CONSENT FORM TO BE PART OF A RESEARCH STUDY

Title of Research: A PHASE I ADAPTIVE, MULTIPLE DOSE PHARMACOKINETIC AND SAFETY ASSESSMENT OF VALACYCLOVIR IN INFANTS AT RISK OF ACQUIRING NEONATAL HERPES SIMPLEX VIRUS DISEASE

UAB IRB Protocol #: IRB-300008028

Principal Investigator: David Kimberlin, MD

Sponsor: National Institutes of Allergy and Infectious Disease

Sponsor Protocol #: DMID 20-0033

For Children (persons under 18 years of age) participating in this study, the term "You" and "Your" addresses both the participant ("you") and the parent or legally authorized representative ("you").

General Information	You are being asked to take part in a research study. This research study is voluntary, meaning you do not have to take part in it. The procedures, risks, and benefits are fully described further in the consent form.
Purpose	The purpose of this study is to determine the dose of medication needed for babies potentially exposed to herpes at the time of delivery.
Duration & Visits	You will be in the study for 42 days. Study visits will be done in person on Days 1 and 5. Study visits may be done in person or by phone on Days 10 and 42. Days 1, 10, and 42 will last about 1 hour and Day 5 will last about 8-10 hours.
Overview of Procedures	We will collect some baseline information about you (date of birth, gender, race, ethnicity, birth weight, weight, length, medical history). You will be on the medication twice a day for 5 days. During the time that you are on the study, we will ask you questions regarding any issues that you have following taking the medication. We will draw blood to monitor your body's reaction to the medication. We will also draw blood to measure the level of medication in your body. See the Study Participation and Procedures section for more details.
Risks	The potential risks with the medication are drop in their white blood cell count, which are the cells that fight off infections, and an increase in creatinine levels (which tells us how well the kidneys are working). The risk with blood drawing is bruising where the blood is collected and discomfort. An infection (rare) or a small clot may also occur. Breach of confidentiality is another risk. See the Risk and Discomforts section for more details on the risks.
Benefits	There is no benefit for participating. The information about how to better treat babies that have been potentially exposed to herpes during birth will be very valuable to the future diagnosis and treatment of these babies.
Alternatives	There are currently no alternative therapies for babies potentially exposed to herpes at the time of delivery due to the mother's history of herpes. If there is no exposure to the herpes at the time of delivery, your pediatrician can discuss options for treatment.

Purpose of the Research

You are invited to take part in a research study. The purpose for this study is to determine the dose of medication (Valacyclovir) needed to prevent an infant from developing herpes simplex virus (HSV) if the infant was potentially exposed to HSV at the time of delivery as they passed through the birth canal. This dose has been studied in patient's age 1 through 11 years old. If this study is successful, treating babies with medication at the time of exposure to HSV would prevent the exposure from progressing on to infection and then HSV disease in the baby. The new drug, Valacyclovir, is investigational and not yet approved for use in babies by the Food and Drug Administration (FDA).

Your doctor suspects that you may have been exposed to HSV at the time of your birth. HSV is a rare disease in babies, but when it occurs it can be harmful. There are about 2,000 babies born each year with HSV disease. The HSV disease can be seen on the skin, eyes, and/or mouth (SEM disease), on the brain (CNS disease), or can involve many organs in the baby's body (disseminated). About 30% (30 out of 100) of babies with disseminated HSV disease in the other organs in the body will not survive even after giving them medication to treat the disease. About 20% (20 out of 100) that live with HSV disease in several of their organs will have long-term issues with normal newborn development. Babies born exposed to HSV at the time of birth without mom having any evidence of HSV are followed by their clinical doctor to see if they develop any symptoms.

Previous research has found that babies exposed to HSV at the time of birth develop HSV disease around 10-19 days of life. We will enroll babies whose mother has a history of genital HSV. They were taking medications to treat HSV for several weeks prior to delivery. These babies are at risk of having been in contact with HSV during the birthing process. Standard of care in these situations is to educate the parents on signs and symptoms to look for HSV disease in their newborns. Treatment or testing of the baby for HSV disease does not occur until the baby has developed some symptoms.

