CLINICAL RESEARCH IN INFECTIOUS DISEASES

STATISTICAL ANALYSIS PLAN
for
DMID Protocol: 20-0033

Study Title:
A Phase 1 Adaptive, Multiple Dose Pharmacokinetic and Safety Assessment of Valacyclovir in Infants at Risk of Acquiring Neonatal Herpes Simplex Virus Disease

NCT05468619

Version 1.0

DATE: 13 JUN 2025

RESTRICTED

STUDY TITLE

Protocol Number Code:	**DMID Protocol: 20-0033**
Development Phase:	Phase 1
Products:	Valacyclovir
Form/Route:	Oral Suspension
Indication Studied:	Herpes Simplex Virus Disease
Sponsor:	Division of Microbiology and Infectious Diseases National Institute of Allergy and Infectious Diseases National Institutes of Health
Clinical Trial Initiation Date:	23SEP2022
Clinical Trial Completion Date:	TBD
Date of the Analysis Plan:	13 JUN 2025
Version Number:	1.0

This study was performed in compliance with Good Clinical Practice.

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LIST OF ABBREVIATIONS

AE	Adverse Event
AIDS	Acquired Immunodeficiency Syndrome
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
ATC	Anatomical Therapeutic Classification
AUC_{12}	Area Under the Concentration-Time Curve from 0 to 12 hours
AUC_{∞}	Area Under the Concentration-Time Curve from 0 to infinity
C	Celsius
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CRF	Case Report Form
CSR	Clinical Study Report
DAIDS	Division of AIDS
DMID	Division of Microbiology and Infectious Diseases
DNA	Deoxyribonucleic Acid
FDA	Food and Drug Administration
HIV	Humans Immunodeficiency Virus
hr	Hour
HSV	Herpes Simplex Virus
ICH	International Conference on Harmonisation
ITT	Intention to Treat
IV	Intravenous
kg	Kilogram
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mL	Milliliter
N	Number (typically refers to participants)
NIH	National Institutes of Health
ng	Nanogram
PCR	Polymerase Chain Reaction

List of Abbreviations *(continued)*

PI	Principal Investigator
PK	Pharmacokinetics
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SEM	Skin, Eye, and Mouth
SDCC	Statistical and Data Coordinating Center
SDTM	Study Data Tabulation Model
SMC	Safety Monitoring Committee
SOC	System Organ Class
UAB	University of Alabama at Birmingham
ULN	Upper Limit of Normal
WBC	White Blood Cell
WHO	World Health Organization

1. PREFACE

The Statistical Analysis Plan (SAP) for "A Phase 1 Adaptive, Multiple Dose Pharmacokinetic and Safety Assessment of Valacyclovir in Infants at Risk of Acquiring Neonatal Herpes Simplex Virus Disease" (DMID Protocol 20-0033) describes and expands upon the statistical information presented in the protocol.

This document describes all planned safety analyses to be performed by the statistical and data coordinating center (SDCC) and provides reasons and justifications for these analyses. It also includes sample tables, listings, and figures planned for the covered analyses. Note that planned pharmacokinetic (PK) analyses are not covered in this SAP and will be provided in a separate PK analysis plan. The PK analysis will be performed by the University of Alabama at Birmingham (UAB).

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 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

Approximately 85% of neonatal Herpes Simplex Virus (HSV) cases acquire the infection in the peripartum period, as they pass through an infected birth canal [1]. Maternal shedding of virus in the genital tract can be symptomatic (visible lesions) or asymptomatic (no visible evidence of HSV infection), and either can result in peripartum transmission. Women with active lesions at the time of labor are delivered by cesarean section [2], and their neonates are managed with preemptive testing and possibly antiviral therapy [3]. However, women with a history of genital HSV but no lesions at delivery have no specific management requirements, and the standard of care for management of their neonates is to educate the parents on manifestations of neonatal HSV disease, to not test the babies for the virus, and to not provide antiviral therapy until evidence of disease manifests [3].

Detection of asymptomatic maternal shedding of HSV at delivery could allow for preemptive antiviral treatment of the exposed neonate, thereby blocking perinatal exposure from progressing to neonatal infection and disease. To accomplish this, a reliable and rapid means of detecting vaginal shedding at delivery is required, and an appropriate antiviral treatment for the at-risk-but-not-yet-sick neonate must be characterized. The former has been accomplished in a recently completed study of a novel point-of-care polymerase chain reaction (PCR) assay for the detection of HSV deoxyribonucleic acid (DNA) in vaginal swabs of pregnant women at delivery (BAA#HHSN272201100034C; DMID Protocol Number 11-0070; ClinicalTrials.gov Identifier NCT01878383). The purpose of the current study is to address the second part of what is needed by determining the dose of oral valacyclovir that produces reliable acyclovir exposure in neonates.

2.1. Purpose of the Analyses

The safety analyses covered in this SAP will assess and describe the safety profile of valacyclovir among treated neonates.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1. Study Objectives

Primary Objective:

- To establish the dose of valacyclovir in neonates that reliably achieves systemic acyclovir exposures comparable to 10 mg/kg of parenterally administered acyclovir.
    - This SAP does not cover the analyses supporting this objective.

Secondary Objectives:

- To define the pharmacokinetic profile of acyclovir in neonates receiving oral valacyclovir.
    - This SAP does not cover the analyses supporting this objective.
- To assess and describe the safety profile of valacyclovir among treated neonates.

3.2. Endpoints

Primary Endpoint:

- Neonatal plasma acyclovir mean area under the concentration-time curve from 0 to 12 hours (AUC_{12}) between 24,000 ngxhr/mL and 48,000 ngxhr/mL.
    - This SAP does not cover the analyses supporting this endpoint.

Secondary Outcome Measures:

- Plasma acyclovir PK parameters including maximum serum concentration, time to the maximum concentration, half-life, oral clearance, and volume of distribution.
    - This SAP does not cover the analyses supporting this endpoint.
- Grade 3 Adverse Events (AEs).
- Grade 4 AEs and Serious Adverse Events (SAEs).

3.3. Study Definitions and Derived Variables

Baseline Value

The baseline value will be defined as the last value obtained prior to the administration of study product.

Post-Baseline Value

Post-Baseline values refer to measurements and assessments collected after the first administration of study product.

Change From Baseline

Change from baseline will be calculated as: (Post-Baseline value) – (Baseline Value). If the baseline value is not available or is indeterminant, change from baseline will be undefined.

Analysis Day

For clinical laboratory data, summaries will be generated by nominal time point corresponding to the study visit day (e.g., Baseline and Day 5). For such summaries, the data point collected within the visit window (see Table 2) will be used as the data point for the time point. In the case of multiple records within a specific visit window, the value that is closest to the targeted study day will be used in the summaries. If observations have the same distance to the scheduled assessment, the latest one will be used. Data from supplemental and/or unscheduled visits may be used to provide a measurement for a time point, if appropriate.

All the recorded data will be included in listings.

Days on Study

The number of days the participant was on study will be calculated as follows:

(Protocol completion date or early termination date) – (Enrollment date) + 1

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design and Plan

This is a Phase 1, open label multicenter trial to assess the safety and PK of oral valacyclovir in neonates who are at risk of acquiring neonatal HSV disease. This study will determine the valacyclovir dose that results in a systemic acyclovir exposure comparable to 10 mg/kg of parenterally administered acyclovir, which is an AUC_{12} of 24,000 ngxhr/mL to 48,000 ngxhr/mL. Neonates whose mothers have a history of genital HSV infection and are receiving oral valacyclovir in the last several weeks of pregnancy, as per the recommendations of the American College of Obstetrics and Gynecology [4], will be eligible for enrollment. The mothers can have no visible evidence of HSV lesions at the time of delivery, and the neonates will have no signs or symptoms of neonatal HSV disease. Neonates born to women with active herpetic lesions will be excluded from the study because their management is determined by the American Academy of Pediatrics algorithm published in 2013 [5] and in the 2015, 2018, and 2021 Red Books [3, 6 ,7]. Likewise, any baby with signs or symptoms suggestive of neonatal HSV disease will be excluded from this study and instead managed per standard of care.

The starting dose regimen of oral valacyclovir assessed will be 10 mg/kg administered two times daily for 5 days (**Cohort 1**) (Table 1). This dosage has been studied in patients 1 year through 11 years of age, who received twice-daily dosing for 3-5 days, while a single dose of 25 mg/kg has been studied down to 1 month of age [8]. Cohort 1 will be comprised of eight participants. Following informed consent, each participant will receive 10 mg/kg of oral valacyclovir and may start taking oral valacyclovir while still in the birth hospital, with subsequent dosing at home, or may start taking oral valacyclovir following discharge from the birth hospital. **Study Day 1** is the day that the first dose of oral valacyclovir is administered. Following signing of informed consent but prior to administration of the first dose of valacyclovir, hematology and chemistry safety labs (white blood cell [WBC] count and differential for absolute neutrophil count [ANC], hemoglobin, platelet count, alanine aminotransferase [ALT], and creatinine) will be obtained and values checked; if no baseline hematology or chemistry values are Grade 1 toxicity or higher then dosing of valacyclovir will proceed; if any value is Grade 1 toxicity or higher, the participant will be withdrawn from the study prior to receiving any doses of study medication. In addition, the participant must have had a first void before receiving a first dose of study medication. A single plasma sample will also be obtained for a baseline acyclovir concentration, since the mothers of enrolled participants will have been taking antiviral medication prior to delivery. Dropouts and withdrawn participants may be replaced to reach the target sample size of eight participants. Participants will return to the study site on Study Day 5 (window: Study Day 4 through Study Day 5), and also will be assessed for AEs and concomitant medications on Study Day 10 (window: Study Day 7 through Study Day 13) and on Study Day 42 (window: Study Day 35 through Study Day 49), although the Study Day 10 and 42 assessments may occur via telephone or in-person study visits. On the Study Day 5 (window: Study Day 4 through Study Day 5) visit, plasma samples for PK assessments will be obtained around dose 7, 8, 9, or 10 of study drug at 0 hour minus 15 minutes (pre-dose), and then 1-2 hours, 4-6 hours, and 8-10 hours following administration of the valacyclovir dose (full PK profile). Safety laboratory assessments (WBC count with differential, hemoglobin, platelet count, ALT, and creatinine) will be obtained at the Study Day 1 (baseline) and Study Day 5 visits. Safety laboratory values will be classified using the Division of AIDS Toxicity Tables (Table 6). Study drug will be stopped following the obtaining of the PK samples on Study Day 5 (window: Study Day 4 through Study Day 5). Criteria for AEs or SAEs leading to halting of the study are detailed in Section 7.1.1 of the protocol. The total number of study days of study drug administration will be 4 or 5 (depending on where in the window the Study Day 5 visit is

conducted), although the total number of doses can be 7, 8, 9, or 10 depending upon when the study drug was started on Study Day 1 and whether the PK blood draws on Study Day 5 (window: Study Day 4 through Study Day 5) are around the first or second dose that day.

