EVALUATION OF THE PHARMACOKINETICS AND PHARMACODYNAMICS OF VALACYCLOVIR IN NEONATES WITH NEONATAL HERPES SIMPLEX VIRUS DISEASE WHO HAVE COMPLETED STANDARD OF CARE TREATMENT WITH ACYCLOVIR

NCT: 04448392

Principal Investigator: **Nicole Samies, D.O.**

Version Number: **1.0**

2 June 2020

STATEMENT OF COMPLIANCE

Each investigator must adhere to the protocol as detailed in this document. Each investigator will be responsible for enrolling only those study participants who have met protocol eligibility criteria. This trial will be conducted in compliance with the protocol, International Conference on Harmonization Good Clinical Practice guidelines (ICH-E6), 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. Refer to http://grants.nih.gov/grants/guide/notice-files/NOT-OD-01-061.html; http://cme.cancer.gov/clinicaltrials/learning/humanparticipant-protections.asp

SIGNATURE PAGE

The signature below constitutes the approval of this protocol "**Evaluation of the Pharmacokinetics and Pharmacodynamics of Valacyclovir in Neonates with Neonatal Herpes Simplex Virus Disease who have Completed Standard of Care Treatment with Acyclovir"** and attachments and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines. It is understood that no deviations from the protocol may be made without permission of the IRB.

Site Investigator:

Signed: _____ Date: _____

Name

_____

Title

_____

Signature

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LIST OF ABBREVIATIONS

AE	Adverse Event/Adverse Experience
AESI	Adverse Event Special Interest
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
AUC	Area Under the Curve
CFR	Code of Federal Regulations
CHRU	Child Health Research Unit
CL	Clearance
Cmax	Maximum serum concentration
CNS	Central Nervous System
CRF	Case Report Form
CSF	Cerebrospinal fluid
eCRF	Electronic Case Report Form
EU	European Union
FDA	Food and Drug Administration
FWA	Federalwide Assurance
GCP	Good Clinical Practice
HSV	Herpes Simplex Virus
ICH	International Conference on Harmonisation
IEC	Independent or Institutional Ethics Committee
IND	Investigational New Drug Application
IRB	Institutional Review Board
IV	Intravenous
KG	Kilogram
MG	Milligram
mL	Milliliter
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
PCR	Polymerase Chain Reaction
PHI	Protected Health Information
PI	Principal Investigator
PK	Pharmacokinetics
SAE	Serious Adverse Event/Serious Adverse Experience
SEM	Skin, Eye, and Mouth Disease
Vd	Volume of distribution
US	United States
WBC	White Blood Cell Count

PROTOCOL SUMMARY

Title:	Evaluation of the Pharmacokinetics and Pharmacodynamics of Valacyclovir in Neonates with neonatal HSV disease who have completed standard of care treatment with acyclovir
Phase:	IB
Population:	Male and female term infants ≥ 34 weeks gestation who have been diagnosed with virologically confirmed neonatal HSV disease via culture or polymerase chain reaction (PCR)
Sample Size:	6 - 10
Number of Sites:	1
Study Duration:	5 years
Subject Participation Duration:	up to 26 days
Description of Agent or Intervention:	Administration of valacyclovir for 2 to no more than 7 days in infants who have completed standard of care treatment course for neonatal HSV disease with high-dose parenteral acyclovir to obtain pharmacokinetic data. After 2 to no more than 7 days, the infant will be switched to the standard-of-care, oral acyclovir, to complete the standard 6 months of suppressive therapy.
Objectives:	Primary: • To define the pharmacokinetics of valacyclovir in neonates 2-12 weeks of age who are ≥ 34 weeks gestation • To assess the safety of valacyclovir in treated infants Secondary: • To assess the pharmacokinetics of high-dose parenteral acyclovir in neonates ≥ 34 weeks gestation with virologically confirmed neonatal HSV disease who are receiving acyclovir as standard of care • To compare the pharmacokinetics of high-dose parenteral acyclovir to the pharmacokinetics of the proposed study dose of valacyclovir (20 mg/kg every 8 hours)

Outcome Measures

Primary Endpoint:

- Plasma pharmacokinetics parameters for valacyclovir AUC_8
- Cumulative incidence of Grade 3 or higher unsolicited adverse events, serious adverse events, or any adverse event that is not recovered / not resolved

Secondary Endpoints:

- Plasma pharmacokinetic parameters for parenteral acyclovir AUC_8
- Comparison of AUC_8 of 20 mg/kg IV acyclovir to the AUC_8 of 20 mg/kg PO valacyclovir

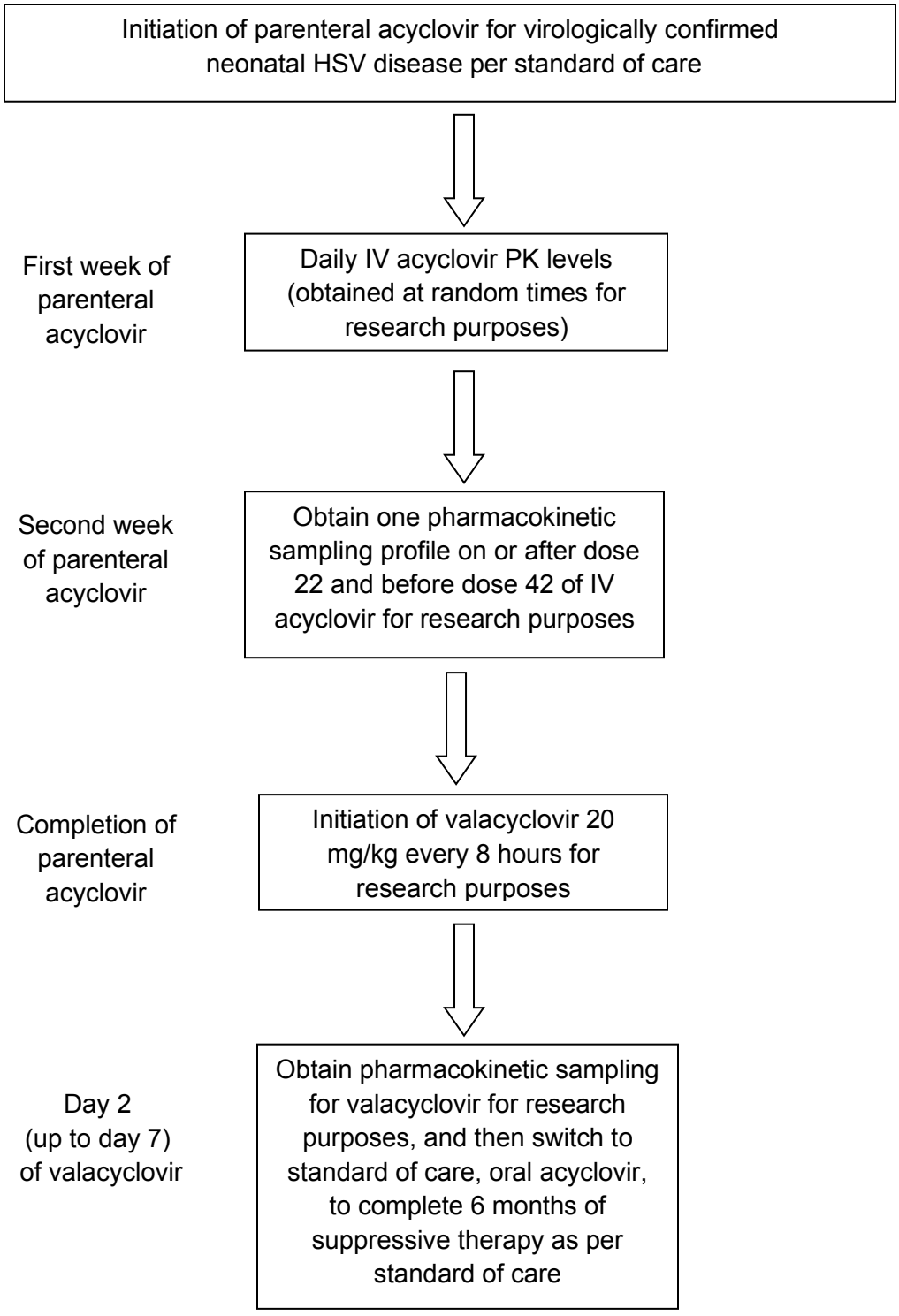
Description of Study Design:

This is an open-label, single center, PK study to assess valacyclovir pharmacokinetics and pharmacodynamics in neonates and compare to the pharmacokinetics and pharmacodynamics of the standard of care treatment dose of intravenous acyclovir. Only those babies with virologically confirmed neonatal HSV disease will be enrolled in the study. The decision to initiate valacyclovir for 2 (up to 7) days will be made by a physician based on inclusion/exclusion criteria, and those who meet entry criteria will be eligible for the study. Those enrolled in the study will have daily random parenteral acyclovir PK levels drawn during the first week of treatment (drawn only at times of other lab draws). These infants will also have a pharmacokinetic sampling profile obtained on or after dose 22 and before dose 42 of intravenous acyclovir. The PK samples for the sampling profile will be collected just prior to the next dose of intravenous acyclovir (within 30 minutes prior to the start of the infusion), within 15 minutes of completion of the infusion, and 3-4 hours after infusion. Upon completion of the recommended treatment course duration with intravenous acyclovir determined by disease classification (SEM, CNS, or disseminated disease), the infant will be started on enteral valacyclovir 20 mg/kg every 8 hours.

On day 2 and no more than day 7 of valacyclovir 20 mg/kg every 8 hours, a pharmacokinetic sampling profile will be obtained. The PK samples will be collected just prior to the

	enteral dose of valacyclovir hour 0 (8 hours after previous dose and immediately before next dose), 1-2 hours after dose, and 3-5 hours after dose. Subjects with inadequate pharmacokinetic data for analysis (e.g., due to dropping out of the study before PK assessments are performed, or blood sampling obtained but is inadequate for analysis) may be replaced and will not count toward the total of 6 (and up to 10) subjects.
Estimated Time to Complete Enrollment:	4.5 years from enrollment of the first study subject

***Schematic of Study Design**:



1 KEY ROLES

Individuals:

Co-Principal Investigator:
Nicole Samies, DO
Protocol Chair
Pediatric Infectious Disease Fellow
The University of Alabama at Birmingham
1600 Sixth Avenue South, CHB 308
Birmingham, AL 35233
Phone: 205-996-6418
Fax: 205-975-6549
e-mail: nsamies@uabmc.edu

Co-Principal Investigator:
David Kimberlin, MD
Co-Principal Investigator, Collaborative Antiviral Study Group
Professor of Pediatrics
Sergio Stagno Endowed Chair in Pediatric Infectious Diseases
The University of Alabama at Birmingham
1600 Seventh Avenue South, CHB 303
Birmingham, AL 35233
Phone: 205-934-5316
Fax: 205-975-9972
e-mail: dkimberlin@peds.uab.edu

Co-Principal Investigator:
Richard Whitley, MD
Co-Principal Investigator, Collaborative Antiviral Study Group
Professor of Pediatrics
Pediatric Infectious Disease Fellow
The University of Alabama at Birmingham
1600 Seventh Avenue South, CHB 303
Birmingham, AL 35233
Phone: 205-996-7878
Fax: 205-975-9972
e-mail: rwhitley@peds.uab.edu

Institutions:

University of Alabama at Birmingham
Nicole Samies, DO

Department of Pediatrics, Division of Infectious Diseases
1600 6th Avenue South, CHB 308 Birmingham, AL 35233
Phone: 205-996-6418
Fax: 205-975-6549
Email: nsamies@uabmc.edu

Optional:

Statistician:
Inmaculada "Chichi" Aban, PhD
Associate Professor
Department of Biostatistics
School of Public Health
The University of Alabama at Birmingham
RPHB 327
Phone: (205) 934-2732
Fax: (205) 975-2541
e-mail: CAban@ms.soph.uab.edu

UAB Antiviral Pharmacology Laboratory:
Edward P. Acosta, Pharm.D.
Professor and Director, Division of Clinical Pharmacology
University of Alabama at Birmingham
School of Medicine
1670 University Blvd, Volker Hall, Room 258
Birmingham, AL 35294-0019
Phone: 205-934-2655
Fax: 205-934-6201
e-mail: eacosta@uab.edu

2 BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 Background Information

Neonatal HSV is an uncommon disease that affects about 1500 infants yearly in the US (1-3) with recent studies indicating an increasing incidence over the last several years (4). Although uncommon, the disease can have devastating outcomes if not detected and treated early. The disease is divided into three classifications: skin, eye, and mouth (SEM), central nervous system (CNS), and disseminated. The classification is predictive of mortality and morbidity, with worse outcomes noted in the CNS and disseminated groups (5). SEM disease accounts for the majority of neonatal HSV disease cases (45%), followed by CNS disease (30%), and then disseminated disease (25%) (6).

Vidarabine was the first antiviral drug recommended for treatment of neonatal HSV disease in the 1970s. Although other antiviral agents were studied prior to vidarabine, they were not recommended for treatment of neonatal HSV disease as a result of their toxic side effects. Vidarabine was later replaced in the 1980s by acyclovir, an acyclic guanine analogue that inhibits viral replication by interfering with viral DNA polymerase (7-10). Although low dose acyclovir (30 mg/kg/day) was equally efficacious and demonstrated no reduction in mortality when compared to vidarabine (5, 6, 11), it was more favorable because of its less toxic profile and easier administration (6). A later study performed by the National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group (CASG) evaluated intermediate dose acyclovir (45 mg/kg/day) and high dose acyclovir (60 mg/kg/day) to determine if outcome could be improved. High dose acyclovir demonstrated the greatest reduction in mortality rate from 14% in CNS disease and 54% in disseminated disease to 4% and 30% respectively (12). Thus, high dose acyclovir became the new standard of treatment for neonatal HSV disease, although the pharmacokinetics of high dose intravenous acyclovir dose were only assessed in two subjects (6, 12).

Currently the standard of care requires that infants diagnosed with neonatal HSV disease are treated with high dose intravenous acyclovir for 14-21 days depending on classification of the disease (6, 13); infants with SEM disease are recommended to receive 14 days of intravenous acyclovir whereas infants with CNS and disseminated disease are recommended to receive at least 21 days of intravenous therapy. Those with CNS disease could potentially require longer than 21 days of therapy as duration of therapy is determined on clearance of viral DNA from the CSF via repeat lumbar puncture performed near the end of the 21 days of therapy(14). If the viral DNA is still detected, intravenous acyclovir is continued for an additional week and another lumbar puncture is performed. Infants remain hospitalized for the entire duration of treatment in order to closely monitor for the potential risk of renal toxicity, a common reversible side effect of intravenous acyclovir. Once the infant has completed the treatment

course of intravenous acyclovir, they are transitioned to oral acyclovir (300 mg/m^2/dose three times a day) and discharged home to complete a total of 6 months of suppressive therapy to prevent further neurologic injury by subclinical viral replication (13, 15). Suppressive therapy has significantly improved neurologic outcome (higher neurodevelopmental scores) in those infants with CNS disease and decreased the number of skin recurrences when started immediately after completion of treatment with IV acyclovir (15, 16).