This study will enroll 16 participants in 2 different groups at multiple research facilities in the US. A third group may be enrolled if the results from the first two groups show that more information is needed. We will enroll 4 participants at UAB. Please read this information and feel free to ask any questions before you agree to take part in the study. Your participation is voluntary. You may refuse to participate in this study and you may leave the study at any time.

Study Participation and Procedures

The first 8 participants (Group 1) enrolled in the study will receive study medication 2 times a day for 5 days in liquid form by mouth. The dose of medication will be based on their weight (10mg/kg). After your baby has taken the medicine, blood samples will be taken to see how much of the medicine is present in the baby's blood. Following enrollment of the first 8 participants in Group 1, the safety data and information on the amount of study drug in the blood will be reviewed. If these data show that it was safe and gave acceptable levels in the baby's blood, we will enroll 8 additional participants (Group 2) using a dose of medication that will be based on the information from the first babies enrolled on the study.

Should the amount of study drug in the blood from the 8 additional babies enrolled in Group 2 not be acceptable, an additional group may be enrolled at a third dose level. Your doctor will tell you if your baby is one of the first eight babies (Group 1), additional eight babies (Group 2), or an additional group

of babies. All babies enrolled on the study will be seen by the study staff on the same schedule and have the same procedures done each visit.

You will be seen by the study team on study Days 1 and, 5. Study Days 10 and 42 may be done on the phone or in the research doctor's clinic. Visits on study Days 1, 10 and 42 will take about 1 hour. The visit on study Day 5 will require you to remain in the clinic area for about 8-10 hours. This will be the day we collect blood at 4 different times to determine the amount of medication in your blood. The study doctor will discuss with you your responsibilities as a participant.

Study Day 1 (1 hour)- This is the day that you sign the consent agreeing to participate in the study.

- You will start taking the study medication by mouth. The medication will be given twice a day based for 8 or 10 doses. The amount of medication is based on how much your baby weighs. The number of doses depends on how many doses you received on study Day 1.
- We will collect some basic information about you such as date of birth, race, sex, birth weight, weight at enrollment, length at enrollment, estimated age at time of delivery and medical conditions that you had prior to being in the study.
- We will collect about ¼ teaspoons of blood to determine how your body's kidneys and liver are functioning, to the check the function of the cells that fight infection, and to see the amount of study medication in your body.
- We will record all medications that you are taking.
- We will check to see if you are having any issues from taking the medication.

Study Day 5 (8-10 hours)-

- We will collect about ¼ teaspoons of blood to determine how your body's kidneys and liver are functioning and check the function of the cells that fight infection.
- We will record any new medications that you have taken since your last visit.
- We will check to see if you are having any issues from taking the medication.
- We will collect a small amount (1/8 teaspoons) of blood at four different times to determine the amount of study medication in your body. Blood will be done about 15 minutes before you take the medication, then 1-2 hours, 4-6 hours and 8-10 hours after you take the medication.
- Study medication will be stopped after the morning dose of study medication.

Study Days 10 and 42 (1 hour) -These visits may be done in the doctor's clinic or via telephone.

- We will record all medications that you have taken since the last visit.
- We will check to see if you are having any issues from taking the medication.

You have an option to complete Study Days 10 and 42 via telephone. If a telephone visit is scheduled for Day 10 and/or Day 42, you will receive a reminder call prior to your visit.

A Study Drug Diary will be provide to help you keep track of the home dosing of the study medication, storage method, any vomiting, and additional comments.

Additional Information:
Your de-identified private information and de-identified biospecimens (private information and biospecimens with all identifiers removed) may be used for future research studies or distributed to

another researcher for future research studies without additional informed consent. **This is only when there are no identifiers associated with the data or biospecimens.**

The blood collections in this study are within the Children's of Alabama blood volume guidelines.

The clinical results (including individual research results) will not be returned to you.