Upon full accrual of Cohort 1, the PK and safety data will be reviewed. If the safety profile and the drug exposure concentrations in Cohort 1 are acceptable, eight new participants will be enrolled in Cohort 2. The dose that these participants will receive will be predicated upon the PK data from Cohort 1. Refer to Section 4.4.5 for the method of dose selection for Cohort 2.

If the targeted exposure is not achieved in Cohorts 1 and 2 and the safety data are acceptable, it is possible, but not anticipated, that additional dosing cohorts could be recommended based upon the results of participants in the first two cohorts. If such a recommendation is made, dose selection and participant enrollment and assessment will follow the approach used for Cohort 2.

The schedule of study procedures is provided in Table 2.

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

The primary objective of this study is to describe the acyclovir AUC_{12} following oral dosing of valacyclovir at the proposed starting dose in Cohort 1 and a linearly adjusted dose in Cohort 2 if required to achieve the targeted exposure. The goal is to generate preliminary PK data in this population to help inform larger dosing/efficacy trials in the future. As such, no comparator arms are included in the design.

4.3. Selection of Study Population

Neonates delivered to mothers receiving oral valacyclovir therapy (or equivalent antiviral drug) for suppression of genital HSV recurrences at the end of pregnancy will be enrolled within the first two days of life.

This pediatric study will not exclude young children, females, or minorities. This study will be inclusive of all children who meet the inclusion/exclusion criteria, regardless of religion, sex, or ethnic background.

Inclusion Criteria:

To be eligible to participate in this study, an individual must meet all of the following criteria:

- Signed informed consent from parent(s) or legal guardian(s)
- Maternal history of genital HSV infection
- Maternal receipt of oral acyclovir, valacyclovir, or famciclovir suppressive therapy for ≥ 7 days prior to delivery
- Gestational age ≥ 38 weeks at birth
- ≤ 2 days of age at study enrollment*
- Weight at study enrollment ≥ 2,000 grams

* For purposes of this study, the calendar day of birth is Day of Life 0.

Exclusion Criteria:

An individual who meets any of the following criteria will be excluded from participation in this study:

- Evidence of neonatal HSV infection
- Evidence of sepsis
- Known renal anomalies or dysfunction
- Maternal genital lesions suspicious for HSV at the time of delivery
- Infants known to be born to women who are human immunodeficiency virus (HIV) positive (but HIV testing is not required for study entry)
- Current receipt in the neonate of acyclovir, ganciclovir, famciclovir, or any investigational drugs

4.4. Treatments

4.4.1. Treatments Administered

The product studied in this trial is Valacyclovir hydrochloride (Valtrex).

4.4.2. Identity of Investigational Product(s)

Valacyclovir hydrochloride (Valtrex) is a white to off-white powder (from tablets) of the hydrochloride salt of the L-valyl ester of acyclovir with the molecular formula $C_{13}H_{20}N_6O_4$•HCl and a molecular weight of 360.80. Each 500 mg tablet (blue, film-coated) contains valacyclovir hydrochloride equivalent to 500 mg valacyclovir and the inactive ingredients carnauba wax, colloidal silicon dioxide, crospovidone, FD&C Blue No. 2 Lake, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, povidone, and titanium dioxide. Valacyclovir tablets will be extemporaneously compounded as an oral suspension using SyrPalta as the oral liquid vehicle. SyrPalta syrup vehicle contains sucrose 83% w/v; Purified Water; Glycerin; Artificial Flavors; 0.2% Alcohol; 0.1% Sodium Benzoate; 0.001% Benzalkonium Chloride as a Preservative. It is the recommended oral liquid vehicle for valacyclovir suspension from the extemporaneous compounding references supported by the FDA Safe Use Initiative: the Michigan Pediatric Safety Collaboration (https://www.mipedscompounds.org/), and the American Society of Health System Pharmacists Standardize 4 Safety Initiative (https://www.ashp.org/-/media/assets/pharmacy-practice/s4s/docs/Compound-Oral-Liquid.ashx).

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

Enrollment will be performed through the enrollment module in the electronic data capture system, maintained by the SDCC. All participants will receive study product; there is no randomization.

4.4.4. Selection of Doses in the Study

Valacyclovir oral suspension has been evaluated in GlaxoSmithKline-sponsored studies in children 1 month to 12 years of age [8], but not in neonates (infants under 1 month of age). In the United States, valacyclovir is licensed for the treatment of pediatric patients with orolabial HSV recurrences (12 years and older) and chickenpox (2 years through 17 years of age). Pediatric valacyclovir dosing is 20 mg/kg per dose (dose not to exceed 1 gram) administered either three times a day (for varicella-zoster virus) or twice a day (for HSV) [8]. Valacyclovir has demonstrated an excellent safety profile over the 20 years since its initial approval in the United States. In order to minimize the likelihood of neutropenia or elevated creatinine in the study

population, the starting valacyclovir dose regimen in this study will be 10 mg/kg/dose, which is one-third of the FDA-approved dose for children 2 years of age and older of 20 mg/kg/dose administered three times per day. Each participant will be carefully monitored for bone marrow toxicity (e.g., neutropenia) and nephrotoxicity (e.g., elevated creatinine) and the drug will be stopped if significant toxicities are encountered in a given participant.

The target concentration of acyclovir following oral valacyclovir dosing is 24,000 ngxhr/mL to 48,000 ngxhr/mL. This range was selected because a normalized dose of 10 mg/kg of parenteral acyclovir produces a mean (± standard deviation [SD]) area under the concentration-time curve from 0 to infinity (AUC_{∞}) of 36,000 (± 12,000) ngxhr/mL in infants 1-2 months of age [8]. This 10 mg/kg parenteral acyclovir dose was the accepted treatment dose for neonatal disease in the 1980s and 1990s [9], and successfully prevents neonatal HSV skin, eye, and mouth (SEM) disease from progressing to disseminated disease [10]. In the current study, antiviral therapy is being used to prevent neonatal exposure from progressing to neonatal infection (and thus to neonatal disease). The drug exposure that prevented less severe disease (SEM disease) from progressing to more severe disease (disseminated disease) has therefore been selected as the target range. Although a 20 mg/kg parenteral acyclovir treatment dose for neonatal disease improves survival in neonatal disease [11], the current study is not proposing to treat disseminated disease but rather to prevent neonatal disease from developing in the first place. Additionally, the amount of virus present on the skin and mucous membranes in exposed neonates will be lower than in 10-19 day old infants who already have neonatal HSV disease, suggesting that lower drug exposure will be sufficient. Finally, this lower exposure has also been selected to minimize likelihood of drug toxicity.

4.4.5. Selection and Timing of Dose for Each Participant

The shelf-life of valacyclovir oral suspension following preparation is 28 days in the refrigerator between 2ºC to 8ºC (36ºF to 46ºF). Study product will be administered by the parent/guardian if participants are at home, or by the hospital staff if participants are in the hospital. Study Cohort 1 will receive valacyclovir at a dose of 10 mg/kg body weight administered two times daily for 5 days. Specific dosing volumes will be provided for each participant based on body weight and valacyclovir oral suspension concentration. Valacyclovir Oral Suspension will be administered into the participant's mouth via an oral dosing syringe. The parent/guardian will be provided with specific dosing, storage, and administration instructions. If the participant vomits or spits up following the dosing, re-dosing for that dose is not allowed.

Dose selection for Cohort 2 will be predicated upon the PK data from Cohort 1. Specifically, the target range of acyclovir exposure is between 24,000 ngxhr/mL and 48,000 ngxhr/mL. If the mean of observed acyclovir exposures of participants in Cohort 1 is below 24,000 ngxhr/mL, AND if no Grade 3 or Grade 4 AEs or SAEs are detected in any of the study participants, then the participants enrolled in Cohort 2 will receive oral valacyclovir at a dose of 20 mg/kg administered two times daily for 5 days. Alternatively, if the mean of observed acyclovir exposures of participants in Cohort 1 is above 48,000 ngxhr/mL AND if no Grade 3 or Grade 4 AEs or SAEs are detected in any of the study participants, then the participants enrolled in Cohort 2 will receive oral valacyclovir at a dose that has been linearly adjusted downward to target 36,000 ngxh/mL $AUC_{0\text{-}12}$. If the mean of observed acyclovir exposures of participants in Cohort 1 is within the target range of 24,000 ngxhr/mL to 48,000 ngxhr/mL, Cohort 2 will not be opened for enrollment unless suggested by the Safety Monitoring Committee (SMC). Based on review of the safety and PK data by the SMC after Cohort 1, it was decided that Cohort 2 would be opened for enrollment and those participants would receive oral valacyclovir at a dose of 20 mg/kg administered two times daily for 5 days.

If the targeted exposure is not achieved in Cohorts 1 and 2 and the safety data are acceptable, it is possible, but not anticipated, that additional dosing cohorts could be recommended based upon the results of participants in the first two cohorts. If such a recommendation is made, dose selection and participant enrollment and assessment will follow the approach used for Cohort 2.

4.4.6. Blinding

This trial is an open-label study so no blinding procedures will be performed.

4.4.7. Prior and Concomitant Therapy

Concomitant medications will be recorded on the specified case report form (CRF) at Study Visit Days 1, 5, 10, and 42.

4.4.8. Treatment Compliance

Assessment of compliance with administration of study medication throughout the 5-day treatment period will be achieved by utilization of a medication diary. The parent(s) or legal guardian(s) will complete this diary daily, indicating the time of drug administration and whether the participant vomited following the dose. The diary will be collected at the Study Day 5 visit and used to complete the Study Drug Administration CRF.

