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 Number: 20-0033

IND Sponsor: National Institute of Allergy and Infectious Diseases (NIAID) Division of Microbiology and Infectious Diseases (DMID), and National Center for Advancing Translational Sciences

Congenital and Perinatal Infections Consortium
Principal Investigator: David W. Kimberlin, MD

Version Number: 4.0
05 March 2024

NIH Funding Mechanism: 1U54AI150225-01

STATEMENT OF COMPLIANCE

Each institution engaged in this research will hold a current Federalwide Assurance (FWA) issued by the Office of Human Research Protection (OHRP) for federally funded research. The Institutional Review Board (IRB) or Independent/Institutional Ethics Committee (IEC) must be registered with OHRP as applicable to the research.

The study will be carried out in accordance with the following as applicable:

- United States Code of Federal Regulations (CFR) 45 CFR Part 46: Protection of Human Subjects
- U.S. Food and Drug Administration (FDA) Regulations: 21 CFR Part 50 (Protection of Human Subjects), 21 CFR Part 54 (Financial Disclosure by Clinical Investigators), 21 CFR Part 56 (Institutional Review Boards), 21 CFR Part 11, and 21 CFR Part 312 (Investigational New Drug Application), and/or 21 CFR 812 (Investigational Device Exemptions)
- The International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) E6(R2) Good Clinical Practice, and the Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, Report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research
- The policies and procedures of National Institutes of Health (NIH) Office of Extramural Research and DMID
- The National Institute of Allergy and Infectious Diseases (NIAID) Terms of Award
- All national and Local Regulations and Guidance applicable at each site

The signature below provides the necessary assurance that this study will be conducted according to all stipulations of the protocol including statements regarding confidentiality, and according to local legal and regulatory requirements, US federal regulations, and ICH E6(R2) Good Clinical Practice (GCP) guidelines.

Site Investigator Signature:

Signed: _____ Date: _____

_____
Name

_____
Title

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1. PROTOCOL SUMMARY

1.1 Synopsis

Rationale for Proposed Clinical Study

Herpes simplex virus (HSV) is a rare cause of disease in neonates, but when it occurs, the sequelae frequently are devastating. Neonatal HSV cases are classified as disease localized to the skin, eyes, and/or mouth (SEM disease), central nervous system disease (CNS disease), or disseminated infection involving multiple organs (disseminated disease). Neonates with disseminated or SEM disease generally present to medical attention at 10-12 days of life, while those with CNS disease on average present somewhat later at 16-19 days of life (1). Approximately 30% of neonates with disseminated neonatal HSV disease die despite 21 days of parenteral antiviral therapy with acyclovir followed by 6 months of oral acyclovir suppression, and approximately 20% of surviving babies will have lifelong neurodevelopmental sequelae (2, 3). For babies with the CNS classification of neonatal HSV disease receiving the same parenteral and suppressive therapy, approximately 5% will die but one-third of survivors will have neurodevelopmental sequelae (2, 3).

Approximately 85% of neonatal HSV cases acquire the infection in the peripartum period, as they pass through an infected birth canal (4). 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 (5), and their neonates are managed with preemptive testing and possibly antiviral therapy (6). 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 (6).

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 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.

Assessment of Potential Risks and Benefits

Valacyclovir is the prodrug of acyclovir and is a marketed antiviral medication with a well-established safety profile. In young infants, the primary toxicities of parenteral acyclovir are: 1) neutropenia, which is reversible with cessation of the drug; and 2) creatinine elevation from crystal formation in the collecting tubules of the kidneys (7). Neither of these complications have been seen in studies of oral valacyclovir in infants and children one month of age and older

(8). 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 administered two time per day, 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 subject 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 subject.

There are no alternative therapies used in neonates potentially exposed to HSV at delivery (because they are born to women with a history of genital HSV and therefore who could be shedding virus in their genital tract) but without known exposure (no active maternal lesions at delivery). Standard of care at the current time in these potential exposures is simply to follow the baby clinically to see if they develop disease. Therefore, participating in this study will not deprive the subjects of any established therapy, and potentially could provide the benefit of preemptive valacyclovir treatment if perinatal exposure had occurred.

Study Design

This is a Phase 1, open label multicenter trial to assess the safety and pharmacokinetics (PKs) of oral valacyclovir in neonates who are at risk of acquiring neonatal herpes simplex virus 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_{0-12} of 24,000 ngxhr/mL to 48,000 ngxhr/mL. Neonates whose mothers have a history of genital HSV infection and received oral valacyclovir in the last several weeks of pregnancy, as per the recommendations of the American College of Obstetrics and Gynecology (ACOG) (9), 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 (10) and in the 2015, 2018, and 2021 Red Books (6, 11, 12). 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**). 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 subjects. Following informed consent, each subject 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 count and differential for absolute neutrophil count, hemoglobin, platelet count, alanine aminotransferase, 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 subject will be withdrawn from the study

prior to receiving any doses of study medication. In addition, the subject 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 subjects will have been taking antiviral medication prior to delivery. Dropouts and withdrawn subjects may be replaced to reach the target sample size of eight subjects. Subjects will return to the study site on Study Day 5 (window: Study Day 4 through Study Day 5), and also will be assessed for adverse events 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 either 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 (white blood cell count with differential, hemoglobin, platelet count, alanine aminotransferase, 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 (Appendix A). 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.

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 subjects will be enrolled in **Cohort 2**. The dose that these subjects will receive will be predicated upon the pharmacokinetic data from Cohort 1. Specifically, the target range of acyclovir exposure following dosing with oral valacyclovir study drug is from 24,000 ngxhr/mL to 48,000 ngxhr/mL. If the mean of observed acyclovir exposures of subjects 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 subjects, then the 8 subjects 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 subjects 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 subjects, then the 8 subjects enrolled in Cohort 2 will receive oral valacyclovir at a dose that has been linearly adjusted downward to target 36,000 ngxh/mL area-under-the-concentration-time curve from 0 to 12 hours (AUC_{12}). The study schedule for subjects in Cohort 2 will be identical to those in Cohort 1, as described above and in the Schedule of Activities table (see Section 1.2). If the mean of observed acyclovir exposures of subjects in Cohort 1 are 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) (see Section 9.4.6).

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

Study Objectives

- **Primary**
  - To establish the dose of valacyclovir in neonates that reliably achieves systemic acyclovir exposures comparable to 10 mg/kg of parenterally administered acyclovir

- **Secondary**
  - To define the pharmacokinetic profile of acyclovir in neonates receiving oral valacyclovir
  - To assess and describe the safety profile of valacyclovir among treated neonates

Study Endpoints

- **Primary**
  - Neonatal plasma acyclovir mean AUC_{12} concentrations between 24,000 ngxhr/mL and 48,000 ngxhr/mL

- **Secondary**
  - Plasma acyclovir PK parameters including maximum plasma concentration (C_{max}), time to the maximum concentration (T_{max}), half-life ($t_{½}$), oral clearance (CL/F), and volume of distribution (V/F)
  - Grade 3 Adverse Events (AEs)
  - Grade 4 Adverse Events and Serious Adverse Events

Inclusion Criteria

1. Signed informed consent from parent(s) or legal guardian(s)
2. Maternal history of genital HSV infection
3. Maternal receipt of oral acyclovir, valacyclovir, or famciclovir suppressive therapy for ≥ 7 days prior to delivery
4. Gestational age ≥ 38 weeks at birth
5. ≤ 2 days of age at study enrollment*
6. Weight at study enrollment ≥ 2,000 grams

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

Exclusion Criteria

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

Study Phase (if applicable)

Phase 1

Study Population
Male and female neonates without signs or symptoms of neonatal herpes simplex virus (HSV) disease and ≤ 2 days of age, and born to women who received anti-herpesviral suppressive therapy due to a history of genital HSV infection will be enrolled. The study plans to enroll a total of 16 neonatal subjects in 2 cohorts, with 8 subjects per cohort. Decision of enrolling Cohort 2 will depend on the safety and PK results of Cohort 1.

Sites
Approximately 10 sites in the United States

Study Intervention:
Study Product Description
Valacyclovir (Valtrex) hydrochloride 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, capsule-shaped tablets) 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. SyrPalta has been studied as a vehicle for extemporaneously prepared valacyclovir (13), and will be used as the oral liquid vehicle to create the valacyclovir formulation for subjects in this study. SyrPalta 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 (ASHP) Standardize 4 Safety Initiative (https://www.ashp.org/-/media/assets/pharmacy-practice/s4s/docs/Compound-Oral-Liquid.ashx). The shelf life following preparation is 28 days. Study product will be administered by the parent/guardian if subjects are at home, or by the hospital staff if subjects 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, while the dose evaluated in Cohort 2 will be predicated upon the exposure levels of subjects enrolled in Cohort 1. Specific dosing volumes will be provided for each subject based on body weight and valacyclovir oral suspension concentration. Valacyclovir Oral Suspension will be administered into the subject's mouth via an oral dosing syringe. The parent/guardian will be provided with specific dosing, storage, and administration instructions. If the subject vomits or spits up following the dosing, re-dosing for that dose is not allowed.