The following information will be obtain from the mother to determine eligibility for the study: 1) history of genital HSV infection; 2) received oral valacyclovir in the last several week of pregnancy; and 3) no visible evidence of HSV lesions at the time of delivery.

Please indicate whether you give permission for the mother's pregnancy/birthing information to be collected by initialing one of the following statements

_____ I agree to allow my pregnancy/birthing information to be collected for this study.

_____ I do not agree to allow my pregnancy/birthing information to be collected for this study.

Risks and Discomforts

There may also be risks that are unknown at this time. You will be given more information if other risks are found.

Study Medication

Valacyclovir, when given by mouth, is a component of the medication called Acyclovir which is used to treat HSV disease. Once valacyclovir is broken down in the body, it becomes the drug acyclovir. For babies with HSV disease, acyclovir is given as standard of care through a catheter called an IV that stays in the arm. IV Acyclovir has been known to cause about 20 out of 100 babies to have problems with lowered white blood cell counts. These are the cells that help the body fight off infection. Once Acyclovir is stopped, the number of cells that fight infection returns to normal. IV Acyclovir has been known to increase the blood test level that looks at how your kidneys are functioning to be elevated. We will monitor you for these problems by drawing your blood on study days 1 and 5. There may be some risk that we are not aware of with valacyclovir.

Blood draw:

There may be discomfort from the needle stick and occasional bruising at the site during or after the blood drawing and rarely an infection. A small clot may form at the site where the needle enters the body. Some people faint when having their blood drawn.

Risks of Storage and Sharing of Samples and Data

When we store your data and samples, we take precautions to protect your information from others that should not have access to it. When we share your data and samples, we will do everything we can to protect your identity by removing information that can identify you. Even with the safeguards we put in place, we cannot guarantee that your identity will never become known or someone may gain unauthorized access to your information. New methods may be created in the future that could make it possible to re-identify your data or samples.

Benefits

There is no direct benefit to you from participating in this study. Information gathered from this study may help doctors take care of babies exposed to herpes simplex virus (HSV) during the birthing process in the future.

Alternatives

The alternative is to not participate in this study. The study doctor will discuss with you the alternatives to participation and their risks and benefits.

Confidentiality and Authorization to Use and Disclose Information for Research Purposes

Federal regulations give you certain rights related to your health information. These include the right to know who will be able to get the information and why they may be able to get it. The study doctor must get your authorization (permission) to use or give out any health information that might identify you.

What protected health information may be used and/or given to others?
All medical information, including but not limited to information and/or records of any diagnosis or treatment of disease or condition, which may include sexually transmitted diseases (e.g., HIV, etc.) or communicable diseases, drug/alcohol dependency, etc.; all personal identifiers, including but not limited to your name, social security number, medical record number, date of birth, dates of service, etc.; any past, present, and future history, examinations, laboratory results, imaging studies and reports and treatments of any kind, including but not limited to drug/alcohol treatment, psychiatric/psychological treatment; financial/billing information, including but not limited to copies of your medical bills; any other information related to or collected for use in the research study, regardless of whether the information was collected for research or non-research (e.g., treatment) purposes; records about any study drug you received or about study devices used; and consent forms from past studies that might be in your medical record.

Your consent form will be placed in your medical record at UAB Health System or Children's of Alabama. This may include either a paper medical record or electronic medical record (EMR). An EMR is an electronic version of a paper medical record of your care within this health system. Your EMR may indicate that you are on a clinical trial and provide the name and contact information for the principal investigator.

If you are receiving care or have received care within this health system (outpatient or inpatient), results of research tests or procedures (i.e. laboratory tests, imaging studies and clinical procedures) may be placed in your existing medical record.

If you have never received care within this health system (outpatient or inpatient), a medical record will be created for you to maintain results of research tests or procedures.

All information within your medical record can be viewed by individuals authorized to access the record.

A description of this clinical trial will be available on www.ClinicalTrials.gov, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

Who may use and give out this information?
Information about your health may be used and given to others by the study doctor and staff. They might see the research information during and after the study.