Administration data that are collected and will be summarized by dose include:

- Dose given/taken
  - Yes/No
  - Numeric, in mL (for first dose only)
- Dose vomited
  - Yes/No

4.5. Safety Variables

4.5.1. Participant Disposition

Participant disposition will include the description of participant status at key study milestones and analysis population eligibilities. For participant status, the key milestone variables are the following:

- Screened
- Enrolled
- Received at least one dose of study product
- Receive all doses of study product
- Discontinued study product and reason for discontinuing study product
- Completed all PK blood draws
- Completing the Day 5 follow-up visit
- Completing the Day 10 follow-up visit
- Completing the last follow-up visit (Day 42)
- Terminated early from the study and reason for early termination

For the analysis populations below, the variables are inclusion and exclusion from the analysis population as well as the reason(s) for exclusion:

- Intention to Treat (ITT) Population
- Safety Population
- Per Protocol Population
- PK Population

4.5.2. Demographics and Other Baseline Characteristics

The following demographics and growth parameters will be collected from the participant's medical records to the extent the information is available, or by direct assessment of the participant and questioning of the parent(s) or legal guardian(s):

- Sex
  - Male or Female
- Age
  - Numeric, in months
- Race
  - American Indian or Alaskan Native; Asian; Native Hawaiian or Other Pacific Islander; Black or African American; White; Multi-Racial; Unknown
  - In accordance with NIH reporting policy, participants may self-designate as belonging to more than one race or may refuse to identify a race, the latter reflected in the CRF as "No" to each racial option.
- Ethnicity
  - Hispanic or Latino; Not Hispanic or Latino; Not Reported; Unknown.
- Weight at enrollment
  - Numeric, in kg
- Length at enrollment
  - Numeric, in cm
- Gestational age at birth
  - Numeric, in weeks
- Weight at birth
  - Numeric, in kg

4.5.3. Adverse Event Assessment

At each study visit following the receipt of first dose of study drug and continuing through four weeks following the final dose of study drug, the study participant will be assessed for any AEs.

An AE is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of medicinal (investigational) product whether or not considered drug related. The occurrence of an AE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

Information to be collected on reportable AEs includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis, which would include MD or DO), and time of resolution/stabilization of the event. All AEs occurring from Study Day 1 through four weeks following the last dose of study drug must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the patient is enrolled should be considered as a baseline condition and not reported as an AE. However, if the event meets the criteria and the grade of the event worsens at any time during the study, it should be recorded as an AE.

The determination of seriousness, severity, and causality will be made by an on-site investigator who is qualified (licensed) to diagnose AE information, provide a medical evaluation of AEs, and classify AEs based upon medical judgment. This includes MD or DO. Events will be identified by assessing the participant at each visit. If a participant is hospitalized, the medical record should be reviewed to identify AEs. The PI is responsible for identifying and reporting AEs according to protocol guidelines.

Unsolicited AEs

All AEs spontaneously reported by the participant and/or in response to an open question from study personnel or revealed by observation, physical examination or other diagnostic procedures must be recorded in the source document and on the appropriate page of the CRF. All reported unsolicited AEs are graded in accordance with the toxicity tables (Table 5 and Table 6).

Serious AEs

An SAE is defined as an AE or suspected AE is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death,
- A life-threatening adverse event*;
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions; or
- A congenital anomaly/birth defect.

  * Life-threatening AE. An AE is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or participant at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death. It does not necessarily include all grade 4 AEs according to the toxicity tables (Table 5 and Table 6).

Important medical events that may not result in death, be life-threatening, or require hospitalizations may be considered serious when, based upon appropriate medical judgment they may jeopardize the patient or participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Severity of AE

All reportable AEs will be graded by the investigator according to the protocol toxicity tables (Table 5 and Table 6) using a four-grade system: Mild, Moderate, Severe, and Potentially Life-Threatening. For safety laboratory results with an absolute number in the toxicity tables (e.g., hemoglobin), grading of the AEs will be according to the toxicity tables and not according to the local laboratory reference range. For safety laboratory results with a reference to the Upper Limit of Normal (ULN) in the toxicity tables (e.g., ALT or SGPT), grading of the AEs will utilize the ULN of the local laboratory reference range in determining grading of the event per the toxicity tables. Grade 4 AEs will be only reported as SAE if the event meets one of the regulatory definitions of SAE described below based on the study site physician judgment. The functional table below should be used to grade the severity of an AE that is not specifically identified in the grading table.

In addition, all deaths related to an AE are to be classified as grade 5.

Relationship to Study Intervention

For each reported adverse reaction, the Principal Investigator (PI) or designee must assess the relationship of the event to the study product using the following guideline:

- **Related** – The AE is known to occur with the study intervention, there is a reasonable possibility that the study intervention caused the AE, or there is a temporal relationship between the study intervention and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the AE.
- **Not Related** – There is not a reasonable possibility that the administration of the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or an alternate etiology has been established.

Time Period and Frequency for AE Assessment and Follow-up

All AEs, including safety laboratory AEs, and all SAEs will be documented from Study Day 1 through four weeks following the last dose of study drug.

All AEs and SAEs will be followed until resolution, even if this extends beyond the study-reporting period, which is 4 weeks following the last dose of study product. Resolution of an AE is defined as the return to pretreatment status or stabilization of the condition with the expectation that it will remain chronic.

At any time after completion of the study, if the investigator becomes aware of an SAE that is suspected to be related to study product, the investigator will report the event.

4.5.4. Concomitant Medications Assessment

At each study visit from the receipt of first dose of study drug and continuing through four weeks following the final dose of study drug, concomitant medications that are being administered to the participant will be recorded.

4.5.5. Laboratory Evaluations

Blood for study-specified laboratory evaluations may be obtained by methods such as the following: venipuncture, heel stick, indwelling intravenous catheter, etc. As detailed below, blood will be obtained for assessment of hematology safety labs, chemistry safety labs, and acyclovir concentrations; blood draws will be attempted a second time if the first attempt is unsuccessful. If an insufficient volume of blood is obtained for all of the tests at any given study visit, the following prioritization as to which tests to send will apply (most important to least important): 1) PK samples for acyclovir plasma concentrations (most important); 2) hematology safety labs (second most important); and 3) chemistry safety labs (third most important). With the exception of the PK samples and the WBC count with differential, those lab tests that are unable to be obtained due to lack of sufficient blood or parental refusal at a given study visit will be noted but will not be reported as protocol deviations. As far as possible, research specimens should be taken to coincide with clinical care.

If a laboratory value is outside of the protocol specified range, then the measurement may be repeated if there is a technical problem with the measurement cause by a laboratory error or a malfunctioning or inappropriate device. Laboratory parameters other than those specified in hematology safety labs and chemistry safety labs as part of the complete blood count and complete metabolic panel need to be evaluated by the site physician, recorded in the source document, and reported as laboratory AEs if clinically significant.

Clinical Laboratory Evaluations

Clinical laboratory results can be used for chemistry and hematology safety labs if collected within the required study window and will be graded according to Table 6. If labs drawn for the study-required assessments are not evaluable, blood draws will not be repeated.

Hematology Safety Labs

All hematology safety laboratory assessments will be conducted at the PI's local lab. They will be obtained on Study Days 1 and 5. The following will be tested: WBC with differential, hemoglobin, and platelet count. From the WBC count and differential, the ANC will be calculated.

Chemistry Safety Labs

All chemistry safety laboratory assessments will be conducted at the PI's local lab. They will be obtained on Study Days 1 and 5. The following will be tested: ALT and creatinine.

5. SAMPLE SIZE CONSIDERATIONS

The sample size will be characterized by the width of a 95% confidence interval (CI) for AUC_{∞} in Cohort 1. As previously noted, in infants 1-2 months of age, the mean (± SD) AUC_{∞} is 36,000 (± 12,000) ngxhr/mL for a normalized dose of 10 mg/kg of intravenous (IV) acyclovir [8]. A higher (lower) dose for Cohort 2 will be considered when observed acyclovir exposures in Cohort 1 are below the mean of 24,000 (above 48,000) ngxhr/mL. Assuming a constant coefficient of variation of 0.3333 in determining the SD of AUC_{∞} for a given mean, a sample size of eight will be characterized in terms of the width of a 95% two-sided CI for the mean. If the observed mean is 24,000 ngxhr/mL and using a SD of 8,000 ngxhr/mL, a two-sided 95% CI for the mean AUC_{∞} is (17,312-30,688), i.e., the true mean can be as low as 17,312 ngxhr/mL but no higher than 30,688 ngxhr/mL. If the observed mean is 48,000 ngxhr/mL and using a SD of 15,998 ngxhr/mL, a two-sided 95% CI for the mean AUC_{∞} is (34,625-61,375), i.e., the true mean can be as high as 61,375 ngxhr/mL but no lower than 34,625 ngxhr/mL. For the CIs for other sample sizes, refer to Table 3.

For the 95% upper bound for the proportion experiencing AEs or SAEs when 0 are observed in a sample size of n. For example, if n=8 and no SAEs are observed, then there is 95% confidence that the rate is no more than 36.9%. If n=10, there is 95% confidence that the rate is not more than 30.8%. The larger the n, the tighter (i.e., closer to 0) the upper bound.

6. GENERAL STATISTICAL CONSIDERATIONS

6.1. General Principles

In general, all data will be listed, sorted by site, dose level, and participant, and when appropriate by visit within participant. All summary tables will be structured with columns for dose level (10 mg/kg, 20 mg/kg) and will be annotated with the total population size relevant to that table/treatment, including any missing observations.

All continuous variables will be summarized using the following descriptive statistics: n (non-missing sample size), mean, SD, median, maximum, and minimum. For laboratory data, 10^{th} and 90^{th} percentiles will be used instead of minimum and maximum. The frequency and percentages (based on the non-missing sample size) of observed levels will be reported for all categorical measures.

Boxplots will be used to display change from baseline summary statistics for continuous variables. For estimating proportion CIs, the Clopper-Pearson method will be utilized, where the confidence level will be at least 95% for estimation.

6.2. Timing of Analyses

The final analyses of safety data will be performed after database lock.

6.3. Analysis Populations

6.3.1. ITT Population

Any child who receives at least one dose of study medication will be included in an ITT analysis of safety.

6.3.2. Safety Population

The Safety Population will consist of all participants who have received at least one dose of study product and for whom any data on safety are available.

6.3.3. Per Protocol Population

The Per Protocol Population will consist of all participants who complete the course of study medication. A complete dose of study medication includes having received 7, 8, 9, or 10 doses.

6.3.4. PK Population

The PK Population will be defined in a separate PK analysis plan.

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

Missing safety data will be assumed to be missing completely at random and will not be imputed.