Although vast advancements have been made in the treatment of neonatal HSV disease to reduce mortality and morbidity, there remains a high emotional burden and demand on families as a result of guilt, lengthy hospitalizations, and frequent administration of medications for a prolonged period of time. There is also a large financial burden on healthcare systems; the estimated costs for treatment of neonatal HSV disease accounting for admission and 6 months of follow up in a cohort of 900 infants from 2009-2015 was more than 60 million dollars (4), which will continue to increase as the incidence of the disease increases. Preventing neonatal HSV disease would be ideal to reduce the emotional stress and demand on families and financial burden on healthcare systems, but until that time, other means of reducing these stressors should be evaluated.

One way to potentially reduce the emotional stress and demands on families would be to decrease the length of hospital stay. Unfortunately, due to oral acyclovir's poor bioavailability of 15-30% (8-10, 17, 18), infant's require intravenous acyclovir for treatment in order to achieve the desired acyclovir plasma concentration. Valacyclovir, on the other hand, offers the possibility of use in infants for a portion of the treatment course as it can achieve similar concentrations to IV acyclovir because of its improved bioavailability of 50-54% (7, 8). Valacyclovir is an enteral prodrug of acyclovir synthesized by the addition of L-valine to acyclovir, and it is commonly used in the treatment and/or suppression of genital herpes in adolescents, adults, and pregnant women (9, 17, 19). Yet, only limited data exists on its use in children. One study performed by Kimberlin et al evaluated the pharmacokinetics of valacyclovir in children ranging from 1 month to 11 years of age. The study was able to recommend a valacyclovir dose of 20 mg/kg two to three times a day in children 3 months of age and older but was unable to recommend a dose for those younger than 3 months of age. This is because only one dose (25 mg/kg) was evaluated in those 1-2 months of age, and the 1-2 month old infants had a significantly higher AUC and C_{max} with a 25 mg/kg/dose of valacyclovir when compared to older infants due to decreased clearance (20). Thus, the pharmacokinetics of valacyclovir 20 mg/kg in infants less than 3 months of age needs to be evaluated in order to determine if valacyclovir can safely be recommended for use in the treatment of neonatal HSV disease. The dose recommended must approximate the plasma serum concentrations achieved with 20 mg/kg/dose of intravenous acyclovir.

UAB has contributed to and led many multi-center pharmacokinetic and pharmacodynamic studies including the study that evaluated the use of valacyclovir in children from 1 month to 11 years of age. Their experience will be extremely helpful in determining the PK data of valacyclovir and its potential use in the treatment course of neonatal HSV disease (specifically

with SEM disease). Due to biochemical properties, a liquid suspension of valacyclovir has not been produced, but the American Society of Health-System Pharmacists provides instructions on how to make an extemporaneously suspension that shows stability for at least 21 days (21).

2.2 Rationale

Valacyclovir is frequently used in adolescents and adults for the treatment and suppression of genital herpes; it is also recommended for use in pregnant women beginning around 36 weeks gestation with a history of genital herpes for suppressive therapy to decrease the risk of developing active lesions at time of delivery (19). In 2010, CASG performed a valacyclovir pharmacokinetic study in children one month to eleven years of age, and the study provided the first recommendations for valacyclovir dosing in children 3 months of age and older. The dose recommended was 20 mg/kg two to three times a day. Unfortunately, dosing recommendations could not be provided for those 1-2 months of age as only the 25 mg/kg dose was studied (20). Therefore, determining if 20 mg/kg every 8 hours is an appropriate dose of valacyclovir in infants less than 3 months of age is necessary before it can be recommended for use in the treatment of neonatal HSV disease. In order to determine if the dose is appropriate, pharmacokinetic data will need to be obtained for valacyclovir and compared to intravenous acyclovir pharmacokinetic data. Since pharmacokinetic data on intravenous high-dose acyclovir is limited to only two patients, this too will need to be evaluated for comparison purposes.

The proposed study is a PK study evaluating the pharmacokinetics of valacyclovir in infants 2-12 weeks of age. Only infants ≤ 42 days of age who have been diagnosed with neonatal HSV disease on intravenous acyclovir per standard of care guidelines will be eligible for participation. The recommended dose of valacyclovir in children 3 months of age and older is 20 mg/kg two to three times a day, and thus, the dose to be studied will be 20 mg/kg/dose every 8 hours. Valacyclovir will be given anywhere from 2 days up to 7 days depending on when the pharmacokinetic data can be obtained. Data will only be obtained during weekday hours in the Child Health Research Unit (CHRU) at the University of Alabama at Birmingham. After pharmacokinetic data has been obtained, the infant will be switched to oral acyclovir per standard of care guidelines to complete 6 months of suppressive therapy. At the completion of the study, the pharmacokinetic data for valacyclovir 20 mg/kg every 8 hours in infants 2-12 weeks of age will be defined and will be evaluated to determine if the recommended dose is comparable to the currently recommended IV acyclovir dose. Results from this research will lay the foundation for future studies evaluating the use of valacyclovir in a portion of the treatment course for neonatal HSV disease - specifically SEM disease - to reduce the number of days an infant requires hospitalization and subsequently decrease the cost of admission. Additional studies will need to be performed to determine the CNS penetration of valacyclovir in order to determine its potential use in infants with CNS disease. All pharmacokinetic assays will be performed in the UAB Antiviral Pharmacology Laboratory, which has developed the methodology to process microspecimens of blood for several different drug concentration studies.

2.3 Potential Risks and Benefits

2.3.1 Potential Risks

One potential risk relates to the blood draws (e.g., bruising at the site, discomfort, infection) required to obtain the pharmacokinetic samples. All infants should have a long-term indwelling intravenous catheter (e.g. PICC) during hospitalization for administration of IV acyclovir through which blood can be withdrawn without risk of discomfort from a needle stick or bruising at the site during or after the blood drawing and rarely infection. However, once the infant is discharged from the hospital the indwelling intravenous catheter will need to be removed to prevent more harm to the infant as the risk of infection is greater when an indwelling catheter is not being used. Thus, valacyclovir pharmacokinetic samples will need to be obtained via a heel or venous stick on day 2 up to day 7 of valacyclovir therapy. Heel warmers or socks can be used prior to the blood draw to increase blood flow to the heel and reduce the amount of discomfort experienced with squeezing of the infant's heel in order to obtain the amount of blood necessary. The weight-based volumes required for the study-specific procedures are less than the limits of the Institutional Review Board and the NIH.

Additionally, daily random pharmacokinetic samples obtained during the first week of IV acyclovir will be obtained only at the time of clinical blood draws (creatinine and/or CBC/diff) to prevent additional venipuncture procedures solely for study purposes. The weight-based volumes required for the study-specific procedures are less than the limits of the Institutional Review Board and the NIH.

Potential risks associated with the use of valacyclovir are comparable to the risks associated with long term use of the current standard of care, oral acyclovir. Therefore, monitoring for adverse events is not necessary for short term use (2 and up to 7 days) of valacyclovir.