Who might get this information?
All individuals/entities listed in the informed consent document(s), including but not limited to, the physicians, nurses and staff and others performing services related to the research (whether at UAB or elsewhere). Your information may also be given to the sponsor of this research. "Sponsor" includes any persons or companies that are working for or with the sponsor, or are owned by the sponsor, or are providing support to the sponsor (e.g., contract research organization).

Information about you and your health which might identify you may be given to:

- the Office for Human Research Protections (OHRP)
- the U.S. Food and Drug Administration (FDA)
- Department of Health and Human Services (DHHS) agencies
- Governmental agencies in other countries
- Governmental agencies to whom certain diseases (reportable diseases) must be reported
- the University of Alabama at Birmingham - the physicians, nurses and staff working on the research study (whether at UAB or elsewhere); other operating units of UAB, UAB Hospital, UAB Highlands Hospital, *University of Alabama Health Services Foundation, Children's of Alabama, Eye Foundation Hospital, and the Jefferson County Department of Heal*th, as necessary for their operations; the UAB IRB and its staff
- the billing offices of *UAB and UAB Health Systems affiliates and/or Children's of Alabama* and its billing agents

Why will this information be used and/or given to others?
Information about you and your health that might identify you may be given to others to carry out the research study. The sponsor will analyze and evaluate the results of the study. In addition, people from the sponsor and its consultants will be visiting the research site. They will follow how the study is done, and they will be reviewing your information for this purpose.

This research is covered by a Certificate of Confidentiality from the National Institutes of Health. The researchers with this Certificate may not disclose or use information, documents, or biospecimens that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other action, suit, or proceeding, or be used as evidence, for example, if there is a court subpoena, unless you have consented for this use. Information, documents, or biospecimens protected by this Certificate cannot be disclosed to anyone else who is not connected with the research except, if there is a federal, state, or local law that requires disclosure (such as to report child abuse or communicable diseases but not for federal, state, or local civil, criminal, administrative, legislative, or other proceedings, see below); if you have consented to the disclosure, including for your medical treatment; or if it is used for other scientific research, as allowed by federal regulations protecting research participants.

The Certificate cannot be used to refuse a request for information from personnel of the United States federal or state government agency sponsoring the project that is needed for auditing or program evaluation by the *National Institutes of Health* which is funding this project or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA). You should understand that a Certificate of Confidentiality does not prevent you from voluntarily releasing

information about yourself or your involvement in this research. If you want your research information released to an insurer, medical care provider, or any other person not connected with the research, you must provide consent to allow the researchers to release it.

The Certificate of Confidentiality will not be used to prevent disclosure for any purpose you have consented to in this informed consent document.

What if I decide not to give permission to use and give out my health information?

By signing this consent form, you are giving permission to use and give out the health information listed above for the purposes described above. If you refuse to give permission, you will not be able to be in this research study.

May I review or copy the information obtained from me or created about me?

You have the right to review and copy your health information. However, if you decide to be in this study and sign this permission form, you will not be allowed to look at or copy your information until after the research is completed.

May I withdraw or revoke (cancel) my permission?

Yes, but this permission will not stop automatically. The use of your personal health information will continue until you cancel your permission.

You may withdraw or take away your permission to use and disclose your health information at any time. You do this by sending written notice to the study doctor. If you withdraw your permission, you will not be able to continue being in this study.

When you withdraw your permission, no new health information which might identify you will be gathered after that date. Information that has already been gathered may still be used and given to others. This would be done if it were necessary for the research to be reliable.

Is my health information protected after it has been given to others?

If you give permission to give your identifiable health information to a person or business, the information may no longer be protected. There is a risk that your information will be released to others. Including others outside of UAB, without your permission.

Voluntary Participation and Withdrawal

Whether or not you take part in this study is your choice. There will be no penalty if you decide to withdraw from the study. If you decide not to be in the study, you will not lose any benefits that you are otherwise owed.

