Official Study Title: HYDROXYUREA THERAPY: OPTIMIZING ACCESS IN PEDIATRIC POPULATIONS EVERYWHERE

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Informed Consent for Research

HYDROXYUREA THERAPY: OPTIMIZING ACCESS IN PEDIATRIC POPULATIONS EVERYWHERE

Note: *When we say "you" in this document, we mean "you or your child."*

1. Why am I being asked to take part in this research study?

You are being asked to volunteer for this research study because you have sickle cell anemia. This consent form gives you information about the study which will be discussed with you. Please take your time making a decision and feel free to discuss it with your friends, family and St. Jude staff. Before agreeing to take part in this research study, it is important that you read this consent form that describes the study. After you understand the study, and if you agree to take part, you will be asked to sign this consent form. You will be given a copy to keep.

2. Why is this study being done?

Children with sickle cell anemia suffer pain, health problems in the lungs, spleen, painful erection, and bleeding or clotting in the brain. If untreated, sickle cell anemia results in organ damage and early mortality. Hydroxyurea (HU) therapy reduces the risk of serious problems and may protect against organ dysfunction and early mortality in children with sickle cell anemia. HU is not yet approved for children with sickle cell anemia, so it is called "investigational" in young patients.

This research study will determine the pharmacokinetics of the liquid form of HU. Pharmacokinetics (PK) is a type of testing that measures the amount of study drug in the blood to see how well the body takes the drug into the blood, delivers the drug through the blood, breaks down or processes the drug and removes it from the blood. The study will also determine the benefits of "sprinkle formulation", a new method to give hydroxyurea to older children. The sprinkle formulation is a white powder that will be mixed with food. We want to see if the sprinkle formulation can deliver the HU to the bloodstream and to see the ability to deliver the drug to the bloodstream in an amount sufficient to cause the desired response.

3. What are my rights in this study?

- Whether or not you agree to take part in this study is entirely up to you.
- You may refuse to be in this research study or stop at any time. The decision will not affect your care or your relationship with your doctor or St. Jude. If available, you may receive routine medical care at St. Jude Children's Research Hospital.
- The study is being sponsored by St. Jude Children's Research Hospital. The sponsor will provide financial support.
- The sponsor will get information about you related to the study.
- The person in charge of the study (called the principal investigator and researcher) is Dr. Jeremie Estepp. This doctor may be reached by phone at 901-595-3300 if you have any questions or concerns about this research.

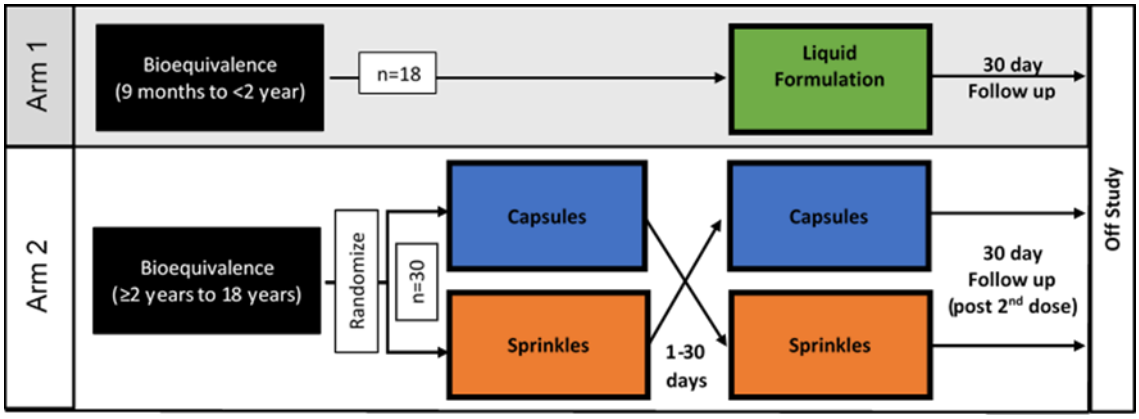
4. What will be done in this study?

The trial will be open label, 2-arm study of HU in 60 children with sickle cell disease.

In Arm 1 of this study, 18 infants ages 9 months up to 2 years will be administered an oral liquid form of HU on a single occasion followed by PK sampling. The dose administered will be around 20 mg/kg/day or the infant's usual daily dose.

In Arm 2 of this study, children who range in age from 2 to 18 years will be given HU, both a sprinkle formulation and capsules (Droxia® 200 mg), on two separate occasions separated by at least 1 but no more than 30 days in a randomized, crossover fashion. Randomization is a process where a computer decides (like drawing a number out of a hat) the order in which you will swallow the capsule whole or take it as a sprinkle formulation. You will not get to choose which order you are assigned. The doses of HU on each occasion will be rounded to the nearest 200 mg and will not exceed 35 mg/kg or 2000mg.

Participants in both arms will be followed up to 30 days from receiving the last HU dose.



You will be allowed clear liquids up to 1 hour before and then one hour after you take the HU. Then you will eat an age appropriate meal 2 hours after taking the HU. See the list of allowed clear liquids below:

Approved Clear Liquids
• Ice chips • Gelatin (Jell-O, etc.; sweetened, with no fruit) • Popsicles (sweetened, made from flavored water) • Beverages made with flavored drink mix (Kool-Aid, etc.) • Soda pop • Clear broth • Sports drinks (Gatorade, etc.) • Other electrolyte drinks (Pedialyte, etc)
*Fruit juice and fruit juice-containing products (including those containing apple juice) are not permitted.