Study Duration
The estimated timeframe from study activation to the last subject's last study day (defined as the time point the final subject will be contacted by the study site) is 18 months.

Participant Duration
42 days

Safety
The trial will be overseen by a Safety Monitoring Committee (SMC).

1.2 Schedule of Activities (SoA)

The study procedures and evaluations are summarized below in the Schedule of Activities table.

Table 1. Schedule of Activities

	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, gender, 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) prior to the first oral dose of valacyclovir being administered on Study Day 1; if any value is Grade 1 toxicity or higher, the subject will be withdrawn from the study and will not receive study medication. In addition, the subject 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 subject 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 subjects with the Study Day 1 hematology and chemistry safety labs.
j) Plasma samples for PK assessments will be obtained from study subjects 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.

2. INTRODUCTION

2.1 Study Rationale

Approximately 85% of neonatal HSV cases acquire the infection in the peripartum period, as they pass through an infected birth canal (4). 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 (5), and their neonates are managed with preemptive testing and possibly antiviral therapy (6). 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 (6).

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 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.

Since the early 1980s, parenteral acyclovir has been the antiviral therapy for neonatal HSV disease (2, 14). While appropriate for the treatment of neonates who already have HSV disease, parenteral acyclovir would not be ideal as preemptive therapy in an exposed neonate because of the risks associated with intravenous access at this very young age. The prodrug valacyclovir is the L-valyl ester of acyclovir that is rapidly converted to acyclovir after oral administration by first-pass metabolism in the liver (15). Its mechanism of action is the same as that of its parent drug, acyclovir. While only 15% to 30% of the oral formulation of acyclovir is absorbed, the bioavailability of valacyclovir in adults exceeds 50% (16). After oral administration of valacyclovir, though, rapid and complete conversion to acyclovir occurs with first-pass intestinal and hepatic metabolism. Peak serum concentrations, attained about 1.5 hours after a dose has been given, are proportional to the amount of drug administered; they range from 0.8 to 8.5 μg/mL for doses of 100 to 2000 mg (17). The area-under-the-concentration-time curve (AUC) approximates that seen after IV acyclovir. All other PK characteristics of oral valacyclovir are similar to those of IV acyclovir.

Valacyclovir oral suspension has been evaluated in GlaxoSmithKline-sponsored studies in children 1 month to 12 years of age (8). Bioavailability was estimated to be 45% to 51% in all age groups except those 3 months through 5 months of age, in whom the bioavailability is lower at 22%. Approximate dose proportionality in C_{max} and AUC was seen across the 10 mg/kg to 25 mg/kg dose range (i.e., dose normalized differences generally within ≤ ~30%) with the exception of children 2 years through 5 years of age, for whom a near doubling in C_{max} and AUC was noted with only a modest increase in dose from 20 to 25 mg/kg (8). Valacyclovir has not been studied in neonates (infants under 1 month of age). In the U.S., 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 VZV) or twice a day (for HSV) (8, 18). Valacyclovir has demonstrated an excellent safety profile over the 20 years since its initial approval in the U.S.

2.2 Background

2.2.1 Purpose of Study

Background of Neonatal Herpes Simplex Virus Disease

Herpes simplex virus (HSV) is a rare cause of disease in neonates, but when it occurs the sequelae frequently are devastating. We recently documented that neonatal HSV disease incidence was approximately 1 in 3,000 deliveries in 2000, but by 2012 had increased by almost 60% to 1 in 1,900 live births (19). With an annual national birth cohort of 3.8 million, this equates to 2,000 babies delivered each year who develop neonatal HSV disease. Neonatal HSV cases are classified as disease localized to the skin, eyes, and/or mouth (SEM disease), central nervous system disease (CNS disease), or disseminated infection involving multiple organs (disseminated disease). Neonates with disseminated or SEM disease generally present to

medical attention at 10-12 days of life, while those with CNS disease on average present somewhat later at 16-19 days of life (1). Approximately 30% of neonates with disseminated neonatal HSV disease die despite 21 days of parenteral antiviral therapy with acyclovir followed by 6 months of oral acyclovir suppression, and approximately 20% of surviving babies will have lifelong neurodevelopmental sequelae (2, 3). For babies with the CNS classification of neonatal HSV disease receiving the same parenteral and suppressive therapy, approximately 5% will die but one-third of survivors will have neurodevelopmental sequelae (2, 3).

Timing of Transmission from Mother to Neonate

The overwhelming majority (85%) of babies with neonatal HSV disease acquire the virus from their mothers during the birth process (4). The mothers of these babies are usually asymptomatically shedding HSV in their genital tract (20-22). Neonates acquiring the virus then present with signs and symptoms of disease at 10 to 19 days of life, as discussed above. While maternal antiviral suppression with oral valacyclovir, the prodrug of acyclovir, is routinely provided near the end of pregnancy to women with a history of genital herpes (9, 23-26), it is ineffective in completely suppressing viral shedding at delivery (25-28) and babies born to women on antiviral suppression can still develop neonatal HSV disease (29).

Definitions Related to HSV Acquisition by Neonate

Since neonatal HSV is acquired perinatally (during the birth process), it is important to use standardized language relating to transmission. Following **neonatal exposure** to HSV during the time of delivery, **neonatal infection** occurs as viral replication occurs over the first several days of life on the neonate's skin and mucous membranes. Neonatal infection then progresses to **neonatal disease** at generally 10 to 19 days of life, as discussed above.

Public Health Impact and Current Standard of Care for Treatment/Prevention of Neonatal HSV Disease

From a study of Medicaid-enrolled children from 2009-2015, costs for care of infants with neonatal HSV over the first six months of life exceeded $60M (19). This large number is only part of the overall public health impact of neonatal HSV, though. Up to 20% of women of reproductive age are infected with HSV type 2 (HSV-2), which virtually exclusively causes genital infection (30). Furthermore, over the past decade 60% to 80% of genital herpes infections are caused by HSV type 1 (HSV-1), which more commonly causes orolabial HSV infection (31, 32). It therefore is estimated that approximately one-third of women of childbearing age have a genital HSV infection, and therefore are at risk of transmitting the virus to their newborn at the time of delivery to cause neonatal HSV disease (4). Knowledge of this can drive pediatric decision-making when neonates are admitted at 2 to 3 weeks of life with fever and undergo a sepsis evaluation, with additional costs incurred in the workup of these babies even if they do not have neonatal HSV disease and therefore are not captured in the costs above.

Acyclovir is the mainstay for the treatment of HSV, both in adults and in neonates. From the 1980s through the 2000s, the precursor of the Congenital and Perinatal Infections Consortium (CPIC), which was known then as the Collaborative Antiviral Study Group (CASG), established the standard of care for the treatment of neonatal HSV disease in a series of studies. The first

established the superiority of a lower dose of parenteral acyclovir (30 mg/kg/day) over an older antiviral drug, vidarabine (14), and the second established the superiority of higher dose parenteral acyclovir (60 mg/kg/day) for a longer duration of treatment (21 days for CNS and disseminated neonatal HSV) (2). The CASG then conducted a placebo-controlled study of oral acyclovir suppressive therapy following treatment of acute neonatal disease (3), in which we determined that babies with neonatal HSV CNS disease had significantly improved neurodevelopmental outcomes when immediately started on active antiviral suppression following parenteral acyclovir therapy of acute disease, compared with babies in whom oral antiviral suppression was deferred until after skin lesions recurred or who only received placebo. Even with use of higher dose parenteral acyclovir followed by immediate antiviral suppression, each year in the United States over 100 babies die from neonatal herpes, and 250 survivors are left with significant neurologic damage (2-4, 20, 33). Approximately 1,000 more survive without neurologic impairment, yet still require two to three weeks of hospitalization for IV therapy of acute disease, which puts significant emotional stress on their families – especially given the fact that this involves a sexually transmitted infection that the mother passed to her newborn (2, 3, 33).

Role of Study in Clinical Development

No new antiviral drugs active against HSV are in advanced stages of development, and use of existing therapies (parenteral acyclovir for treatment of acute neonatal HSV disease followed by oral acyclovir suppression) has been maximized already. Therefore, our strategy to decrease the deaths and neurologic morbidity caused by HSV in the neonatal population has shifted to preventing **neonatal exposure** to HSV in the maternal genital tract at the time of delivery from progressing to **neonatal infection** and subsequently to **neonatal disease** at 10-19 days of life. The current study will provide critical data needed in this prevention strategy by determining the appropriate dose of oral antiviral medication that can be expected to halt viral replication on the skin or mucous membranes of newborns exposed to HSV at delivery, thereby preventing the HSV exposure from ever progressing to infection or neonatal HSV disease.