2.3.2 Known Potential Benefits

Knowledge of the pharmacokinetic profile will aid in determining if 20 mg/kg/dose every 8 hours is the most appropriate dose of valacyclovir to be used in infants (≤ 84 days of age) for treatment of neonatal SEM HSV disease. It will also provide further baseline information for future studies to evaluate the use of valacyclovir in infants with neonatal HSV CNS disease. This information can aid in decreasing the length of hospitalization, emotional burden on families, and ultimately health care costs. Participants will not directly benefit themselves from participating, though.

3 OBJECTIVES

3.1 Study Objectives

Primary:

- To define the pharmacokinetics of valacyclovir in neonates (≥ 34 weeks gestational age at birth and ≥ 2000 g)
- To assess safety of valacyclovir administration

Secondary:

- To assess the pharmacokinetics of high-dose parenteral acyclovir in neonates ≥ 34 weeks gestation with virologically confirmed neonatal HSV disease who are receiving acyclovir as standard of care
- To compare the pharmacokinetics of high-dose parenteral acyclovir to the pharmacokinetics of the proposed study dose of valacyclovir (20 mg/kg every 8 hours)

3.2 Study Outcome Measures

3.2.1 Primary Outcome Measures

Primary Endpoint:

- Plasma pharmacokinetic parameters for valacyclovir AUC_8
- Cumulative incidence of Grade 3 or higher unsolicited adverse events, serious adverse events, or any adverse event that is not recovered / not resolved

3.2.2 Secondary Outcome Measures

Secondary Endpoints:

- Plasma pharmacokinetic parameters for parenteral acyclovir AUC_8
- Comparison of AUC_8 of 20 mg/kg IV acyclovir to the AUC_8 of 20 mg/kg PO valacyclovir

4 STUDY DESIGN

This study is an open-label, single-center, pharmacokinetic study of valacyclovir pharmacokinetics in male and female infants ≥ 34 weeks gestation, ≤ 42 days of age at initiation of intravenous acyclovir, and ≥ 2000 g who have been diagnosed with virologically confirmed neonatal HSV disease via culture or polymerase chain reaction (PCR). Infants who meet the inclusion criteria will be eligible for the study, and informed consent will be obtained by the infant's parent(s) or legal guardian(s).

Subjects meeting enrollment criteria will be enrolled in this clinical trial. The total sample size will be 6 and up to 10 infants diagnosed with any of the 3 disease classifications of neonatal HSV disease. Following enrollment, infants during the first week of treatment with intravenous acyclovir as per standard of care will have daily random pharmacokinetic levels (population based pharmacokinetics) obtained at the same time of clinical blood draws (e.g. creatinine and/or CBC/diff), namely using remnant specimens. During the second week of treatment with IV acyclovir (between dose 22 and 42) infants will have one pharmacokinetic sampling profile obtained. The plasma specimens for the pharmacokinetic sampling profile will be drawn immediately prior to next dose (within 30 minutes prior to the start of infusion and 8 hours after previous dose) for an 8 hour trough, a post-infusion peak obtained within 15 minutes following completion of infusion, and 3-4 hours after infusion. Once these samples are obtained, the infant will complete the course of IV acyclovir per the standard of care guidelines.

Upon completion of the intravenous acyclovir per standard of care, the infant will be switched to valacyclovir 20 mg/kg every 8 hours for 2 and up to 7 days depending upon availability of the CHRU. The first dose of valacyclovir is to be given 8 hours after completion of the last dose of IV acyclovir. On day 2 (up to 7), the infant will return to UAB's CHRU for a PK profile to be obtained. The plasma specimens for the pharmacokinetic profile will be drawn at hour 0 (just prior to the scheduled valacyclovir dose and 8 hours after the last dose), at 1-2 hours after dose for a peak level, and 3-5 hours after dose. Once the infant completes the pharmacokinetic sampling, the infant will have completed the study and will be switched to oral acyclovir per standard of care guidelines to complete 6 months of oral suppressive therapy for neonatal HSV disease. The parent(s) or guardian will be instructed to have the infant follow with an infectious disease specialist for appropriate follow up of neonatal HSV disease while on suppressive therapy.

All participants will receive the standard of care treatment with 14 to 21 days of IV acyclovir (depending on disease classification) followed by 6 months of oral antiviral suppression. The only change is that the first few days or oral suppression with be with valacyclovir instead of acyclovir. Subjects with inadequate pharmacokinetic data for analysis (e.g., due to dropping out of the study before PK assessments are performed or blood sampling obtained but is

inadequate for analysis) may be replaced and will not count toward the total of 6 and up to 10 subjects.

Treatment Day 1 is the calendar day when the first dose of parenteral acyclovir was administered to the study subject for clinical purposes and will be the date against which follow-up visits will be defined. **Treatment Dose 1** corresponds to the first dose of parenteral acyclovir given to the study subject for clinical purposes. The study enrollment day is unlikely to be the same day as Treatment day 1 as individuals will need confirmation of neonatal HSV infection in order to be enrolled. Participants can enroll on or before treatment day 14. **Study Assessment Day 1** is the calendar day when the participant is enrolled in the study.

The study will be divided up into 3 periods: **Period 1** will consist of **Treatment Day 1 through Treatment Day 7**, **Period 2** will consist of **Treatment Day 8 through Treatment Day 14 (or 21 if being treated for CNS or disseminated infection),** and **Period 3** will be from the initiation of valacyclovir (started after completion of IV acyclovir) until the collection of PK valacyclovir specimens. Although it is anticipated, but not required, that patients are enrolled in the study prior to treatment day 7 in order to participate in all 3 periods, all patients will be enrolled on or before treatment day 14 and will included in all eligible periods based on pre-determined classification.

During **Period 1,** daily pharmacokinetic specimens will be obtained randomly but only at times of other clinical blood draws. The acyclovir dose, time of last acyclovir infusion prior to blood draw, and time of blood draw will be recorded. During **Period 2**, only one pharmacokinetic sampling profile will be obtained between **Treatment Dose 22 and Treatment Dose 42**. The pharmacokinetic specimens for the profile will be obtained at hour 0 (within 30 minutes of the next parenteral acyclovir dose), within 15 minutes of completion of parenteral acyclovir infusion, and 3-4 hours after infusion.

During **Period 3**, a pharmacokinetic sampling profile will be obtained while the infant is on valacyclovir. Pharmacokinetic specimens will be obtained at hour 0 (immediately prior to next valacyclovir dose; window: -15 min), 1-2 hours post dose, and 3-5 hours post dose. Valacyclovir dose, date, time of last valacyclovir dose, and time of blood draw will be recorded.

All pharmacokinetic specimens will be taken to the UAB Antiviral Pharmacology Laboratory for processing. No additional blood samples will be required for research purposes.

5 STUDY ENROLLMENT AND WITHDRAWAL

Male and female infants ≥ 34 weeks gestation of any ethnicity with virologically confirmed neonatal HSV disease via culture- or polymerase chain reaction (PCR). The study population will be drawn from the in-hospital setting. Potential subjects will be identified by the site investigators and the study coordinators. Patients meeting study eligibility criteria will be offered enrollment into the trial. Informed consent signed by study subject's parent(s) or guardian(s) must be obtained prior to study enrollment. Site investigators are all clinicians who have direct access to the study population.