6.6. Interim Analyses and Data Monitoring

The initial oral valacyclovir dose will be 10 mg/kg administered two times daily for 5 days (Cohort 1). The target exposure for acyclovir following oral valacyclovir dosing is 36,000 ngxhr/mL with a range of 24,000 ngxhr/mL to 48,000 ngxhr/mL. Upon full accrual and follow-up of Cohort 1, the PK and safety data will be reviewed by the SMC, using the approved report shell. If the mean of observed acyclovir exposures of participants in Cohort 1 are below 24,000 ngxhr/mL, AND if no Grade 3 or Grade 4 AEs or SAEs are detected in any of the study participants, then the participants enrolled in Cohort 2 will receive oral valacyclovir at a dose of 20 mg/kg administered two times daily for 5 days. Alternatively, if the mean of observed acyclovir exposures of participants in Cohort 1 are above 48,000 ngxhr/mL AND if no Grade 3 or Grade 4 AEs or SAEs are detected in any of the study participants, then the participants enrolled in Cohort 2 will receive oral valacyclovir at a dose that has been linearly adjusted downward to target 36,000 ngxh/mL AUC_{12}. The SMC retains the ability to suggest an alternative dose be studied in Cohort 2 if the mean AUC_{12} from Cohort 1 is within but at or near the lower or upper ranges in order to attain an AUC_{12} closer to the 36,000 ngxhr/mL target. Based on review of the safety and PK data by the SMC after Cohort 1, it was decided that Cohort 2 would be opened for enrollment and those participants would receive oral valacyclovir at a dose of 20 mg/kg administered two times daily for 5 days.

If the targeted exposure is not achieved in Cohorts 1 and 2 and the safety data are acceptable, it is possible, but not anticipated, that additional dosing cohorts could be recommended based upon the results of participants in the first two cohorts. If such a recommendation is made, dose selection and participant enrollment and assessment will follow the approach used for Cohort 2.

The SMC will also conduct ad hoc meetings if trial-level halting criteria are met or at the request of DMID to review a potential safety concern identified by either the lead PI, DMID Medical Monitor, or protocol team. Additional data may be requested by the SMC, and interim statistical reports may be generated as deemed necessary and appropriate by the SMC.

There are no other planned interim analyses.

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 product administration and assessment of unsolicited AEs, and the study relies on central laboratories for the assessment of PK endpoints.

6.8. Multiple Comparisons/Multiplicity

No adjustments for multiple testing are planned.

7. STUDY PARTICIPANTS

7.1. Disposition of Participants

The disposition of participants in the study will be tabulated by dose level, providing summaries of the disposition metrics noted in Section 4.5.1 (Table 7). The composition of analysis populations, including reasons for participant exclusion, by dose level, will also be summarized (Table 8). Reasons participants were screened but not enrolled will be summarized (Table 9).

A flowchart showing the disposition of study participants, adapted from the Consort Statement will be generated (Figure 1). This figure will present the number of participants screened, enrolled, lost to follow-up, and analyzed, by dose level.

A listing of participants who received study product will be generated (Listing 1). Participants who terminated early and/or discontinued study product will be listed (Listing 2). A listing of participants excluded from analyses will be generated (Listing 5).

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 level for all participants (Table 4). This table will provide the number of participants and the number of deviations for each deviation and deviation type. All participant-specific protocol deviations and non-participant specific protocol deviations will be included in participant listings (Listing 3 and Listing 4, respectively).

All protocol deviations will be classified as either a major or minor deviation and summarized accordingly. As the question of a major or minor deviation was not included on the protocol deviation CRFs, the following process will be used to classify the deviations: (1) Prior to database lock, the SDCC will generate a spreadsheet of all protocol deviations (participant-specific and non-participant specific separately) and will assign major/minor according to the major protocol deviation list finalized with DMID; (2) DMID will review the list and confirm the agreement or not; (3) Once the classifications are completed and finalized, the SDCC will incorporate this spreadsheet into their programming.

8. EFFICACY EVALUATION

There are no efficacy objectives/endpoints for this study.

9. SAFETY EVALUATION

9.1. Demographic and Other Baseline Characteristics

Summaries of the demographic and baseline characteristics noted in Section 4.5.2 will be summarized by study site (Table 10 and Table 11) and dose level (Table 12 and Table 13).

Individual participant listings will be generated for all demographic and growth parameters (Listing 6).

9.1.1. Prior and Concurrent Medical Conditions

All current illnesses and past pre-existing medical conditions will be coded using Medical Dictionary for Regulatory Activities (MedDRA) dictionary version 27.0 or higher.

Summaries of participants' pre-existing medical conditions will be presented by dose level (Table 14).

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

9.1.2. Prior and Concomitant Medications

Summaries of medications that were started prior to dosing and continuing at the time of dosing will be presented by WHO Drug Terms 2 and 3 and dose level (Table 27).

Individual participants listings will be generated for all concomitant medications (Listing 11).

9.2. Measurements of Treatment Compliance

A listing of the treatment compliance data noted in Section 4.4.8 will be generated (Listing 8).

Section 7.1 describes the additional tabular and listing output for compliance data.

9.3. Adverse Events

Safety evaluations will be based on the incidence, severity, and type of AEs. Safety variables will be tabulated and presented for all participants in the safety population.

When calculating the incidence of AEs (i.e., on a per participant basis), each participant will only be counted once and any repetitions of AEs within a participant will be ignored; the denominator will be the total population size. All AEs reported will be included in the summaries and analyses.

9.3.1. Unsolicited Adverse Events

An overall summary of unsolicited AEs will be generated which includes the following participant-level counts in each dose level: the number of participants reporting at least one AE, related AE, SAE, related SAE, and AE leading to early termination from the study (Table 15).

The number and percentage of participants reporting at least one unsolicited AE will be summarized by MedDRA System Organ Class (SOC) and Preferred Term (PT) (Table 16). The number of events within each SOC and PT will also be presented with the participant-level counts in this table. Counts and percentages will also be broken out by severity (Table 17). Related AEs will be summarized similarly (Table 18). Tabular summaries will be supplemented by the following graphical summaries:

- Event-level counts of AEs by SOC and severity (Figure 2)
- Event-level counts of related AEs by SOC and severity (Figure 3)
- Participant-level counts of AEs by SOC and maximum severity (Figure 4)
- Participant-level counts of related AEs by SOC and maximum severity (Figure 5)

The following participant listings will be generated:

- Unsolicited AEs (Listing 9)
- SAEs (Table 19)
- Non-serious unsolicited AEs of moderate or greater severity (Table 20)

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

A participant listing of SAEs, including deaths, will be generated (Table 19).

9.5. Pregnancies

Not applicable.

9.6. Clinical Laboratory Evaluations

Laboratory results will be summarized separately for chemistry and hematology parameters. Laboratory data summaries will include:

- Results by time point and severity (Table 23 and Table 25).
- Descriptive statistics including mean, SD, and change from baseline by time point (Table 24 and Table 26)
- Graphical summary of the change from baseline (Figure 6 and Figure 7)

Participant listings of clinical laboratory results will be generated for abnormal values, including results that are outside the normal range, (Table 21 and Table 22) and all values (Listing 10 and Listing 11).

9.7. Vital Signs and Physical Evaluations

Vital sign measurements are not collected, and physical examinations are not performed in this study. Length and weight are summarized with demographics.

9.8. Concomitant Medications

Concomitant medications will be coded to the Anatomical Therapeutic Classification (ATC) 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 ATC1, ATC2 code and dose level for the Safety population (Table 27).

Individual participant listings will be generated for all concomitant medications (Listing 12).

10. PHARMACOKINETICS

The analyses of PK endpoints are not provided by this SAP and will be provided in a separate PK analysis plan. The PK analysis will be performed by UAB, and results from this analysis will be transferred to the SDCC upon completion. The SDCC is responsible for mapping these results to Clinical Data Interchange Standards Consortium (CDISC) study data tabulation model (SDTM) datasets but will not validate any analysis performed by UAB.

11. IMMUNOGENICITY

Not Applicable.

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. 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%.

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

There are no changes in the conduct of the study or planned analyses to report.

16. REFERENCES

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17. LISTING OF TABLES, FIGURES, AND LISTINGS

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

APPENDICES

APPENDIX 1. TABLE MOCK-UPS

LIST OF TABLES

9.1 Overall Study Design and Plan Description

Table 1: Dosing and Administration

Cohort	Product Name	Dose	Route	Frequency of Administration	Duration of Therapy
1	Valacyclovir	10 mg/kg	Oral	bid	5 days
2	Valacyclovir	20 mg/kg	Oral	bid	5 days

9.5.1 Pharmacokinetic and Safety Measurements Assessed and Flow Chart

Table 2: Schedule of Study Procedures

	Study Day (window)			
	1	**5 (- 1 day)**	**10 (± 3 days)**	**42 (± 7 days)**
Informed consent	X			
Baseline demographics[a]	X			
Hematology safety labs[b]	X	X		
Chemistry safety labs[c]	X	X		
Adverse Event assessment	X[d]	X	X[e]	X[e]
Concomitant medications	X	X	X[e]	X[e]
Oral valacyclovir administration BID[f,g]	←	→		
PK assessment[h]	X[i]	X[j]		
Total volume of blood required for study	1.7 mL	2.3 mL	0.0 mL	0.0 mL

[a]Gestational age at delivery, date of birth, sex, race, ethnicity, birth weight, weight at enrollment, length in centimeters at enrollment, and baseline conditions prior to study enrollment, by body system.
[b]WBC with differential, Hemoglobin, Platelets (approximate total blood needed for these tests is 0.5 mL).
[c]Alanine aminotransferase (ALT) and creatinine (approximate total blood needed for these tests is 1.0 mL).
[d]Adverse events that occur following the first dose of study medication.
[e]This assessment may occur via telephone or an in-person study visit.
[f]Oral valacyclovir will be administered as 10 mg/kg/dose two times per day (Cohort 1) or as 20 mg/kg/dose two times per day (or an adjusted dose, as detailed above in Study Design) (Cohort 2). Hematology and chemistry safety labs will be confirmed to have no ≥ Grade 1 values utilizing the DAIDS Toxicity Tables (Appendix A in the protocol) prior to the first oral dose of valacyclovir being administered on Study Day 1; if any value is Grade 1 toxicity or higher, the participant will be withdrawn from the study and will not receive study medication. In addition, the participant must have had a first void before receiving a first dose of study medication. Total number of study days of study drug administration will be 4 or 5 (depending on where in the window the Study Day 5 visit is conducted), although the total number of doses can be 7, 8, 9, or 10 depending upon when the study drug was started on Study Day 1 and whether the PK blood draws on Study Day 5 (window: Study Day 4 through Study Day 5) are around the first or second dose that day. Study drug will be stopped following the obtaining of the PK samples on Study Day 5 (window: Study Day 4 through Study Day 5).
[g]Assessment of compliance with administration of study medication throughout the 5-day treatment period will be achieved by utilization of a medication diary. The parent(s) or legal guardian(s) will complete this diary daily, indicating the time of drug administration and whether the participant vomited following the dose. The diary will be collected at the Study Day 5 visit.
[h]A minimum of 200 µL (0.2 mL) of whole blood is required for collection at each time point for plasma acyclovir concentration determination.
[i]A single 0.2 mL whole blood sample for PK assessment will be obtained from study participants with the Study Day 1 hematology and chemistry safety labs.
[j]Plasma samples for PK assessments will be obtained from study participants around dose 7, 8, 9, or 10 of study drug at 0 hour -15 minutes (pre-dose), and then 1-2 hours, 4-6 hours, and 8-10 hours following administration of the dose. This will be a total blood volume of 0.8 ml if all four PK time points are collected.