Description of Study Product

Oral valacyclovir has a much more favorable bioavailability than oral acyclovir in all age groups studied to date. Only 15% to 30% of oral acyclovir is absorbed (34, 35). In contrast, the oral bioavailability of valacyclovir in adults exceeds 50% (16), and in young infants 1-2 months of age is 45% (8). Valacyclovir is the L-valyl ester prodrug of acyclovir, and following absorption in the gastrointestinal tract is rapidly converted to acyclovir by first-pass metabolism in the liver (15). Thus, oral valacyclovir is a more efficient way to deliver acyclovir systemically compared with oral acyclovir. The active metabolite of valacyclovir is a deoxyguanosine analogue with an acyclic side chain that lacks the 3′-hydoxyl group of natural nucleosides (34). Following preferential uptake by infected cells, acyclovir is monophosphorylated by HSV-encoded thymidine kinase. Subsequent diphosphorylation and triphosphorylation are catalyzed by host cell enzymes, resulting in acyclovir triphosphate concentrations that are 40 to 100 times higher in HSV-infected cells than in noninfected cells (36). Acyclovir triphosphate prevents viral DNA synthesis by inhibiting the viral DNA polymerase. In vitro, acyclovir triphosphate competes with deoxyguanosine triphosphate as a substrate for viral DNA polymerase. Because acyclovir triphosphate lacks the 3′-hydroxyl group required for elongation of the DNA chain, the growing

chain of DNA is terminated. In the presence of the deoxynucleoside triphosphate complementary to the next template position, the viral DNA polymerase is functionally inactivated (37). In addition, acyclovir triphosphate is a much better substrate for the viral polymerase than for cellular DNA polymerase, resulting in little incorporation of acyclovir into host cellular DNA. The higher concentration of the active triphosphate anabolite in infected cells plus the affinity for viral polymerases result in the very low toxicity of acyclovir in noninfected host cells.

Prior Studies of the Study Product

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 VZV) or twice a day (for HSV) (8). Valacyclovir oral suspension has been evaluated in company-sponsored studies in 112 children 1 month through 11 years of age (8, 18). Dosing regimens evaluated were 25 mg/kg as a single dose in 1 month old through 23 month old subjects, 10 mg/kg as a twice-daily dose for 3–5 days in 1 year old through 11 year old subjects, and 20 mg/kg as a 3-times-daily dose for 5 days in 1 year old through 11 year old subjects (8). Bioavailability was estimated to be 45% to 51% in all age groups except those 3 months through 5 months of age, in whom the bioavailability is lower at 22%. Approximate dose proportionality in C_{max} and area-under-the-curve (AUC) was seen across the 10 mg/kg to 25 mg/kg dose range (i.e., dose normalized differences generally within ≤ ~30%) with the exception of children 2 years through 5 years of age, for whom a near doubling in C_{max} and AUC was noted with only a modest increase in dose from 20 to 25 mg/kg (8). Valacyclovir has not been studied in neonates (infants under 1 month of age), which is the purpose of this study. GlaxoSmithKline has provided to us the patient-level data from their prior pediatric PK studies of valacyclovir in children 1 month through 11 years of age (8), which we have utilized along with our prior data on the pharmacokinetics of parenteral acyclovir in neonates (2) to identify the doses of valacyclovir being evaluated in this study.

2.3 Risk/Benefit Assessment

2.3.1 Known Potential Risks

Valacyclovir is the prodrug of acyclovir and is a marketed antiviral medication with a well-established safety profile. In young infants, the primary toxicities of parenteral acyclovir are: 1) neutropenia, which is reversable with cessation of the drug; and 2) creatinine elevation from crystal formation in the collecting tubules of the kidneys (7). Neither of these complications have been seen in studies of oral valacyclovir in infants and children one month of age and older (8). 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 administered two times per day, 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 subject 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 subject.

There are no alternative therapies used in neonates potentially exposed to HSV at delivery (because they are born to women with a history of genital HSV and therefore who could be shedding virus in their genital tract) but without known exposure (no active maternal lesions at delivery). Standard of care at the current time in these potential exposures is simply to follow the baby clinically to see if they develop disease. Therefore, participating in this study will not deprive the subjects of any established therapy.

Risks to Privacy: Subjects will be asked to provide personal health information (PHI). All attempts will be made to keep this PHI confidential within the limits of the law. However, there is a chance that unauthorized persons will see the subject's PHI. All study records will be kept in a locked file cabinet or maintained in a locked room at each participating clinical site. Electronic files will be password protected. Only people who are involved in the conduct, oversight, monitoring, or auditing of this trial will be allowed access to the PHI that is collected. Any publications from this trial will not use information that will identify subjects by name. Organizations that may inspect and/or copy research records maintained at the participating site for quality assurance and data analysis include groups such as the IRB, NIAID, and the FDA.

2.3.2 Known Potential Benefits

There may be no direct benefit from the experimental treatment to the neonates potentially exposed to HSV at the time of delivery. This trial will determine what dose of oral valacyclovir provides the desired acyclovir systemic concentrations to effectively prevent infection from developing following an exposure to the virus at birth. Subjects who participate will contribute to the knowledge about the safety and pharmacokinetics of valacyclovir in neonates. We have selected the study population for this Phase 1 study carefully and deliberately, to include only those neonates whose mothers have a history of genital HSV and are on oral antiviral suppressive therapy for the last several weeks of pregnancy, as is recommended by the American College of Obstetricians and Gynecologists (ACOG) (9). However, women with a history of genital HSV infection may still shed HSV asymptomatically at delivery even when receiving antiviral suppression (25-28, 38). Babies born to these women can develop neonatal HSV disease (29), which documents that they remain at risk of acquiring neonatal HSV even when the mothers do not have active lesions at delivery. By requiring that subjects enrolled on this study be delivered to women on oral antiviral suppressive therapy, we have deliberately selected a population that could potentially benefit from participation on the study if they are exposed to HSV at delivery and if the oral valacyclovir study drug that they will receive in the study provides benefit in preventing that exposure from progressing to neonatal infection and disease

2.3.3 Assessment of Potential Risks and Benefits

Participation in this study will not adversely increase the risk that newborns face when exposed to HSV at the time of delivery without treatment. This study will lead to the knowledge that can be used to determine the correct dosage of valacyclovir that is needed to effectively preemptively treat HSV-exposed neonates at the time of delivery. Known exposure to HSV at delivery is an exclusion criterion for study enrollment.

3. OBJECTIVES AND ENDPOINTS

Table 2. Objectives and Endpoints

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
Primary	
• To establish the dose of valacyclovir in neonates that reliably achieves systemic acyclovir exposures comparable to 10 mg/kg of parenterally administered acyclovir	• Neonatal plasma acyclovir mean AUC_{12} concentrations between 24,000 ngxhr/mL and 48,000 ngxhr/mL
Secondary	
• To define the pharmacokinetic profile of acyclovir in neonates receiving oral valacyclovir	• Plasma acyclovir PK parameters including maximum serum concentration (C_{max}), time to the maximum concentration (T_{max}), half-life ($t_{1/2}$), oral clearance (CL/F), and volume of distribution (V/F)
• To assess and describe the safety profile of valacyclovir among treated neonates	• Grade 3 Adverse Events (AEs) • Grade 4 Adverse Events and Serious Adverse Events

4. STUDY DESIGN

4.1 Overall Design

This is a Phase 1, open label multicenter trial to assess the safety and pharmacokinetics of oral valacyclovir in neonates who are at risk of acquiring neonatal herpes simplex virus 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_{0-12} 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 (ACOG) (9), 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 (10) and in the 2015, 2018, and 2021 Red Books (6, 11, 12). 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**). 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 subjects. Following

informed consent, each subject 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 count and differential for absolute neutrophil count, hemoglobin, platelet count, alanine aminotransferase, 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 subject will be withdrawn from the study prior to receiving any doses of study medication. In addition, the subject 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 subjects will have been taking antiviral medication prior to delivery. Dropouts and withdrawn subjects may be replaced to reach the target sample size of eight subjects. Subjects will return to the study site on Study Day 5 (window: Study Day 4 through Study Day 5), and also will be assessed for adverse events 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 (white blood cell count with differential, hemoglobin, platelet count, alanine aminotransferase, 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 (Appendix A). 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. 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.

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 (± SD) 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 (14), and successfully prevents neonatal HSV SEM disease from progressing to disseminated disease (20). 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 (2), 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.

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 subjects will be enrolled in **Cohort 2**. The dose that these subjects will receive will be predicated upon the pharmacokinetic data from Cohort 1. If the mean of observed acyclovir exposures of subjects 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 subjects, then the 8 subjects 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 subjects 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 subjects, then the 8 subjects enrolled in Cohort 2 will receive oral valacyclovir at a dose that has been linearly adjusted downward to target 36,000 ngxh/mL area-under-the-concentration-time curve from 0 to 12 hours (AUC_{12}). The study schedule for subjects in Cohort 2 will be identical to those in Cohort 1, as described above and in the Schedule of Activities table (see Section 1.2). If the mean of observed acyclovir exposures of subjects in Cohort 1 are 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) (see Section 9.4.6).

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 subjects in the first two cohorts. If such a recommendation is made, dose selection and subject enrollment and assessment will follow the approach used for Cohort 2.

Schedule of assessments can be found in **Section 1.2, Schedule of Activities**. Dose escalation or dose-ranging details are found in **Section 6.1.2, Dosing and Administration**. Full details of interim analysis are found in **Section 9.4.6, Planned Interim Analysis**

4.2 Justification for Dose

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 U.S., 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 VZV) or twice a day (for HSV) (8). Valacyclovir has demonstrated an excellent safety profile over the 20 years since its initial approval in the U.S. 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 subject 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 subject.