5.1 Subject Inclusion Criteria

1. Signed informed consent from parent(s) or legal guardian(s)
2. Confirmation of HSV infection from surface culture/PCR, skin lesion culture/PCR, blood PCR, or CSF PCR (performed at UAB Virology lab)
3. ≥ 34 weeks gestational age at birth
4. Weight at study enrollment is ≥ 2000 grams
5. Receiving intravenous acyclovir, prescribed by the patient's physician for ≤ 14 days
6. ≤ 42 days of age at initiation of parenteral acyclovir
7. Creatinine ≤ 1.2

5.2 Subject Exclusion Criteria

1. Imminent demise
2. Current receipt of other investigational drugs
3. Major congenital anomaly that in the site investigator's opinion may impact drug metabolism or the patient's volume of distribution
4. Creatinine of > 1.2 prior to initiation of valacyclovir
5. Evidence of immunosuppression (HIV infected, immune deficiencies, etc.)
6. Any condition that, in the opinion of the investigator, would place the subject at an unacceptable injury risk or that may interfere with successful study completion
7. > 42 days of age at initiation of parenteral acyclovir
8. Concern for parental/guardian compliance

5.3 Treatment Assignment Procedures

5.3.1 Randomization Procedures

Since this is a pharmacokinetic sampling study evaluating valacyclovir with no therapeutic intervention or investigation, no randomization procedures are required.

5.3.2 Reasons for Delaying Study-Related Procedures

Study related laboratory draws will be delayed or deferred if the investigator believes that obtaining them might increase subject risk. If a study related laboratory draw is delayed or deferred, study staff will document this on a source document.

5.3.3 Reasons for Withdrawal

The criteria for discontinuations during the study include:

- Study subject (parent/legal guardian) wishes to withdraw
- An alternate cause of disease (bacterial or other viral) is identified and acyclovir is discontinued
- Non-compliance with study procedures
- Trial termination (by UAB, or agreement of all investigators)
- Any other reason which, in the opinion of the investigator, precludes the study subject's participation in the study. The principal investigator must call the Protocol Chair prior to discontinuing a study subject for this reason.

5.3.4 Handling of Withdrawals

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. If subject withdraws before collection of the pharmacokinetic collection, this subject may be replaced (see Section 4).

5.3.5 Termination of Study

The PI and study team have the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- Study subject enrollment is unsatisfactory
- Data recording is inaccurate or incomplete
- Investigators do not adhere to the protocol or applicable regulatory guidelines in conducting the study.

6 STUDY INTERVENTION/INVESTIGATIONAL PRODUCT

Although valacyclovir does not currently have a recommended dose for infants 2 months and younger, this study is mainly a pharmacokinetic sampling study of valacyclovir in infants 2 months and younger and is not being used for a therapeutic intervention. Currently intravenous acyclovir is recommended for treatment of neonatal HSV disease, which these infants will receive per standard of care guidelines. The infants will only receive a short course of valacyclovir (2 and up to 7 days) in order to obtain the pharmacokinetic profile and then will be switched to the standard of care oral acyclovir to complete 6 months of suppressive therapy. The only change is that the first few days or oral suppression with be with valacyclovir instead of acyclovir.

6.1 6.1. Study Product Description

6.1.1 Acquisition

Valacyclovir will be resourced from COA's wholesaler.

6.1.2. Formulation, Packaging, and Labeling

A pharmaceutically-manufactured liquid formulation of valacyclovir does not exist at this time, but the American Society of Health-System Pharmacists provides instructions on how to make an extemporaneous preparation of oral suspension from 500 mg caplets. COA's Investigational Drug Pharmacy will prepare, package, and label the study medication. Valacyclovir is supplied in amber glass medicine bottles. It will be labeled as an investigational product.

6.1.3. Product Storage and Stability

The valacyclovir caplets should be stored at 15° – 25° C (59° – 77° F). Adherence to the USP Controlled Room Temperature is required. After constituting the study drug, it can be used within 21 days of preparation. The constituted study drug should be stored under refrigeration (2° – 8° C or 36° – 46° F) in a refrigerator. The constituted study drug must not be frozen.

6.2 6.2. Dosage, Preparation and Administration of Study Investigational Product

The dose of valacyclovir to be evaluated is 20 mg/kg every 8 hours to correlate with 20 mg/kg every 8 hours of intravenous acyclovir that is already used as standard of care for treatment of neonatal HSV disease. The subject enrolled in the study will receive anywhere from 2 up to 7 days (6-21 doses) of valacyclovir depending upon availability of the CHRU.

6.2.1. Preparation of Study Drug

Valacyclovir extemporaneously oral suspension will be reconstituted by COA's research or designated pharmacist. The extemporaneous suspension will be prepared following the instructions from the American Society of Health-System Pharmacists.

6.2.2. Administration of Study Drug

Valacyclovir may be given with or without food. The route of administration of study drug will be recorded (orally, nasogastric tube, orogastric tube, etc.).

6.3 6.3. Drug Accountability

After receipt of the investigational drug, the pharmacist will be responsible for and maintain logs of receipt, dispensation, storage conditions, and disposal of study drug. All original documents will be provided to the PI and will be maintained in a secure and accessible location.

Used and unused study product will not be disposed of or returned until the study monitor reviews and confirms the drug accountability.

- Used or partially used study product will be disposed of by the local site pharmacy in accordance with local regulations after completion of drug accountability by the study monitor.

6.4 6.4. Concomitant Medications

Concomitant medications not be recorded as this is only a PK sampling study.

6.5 6.5. Prohibited Medications

No drugs are prohibited while taking valacyclovir as there are no clinically significant drug-drug interactions.

7 STUDY SCHEDULE

7.1 Screening

Potential subjects will be identified by the site investigators and the study coordinators. Informed consent signed by study subject's parent(s) or guardian(s) must be obtained prior to study enrollment.

7.2 Enrollment/Baseline

7.2.1. Baseline Assessment (Window: Treatment Day 1 through Treatment day 14)

- Confirm that informed consent has been obtained from parent or legally authorized representative

- Document baseline demographics
  - Gestational age at delivery
  - Date of birth
  - Day of life at initiation of IV acyclovir therapy
  - Gender
  - Race
  - Ethnicity
  - Birth weight
  - Weight at enrollment
  - Length in centimeters at enrollment
  - Type of neonatal HSV
  - HSV diagnostic results (surface culture and/or PCR, HSV CSF PCR, HSV blood PCR, and/or lesion culture and/or PCR)

- Hematology labs
  - WBC with differential drawn for clinical purposes will be recorded

- Chemistry labs
  - All creatinine and alanine aminotransferase (ALT) values obtained for clinical purposes will be recorded

7.3 Study Follow-up

7.3.1. Period 1 (Treatment Day 1 through Treatment Day 7)

- Hematology labs

- WBC with differential will be recorded if being drawn for clinical reasons (any laboratory value obtained during the window will suffice, with an effort being made to capture the most abnormal value)

- Chemistry labs
  - Creatinine and alanine aminotransferase (ALT) values will be recorded if being drawn for clinical reasons

- Acyclovir pharmacokinetics
  - A single blood sample for PK determination will be obtained daily at random time intervals as able
  - Timepoints for pharmacokinetic draws will occur at random time intervals
    - Date and time of lab draw for PK specimen will be recorded
    - Date and time of last acyclovir infusion prior to PK lab draw will be recorded
    - Most recent patient weight, acyclovir dose received, and serum creatinine value will be recorded
  - Required amount of whole blood for plasma acyclovir determination at each timepoint is 200 μL (0.2 mL)