9.7.1 Sample Size

Table 3: Sample Size Determination

N	95% Confidence Bound for Event Rates*	95% CI for Mean AUC∞ Assuming a Sample Mean of 24,000 and SD=8,000		95% CI for Mean AUC∞ Assuming a Sample Mean of 48,000 and SD=15,998	
		Lower	Upper	Lower	Upper
5	0.5218	14,066.69	33,933.31	28,135.86	67,864.14
6	0.4593	15,604.52	32,395.49	31,211.13	64,788.87
7	0.4096	16,601.23	31,398.77	33,204.32	62,795.68
8	0.3694	17,311.83	30,688.17	34,625.34	61,374.66
9	0.3363	17,850.66	30,149.34	35,702.85	60,297.15
10	0.3085	18,277.15	29,722.86	36,555.72	59,444.28
11	0.2849	18,625.53	29,374.47	37,252.40	58,747.60
12	0.2646	18,917.04	29,082.96	37,835.36	58,164.64
13	0.2471	19,165.65	28,834.35	38,332.51	57,667.49
14	0.2316	19,380.94	28,619.06	38,763.03	57,236.97
15	0.2180	19,569.75	28,430.25	39,140.60	56,859.40

*When no events are observed.

10.2 Protocol Deviations

Table 4: Protocol Deviations by Classification, Category, Type, and Dose Level, All Enrolled Participants

Category	Deviation Type	10 mg/kg (N=X)		20 mg/kg (N=X)		All Participants (N=X)	
		No. of Pts.	No. of Dev.	No. of Pts.	No. of Dev.	No. of Pts.	No. of Dev.
Major Protocol Deviations							
Eligibility/ enrollment	Any type						
	Did not meet inclusion criterion	x	x	x	x	x	x
	Met exclusion criterion						
	ICF not signed prior to study procedures						
	Other						
Treatment administration schedule	Any type						
	Out of window visit						
	Missed visit/visit not conducted						
	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						
	Incorrect version of ICF signed						
	Blood not collected						
	Other specimen not collected						
	Too few aliquots obtained						
	Specimen result not obtained						
	Required procedure not conducted						
	Required procedure done incorrectly						
	Study product temperature excursion						
	Specimen temperature excursion						
	Other						
Treatment administration	Any type						
	Required procedure done incorrectly						
	Study product temperature excursion						
	Other						
Minor Protocol Deviations							
Eligibility/ enrollment	Any type						
	Did not meet inclusion criterion						
	…						
…	…						
Note: N = Number of enrolled participants.							

12.2.2 Displays of Adverse Events

Table 5: Adverse Event Grading Scale

PARAMETER	GRADE 1/ MILD	GRADE 2/ MODERATE	GRADE 3/ SEVERE	GRADE 4/ POTENTIALLY LIFE- THREATENING
Diarrhea *< 1 year of age*	Liquid stools (more unformed than usual) but usual number of stools	Liquid stools with increased number of stools OR Mild dehydration	Liquid stools with moderate dehydration	Life-threatening consequences (e.g., liquid stools resulting in severe dehydration, hypotensive shock)
Vomiting	Transient or intermittent AND No or minimal interference with oral intake	Frequent episodes with no or mild dehydration	Persistent vomiting resulting in orthostatic hypotension OR Aggressive rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)

12.4.1 Individual Laboratory Measurements and Abnormal Laboratory Values

Table 6: Laboratory Toxicity Grading Scale

PARAMETER	GRADE 1\/ MILD	GRADE 2/ MODERATE	GRADE 3/ SEVERE	GRADE 4/ POTENTIALLY LIFE- THREATENING
ALT or SGPT, High *Report only one*	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Creatinine, High	1.1 to 1.3 x ULN	> 1.3 to 1.8 x ULN OR Increase of > 0.3 mg/dL above baseline	> 1.8 to < 3.5 x ULN OR Increase of 1.5 to < 2.0 x above baseline	≥ 3.5 x ULN OR Increase of ≥ 2.0 x above baseline
Absolute Neutrophil Count (ANC), Low (cells/mm^3; *cells/L*) *> 7 days of age*	800 to 1,000 *0.800 x 10^9 to 1.000 x 10^9*	600 to 799 *0.600 x 10^9 to 0.799 x 10^9*	400 to 599 *0.400 x 10^9 to 0.599 x 10^9*	< 400 *< 0.400 x 10^9*
2 to 7 days of age	1,250 to 1,500 *1.250 x 10^9 to 1.500 x 10^9*	1,000 to 1,249 *1.000 x 10^9 to 1.249 x 10^9*	750 to 999 *0.750 x 10^9 to 0.999 x 10^9*	< 750 *< 0.750 x 10^9*
≤ 1 day of age	4,000 to 5,000 *4.000 x 10^9 to 5.000 x 10^9*	3,000 to 3,999 *3.000 x 10^9 to 3.999 x 10^9*	1,500 to 2,999 *1.500 x 10^9 to 2.999 x 10^9*	< 1,500 *< 1.500 x 10^9*
Hemoglobin, Low (g/dL; *mmol/L*) *≥ 13 years of age (male only)*	10.0 to 10.9 *6.19 to 6.76*	9.0 to < 10.0 *5.57 to < 6.19*	7.0 to < 9.0 *4.34 to < 5.57*	< 7.0 *< 4.34*
≥ 13 years of age (female only)	9.5 to 10.4 *5.88 to 6.48*	8.5 to < 9.5 *5.25 to < 5.88*	6.5 to < 8.5 *4.03 to < 5.25*	< 6.5 *< 4.03*
57 days of age to < 13 years of age (male and female)	9.5 to 10.4 *5.88 to 6.48*	8.5 to < 9.5 *5.25 to < 5.88*	6.5 to < 8.5 *4.03 to < 5.25*	< 6.5 *< 4.03*
36 to 56 days of age (male and female)	8.5 to 9.6 *5.26 to 5.99*	7.0 to < 8.5 *4.32 to < 5.26*	6.0 to < 7.0 *3.72 to < 4.32*	< 6.0 *< 3.72*
22 to 35 days of age (male and female)	9.5 to 11.0 *5.88 to 6.86*	8.0 to < 9.5 *4.94 to < 5.88*	6.7 to < 8.0 *4.15 to < 4.94*	< 6.7 *< 4.15*
8 to ≤ 21 days of age (male and female)	11.0 to 13.0 *6.81 to 8.10*	9.0 to < 11.0 *5.57 to < 6.81*	8.0 to < 9.0 *4.96 to < 5.57*	< 8.0 *< 4.96*
≤ 7 days of age (male and female)	13.0 to 14.0 *8.05 to 8.72*	10.0 to < 13.0 *6.19 to < 8.05*	9.0 to < 10.0 *5.59 to < 6.19*	< 9.0 *< 5.59*
Platelets, Decreased (cells/mm^3; *cells/L*)	100,000 to < 124,999 *100.000 x 10^9 to < 124.999 x 10^9*	50,000 to < 100,000 *50.000 x 10^9 to < 100.000 x 10^9*	25,000 to < 50,000 *25.000 x 10^9 to < 50.000 x 10^9*	< 25,000 *< 25.000 x 10^9*
WBC, Decreased (cells/mm^3; *cells/L*) *> 7 days of age*	2,000 to 2,499 *2.000 x 10^9 to 2.499 x 10^9*	1,500 to 1,999 *1.500 x 10^9 to 1.999 x 10^9*	1,000 to 1,499 *1.000 x 10^9 to 1.499 x 10^9*	< 1,000 *< 1.000 x 10^9*
≤ 7 days of age	5,500 to 6,999 *5.500 x 10^9 to 6.999 x 10^9*	4,000 to 5,499 *4.000 x 10^9 to 5.499 x 10^9*	2,500 to 3,999 *2.500 x 10^9 to 3.999 x 10^9*	< 2,500 *< 2.500 x 10^9*

14.1 Description of Study Participants

14.1.1 Disposition of Participants

Table 7: Participant Disposition by Dose Level, All Enrolled Participants

Participant Disposition	10 mg/kg (N=X)		20 mg/kg (N=X)		All Participants (N=X)	
	n	%	n	%	n	%
Screened	--	--	--	--	x	--
Enrolled	x	100	x	100	x	100
Received at least One Dose of Study Product	x	xx	x	xx	x	xx
Received Complete Dose of Study Product[a]	x	xx	x	xx	x	xx
Discontinued Study Product						
[Reason 1]						
[Reason 2]						
…[etc.]						
Completed All PK Blood Draws						
Completed Study Day 5 Visit						
Completed Study Day 10 Visit						
Completed Study Day 42 Visit						
Terminated Early from Study						
[Reason 1]						
[Reason 2]						
…[etc.]						

Note: N = Number of enrolled participants.
[a]Complete dose of study product includes having received 7, 8, 9, or 10 doses.

Table 8: Analysis Populations by Dose Level, All Enrolled Participants

[Implementation Note: Add rows for PK Population, per definition provided in the PK analysis plan.]

Analysis Populations		10 mg/kg (N=X)		20 mg/kg (N=X)		All Participants (N=X)	
		n	%	n	%	%	n
ITT Population	Included	x	xx	x	xx	x	xx
	Excluded						
	Did not receive study product						
Safety Population	Included						
	Excluded						
	Did not receive study product						
	Does not have any safety data						
Per Protocol Population	Included						
	Excluded						
	Did not receive a complete dose of study product[a]						

Note: N = Number of enrolled participants.
[a]Complete dose of study product includes having received 7, 8, 9, or 10 doses.

Table 9: Screen Failures

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

[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: Categorical Demographic and Baseline Characteristics by Site, All Enrolled Participants

[Implementation Note: Only include sites that enrolled participants. If too many sites enrolled participants to fit across, rows and columns can be switched.]