5. 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.

5.1 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

5.2 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 HIV positive (but HIV testing is not required for study entry)
- Current receipt in the neonate of acyclovir, ganciclovir, famciclovir, or any investigational drugs

5.2.1 Exclusion of Specific Populations

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, gender, or ethnic background.

5.3 Inclusion of Vulnerable Participants

Not applicable

5.4 Lifestyle Considerations

Not applicable

5.5 Screen Failures

The investigator or designee is to review the inclusion/exclusion criteria and determine the subject's eligibility for study participation. Only the following information will be collected on screen failures: demographics (age, screen number, sex, ethnicity, and race) and reason for ineligibility. The parent(s)/guardian(s) of subjects who are found to be ineligible will be told the reason for ineligibility.

5.6 Strategies for Recruitment and Retention

5.6.1 Recruitment

Each site participating in this study will develop an individual recruitment plan that is specific to their region and facility requirements. Recruitment materials may be delivered in prenatal and postnatal settings.

5.6.2 Retention

Enrolled subjects will be followed for only 42 days. Challenges with subject retention are therefore not anticipated.

5.6.3 Compensation Plan for Subjects

Study subject compensation, if any, will be determined by the individual sites. The compensation plan will be in accordance with local IRB requirements and subject to local IRB approval.

5.6.4 Costs

There is no cost to subjects for the research tests, procedures, and study product while taking part in this trial. Procedures and treatment for clinical care may be billed to the subject, subject's insurance or third party.

6. STUDY PRODUCT

6.1 Study Product(s) and Administration

6.1.1 Study Product Description

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 (18). Valacyclovir tablets will be extemporaneously compounded as an oral suspension using SyrPalta as the oral liquid vehicle (13). 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 (ASHP) Standardize 4 Safety Initiative (https://www.ashp.org/-/media/assets/pharmacy-practice/s4s/docs/Compound-Oral-Liquid.ashx).

6.1.2 Dosing and Administration

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 subjects are at home, or by the hospital staff if subjects 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, while the dose evaluated in Cohort 2 will be predicated upon the exposure levels of subjects enrolled in Cohort 1. Specific dosing volumes will be provided for each subject based on body weight and valacyclovir oral suspension concentration. Valacyclovir Oral Suspension will be administered into the subject's mouth via an oral dosing syringe. The parent/guardian will be provided with specific dosing, storage, and administration instructions. If the subject vomits or spits up following the dosing, re-dosing for that dose is not allowed.

Table 3. 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	TBD	Oral	bid	5 days

6.1.3 Dose Escalation

Dose selection for Cohort 2 will be predicated upon the pharmacokinetic 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 subjects 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 subjects, then the 8 subjects 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 subjects 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 subjects, then the 8 subjects enrolled in Cohort 2 will receive oral valacyclovir at a dose that has been linearly adjusted downward to target 36,000 ngxh/mL area-under-the-concentration-time curve from 0 to 12 hours (AUC_{12}). If the mean of observed acyclovir exposures of subjects in Cohort 1 are 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) (see Section 9.4.6).

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 subjects in the first two cohorts. If such a recommendation is made, dose selection and subject enrollment and assessment will follow the approach used for Cohort 2.

6.1.4 Dose Modifications

Valacyclovir will be dosed according to the study cohort into which the subject enrolls. Study Cohort 1 will receive 10 mg/kg body weight administered two times daily for 5 days, while the dose for Cohort 2 will be predicated upon the pharmacokinetic results of subjects enrolled in Cohort 1, as detailed in Section 4.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Acquisition and Accountability

Acquisition:
Commercial brand name (Valtrex) valacyclovir (500 mg tablets) and SyrPalta syrup vehicle will be shipped to the participating sites from the DMID Clinical Material Services (CMS). Ancillary supplies for oral administration, such as amber bottles and oral dosing syringes, will be provided by the clinical research site. Multiple lots may be provided. The study products will be open label and not kit specific. Extemporaneous preparation of the suspension formulation will be performed by the site's research pharmacist following enrollment of a subject (13).

Accountability:
After receipt of the study product, the site principal investigator (PI) is responsible for study product distribution and disposition and has ultimate responsibility for study product accountability. The Site PI will delegate to the site Research Pharmacist the responsibility for study product accountability. Each pharmacist will be responsible for and will maintain logs of receipt, accountability, dispensation, storage conditions, and disposal of study drug. All study product, whether administered or not, must be documented on the appropriate study product accountability record or dispensing log. Parents/guardians will be instructed to return the used bottle and medication diary to the PI at Study Day 5.

Unused (e.g., returned) study product will be retained at the site until further instruction from the Sponsor or its designee. Upon study completion, or termination and final monitoring visit, the Sponsor or its designee will provide instructions for the return of any remaining unused study product to the repository or destroyed according to site procedures with a second staff member observing and verifying the destruction. Used study product will be destroyed at the site in accordance with standard site procedures following monitoring and release for destruction, unless the site's local storage policy prohibits retention of used IP. In that event, used study product may be destroyed on-site following applicable site procedures with a second staff member observing and verifying the destruction.

At study completion, the sites will be required to return the drug accountability log to the UAB Central Unit (CU) upon request, retaining a copy of the drug accountability form in their study files.

6.2.2 Formulation, Appearance, Packaging, and Labeling

Commercial valacyclovir tablets 500 mg (Valtrex) will be supplied for extemporaneous preparation of the suspension formulation by the Research Pharmacist. Valacyclovir

hydrochloride is a white to off-white powder (from tablets) of the hydrochloride salt of the L-valyl ester of acyclovir. The blue, film-coated tablets are printed with edible white ink. Commercial SyrPalta will be supplied as the vehicle for the valacyclovir suspension and is a clear liquid (13). Valacyclovir oral suspension will be stored in an amber medicine bottle with a child-resistant closure. The final prepared oral suspension will be labeled with the FDA-required cautionary statement "Caution: New Drug Limited by Federal Law to Investigational Use".

6.2.3 Product Storage and Stability

Valacyclovir tablets will be stored at 15°C to 25°C (59°F to 77°F). SryPalta syrup vehicle will be stored between 13°C to 29°C (56°F to 85°F). The final prepared valacyclovir oral suspension will be stored refrigerated between 2°C and 8° C (36° to 46°F) in the pharmacy and subject's home. Shake well before using. Discard after 28 days.

6.2.4 Preparation

Valacyclovir Oral Suspension will be extemporaneously prepared by the site Research Pharmacist following the instructions in the Manual of Procedures for dispensing to the study subject. One bottle will be compounded and dispensed at study enrollment and will suffice for the full 5-day treatment period. Resupply will only be provided in the event of loss of the product by the family. Additional details regarding preparation and procedures for dispensing or administration of study product will be described in the protocol-specific Manual of Procedures.

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Treatment Assignment Procedures

Not applicable. All subjects will receive study product.

6.3.2 Randomization and Blinding

Not Applicable

6.3.3 Blinding and Masking Procedures

Not applicable. No masking procedures will be done.

6.4 Study Intervention 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 subject vomited following the dose. The diary will also note the storage conditions of the product (e.g. refrigerated). The diary will be collected at the Study Day 5 visit.

6.5 Concomitant Therapy

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

6.5.1 Rescue Medicine

Not applicable

7. STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Halting Criteria and Discontinuation of Study Intervention

7.1.1 Study Halting Criteria

Enrollment and study product administration will be halted for SMC review/recommendation if any of the following is reported:

- Any subject experiences an SAE after study product administration that is considered related to the study product.
- Two subjects experience an AE Grade 2 or higher from the same organ class, deemed to be a study product-related unsolicited AE.
- Two subjects experience the same Grade 2 or higher study product-related safety laboratory AE.

Additionally, DMID and the Central Unit may interrupt study dosing and/or study entry at any time if medically indicated. To minimize risk, the medical monitor will review real-time safety data and the SMC will review cumulative safety data. If enrollment is halted based upon the study halting criteria above or the review of the safety data, upon completion of the review and receipt of advice of the SMC, DMID and the Central Unit Administration will determine if study entry or study dosing may continue according to the protocol.

7.1.2 Individual Halting Criteria

Subjects with any initial (pre-dosing) hematology or chemistry safety lab that is ≥ Grade 1 in value utilizing the DAIDS Toxicity Tables (Appendix A) will be withdrawn from the study and will not receive study medication. During the 5 days of study product dosing, a Grade 2 or higher AE, including a laboratory AE, will result in halting of study product administration for the subject. If a subject develops signs/symptoms of HSV infection, study medication will be stopped and standard antiviral therapy will be administered.

7.1.3 Criteria for Continuation of Dosing and Redosing

In the event a halting rule is met:

- An unscheduled safety analysis by the SMC will be required for approval of further enrollment, and
- Further administration of the study product is suspended for ALL subjects until an assessment by the SMC takes place.

7.1.4 Follow up for subjects that discontinue study intervention

Study subjects that discontinue study drug will be offered an opportunity to complete the follow-up study visits through study day 42. They will complete all follow-up visits as outlined in the study Schedule of Activities in Section 1.2.