  Note: blood for PK assessments will be obtained at the time that a clinical blood draw is being performed, or through the indwelling intravenous catheter, so that no additional venipuncture procedures solely for study purposes will be required

7.3.2. Period 2 (Treatment Day 8 through Treatment Day 14 for SEM disease and Treatment Day 21 for CNS and disseminated disease)

- Hematology labs
  - WBC with differential will be recorded if being drawn for clinical reasons (any laboratory value obtained during the window will suffice, with an effort being made to capture the most abnormal value)

- Chemistry labs
  - Creatinine and alanine aminotransferase (ALT) values will be recorded if being drawn for clinical reasons

- Acyclovir pharmacokinetics
  - One acyclovir PK sampling profile will be performed after dose 22 and before dose 42
  - Acyclovir concentrations will be obtained at specified timepoints
  - Timepoints for pharmacokinetic draws: 0h (within 30 minutes prior to the start of the infusion of acyclovir), within 15 minutes after completion of the infusion, and 3-4 hours after infusion
  - Most recent patient weight, acyclovir dose received, and serum creatinine value will be recorded
  - Required amount of whole blood for plasma acyclovir determination at each timepoint is 200 μL (0.2 mL)

Note: blood for PK assessments will be obtained at the time that a clinical blood draw is being performed, or through the indwelling intravenous catheter, so that no additional venipuncture procedures solely for study purposes will be required

7.3.3. Period 3 (Day 2 and up to 7 of valacyclovir)

- Valacyclovir pharmacokinetics
  - One valacyclovir PK sampling profile will be performed on Day 2 (and up to day 7) of valacyclovir
  - Acyclovir concentrations will be obtained at specified timepoints
  - Timepoints for pharmacokinetic draws: 0h (immediately prior to valacyclovir dose; window: -15 min), 1-2 hours after dose, and 3-5 hours after dose
  - Date and time of last valacyclovir dose prior to PK lab draw will be recorded
  - Date and time of valacyclovir dose given in the CHRU will be recorded
  - Required amount of whole blood for plasma acyclovir determination at each timepoint is 200 μL (0.2 mL)

  Note: blood for PK assessments will be obtained either via venous/heel stick; will attempt to reduce discomfort experienced with heel sticks by using a heel warmer prior to blood draw

- Initiation of oral acyclovir per standard of care guidelines to complete 6-month course of oral suppressive therapy at recommended dose of 300 mg/m^2/dose every 8 hours) after last PK lab is drawn. Prescription for oral acyclovir to be written and prescription filled by outpatient pharmacy and billed to patient's insurance prior to leaving the hospital

7.4 Early Termination Visit

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. SAEs and AEs will be followed according to guidelines in Section 9. Upon withdrawal from the study, the infant should follow the standard of care guidelines for neonatal HSV disease.

7.5 Unscheduled Visit

Should an unscheduled visit occur, the study subject will be assessed as standard of care.

8 STUDY PROCEDURES/EVALUATIONS

The study procedures and evaluations are summarized in Appendix A: Schedule of Events. In the conduct of this study, hospital staff may perform research activities (e.g., pharmacokinetic blood draw collection) under the direction of the Principal Investigator or designee.

8.1 Clinical Evaluations

8.1.1. Baseline Demographics

To characterize the study subjects, information will be recorded at the baseline study visit following the obtaining of informed consent. Data collected will include basic demographics and birth history (date of birth; gestational age at delivery; gender; race; ethnicity; birth weight; weight at enrollment; length in centimeters at enrollment; all HSV diagnostic tests, CSF indices from lumbar puncture(s); classification of neonatal HSV disease, age at diagnosis; day of life at initiation of IV acyclovir therapy; acyclovir dose and dosing frequency).

8.2 Laboratory Evaluations

All chemistry labs (serum creatinine, ALT) will be recorded on eCRFs if they have been drawn for clinical reasons; only the most abnormal value for hematology labs (WBC with differential) will be recorded on eCRFs if they have been drawn for clinical reasons

8.2.1 Special Assays or Procedures

Research assays (Pharmacokinetics will be conducted at the respective UAB lab).

8.2.1.1. Acyclovir Pharmacokinetics

Assessment of acyclovir plasma concentrations will be conducted at the UAB Pharmacokinetic Laboratory. Acyclovir concentrations will be obtained on a daily basis at random time intervals during Period 1 (Treatment Day 1 through Treatment Day 7). One PK sampling profile will then be completed during Period 2 (between Treatment Day 8 and Treatment Day 14). Timepoints for pharmacokinetic draws for Period 2 are as follows: 0 hours (within 30 minutes prior to the start of the infusion), within 15 minutes after completion of the infusion, and 3-4 hours after infusion.

Pharmacokinetic specimens will also be obtained during Period 3 (Day 2 up to Day 7 of valacyclovir). The timepoints for the lab draws for Period 3 are as follows: 0 hours (just prior to the enteral dose of valacyclovir and approximately 8

hours after previous dose), 1-2 hours after dose, and 3-5 hours after dose. The required amount of whole blood for plasma acyclovir determination at each time point is 200μL (0.2 mL). Specimens will be processed to separate the plasma, and then will be transported to the UAB Pharmacokinetic Laboratory. Most recent patient weight, valacyclovir dose received, timing of dose, sample collection time, WBC, percentage neutrophils, ANC, ALT, and serum creatinine value will be recorded.

9 ASSESSMENT OF SAFETY

Regulatory requirements including the Food and Drug Administration (FDA) regulations, International Conference on Harmonisation (ICH) Guidelines for Good Clinical Practice (GCP), and European Union (EU) Clinical Trials Directive set forth safety monitoring and reporting responsibilities of sponsors and investigators to ensure the safety and protection of human subjects participating in clinical trials.

Any other adverse events that meet the reporting requirements of the Institutional Review Board will be documented and reported to Protocol Chair.

9.1 Safety Reporting: Adverse Events of Special Interest (AESI)

The investigator must also report the following AESI on the AESI case report form:

- AEs associated with blood draws
- All adverse events that meet the reporting requirements of the Institutional Review Board (which will also be reported to Protocol Chair).

The risks associated with participation in the clinical trial are associated with blood draws and potential side effects to valacyclovir. However, the potential drug risks for valacyclovir are comparable to the risks associated with long term use of the current standard of care, oral acyclovir. Therefore, monitoring for adverse events is not necessary for short term use (2 and up to 7 days) of valacyclovir. In an effort to document only untoward medical events that have a greater likelihood of being study-related, only adverse events associated with blood draws will be considered adverse events for the purposes of this protocol.

9.2 Type and Duration of Follow-up of Subjects after Adverse Events

All AEs as described above will be followed until resolved or considered stable.

9.3 Halting Rules

9.3.1 Discontinue of Study participation for individual subject

Subjects who experience significant problems with blood draws may be withdrawn from any future sampling.

9.4 FDA MedWatch Adverse Event Reporting Program

Reporting of adverse events related to drug administration is not part of the protocol. The reporting is in support of the FDA post-marketing safety surveillance program and is encouraged.

The FDA MedWatch adverse event reporting program allows health care professionals to voluntarily report a serious adverse event, product quality problem or product use error that is suspected to be associated with the use of an FDA-regulated drug, biologic, medical device or dietary supplement. This system is for the reporting of adverse events noted spontaneously in the course of clinical care, and not for events that occur during clinical trials under an Investigational New Drug (IND) application.