Variable	Characteristic	[Site 1] (N=X)		[Site 2] (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						
	Unknown						
Race	American Indian or Alaska Native	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 enrolled participants.							

Table 11: Continuous Demographic and Baseline Characteristics by Site, All Enrolled Participants

[Implementation Note: Only include sites that enrolled participants. If too many sites enrolled participants to fit across, rows and columns can be switched.]

Variable	Statistic	[Site 1] (N=X)	[Site 2] (N=X)	All Participants (N=X)
Age (days)	n	xx	xx	xx
	Mean	xx	xx	xx
	Standard Deviation	xx	xx	xx
	Median	x	x	x
	Minimum	x	x	x
	Maximum	x	x	x
Weight at Enrollment (kg)	n	xx	xx	xx
	Mean			
	Standard Deviation	xx	xx	xx
	Median	x	x	x
	Minimum	x	x	x
	Maximum	x	x	x
Length at Enrollment (cm)	n			
	Mean			
	Standard Deviation			
	Median			
	Minimum			
	Maximum			
Gestational Age at Birth (weeks)	n			
	Mean			
	Standard Deviation			
	Median			
	Minimum			
	Maximum			
Weight at Birth (kg)	n			
	Mean			
	Standard Deviation			
	Median			
	Minimum			
	Maximum			

Notes: N = Number of enrolled participants.
n = Number of participants with known characteristic.

Table 12: Categorical Demographic and Baseline Characteristics by Dose Level, All Enrolled Participants

Variable	Characteristic	10 mg/kg (N=X)		20 mg/kg (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						
	Unknown						
Race	American Indian or Alaska Native	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 enrolled participants.

Table 13: Continuous Demographic and Baseline Characteristics by Dose Level, All Enrolled Participants

Variable	Statistic	10 mg/kg (N=X)	20 mg/kg (N=X)	All Participants (N=X)
Age (days)	n	xx	xx	xx
	Mean	xx	xx	xx
	Standard Deviation	xx	xx	xx
	Median	x	x	x
	Minimum	x	x	x
	Maximum	x	x	x
Weight at Enrollment (kg)	n	xx	xx	xx
	Mean			
	Standard Deviation	xx	xx	xx
	Median	x	x	x
	Minimum	x	x	x
	Maximum	x	x	x
Length at Enrollment (cm)	n			
	Mean			
	Standard Deviation			
	Median			
	Minimum			
	Maximum			
Gestational Age at Birth (weeks)	n			
	Mean			
	Standard Deviation			
	Median			
	Minimum			
	Maximum			
Weight at Birth (kg)	n			
	Mean			
	Standard Deviation			
	Median			
	Minimum			
	Maximum			

Notes: N = Number of enrolled participants.
n = Number of participants with known characteristic.

14.1.3 Prior and Concurrent Medical Conditions

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

MedDRA System Organ Class	10 mg/kg (N=X)		20 mg/kg (N=X)		All Participants (N=X)	
	n	%	n	%	n	%
Any SOC	x	xx	x	xx	x	xx
[SOC 1]						
[SOC 2]						
[etc…]						

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

14.2 Pharmacokinetic Data

Not Applicable. Please see the PK analysis plan.

14.3 Safety Data

14.3.1 Displays of Adverse Events

Table 15: Overall Summary of Adverse Events, Safety Population

Participants[a] with	10 mg/kg (N = xx)		20 mg/kg (N = xx)		All Participants (N = xx)	
	n	%	n	%	n	%
At least one unsolicited adverse event	x	x	x	x	x	x
At least one related unsolicited adverse event	x	x	x	x	x	x
Mild (Grade 1)	x	x	x	x	x	x
Moderate (Grade 2)	x	x	x	x	x	x
Severe (Grade 3)	x	x	x	x	x	x
Life-Threatening (Grade 4)	x	x	x	x	x	x
At least one severe (Grade 3) or higher unsolicited adverse event	x	x	x	x	x	x
Related	x	x	x	x	x	x
Unrelated	x	x	x	x	x	x
At least one serious adverse event	x	x	x	x	x	x
At least one related, serious adverse event	x	x	x	x	x	x
At least one adverse event leading to early termination	x	x	x	x	x	x

Note: N = Number of participants in the Safety Population.
[a]Participants are counted once for each category regardless of the number of events.

Table 16: Summary of Adverse Events by MedDRA System Organ Class and Preferred Term, and Dose Level, Safety Population

MedDRA System Organ Class	MedDRA Preferred Term	10 mg/kg (N=X)			20 mg/kg (N=X)			All Participants (N=X)		
		n (%)	95% CI[a]	m	n (%)	95% CI[a]	m	n (%)	95% CI[a]	m
Any SOC	Any PT	x	x	x	x	x	x	x	x	x
[SOC 1]	Any PT	x	x	x	x	x	x	x	x	x
	[PT 1]	x	x	x	x	x	x	x	x	x
	[Etc.]	x	x	x	x	x	x	x	x	x
[SOC 2]	Any PT	x	x	x	x	x	x	x	x	x
	[PT 1]	x	x	x	x	x	x	x	x	x
	[Etc.]	x	x	x	x	x	x	x	x	x
Etc	Etc	x	x	x	x	x	x	x	x	x

Notes: N = Number of participants in the Safety Population.
n = Number of participants reporting event.
m = Total frequency of events reported.
A participant is only counted once per PT.
[a]Exact Clopper-Pearson Confidence Interval.

14.3.1.1 Solicited Adverse Events

Not Applicable.

14.3.1.2 Unsolicited Adverse Events

Table 17: Unsolicited Adverse Events by MedDRA System Organ Class and Preferred Term, Maximum Severity, and Dose Level, Safety Population

MedDRA System Organ Class	MedDRA Preferred Term	Severity	10 mg/kg (N=X) n (%)	20 mg/kg (N=X) n (%)	All Participants (N=X) n (%)
Any SOC	Any PT	Any Severity	x (x)	x (x)	x (x)
		Mild	x (x)	x (x)	x (x)
		Moderate	x (x)	x (x)	x (x)
		Severe	x (x)	x (x)	x (x)
		Life-Threatening	x (x)	x (x)	x (x)
[SOC 1]	Any PT	Any Severity	x (x)	x (x)	x (x)
		…			
	[PT 1]	Any Severity	x (x)	x (x)	x (x)
		…			
	[PT 2]	Any Severity	x (x)	x (x)	x (x)
		…			
	[Additional PTs Reported]	Any Severity	x (x)	x (x)	x (x)
		…			
[SOC 2]	Any PT	Any Severity	x (x)	x (x)	x (x)
		…			
	[PT 1]	Any Severity	x (x)	x (x)	x (x)
		…			
	[Additional PTs Reported]	Any Severity	x (x)	x (x)	x (x)
		…			

Notes: N = Number of participants in the Safety Population.
n = Number of participants with an event in the SOC/PT.
A participant is only counted once per PT and dose level, in the highest severity reported.

Table with similar format:

Table 18: Related Unsolicited Adverse Events by MedDRA System Organ Class and Preferred Term, Maximum Severity, and Dose Level, Safety Population

14.3.2 Listing of Deaths, Other Serious and Significant Adverse Events

Table 19: Listing of Serious Adverse Events, Safety Population

[Implementation Note: Listing will be sorted by Dose Level, Participant ID, AE Number.]

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

Table 20: Listing of Non-Serious, Unsolicited, Moderate, Severe, or Life-Threatening Adverse Events, Safety Population

[Implementation Note: Listing will be sorted by Dose Level, Participant ID, AE Number.]

Adverse Event	No. of Days Post First Dose	Duration (Days)	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 Preferred Term
Dose Level: , Participant ID: , AE Number:										
Comments:										
Dose Level: , Participant ID: , AE Number:										
Comments:										

14.3.3 Narratives of Deaths, Other Serious and Significant Adverse Events

This is a placeholder for the CSR.

14.3.4 Abnormal Laboratory Value Listings (by Participant)

Table 21: Listing of Abnormal Laboratory Results – Chemistry, Safety Population

[Implementation Note: This listing will include any chemistry result outside of normal range, including ONRs and graded events. Listing will be sorted by Dose Level, Participant ID, Study Day, Parameter.]

Dose Level	Participant ID	Sex	Age at Study Day (days)	Study Day	Laboratory Parameter (Units)	Result (Severity)	Reference Range Low	Reference Range High	Relationship to Treatment	If Not Related, Alternate Etiology	Action Taken with Study Treatment	Participant Discontinued Due to Result?	Clinically Significant?

Table 22: Listing of Abnormal Laboratory Results – Hematology, Safety Population

[Implementation Note: This listing will include any hematology result outside of normal range, including ONRs and graded events. Listing will be sorted by Dose Level, Participant ID, Study Day, Parameter.]

Dose Level	Participant ID	Sex	Age at Study Day (days)	Actual Study Day	Laboratory Parameter (Units)	Result (Severity)	Reference Range Low	Reference Range High	Relationship to Treatment	If Not Related, Alternate Etiology	Action Taken with Study Treatment	Participant Discontinued Due to Result?	Clinically Significant?

14.3.5 Displays of Laboratory Results

14.3.5.1 Chemistry Results

Table 23: Chemistry Results by Parameter, Time Point, Severity, and Dose Level, Safety Population

[Implementation Note: If no Life-Threatening/Grade 4 events were reported, then that column will be omitted. If there are no graded events at any scheduled post-baseline study visit (i.e., Day 5) within a parameter, then only the "Baseline" and "Max Post-Baseline" rows will be displayed.

Parameters will be shown in the following order: Any Parameter, ALT, Creatinine.]

Parameter (Units)	Time Point	Dose Level	N	None n (%)	Mild/Grade 1 n (%)	Moderate/Grade 2 n (%)	Severe/Grade 3 n (%)	Life-Threatening/Grade 4 n (%)
Any Parameter	Baseline	All Participants	x	x (x)	x (x)	x (x)	x (x)	x (x)
		10 mg/kg	x	x (x)	x (x)	x (x)	x (x)	x (x)
		20 mg/kg	x	x (x)	x (x)	x (x)	x (x)	x (x)
	Day 5	All Participants	x	x (x)	x (x)	x (x)	x (x)	x (x)
		10 mg/kg	x	x (x)	x (x)	x (x)	x (x)	x (x)
		20 mg/kg	x	x (x)	x (x)	x (x)	x (x)	x (x)
	Max Post-Baseline	All Participants	x	x (x)	x (x)	x (x)	x (x)	x (x)
		10 mg/kg	x	x (x)	x (x)	x (x)	x (x)	x (x)
		20 mg/kg	x	x (x)	x (x)	x (x)	x (x)	x (x)
[Parameter 1]	Baseline	All Participants	x	x (x)	x (x)	x (x)	x (x)	x (x)
	…	…						
[Additional Parameters]								

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

Table 24: Chemistry Summary Statistics by Parameter, Time Point, and Dose Level, Safety Population

[Implementation Note: Parameters will be shown in the following order: ALT, Creatinine.]