7.2 Participant Withdrawal from the Study and Replacement

Study subjects may withdraw voluntarily from participation in the study at any time. If a study subject withdraws or is discontinued from the study at any time prior to completion of the study, the reason for this decision will be recorded on the eCRFs. Should a study subject's therapy be discontinued prematurely, all clinical and laboratory evaluations scheduled during the next study visit will be completed on the day the study subject is discontinued, if possible. Dropouts and withdrawn subjects may be replaced to reach the target of sample size.

7.3 Lost to Follow-Up

A participant will be considered lost to follow-up if he or she fails to return for more than one scheduled visit and is unable to be contacted by the study site staff. These efforts will be documented in the subject's study record.

8. STUDY ASSESSMENTS AND PROCEDURES

The study procedures and evaluations are summarized in the Schedule of Activities in Section 1.2.

8.1 Screening Procedures

It is anticipated that screening will occur either in the final weeks of pregnancy or at the time of delivery by identifying pregnant women who are receiving antiviral suppressive therapy for genital HSV infections. Each site will determine the manner by which patients who could be eligible for study enrollment are identified and their mothers approached for discussion of participating in the study.

8.2 Efficacy / Immunogenicity Assessments

Not applicable

8.2.1 Efficacy / Immunogenicity Evaluations

Not applicable

8.3 Safety and Other Assessments

Baseline Demographics

The following information will be collected from the subject's medical records to the extent the information is available, or by direct assessment of the subject and questioning of the parent(s) or legal guardian(s): Gestational age at delivery, date of birth, gender, race, ethnicity, birth weight, weight at enrollment, length in centimeters at enrollment, and baseline conditions prior to study enrollment, by body system.

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 subject will be assessed for any adverse events.

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 subject will be recorded.

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) pharmacokinetic 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 pharmacokinetic samples and the white blood cell 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.

Clinical Laboratory Evaluations

The breakdowns of the amount of blood for individual tests are provided in the Schedule of Activities in Section 1.2. Clinical laboratory results can be used for chemistry and hematology safety labs if collected within the required study window. 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: white blood cell count (WBC)

with differential, hemoglobin, and platelet count. From the WBC count and differential, the absolute neutrophil count (ANC) will be calculated (39).

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: alanine aminotransferase (ALT) and creatinine.

Special Assays or Procedures: Pharmacokinetic Testing
Assessment of acyclovir plasma concentrations will be conducted at the UAB Central Pharmacokinetic Laboratory. On Study Day 1, a blood sample will be obtained at the same time as the Study Day 1 hematology and chemistry safety labs. On Study Day 5 (window: Study Day 4 through Study Day 5), blood will be obtained around dose 7, 8, 9, or 10 of study drug at 15 minutes before the dose (pre-dose), and then 1-2 hours, 4-6 hours, and 8-10 hours following administration of the dose. Specific instructions for shipping PK samples are found in the MOP.

8.3.1 Procedures to be Followed in the Event of Abnormal Laboratory Test Values or Abnormal Clinical Findings

If a physical parameter or 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 CBC 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.

8.4 Adverse Events and Serious Adverse Events

8.4.1 Definition of Adverse Events (AE)

An Adverse Event 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 recipient presenting for medical care, or upon review by a study monitor.

Investigators participating in this clinical trial are responsible for and will:
- Evaluate subject safety including assessment of adverse events (AEs) for seriousness, severity, and causality;
- Notify the Central Unit, CROMS PVG, and EMMES of protocol-defined serious adverse events (SAEs) within 24 hours; (details provided in the MOP)
- Provide detailed written reports, including necessary documentation requested by the sponsor or institutional review board (IRB)/independent ethics committee (IEC), promptly following immediate initial reports; and
- Inform the IRB/IEC of AEs as required by applicable regulatory requirements.

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 subject at each visit. If a subject is hospitalized, the medical record should be reviewed to identify AEs. The PI is responsible for identifying and reporting AEs according to protocol guidelines.

8.4.1.1 Solicited Adverse Events

Solicited adverse events are anticipated local and systemic adverse events for which consistent collection of information is desired. This may include:

- Common and expected according to the available knowledge about the product, or
- Specific events of concern that should be ascertained on every participant.

8.4.1.2 Unsolicited Events

All AEs spontaneously reported by the subject 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 case report form. All reported unsolicited AEs are graded in accordance with the protocol toxicity tables.

8.4.1.3 Special Reporting of Adverse Events

Not applicable

8.4.2 Definition of Serious Adverse Events

An SAE is defined as an adverse event or suspected adverse reaction 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 adverse event. An adverse event is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event 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 in Appendix A.

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

All SAEs will be:

- Recorded on the appropriate SAE eCRF;
- Followed through resolution or stabilization by a licensed study physician (listed on the Form 1572 as the site PI or Sub-Investigator);
- Reviewed and evaluated by DMID, and will be sent to the SMC (for periodic review) and the IRB.

Relationship to Study Products: The physician's assessment of an AE's relationship to valganciclovir study drug is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported. All AEs must have their relationship to study product assessed using the terms "related" or "not related," and should be followed through resolution or stabilization. In a clinical trial, the study product must always be suspect.

The investigator must provide an assessment of relationship of AEs to the study product based on:

- Temporal relationship of the event to the administration of study product;
- Whether an alternative etiology has been identified;
- Biological plausibility; and
- Existing therapy, and/or concomitant medications.

To help assess, the following guidelines are used:

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

8.4.2.1 Suspected Unexpected Serious Adverse Reactions (SUSAR)

A SUSAR is any SAE where a causal relationship with the study product is at least a reasonably possible but is not listed in the Investigator Brochure, Package Insert, and/or Summary of Product Characteristics.

8.4.3 Classification of an Adverse Event

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 but is not limited to physicians, physician assistants, and nurse practitioners.

8.4.3.1 Severity of Event

All reportable AEs will be graded by the investigator according to the protocol toxicity tables (Appendix A) using a four-grade system (Table 1). 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 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.

Table 4. Protocol Toxicity Table

(Four-grade system utilized for this trial [see also Appendix A])

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Clinical adverse event **NOT** identified elsewhere in the grading table	Mild symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated	Moderate symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated	Severe symptoms causing inability to perform usual social & functional activities with intervention or hospitalization indicated	Potentially life-threatening symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability, or death

8.4.3.2 Relationship to Study Intervention

For each reported adverse reaction, the Principal Investigator 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.

8.4.4 Time Period and Frequency for Event 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.

8.4.5 Adverse Event Reporting

8.4.5.1 Investigators Reporting of AEs

Information on all AEs should be recorded on the eCRF. All clearly related signs, symptoms, and results of diagnostic procedures performed because of an AE should be grouped together and recorded as a single diagnosis. If the AE is a laboratory abnormality that is part of a clinical condition or syndrome, it should be recorded as the syndrome or diagnosis rather than the individual laboratory abnormality. Each AE will also be described in terms of duration (start and stop date), severity, association with the study product, action(s) taken, and outcome.

8.4.6 Serious Adverse Event Reporting

8.4.6.1 Investigators Reporting of SAEs

Any AE that meets the protocol defined criterion as an SAE must be submitted immediately (within 24 hours of identification) on an SAE form to the DMID Pharmacovigilance Group at the following address:

DMID Pharmacovigilance Group
Clinical Research Operations and Management Support (CROMS)
6500 Rock Spring Dr., Suite 650
Bethesda, MD 20817, USA

SAE Hot Line: 1-800-537-9979 (US) or 1-301-897-1709 (outside US)
SAE FAX Phone Number: 1-800-275-7619 (US) or 1-301-897-1710 (outside US)
SAE Email address: PVG@dmidcroms.com

The DMID Serious Adverse Event form can be found at https://www.dmidcroms.com/CRS/PVG/PVG_Public/SAE%20Form_V%204.0.pdf.

The Investigator will call the Clinical Studies Administrator at the Central Unit to notify them that an SAE has been identified. Other supporting documentation of the event may be requested by the DMID Pharmacovigilance Group and should be provided as soon as possible. The DMID medical monitor will review and assess the SAE for regulatory reporting and potential impact on study subject safety and protocol conduct. 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 to the DMID Pharmacovigilance Group.

8.4.6.2 Regulatory Reporting of SAEs

Following notification from the site Principal Investigator or appropriate sub-investigator, DMID, as the IND sponsor, will report any suspected unexpected serious adverse event (SUSAR) as an IND safety report to the FDA and will notify all participating site Principal Investigators (i.e., all Principal Investigators to whom the sponsor is providing drug under its IND(s) or under any Principal Investigator's IND(s)of potential serious risks from clinical studies or any other source, as soon as possible. DMID will report to the FDA any unexpected fatal or life-threatening suspected adverse reaction as soon as possible, but in no case later than 7 calendar days after the sponsor's initial receipt of the information. If the event is not fatal or life-threatening the IND safety report will be submitted within 15 calendar days after the sponsor determines that the information qualifies for reporting as specified in 21 CFR Part 312.32. Relevant follow up information to an IND safety report will be submitted as soon as the information is available. Upon request from FDA, DMID will submit to the FDA any additional data or information that the agency deems necessary, as soon as possible, but in no case later than 15 calendar days after receiving the request.