The MedWatch Website, http://www.fda.gov/Safety/MedWatch/HowToReport/ucm085568.htm can be used to voluntarily report a serious adverse event, product quality problem or product use error that is suspected to be associated with the use of an FDA-regulated drug, biologic, medical device, dietary supplement or cosmetic. FDA uses these data to maintain safety surveillance of all FDA-regulated products. A health care professional report may be the critical action that prompts a modification in use or design of the product, improves the safety profile of the drug or device and leads to increased patient safety.

10 CLINICAL MONITORING

10.1 Monitoring Plan

Monitoring of study will be conducted to ensure that human subject protection, study procedures, laboratory procedures, study intervention administration, and data collection processes are of high quality and meet regulatory guidelines, and that the study is conducted in accordance with the protocol and study manuals. A Clinical Monitoring Plan will not be developed.

If conducted, monitoring visits will include but are not limited to review of regulatory files, case report forms, informed consent forms, medical and laboratory reports, and protocol compliance. COA research nurses will meet with investigators to discuss any problems and actions to be taken and document visit findings and discussions.

Every effort will be made to maintain the anonymity and confidentiality of subjects during this study.

11 STATISTICAL CONSIDERATIONS

11.1 Study Hypotheses

Our primary hypothesis is that valacyclovir at 20 mg/kg every 8 hours when administered to very young infants will provide adequate exposure to the active metabolite, acyclovir, and be comparable to intravenous acyclovir 20 mg/kg every 8 hours.

11.2 Sample Size Considerations

The primary endpoint for this study is to determine if 20 mg/kg of valacyclovir every 8 hours is comparable to 20 mg/kg of intravenous acyclovir every 8 hours. Thus, based on investigator experience, feasibility, and low kinetic variability secondary to renal excretion, a sample size of 6 and up to 10 subjects will be enrolled. Data will be collected on standardized case report forms. Standard non-compartmental techniques will be used initially to estimate pharmacokinetic parameters derived from the acyclovir concentration time data. The resource utilized for pharmacokinetic analysis is WinNonlin version 5.3, Pharsight Corporation, Mountain View, CA.

11.3 Planned Interim Analyses (if applicable)

There are no planned interim analyses for this trial.

11.4 Final Analysis Plan

Descriptive statistics will be represented by means, standard deviations, and confidence intervals for continuous variables and counts and proportions for categorical variables.

Primary analysis: Acyclovir and valacyclovir pharmacokinetic parameters will initially be determined using non-compartmental analysis (WinNonlin v5.3) for each individual subject. The parameters (AUC_8, CL, Vd, etc.) will be summarized and further used for exploratory pharmacodynamic analysis.

To compare how the valacyclovir PK as measured by AUC_8 in infants diagnosed with neonatal HSV disease differ from acyclovir PK as measured by AUC_8 in the same subset of patients, we will construct 95% confidence intervals around the mean AUC_8 and compare these means across the subset of patients. Additional pharmacokinetic parameters that compose analyses for secondary endpoints include C_{max}, $T_{1/2}$,CL, and Vd.

12 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

The PI is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. The site will maintain appropriate medical and research records for this trial, in compliance with ICH E6, Section 4.9 and regulatory and institutional requirements for the protection of confidentiality of subjects. Data reported in the eCRF derived from the data collection forms should be consistent with the source documents or the discrepancies should be explained.

Documentation of source data is necessary for the reconstruction, evaluation, and validation of clinical findings, observations, and other activities during a clinical trial. Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to, Source Document Worksheets, hospital records, clinical and office charts, laboratory notes, memoranda, subjects' evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and subject files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial. Source documentation serves to substantiate the integrity of trial data, confirms observations that are recorded, and confirm the existence of study participants. This standard also serves to ensure data quality by creating audit trails and enabling verification that data are present, complete, and accurate.

13 QUALITY CONTROL AND QUALITY ASSURANCE

The study site will implement a quality management plan. The quality management procedures are described herein. Data will be evaluated for compliance with the protocol and accuracy in relation to source documents. The study will be conducted in accordance with procedures identified in the protocol. Items to be reviewed include, but are not limited to: eligibility (including informed consent), AE reporting, study/clinical endpoints, follow-up visits, regulatory documents, missed visits, and review of clinical records. Data that will be reviewed, who is responsible for implementation, and the schedule for internal reviews will be specified or referenced in the quality management plan.

The CASG research nurses will verify that the clinical trial is conducted and data are generated, documented, and reported in compliance with the protocol, ICH E6(R1), and the applicable regulatory requirements.

14 ETHICS/PROTECTION OF HUMAN SUBJECTS

14.1 Ethical Standard

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).

14.2 Institutional Review Board

Reviewing IRBs must be registered with the OHRP to conduct studies. In the United States and in other countries, institutions are required to hold a current US Federal wide Assurance (FWA) issued by OHRP.

This protocol, informed consent documents, relevant supporting information, and all volunteer recruitment or advertisement information will be submitted to the Institutional Review Board (IRB) for review and must be approved before the study is initiated. Any amendments to the protocol must also be approved by the IRB prior to implementing changes in the study.

The investigator is responsible for keeping the IRB apprised of the progress of the study and of any changes made to the protocol as deemed appropriate, but in any case at least once per year. The investigator must also keep the IRB informed of any significant AEs.

All IRB approved documents as well as relevant study correspondence should be copied and sent to the UAB Central Unit.

14.3 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 COA research nurses at any time.

The investigational nature and research objectives of this trial, the procedure, 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, AEs, or toxicities, 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).

Subject's parent(s)/legal guardian(s) will sign the informed consent document prior to any procedures being done specifically for the study. 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. Subject's parent(s)/legal guardian(s) may withdraw consent at any time throughout the course of the trial. 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.

14.3.1 Informed Consent/Assent Process (in Case of a Minor)

If required by the site's IRB, the parent or legal guardian will sign a waiver of assent for the minor due to the study participant's age. Assent age will be determined by the local IRB. Appropriate documentation will be required for subjects who are the age of assent, whether mature enough to read and capable of providing signed assent, or whether too young to read but capable of providing verbal assent, as determined by the local IRB in compliance with 45CFR46. Local IRBs will review and assign the risk level.

14.4 Exclusion of Women, Minorities, and Children (Special Populations)

This study will be conducted solely in infants. The study will not exclude young children, females, or minorities.

14.5 Subject Confidentiality

The information obtained during the conduct of this clinical 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 investigators 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.

The study investigator is obliged to provide complete test results and all data developed in this study. The PI/study investigators may disclose this information to appropriate regulatory authorities or clinical practice management groups (such as 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, UAB personnel, and the IRB/IEC for the study site.

14.6 Study Discontinuation

Infants enrolled in the study will follow the standard of care guidelines for treatment of neonatal HSV disease, and upon completion of treatment with IV acyclovir, will be switched to valacyclovir for 2 days (and up to 7 days) prior to initiating oral acyclovir for suppressive therapy as per the standard of care. Therefore, if the study is discontinued, infants must follow the standard of care guidelines for both treatment and suppressive therapy of neonatal HSV disease.

14.7 Future Use of Stored Specimens

Remnant specimens will be held in case assays need to be repeated, and some of the specimens obtained from study participants during this study will be stored indefinitely in the UAB Central Laboratory at the University of Alabama at Birmingham and may be used in future virology research. These specimens will be labeled with a code number and not with the study participant's name. At the time of consent for study participation, study participant's parent/legal guardian will have the opportunity to either agree to have their specimens used in future virology research or decline to have their specimens used in future virology 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, "Future Use of Specimens". Non-protocol designated, future testing of samples will be performed only on samples from study participants who have consented for future testing of samples. Residual specimens from subject who decline future use will be destroyed after the study, final analysis and report writing is complete.