Parameter (Units)	Time Point	Dose Level	Value at Visit				Change from Baseline			
			n	Mean (SD)	Median	10th Percentile, 90th Percentile	n	Mean (SD)	Median	10th Percentile, 90th Percentile
[Parameter 1]	Baseline	All Participants (N = X)	x	x.x (x.x)	x.x	x.x, x.x	-	-	-	-
		10 mg/kg (N = X)	x	x.x (x.x)	x.x	x.x, x.x	x	x.x (x.x)	x.x	x.x, x.x
		20 mg/kg (N = X)	x	x.x (x.x)	x.x	x.x, x.x	x	x.x (x.x)	x.x	x.x, x.x
	Day 5	All Participants (N = X)	x	x.x (x.x)	x.x	x.x, x.x	x	x.x (x.x)	x.x	x.x, x.x
		10 mg/kg (N = X)	x	x.x (x.x)	x.x	x.x, x.x	x	x.x (x.x)	x.x	x.x, x.x
		20 mg/kg (N = X)	x	x.x (x.x)	x.x	x.x, x.x	x	x.x (x.x)	x.x	x.x, x.x
[Additional Parameters]										

Notes: N = Number of participants in the Safety Population.
n = Number of participants with data recorded at the respective time point. For the change from baseline, n represents the number of participants with non-missing data at baseline and the respective visit.
SD = Standard Deviation.

14.3.5.2 Hematology Results

Table 25: Hematology Results by Parameter, Time Point, Severity, and Dose Level, Safety Population

Similar shell as to Table 25. Parameters will be shown in the following order: Any Parameter, Absolute Neutrophil Count (ANC), Hemoglobin, Platelets, WBC.

Table 26: Hematology Summary Statistics by Parameter, Time Point, and Dose Level, Safety Population

Similar shell as to Table 26. Parameters will be shown in the following order: Absolute Neutrophil Count (ANC), Hemoglobin, Platelets, WBC.

14.3.6 Displays of Vital Signs

Not Applicable.

14.4 Summary of Prior and Concomitant Medications

Table 27: Prior and Concurrent Medications by WHO Drug Classification and Dose Level, All Enrolled Participants

WHO Drug Code Level 1, Anatomic Group	WHO Drug Code Level 2, Therapeutic Subgroup	10 mg/kg (N=X)		20 mg/kg (N=X)		All Participants (N=X)	
		n	%	n	%	n	%
Any Level 1 Codes	Any Level 2 Codes	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]	Any [ATC 1 - 2]						
	[ATC 2 - 1]						
	[ATC 2 - 2]						
	[ATC 2 - 3]						

Notes: N = Number of enrolled participants.
n = Number of participants reporting taking at least one medication in the specific WHO Drug Class. A participant is counted once per group/subgroup.

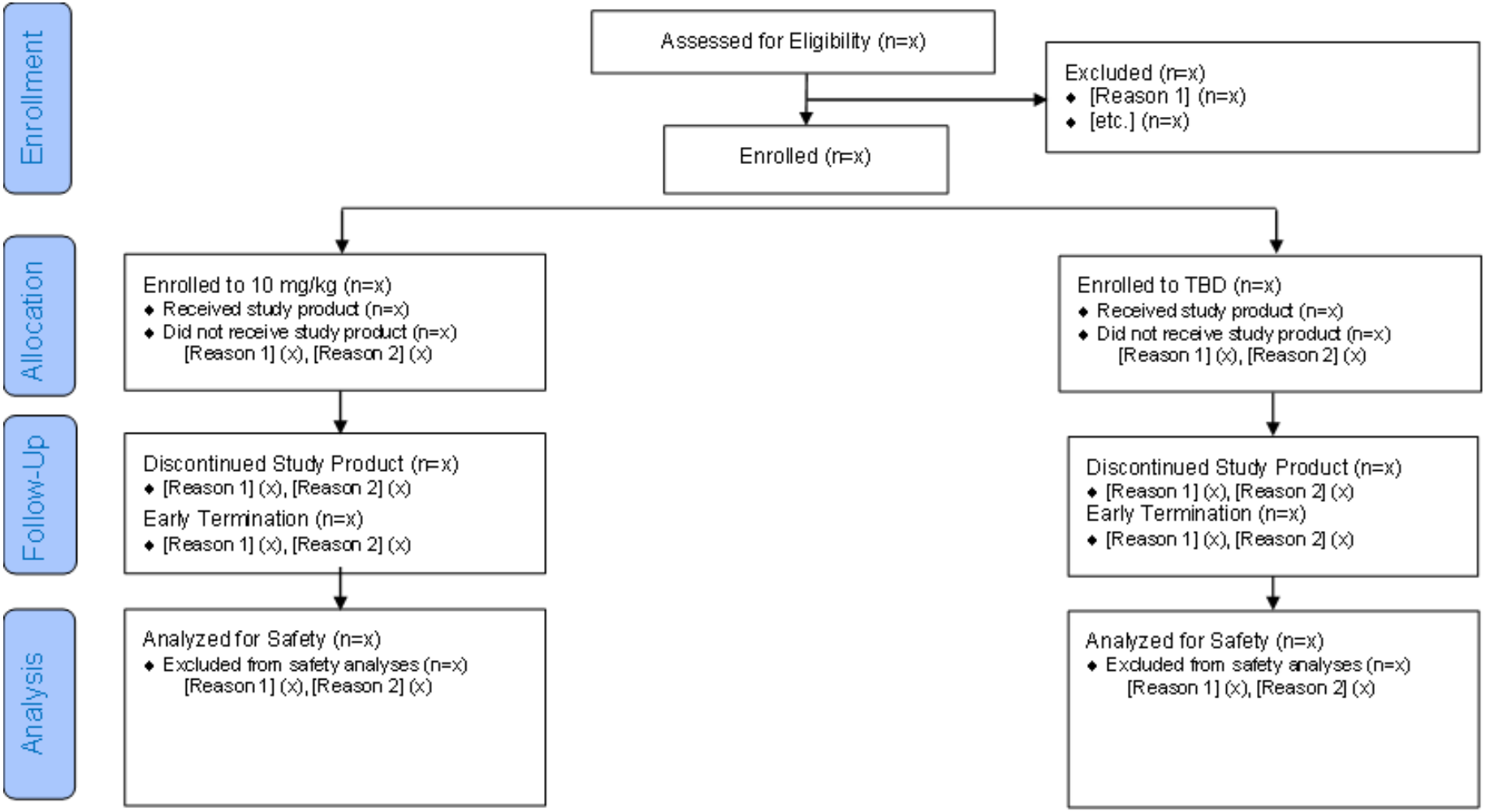
APPENDIX 2. FIGURE MOCK-UPS

LIST OF FIGURES

10.1 Disposition of Participants

Figure 1: CONSORT Flow Diagram

[Implementation Note: Update TBD to 20 mg/kg. Include Analyzed for PK under analysis.]



14.2.2 Pharmacokinetic Response Figures by Measure, Treatment, and Time Point

Not Applicable.

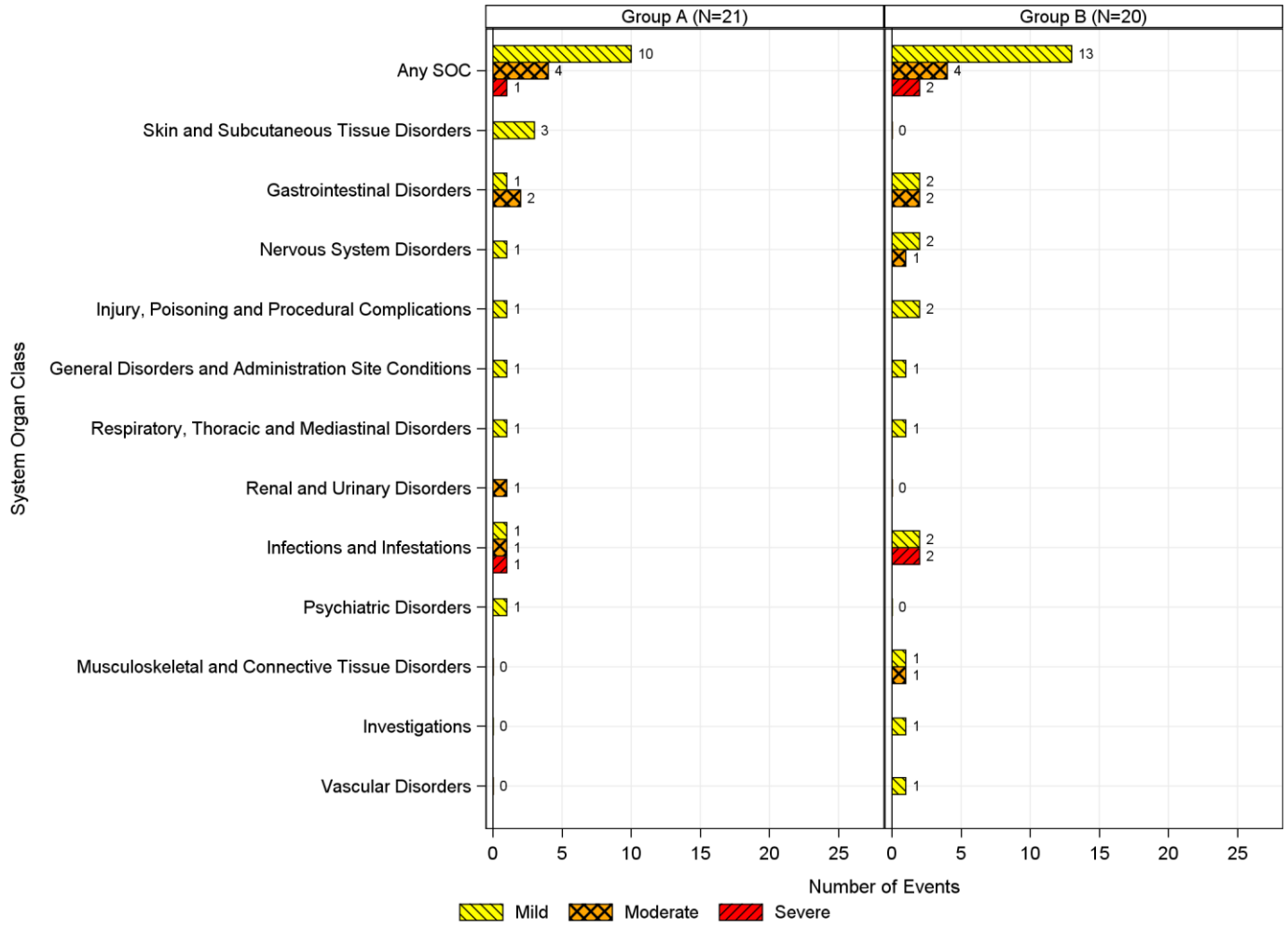
14.3.1.1 Solicited Adverse Events

Not Applicable.