SAEs that are not SUSARs will be reported to the FDA at least annually in a summary format which includes all SAEs.

8.4.7 Reporting Events to Participants

Not applicable

8.4.8 Adverse Events of Special Interest

Not applicable

8.4.9 Reporting of Pregnancy

Not applicable

8.5 Unanticipated Problems

8.5.1 Definition of Unanticipated Problems (UP)

Not applicable

8.5.2 Unanticipated Problem Reporting

Not applicable

8.5.3 Reporting Unanticipated Problems to Participants

Not applicable

9. STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

We hypothesize that the pharmacokinetics (PK) of acyclovir in neonates, following administration of the prodrug valacyclovir, are definable in an adaptive, dose-escalation study with sparse and intensive concentration-time assessments.

9.2 Sample Size Determination

The sample size will be characterized by the width of a 95% confidence interval 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 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 standard deviation of AUC_∞ for a given mean, a sample size of 8 will be characterized in terms of the width of a 95% two-sided confidence interval for the mean. If the observed mean is 24,000 ngxhr/mL and using a standard deviation of 8,000 ngxhr/mL, a two-sided 95% confidence 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 standard deviation of 15,998 ngxhr/mL, a two-sided 95% confidence interval 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 confidence intervals for other sample sizes, please see table below.

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.

Table 5. 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

9.3 Populations for Analyses

Intent to Treat Population
Any child who receives at least one dose of study medication will be included in an intention to treat (ITT) analysis of safety.

Per Protocol Population
Children who complete the course of study medication will be included in a per protocol (PP) analysis of pharmacokinetics.

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

9.4 Statistical Analyses

The primary objective of this study is to describe the acyclovir AUC12 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. As such, only descriptive statistics will be needed to summarize the pharmacokinetic data. This is an observational pharmacokinetic study with no comparator arms. Our goal is to generate preliminary pharmacokinetic data in this population to help inform larger dosing/efficacy trials in the future. The AUC12 will be the primary parameter summarized, but secondary objective pharmacokinetic parameters such as CL/F, T1/2, Cmax, V/F, and others will also be summarized using descriptive statistics. These statistics will include at least the mean, standard deviation, coefficient of variation, median, range, and mean.

The low valacyclovir dose that is being assessed is expected to produce exposures well within a clinically acceptable range for older neonates receiving IV acyclovir dosing. Therefore, any AEs are expected to be similar in frequency and severity to what is already known about the drug within this exposure range. Any AEs will be summarized by grade and frequency (percent). Symptoms and toxicities (e.g., AEs) will be listed and the counts and proportion computed by dose cohort. The Clopper-Pearson method will be used to estimate 95% confidence intervals (or upper bound) around the estimates of these proportions and Fisher's exact test to compare the proportions between dose cohorts. Summary statistics for continuous laboratory safety parameters will be presented. The data also will be presented using appropriate graphical tools to help compare the different dose cohorts. The exact Wilcoxon test will be used to compare between dose cohorts at a given time point or area under the curve for variables collected over time (e.g., laboratory parameters). For area under the curve, the average will be taken to adjust for shortened length of follow-up for dropouts. Linear mixed model with random intercept may be considered to analyze data collected over time to account for correlation of data from the same subject. This method provides another perspective of comparing the treatment cohorts as area under the curve due to being a summary statistic may miss important features of the data that mixed model may detect. The generalized linear mixed model can handle continuous, binary and count data. To measure strength of correlation between continuous variables, the Pearson correlation (or Spearman rank correlation for variables not distributed normally) will be used. Analyses will be done using SAS version 9.4.

9.4.1 General Approach

Data will be summarized using mean, standard deviation, median, minimum and maximum for continuous variables and count and percentages for categorical variables. For laboratory data, 10^{th} and 90^{th} percentiles will be used instead of minimum and maximum. Mean plots and boxplots will be used to display summary statistics over time for continuous variables. For comparing the demographic and laboratory variables between cohorts at a given time point, exact two-tailed Wilcoxon test will be used to compare the two cohorts for continuous variables, due to small sample size and indication of nonnormality, and two-tailed Fisher's exact test for categorical variables. For estimating proportions, Clopper-Pearson method will be utilized. For investigating the change in hematology and chemistry parameters collected over time, generalized linear mixed model with random effects may be utilized to compare the cohorts. Confidence level will be at least 95% for estimation and significance level will be at most 5% for test of hypothesis, respectively. There will be no adjustments for multiple intervals or testing.

9.4.2 Analysis of the Primary Endpoint(s)

Standard noncompartmental techniques will be used to assess pharmacokinetic parameters derived from the full PK profile obtained on Study Day 5 (window: Study Day 4 through Study Day 5). The resource utilized for pharmacokinetic analysis is Phoenix WinNonlin v8.3.1 (or later), Certara USA, Inc. (Princeton, NJ). AUC_{12} is the primary objective, which will be determined using the linear-log trapezoidal rule. In addition, a population PK analysis may be conducted at the end of the study.

9.4.3 Analysis of the Secondary Endpoint(s)

Secondary objectives include calculation of additional pharmacokinetic parameters other than AUC_{12}, including (but not limited to): AUC_{∞}, C_{max}, $t_{1/2}$, T_{max}, k_e, CL/F, V/F, C_{12h}, and T_{last}. C_{max} will be taken as the maximum observed concentration. T_{max} is the time at which C_{max} occurs. Oral clearance (CL/F) will be calculated as dose/AUC_{12}. The elimination half-life ($t_{1/2}$) is a secondary parameter that will be determined using regression analysis of the terminal elimination phase concentration-time points. This will also be accomplished using Phoenix WinNonlin (see section 9.4.2 for additional details).

Grade 3 AEs and 4 AEs and SAEs are also secondary endpoints. See Section 9.4.4 for details of their analyses.

9.4.4 Safety Analyses

Safety evaluations will be based on the incidence, severity, and type of AEs. Safety variables will be tabulated and presented for all subjects in the safety population. All tests will use a 5% significance level, i.e., p-values < 0.05 will be considered significant, and for estimation a 95% confidence level will be used.

Symptoms and toxicities will be listed and the counts and proportion computed by dose cohort. Clopper-Pearson method will be used to estimate confidence intervals (or upper bound) around the estimates of these proportions and Fisher's exact test to compare the proportions between dose cohorts. Summary statistics will be presented for continuous laboratory safety parameters. Data will be presented using appropriate graphical tools to help compare the different dose cohorts. The exact Wilcoxon test will be used to compare between dose cohorts at a given time point or area under the curve for variables collected over time (e.g., laboratory parameters). For area under the curve, the average will be taken to adjust for shortened length of follow-up for dropouts. Linear mixed model with random intercept may be considered to analyze data collected over time to account for correlation of data from the same subject. This method provides another perspective of comparing the treatment cohorts as area under the curve due to being a summary statistic may miss important features of the data that mixed model may detect. The generalized linear mixed model can handle continuous, binary and count data. To measure strength of correlation between continuous variables, the Pearson correlation (or Spearman rank correlation for variables not distributed normally) will be used. Analyses will be done using SAS version 9.4.

9.4.5 Baseline Descriptive Statistics

Baseline characteristics will be summarized. For both continuous and categorical variables, appropriate summary statistics will be applied. For continuous variables, descriptive statistics will include the number of non-missing values, mean, standard deviation, median, minimum, and maximum. For categorical variables, descriptive statistics will include counts and percentages per category.

9.4.6 Planned Interim and Early Analyses

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 of Cohort 1, the PK and safety data will be reviewed. If the mean of observed acyclovir exposures of subjects 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 subjects, then the 8 subjects 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 subjects 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 subjects, then the 8 subjects enrolled in Cohort 2 will receive oral valacyclovir at a dose that has been linearly adjusted downward to target 36,000 ngxh/mL area-under-the-concentration-time curve from 0 to 12 hours (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. After assessment of drug exposure and safety in Cohort 1, eight new subjects will be enrolled in **Cohort 2**, with the dose that these subjects will receive being predicated upon the pharmacokinetic data from Cohort 1.

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 subjects in the first two cohorts. If such a recommendation is made, dose selection and subject enrollment and assessment will follow the approach used for Cohort 2.

9.4.6.1 Interim Safety Analyses

See Section 9.4.6.

9.4.6.2 Interim Immunogenicity or Efficacy Review

Not Applicable

9.4.7 Sub-Group Analyses

Not Applicable

9.4.8 Tabulation of Individual Participant Data

Individual participant data will be listed by measure of pharmacokinetic parameter, including demographic characteristics.

9.4.9 Exploratory Analyses

Not applicable

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Regulatory, Ethical, and Study Oversight Considerations

Ethical Consideration

This trial will be conducted in compliance with the protocol, International Conference on Harmonization Good Clinical Practice E6 (ICH-GCP), and the applicable regulatory requirements, including:

- U.S. Code of Federal Regulations applicable to clinical studies (45 CFR 46 and 21 CFR including parts 50 and 56 concerning informed consent and IRB regulations, if under IND, 21 CFR 312).
- Completion of Human Subjects Protection Training.