A repository for residual samples will be established according to OHRP guidelines ensuring that codes or other personally identifying links will not be distributed to future researchers.

The specimens will be stored indefinitely in the UAB Central Laboratory at the University of Alabama at Birmingham. HSV specimens from study participants will be labeled and coded without study participant's identifiers. If the study participant's parent/legal guardian has indicated in the signed consent form that he/she does not agree to allow the future use of

specimens for future virology research, then his/her child's specimens will be destroyed at the completion of the study.

15 DATA HANDLING AND RECORD KEEPING

The investigator is responsible to ensure the accuracy, completeness, legibility, and timeliness of the data reported.

Electronic case report forms (eCRFs) will be developed. Original data will be recorded on source documents (e.g., medical records, research progress notes, Source Document Worksheets documenting research related procedures). Source Document Worksheets that mirror each data field on the eCRF will be available for use as a tool to record and maintain data for each study participant enrolled in the study when other source documents are not used to collect original data. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. When making a change or correction, cross out the original entry with a single line and initial and date the change. Do not erase, overwrite, or use correction fluid or tape on the original.

Data recorded on the eCRF that differ from source documents must be explained on the Comments eCRF and in the subject's source documents.

15.1 Data Management Responsibilities

All eCRFS must be reviewed by the investigator's research team, under the supervision of the investigator, who will ensure that they are accurate and complete. All data must be supported by source documents, which will remain available for review by regulatory personnel and monitors. Adverse events must be graded, assessed for intensity and causality, and reviewed by the site investigator or designee.

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site PI. During the study, the investigator must maintain complete and accurate documentation for the study.

The PI with the help of the statisticians will be responsible for analysis of the study data and writing of the clinical study report.

15.2 Data Capture Methods

Clinical and laboratory data will be entered into a 21 CRF Part 11 compliant electronic Data Entry System (eDES). The data system includes password protection and internal quality checks, such as automated range checks, to identify data that appear to be inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

15.3 Types of Data

Data for this study will include clinical laboratory, pharmacokinetic, virologic results, and clinical and outcome measures (e.g., PK, weight, and virology).

15.4 Timing/Reports

There are no planned interim analyses or safety reviews for this trial.

15.5 Study Records Retention

Records and documents pertaining to the conduct of this study, including source documents, consent forms, laboratory test results, and medication inventory records, must be retained by the investigator for at least 2 years following completion of the study. No study records shall be destroyed without prior authorization. These documents should be retained for a longer period, however, if required by local regulations.

15.6 Protocol Deviations

Each investigator must adhere to the protocol as detailed in this document and agree that any changes to the protocol must be approved by the PI prior to seeking approval from the IRB/IEC. Each investigator will be responsible for enrolling only those study participants who have met protocol eligibility criteria.

A protocol deviation is any noncompliance with the clinical trial protocol. 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.

These practices are consistent with ICH E6 GCP sections:

4.5 Compliance with Protocol, Sections 4.5.1, 4.5.2, and 4.5.3

5.1 Quality Assurance and Quality Control, Section 5.1.1

5.20 Noncompliance, Sections 5.20.1 and 5.20.2.

It is the responsibility of the site 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 PI.

All deviations from the protocol must be addressed in the source documents. Protocol deviations must be sent to the local IRB per the IRB's guidelines. The site PI/study staff is responsible for knowing and adhering to their IRB/IEC requirements.

16 PUBLICATION POLICY

Following completion of this study, the investigators are expected to publish the results in a scientific journal.

The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a trials-registration policy as a condition for publication. This policy requires that all clinical trials be registered in a public trials registry such as ClinicalTrials.gov, which is sponsored by the National Library of Medicine. Other biomedical journals are considering adopting similar policies.

Unless exempted, this trial will be registered prior to enrollment of study subjects. It is the responsibility of the study's PI (e.g., Dr. Samies) to register the non-exempted trials and post results in compliance with Public Law 110-85, the Food and Drug Administration Amendments Act of 2007 (FDAAA).

17 LITERATURE REFERENCES

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SUPPLEMENTS/APPENDICES

APPENDIX A: SCHEDULE OF EVENTS (FOLLOWING ACQUISITION OF INFORMED CONSENT)

Blue font represents tests being obtained for clinical purposes
Gray boxes represent infants being treated for CNS or disseminated disease (these infants receive 21 days of therapy vs SEM disease patients who receive 14 days of therapy). No research labs will be obtained during this time.

	Treatment Day									
	Period 1							Period 2		Period 3
	1	2	3	4	5	6	7	8 - 14	15 - 21	Day 2 (up to 7) of valacyclovir
Study Enrollment[a]	X									
Baseline demographics[b]	X									
Neonatal HSV disease Classification[c]	X									
Hematology labs[d]				X				X		
Chemistry labs[e]				X				X		
Acyclovir pharmacokinetics[f]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X[h]		
Valacyclovir pharmacokinetics[i]										X[j]
IV acyclovir administration	←							→		
Oral valacyclovir administration every 8 hours										← →
Total volume of blood required for study	0.2 mL	0.2 mL	0.2 mL	0.2 mL	0.2 mL	0.2 mL	0.2 mL	0.6 mL		0.6 mL

a) Participants can enroll in the study on or before treatment day 14, and therefore, data collected for each infant will be dependent on date of enrollment.
b) Gestational age at delivery, postmenstrual age at delivery, date of birth, day of life at initiation of IV acyclovir therapy, gender, race, ethnicity, birth weight, weight at enrollment, length in centimeters at enrollment, acyclovir dose and frequency
c) Treating physician's assessment of Skin-eye-mouth (SEM), central nervous system (CNS), or Disseminated neonatal HSV disease, based upon clinical assessments of skin lesions, skin viral studies, mucous membrane viral studies, CSF PCR, blood PCR, transaminitis, seizures, pneumonitis, coagulopathy, etc.
d) WBC with differential, hemoglobin, platelet will be recorded if drawn for clinical purposes (any laboratory value obtained during the window will suffice, with an effort being made to capture the most abnormal value)

e) All creatinine values will be recorded if drawn for clinical purposes. Any alanine aminotransferase (ALT) value obtained during the window will suffice, with an effort being made to capture the most abnormal value)
f) A minimum of 200 μL (0.2 mL) of whole blood is required for plasma PK analyses for acyclovir
g) A single plasma sample for PK determination will be obtained at each visit marked on the Schedule of Events. These samples will be obtained at random time intervals, but only at the time that a clinical blood draw is being performed, or through the indwelling intravenous catheter, so that no additional venipuncture solely for study purposes will be required; most recent weight, acyclovir dose received (date, time, and mg dose), and serum creatinine value will be recorded.
h) Acyclovir concentrations will be obtained with one of the Study Assessment Doses between dose 22 and 42 (Study Day 8 through Study Day 14) at the following time points: 0h (within 30 minutes prior to the start of acyclovir infusion), within 15 minutes after completion of the infusion, and 3-4 hours after infusion.
i) A minimum of 200 μL (0.2 mL) of whole blood is required for plasma PK analyses for acyclovir
j) Acyclovir concentrations will be obtained with one of the valacyclovir Study Assessment Doses (after dose 3 of valacyclovir) at the following time points: 0 hr (8 hours after previous dose), 1-2 hours after dose, and 3-5 hours after dose.