14.3.1.2 Unsolicited Adverse Events

Figure 2: Adverse Events by MedDRA System Organ Class and Severity (Event-Level), Safety Population

[Implementation Note: This is a generic shell. Group A will be "10 mg/kg" and Group B will be "20 mg/kg".]



Figures with similar format:

Figure 3: Related Adverse Events by MedDRA System Organ Class and Severity (Event-Level), Safety Population

Figure 4: Adverse Events by MedDRA System Organ Class and Maximum Severity (Participant-Level), Safety Population

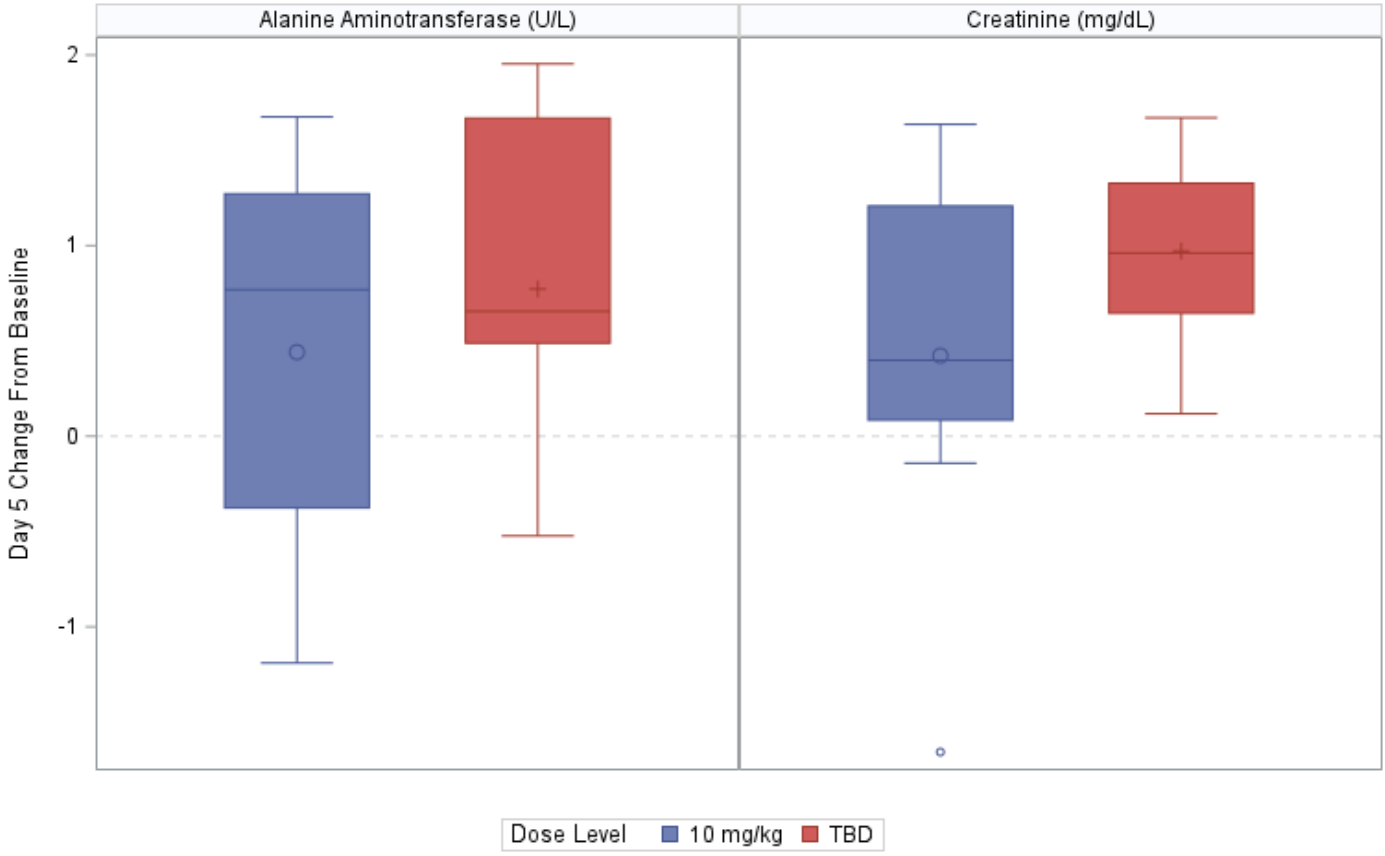
Figure 5: Related Adverse Events by MedDRA System Organ Class and Maximum Severity (Participant-Level), Safety Population

[Implementation Notes for Figures 4 and 5: The x-axis will be the "Percentage of Participants"]

14.3.5 Displays of Laboratory Results

Figure 6: Chemistry Mean Changes from Baseline at Day 5 by Parameter and Dose Level, Safety Population

[Implementation Note: Each panel will be a separate parameter. Update "TBD" to "20 mg/kg".]



Figures with similar format:

Figure 7: Hematology Mean Changes from Baseline at Day 5 by Parameter and Dose Level, Safety Population

APPENDIX 3. LISTINGS MOCK-UPS

LISTINGS

Listing 1: 16.1.6: Listing of Participants Receiving Study Product

[Implementation Note: Listing will be sorted by Dose Level and Participant ID.]

Dose Level	Participant ID

16.2 Database Listings by Participant

16.2.1 Discontinued Participants

Listing 2: 16.2.1: Early Terminations and Study Product Discontinuations

[Implementation Notes: Listing will be sorted by Dose Level, Participant ID, Category (Discontinued Study Product listed first). Participants who discontinued study product and later terminated early will have two records in the listing: one for the termination and one for the study product discontinuation. Days on Study defined in Section 3.3.]

Dose Level	Participant ID	Category	Reason for Early Termination or Treatment Discontinuation	Days on Study	Number of Doses Received

16.2.2 Protocol Deviations

Listing 3: 16.2.2.1: Participant-Specific Protocol Deviations

[Implementation Note: Listing will be sorted by Dose Level, Participant ID, DV Number.]

Dose Level	Participant ID	DV Number	Deviation	Deviation Category	Study Day	Reason for Deviation	Deviation Resulted in AE?	Deviation Resulted in Participant Termination?	Deviation Affected Product Stability?	Deviation Resolution	Deviation Classification (Major/Minor)	Comments

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

[Implementation Note: Listing will be sorted by Site, Start Date.]

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

16.2.3 Participants Excluded from the Pharmacokinetic and Safety Analyses

Listing 5: 16.2.3: Participants Excluded from the Analysis Populations

[Implementation Note: This listing should be congruent with "Analysis Populations by Dose Level (Table 8). Only participants who were excluded from at least one analysis population will be included in this listing.

Listing will be sorted by Dose Level, Participant ID.]

Dose Level	Participant ID	Analysis in which Participant is Included	Analysis from which Participant is Excluded	Reason Participant Excluded
		[e.g., ITT, Safety, Per Protocol, PK]		Safety: Did not receive study product PK: Did not receive a complete dose of study product

16.2.4 Demographic Data

Listing 6: 16.2.4.1: Demographics and Growth Parameters

[Implementation Note: Listing will be sorted by Dose Level, Participant ID.]

Dose Level	Participant ID	Sex	Age at Enrollment (days)	Ethnicity	Race	Weight (kg)	Length (cm)	Gestational age at birth (weeks)	Weight at birth (kg)

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

[Implementation Note: Listing will be sorted by Dose Level, Participant ID, MH Number.]

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

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

Listing 8: 16.2.5: Study Drug Compliance Data

[Implementation Note: Listing will be sorted by Dose Level, Participant ID, Dose Number.]

Dose Level	Participant ID	Dose Number	Study Day	Time of Dose	Dose Taken?	Did the participant vomit or spit up within 30 minutes following the dose?
				hh:mm		

16.2.6 Individual Pharmacokinetic Response Data

Not Applicable. Please see the PK analysis plan.

16.2.7 Adverse Events

Listing 9: 16.2.7.2: Unsolicited Adverse Events

[Implementation Note: Listing will be sorted by Dose Level, Participant ID, AE Number.]

Adverse Event	No. of Days Post First Dose (Duration)	Severity	SAE?	Relationship to Study Treatment	In Not Related, Alternative Etiology	Action Taken with Study Treatment	Participant Discontinued Due to AE	Outcome	MedDRA System Organ Class	MedDRA Preferred Term
Dose Level: Participant ID: AE Number:										
Comments:										
Dose Level: Participant ID: AE Number:										
Comments:										
Note: For additional details about SAEs, see Section 14.3.2.										

16.2.8 Individual Laboratory Measurements and Other Safety Related Assessments

16.2.8.1 Individual Laboratory Measurements

Listing 10: 16.2.8.1.1: Clinical Laboratory Results – Chemistry

[Implementation Note: Listing will be sorted by Dose Level, Participant ID, Study Day, Parameter.]

Dose Level	Participant ID	Sex	Age at Study Day (days)	Study Day	Laboratory Parameter (Units)	Result (Severity)	Reference Range Low	Reference Range High

Listing 11: 16.2.8.1.2: Clinical Laboratory Results – Hematology

[Implementation Note: Listing will be sorted by Dose Level, Participant ID, Study Day, Parameter.]

Dose Level	Participant ID	Sex	Age at Study Day (days)	Study Day	Laboratory Parameter (Units)	Result (Severity)	Reference Range Low	Reference Range High

16.2.8.2 Prior and Concomitant Medications

Listing 12: 16.2.8.2: Prior and Concomitant Medications

[Implementation Note: Listing will be sorted by Dose Level, Participant ID, CM Number.]

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