The investigator will ensure that this study is conducted in full conformity with the principles set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research of the US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (April 18, 1979) and codified in 45 CFR Part 46 and/or the ICH E6; 62 Federal Regulations 25691 (1997).

Institutional Review Board

The UAB Central Unit will identify the IRB that will serve as the Single (Central) IRB of record for the U.S. sites participating in this study. Only institutions holding a current US Federalwide Assurance (FWA) issued by OHRP will be allowed to participate in this study.

This protocol, informed consent documents, relevant supporting information, and all types of volunteer recruitment or advertisement information will be submitted to the Single IRB of record for review and must be approved before the study is initiated. Any amendments to the protocol must also be approved by the Single IRB of record prior to implementing changes in the study. The UAB Central Unit will inform the Single IRB of record of the progress of the study and of any changes made to the protocol as deemed appropriate, but at least once per year.

The site investigator is responsible for keeping their local IRB apprised of the progress of the study and of any changes made to the protocol as deemed appropriate, but at least once per year. All IRB approved documents as well as relevant study correspondence should be copied and sent to the UAB Central Unit.

10.1.1 Informed Consent Process

The process of obtaining informed consent must be documented in the medical records, clinic chart, and/or research chart. The consent form must be signed and dated by the subject's parent(s)/legal guardian(s) before participation in the study. A copy of the signed consent form must be provided to the subject's parent(s)/legal guardian(s). Signed consent forms must remain

in each study participants study file and must be available for verification by study monitors at any time.

The investigational nature and research objectives of this study, its procedures, and its attendant risks and discomforts will be carefully explained to the subject's parent(s)/legal guardian(s). A signed informed consent document will be obtained from each subject's parent(s)/legal guardian(s) prior to entry into this study. At any time during participation in the protocol, if new information becomes available relating to risks, this information will be provided orally or in writing to all enrolled or prospective subject's parent(s)/legal guardian(s). Documentation will be provided to the IRB and, if necessary, the informed consent will be amended to reflect any relevant information.

An investigator shall seek such consent only under circumstances that provide the subject's parent(s)/legal guardian(s) sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence. The information that is given to the subject's parent(s)/legal guardian(s) shall be in language understandable to the subject's parent(s)/legal guardian(s).

The subject's parent(s)/legal guardian(s) will sign the informed consent document prior to any procedures being done specifically for the study. The subject's parent(s)/legal guardian(s) should have the opportunity to discuss the study with their family, friends or personal physician, or think about it prior to agreeing to participate. The subject's parent(s)/legal guardian(s) may withdraw consent at any time throughout the course of the study. A copy of the informed consent document will be given to the subject's parent(s)/legal guardian(s) for their records. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

10.1.1.1 Requirements for Permission by Parents/Guardians and Assent by Children (in case of a minor)

If required by the IRB, the parent or legal guardian will sign a waiver of assent for the minor due to the study participant's age.

10.1.1.2 Other Informed Consent Procedures

Not applicable

10.1.2 Study Termination and Closure

The NIH or study Principal Investigator have the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to study participants.
- Study participant enrollment is unsatisfactory.
- Data recording is inaccurate or incomplete.
- Investigators do not adhere to the protocol or applicable regulatory guidelines in conducting the study.
- Regulatory authority action.

The sponsor will notify regulatory authorities as applicable.

10.1.3 Confidentiality and Privacy

Subject confidentiality will be held in trust by the participating investigators, their staff, the Sponsor and their agents. This confidentiality is extended to cover clinical information related to subjects, test results of biological samples and all other information generated during this study.

This research is covered by a Certificate of Confidentiality from the National Institutes of Health. The information obtained during the conduct of this natural history study is confidential, and disclosure to third parties other than those noted below is prohibited. The results of the research study may be published, but study participant's names or identities will not be revealed. Records will remain confidential. To maintain confidentiality, the principal investigator at each site will keep records in locked cabinets or locked rooms, and the results of tests will be coded to prevent association with volunteers' names. Data entered into computerized files will be accessible only by authorized personnel directly involved with the study and will be encoded. Data received by DMID will not include subject specific data but only encoded data.

The study investigator is obliged to provide the UAB Central Unit and NIAID/DMID with complete test results and all data developed in this study; no direct identifiers will be shared. NIH/NIAID/DMID or UAB may disclose this information to appropriate regulatory authorities or clinical practice management groups (e.g., American Academy of Pediatrics, Pediatric Infectious Disease Society) as deemed necessary.

Subject-specific information may be provided to other appropriate medical personnel only with the study participant's parent/legal guardian permission. To ensure compliance with current ICH guidelines, data generated by this study must be available for inspection upon request by representatives of national and local health authorities, the NIH/NIAID/DMID, UAB Central Unit personnel, and the IRB/IEC for each study site.

Data may be shared within the NIH/NCATS Rare Diseases Clinical Research Network, as required by NCATS or posted on NIH datasharing websites. No direct identifiers will be shared.

10.1.4 Secondary Use of Stored Specimens and Data

10.1.4.1 Samples for Secondary Research

Secondary Human Subject Research is the re-use of identifiable data or identifiable biospecimens that were collected from some other "primary" or "initial" activity, such as the data and samples collected in this protocol. Any use of the sample or data for secondary research purposes, however, will be presented in a separate protocol and require separate IRB approval. Some of the information and specimens obtained from study participants during this study will be stored indefinitely in the UAB Central Laboratory at the University of Alabama at Birmingham in accordance with OHRP guidelines ensuring that codes or other personally identifying links will not be distributed to future researchers and may be used in secondary microbial or antiviral research. The information and specimens will be labeled with a code number linking them to the participant but not with the study participant's name or other

identifiers. At the time of consent for study participation, study participant's parent/legal guardian will have the opportunity to either agree to have their baby's information and specimens be stored and used in future research or decline storing and sharing for future research. The study participant's parent/legal guardian will indicate his/her preference by initialing the appropriate line or checking the appropriate box of the Consent Form in the section entitled "Use of Samples or Data in Other Research Studies". Future testing of samples will be performed only on samples from study participants who have consented for future storage and testing of samples. Residual research specimens from subject who decline future use will be destroyed after the study, final analysis and report writing have all been completed.

Samples will be collected with the subjects' consent in this protocol with the intent to store for additional research (i.e. samples collected beyond those needed for primary research) and will be used in future studies on microbial or antiviral research. Specimens will be labeled only with a barcode and a unique tracking number to protect subject confidentiality. Secondary research with coded samples and data may occur, but subject confidentiality will be maintained as described for this protocol. Any future testing laboratory will not have access to the code, and therefore will not be able to identify study participants. Genetic testing on these samples will not be performed. An IRB review of the secondary research using coded specimens is required.

10.1.4.2 Data Sharing for Secondary Research

Data from this study may be used for secondary research. All the individual participant data collected during the trial will be made available after de-identification. The Statistical Analysis Plan and Analytic Code will also be made available. These data will be available immediately following publication, with no end date. At the end of the trial, the data may be made available to researchers who provide a methodologically sound proposal. The data will be available for any purpose outlined in the approved proposal. Proposals should be directed to David Kimberlin, MD (Principal Investigator for this study) at dkimberlin@peds.uab.edu. To gain access, data requestors will need to sign a data access agreement. An investigator may request removal of data on individual study subjects from NIH data repositories in the event that a research subject withdraws or changes his/her consent. However, some data that have been distributed for approved research use cannot be retrieved.

10.1.5 Key Roles and Study Governance

The study is sponsored by DMID. Decisions related to the study will be made by the protocol team. All study team members and roles are listed in the Manual of Procedures (MOP).

10.1.6 Safety Oversight

The DMID Medical Monitor will be responsible for reviewing SAEs in real time and all safety data. The Lead PI will also review the SAEs and AE listings as needed to ensure the safe conduct of this trial.

Safety oversight will be conducted by a Safety Monitoring Committee (SMC) that is an independent group of experts that monitors subject safety and advises DMID. The SMC

members will be separate and independent of study personnel participating in this trial and should not have scientific, financial or other conflict of interest related to this trial. The SMC will consist of members with appropriate expertise to contribute to the interpretation of the data from this trial. The SMC will operate under the rules of a SMC-approved charter that will be written at the organizational meeting of the SMC. The SMC will review AEs and SAEs on a regular and ad hoc basis during the trial.

The SMC will conduct the following reviews:
- After each cohort of 8 subjects has completed dosing and been followed for 42 days.
- Ad hoc meeting:
  - When trial-level halting criteria are met
  - At the request of DMID to review a potential safety concern identified by either the lead PI, DMID Medical Monitor, or protocol team
- A final review meeting to review the cumulative safety data for this trial.

The study will not stop enrolled awaiting the regularly scheduled SMC reviews, although the SMC may recommend temporary or permanent cessation of enrollment based on their safety reviews.

Additional data may be requested by the SMC, and interim statistical reports may be generated as deemed necessary and appropriate by SMC. The SMC may receive data in aggregate and presented by treatment arm. The SMC may also be provided with expected and observed rates of the expected AEs. The SMC will review grouped data in the closed session only. As an outcome of each review/meeting, the SMC will make a recommendation as to the advisability of proceeding with study interventions (as applicable), and to continue, modify, or terminate this trial.