You are free to withdraw from this study at any time. Your choice to leave the study will not affect your relationship with this institution. However, you should return to see the study doctor for safety reasons so you can be taken off the study drug and referred for follow-up care. Contact the study doctor if you want to withdraw from the study.

You may be removed from the study without your consent if the sponsor ends the study, if the study drug is approved by the FDA, if the study doctor decides it is not in the best interest of your health, or if you are not following the study rules.

Cost of Participation

There will be no cost to you for taking part in this study.

Payment for Participation in Research

You will be paid $50 for each study visit completed on Day 1, Day 10 and Day 42. On Study Day 5, you will be paid $100. If you complete the entire study, you will be paid $250. If you do not finish the entire study, you will be paid at the time you decide to stop taking part in this study. Ask the study staff about the method of payment that will be used for this study (e.g., check, cash, gift card, direct deposit).

You are responsible for paying any state, federal, Social Security or other taxes on the payments you receive. You will receive a form 1099 in January of the year following your participation in this study. This form is also sent to the IRS to report any money paid to you. No taxes are kept from your payment.

Payment for Research-Related Injuries

UAB and NIAID have not provided for any payment if you are harmed as a result of taking part in this study. If such harm occurs, treatment will be provided. However, this treatment will not be provided free of charge.

New Findings

You will be told by the study doctor or the study staff if any new information becomes available that might affect your willingness to stay in the study.

Questions

If you have any questions, concerns, or complaints about the research or a research-related injury including available treatments, please contact the research doctor, Dr. Kimberlin**.** Your doctor will be glad to answer any of your questions. Dr. Kimberlin's phone number is 205-638-2530. Dr. Kimberlin may also be reached after hours by paging him at 205-934-3411.

If you have questions about your rights as a research participant, or concerns or complaints about the research, you may contact the UAB Office of the IRB (OIRB) at (205) 934-3789 or toll free at 1-855-860-3789. Regular hours for the OIRB are 8:00 a.m. to 5:00 p.m. CT, Monday through Friday.

Optional

Future Research Use of Identifiable Private Information and/or Identifiable Biospecimens

We would like your permission to keep your private information (data containing personal information) and biospecimens (blood) collected in this study for future research. The future research may be similar

to this study or may be completely different. Your private information and biospecimens will be stored indefinitely or until used.

Your private information and biospecimens will be identifiable. Results of any future research will not be given to you or your doctor

You can take part in this study even if you decide not to let us keep your identifiable private information and identifiable biospecimens for future research.

If you give us permission now to keep your identifiable private information and identifiable biospecimens, you can change your mind later and ask us to destroy it. However, once we have analyzed your private information and biospecimens, we may not be able to take it out of our future research.

We may share your identifiable private information and identifiable biospecimens, so that others can use it in their research. Their research may be similar to this study or may be completely different. Once we have shared your identifiable private information and identifiable biospecimens with other researchers, we will not be able to get it back.

Future research use of your identifiable private information and identifiable biospecimens will be conducted in compliance with applicable regulatory requirements.

You will not find out the results of the future research. Allowing us to do future research on your identifiable private information and identifiable biospecimens will not benefit you directly.

The identifiable private information and identifiable biospecimens used for future research may be used for commercial profit. There are no plans to provide financial compensation to you should this occur.

Initial your choice below:

___ I agree to allow my identifiable private information and identifiable biospecimens to be kept and used for future research on viral research.

___ I do not agree to allow my identifiable private information and identifiable biospecimens to be kept and used for future research.

If, in the future, you decide that you do not want your identifiable private information and identifiable biospecimens used for viral research, please notify Dr. Kimberlin or his study team at 205-638-2530 and your specimens will be destroyed once all study test are completed.

Legal Rights

You are not waiving any of your legal rights by signing this consent form.

Signatures

You are making a decision whether or not to participate in this study. Your signature indicates that you have read (or have been read) the information provided above and decided to participate. You will receive a copy of this signed consent form.

Signature of Parent or Guardian Date

Signature of Person Obtaining Consent Date