10.1.7 Clinical Monitoring

Clinical site monitoring will be conducted to ensure that the rights and well being of study subjects are protected and that the reported trial data are accurate, complete and verifiable. Clinical site monitoring also ensures that the conduct of the trial is in compliances with the currently approved protocol/amendment(s), ICH, GCP and with applicable regulatory requirements(s) and sponsor requirements. Clinical monitoring will also verify that any critical study procedures are completed following specific instructions in the protocol specific MOP. DMID, the sponsor of this study, or its designee will conduct site monitoring visits as detailed in the clinical monitoring plan (CMP).

Site visits will be made at standard intervals in accordance with the monitoring plan. More frequent visits may be made if needed. Monitoring visits will include, but are not limited to, review of regulatory files, product accountability records, CRFs, ICFs medical and laboratory reports, study site product storage records, and protocol and GCP compliance. Site monitors will have access to each participating site, study personnel, and all study documentation according to the DMID-approved site monitoring plan. Remote or on-site monitoring may be used. Study monitors will meet with the site PIs to discuss any problems and outstanding issues and will

document site visit findings and discussions. The UAB Central Unit will work with the sites to address all monitoring findings.

10.1.8 Quality Assurance and Quality Control

Each study site will have a quality management plan. Following a written DMID-accepted site quality management plan, the investigational site is responsible for conducting routine quality assurance and quality control activities to internally monitor study progress and protocol compliance. The PI will provide direct access to all trial-related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities. The PI will ensure all study personnel are appropriately trained and applicable documentation is maintained on site.

The SDCC will implement quality control procedures beginning with the data entry system and generate data quality control checks that will be run on the database. Any missing data or data anomalies will be communicated to the site(s) for clarification and resolution.

10.1.9 Data Handling and Record Keeping

10.1.9.1 Data Collection and Management Responsibilities

Data collection is the responsibility of the study personnel at the participating clinical study site under the supervision of the site PI. The site PI must maintain complete and accurate source documentation. At the end of the study, the PI will attest to the accurateness of data collected at the study site.

Clinical data from source documentation (including, but not limited to, AEs/SAEs, concomitant medications, medical history, physical assessments, clinical and research laboratory data) will be entered into CRFs via a 21 CFR Part 11-compliant Internet Data Entry System (IDES) provided by the SDCC. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. AEs and concomitant medications will be coded according to the most current versions of MedDRA and WhoDrug, respectively.

The SDCC for this study will be responsible for data management, quality review, analysis and reporting of the study data.

AEs will be coded according to the MedDRA dictionary version 23.0 or higher. A separate study specific Study Data Standardization Plan (SDSP) appendix will be developed which describes the technical recommendations for the submission of human study data and related information in a standardized electronic format throughout product development. At the end of the study, a copy of all datasets including annotated CRFs and data dictionary will be provided to DMID and to the lead PI.

10.1.9.2 Study Record Retention

Study related records and documents pertaining to the conduct of this study, including subject source documents and electronic records, consent forms, the regulatory file, laboratory test results, and study product accountability records, must be retained by the investigator for at least 2 years following completion of the study. No study records shall be destroyed without written authorization from the UAB Central Unit and NIAID/DMID. These documents should be retained for a longer period, however, if required by local regulations. Consent forms with specimen retention linked to identifiable specimens will be maintained for as long as the specimens remain in identifiable format and a minimum of three years after use of the identifiable specimens in nonexempt human subject research. It is the responsibility of the sponsor to notify the UAB Central Unit, which will notify the investigators, when these documents no longer need to be retained.

10.1.9.3 Source Records

Source data are all information in original records (and certified copies of original records) of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Each participating site will maintain appropriate medical and research records for this trial, in compliance with ICH GCP, regulatory, and institutional requirements. Data recorded in the CRF derived from source documents should be consistent with the data recorded on the source documents. Data collection forms used as source documents will be derived from the eCRFs and be provided by the SDCC.

10.1.10 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trials protocol, GCP, or Manual of Procedures requirements. The noncompliance may be either on the part of the study participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly. All individual protocol deviations will be addressed in study subject records.

It is the responsibility of the site PI and study personnel to use continuous vigilance to identify and report deviations within 1 business day of identification of the protocol deviation that increases subject risk. Deviations that do not increase subject risk can be reported within 5 business days of knowledge of the event. All deviations must be promptly reported to the Sponsor DMID per the protocol deviation reporting procedures.

A completed copy of the DMID protocol deviation form must be maintained in the regulatory file (Project Notebook or designated location) as well as in the subject's source documents. Protocol deviations must be sent to the Single (Central) IRB and the local IRB per the IRB's guidelines. The site PI/study staff is responsible for knowing and adhering to their IRB/IEC requirements.

10.1.11 Publication and Data Sharing Policy

This trial will be registered in the public registry ClinicalTrials.gov per NIH policy. Results from the trial will be published on ClinicalTrials.gov in accordance with the policy and U.S. law and will be published in a scientific journal.

10.1.12 Human Data Sharing Plan

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

- National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

As this study is conducted as part of the National Center for Advancing Translational Science (NCATS) Rare Diseases Clinical Research Network (RDCRN), data may be shared with a common data repository maintained by NCATS and managed by the Data Management and Coordinating Center (DMCC).

10.1.13 Genomic Data Sharing Plan

Not applicable

10.1.14 Publication

Following completion of this study, the investigators are expected to publish the results in a scientific journal. The study will adhere to the following publication and data sharing policies and regulations:

- This study will comply with the NIH Public Access Policy, which ensures that the public has access to the published results of NIH funded research. As such, the final peer reviewed journal manuscripts will accessible to the public on PubMed Central no later than 12 months after publication.

10.1.15 Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. DMID has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

10.2 Additional Considerations

10.2.1 Research Related Injuries

For any potential research related injury, the site principal investigator or designee will assess the subject. Study personnel will try to reduce, control, and treat any complications from this study. Immediate medical treatment may be provided by the participating study site. As needed, referrals to appropriate health care facilities will be provided to the subject.

The site principal investigator should then determine if an injury occurred as a direct result of the tests or treatments that are done for this trial. If the site PI determines that the injury occurred to a subject as a direct results of the tests or treatments, then immediate medical treatment may be provided, such as giving emergency medications to stop allergic reactions. Referrals to appropriate health care facilities will be provided. No financial compensation will be provided by the NIAID, NIH, the federal government, or the participating site to the subject, for any injury suffered due to participation in this trial.

10.3 Abbreviations

Table 6. Abbreviations

ACOG	American College of Obstetrics and Gynecology
AE	Adverse Event
ALT	Alanine Transaminase
ANCOVA	Analysis of Covariance
AUC	Area Under the Curve
BID	Twice daily
CASG	Collaborative Antiviral Study Group
CBC	Complete Blood Count
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CI	Confidence Interval
CLIA	Clinical Laboratory Improvement Amendments
CMS	Clinical Material Services
CNS	Central Nervous System
CPIC	Congenital and Perinatal Infections Consortium
CRF	Case Report Form
CROMS	Clinical Research Operations and Management Support
CU	Central Unit
DCC	Data Coordinating Center
DMID	Division of Microbiology and Infectious Diseases
DSMB	Data Safety Monitoring Board
eCRF	Electronic Case Report Forms
eDES	Electronic Data Entry System
FDA	Food and Drug Administration
FWA	Federal Wide Assurance

GCP	Good Clinical Practice
GCSF	Granulocyte colony-stimulating factor
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HSV	Herpes Simplex Virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IEC	Independent or Institutional Ethics Committee
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ISO	International Organization for Standardization
ITT	Intent To Treat
MedDRA	Medical Dictionary for Regulatory Activities
MedDRAÒ	Medical Dictionary for Regulatory Activities
Mg	Milligram
MOP	Manual of Procedures
N	Number (typically refers to subjects)
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
PCR	Polymerase Chain Reaction
PI	Principal Investigator
PMTCT	Prevention of mother-to-child transmission
PK	Pharmacokinetics
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SDCC	Statistical and Data Coordinating Center
SEM	Skin, Eye, Mouth
SMA	Secondary Medical Assessor
SMC	Safety Monitoring Committee
SOA	Schedule of Activities
SOP	Standard Operating Procedure
UAB CU	University of Alabama at Birmingham Central Unit
ULN	Upper limit of normal
UP	Unanticipated Problem
US	United States
VZV	Varicella-zoster virus
WBC	White Blood Cell

10.4 Protocol Amendment History

Table 7. Protocol Amendment History

Version	Date	Description of Change	Brief Rationale
4.0	05 March 2024	• Clarification of number of doses a subject may receive • Clarification of dose around which PK samples should be obtained • Clarification that an SMC will be overseeing the study rather than a DSMB • Addition of the web link to the DMID Serious Adverse Event form	There were internal discrepancies in v3.0 of the protocol. These have been corrected in v4.0.

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12. APPENDIX A: (ADAPTED FROM) DIVISION OF AIDS TOXICITY TABLES

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*

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
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*
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)