Regular routine tests and research tests will be performed during the study. We will make every effort to reduce the number of your needle sticks by obtaining all research blood samples at the same time routine blood tests are collected. Procedures and tests that will be done during this study:

ROUTINE TESTS (Tests done as a regular part of clinical care)	**WHEN**
Physical Examinations (including heart rate, respiratory rate, blood pressure, temperature, height, weight, and medical history)	(ES*, BE*, Day 1, Day2-30****, Follow-up)
Blood tests	BE*, Day 2-30****
Pregnancy Test (for participants that have child bearing potential) if you are female and of age deemed able to become pregnant, you will be tested to ensure you are not pregnant, as pregnancy would preclude you from participating in the study. Girls or women of childbearing potential must have a negative serum (blood) pregnancy test prior to the first dose of study medication. You will have a blood sample drawn to confirm you are not pregnant at screening Visit. All female patients who can become pregnant and are sexually active will be required to use an effective method of birth control throughout the study and for up to 30 days following termination of treatment.	BE*
RESEARCH TESTS (Tests done in addition to your clinical care)	**WHEN**
Hemoglobin identification**	ES*
Pharmacokinetic Sampling Pre-dose Post-dose***	Day 1, Day 2-30***
Palatability Questionnaire***	Day 1, Day 2-30***

*ES, eligibility screening (-4 to 0 weeks); BE, baseline evaluation (0 week); ES and BE may be performed at the same time.
**Hemoglobin identification at the ES visit only needs to be done if a previous result is not already in your medical record.
***Only for Arm 2.

Hemoglobin identification
This blood test measures and identifies the different types of red blood cells in your bloodstream. If this test is done as a regular part of clinical care at the time of the visit it does not need to be performed again for HOPE18.

Pharmacokinetic Sampling:
Blood sampling for HU levels will occur through a catheter at pre-dose, then 10 minutes, 15 minutes, 30 minutes, 45 minutes, and 1,1.5, 2, 4, 6, and 8 hours after a directly observed dose of HU. At each time point, 1 ml of blood will be collected.

Palatability Questionnaire for Arm 2:
You will be asked to answer some questions about the taste of the HU "sprinkle formulation."

5. What are my other choices if I do not take part in this study?

You may choose not to take part in this study. You do not have to be in this study to get your regular medical care. Your study doctor can discuss the alternatives and the risks and benefits of other forms of treatment with you.

6. How many people will take part in this study?

Up to 48 children with sickle cell disease will take part in this study. Arm 1 will have 18 infants from age 9 months to 2 years. Arm 2 will have 30 children who range in ages from 2 years to 18 years.

7. How long will I be in the study?

You will be in the study for up to 60 days including 30 days of side effects follow up.

8. What risks can I expect from taking part in this study?

These are the risk(s) of this study:

Research studies in adults and children with sickle cell anemia have shown that HU usually has only mild side effects that quickly get better. A major effect of HU is to reduce the bone marrow production of white blood cells, and sometimes red blood cells and blood platelets. This drop in blood counts is expected and is how HU works. However, a large drop in the white blood cell count can increase your risk for infection, including life-threatening infection. Similarly, lowering the platelet count by a large amount can increase the risk of bleeding and lowering the red blood cell count (anemia) can cause you to be more fatigued and dizzy.

- Having blood samples taken: brief stinging pain, bruising, slight bleeding at needle site, and rarely, infection. Risks will be decreased by using sterile needles and

antiseptic wipes. To lower the number of needle sticks, we will use a catheter to take the PK sampling draws for this research.

- For the questionnaire, you may become upset by some of the questions or not want to answer them. If you do not want to answer a question for any reason, please tell us, and we will skip it. If you become upset, study staff will be there for you to discuss your feelings. You may quit the study at any time.

- Loss of privacy: Very rarely, personal information could be given out by accident. This might make you upset, embarrass you or affect your ability to get insurance. To stop this from happening, we:

  - Store records apart from names or other personal information
  - Only allow members of the study team to see the records
  - Store electronic data only on computers protected with a password and encryption software
  - Report study results on the whole group and never identify one single person in any reports

Reproductive risks:

Females: If you are sexually active, you must agree to use a reliable method of birth control during the study. You must have a negative pregnancy test at the time of enrollment.

You should not become pregnant or breastfeed a child while in this study. The best way to not become pregnant is not to have vaginal sex (intercourse). If you are sexually active, you should talk with your doctor about the types of birth control that are best for you and your partner. Tell your doctor right away if you become pregnant or think you are pregnant, as the risk of HU to an unborn child is unknown.

Males: You should not father a baby while in this study. Talk to your doctor about the types of birth control that might be best for you and your partner. Tell the doctor right away if your partner becomes pregnant or thinks she may be pregnant.

9. What are the possible benefits of the study?

There is no direct benefit to the participants. This study will help us learn more information about HU in the sprinkle formulation.

10. Can I stop taking part in this study?

You can decide to stop your participation at any time. If you decide to stop for any reason, it is important to let the study doctor know as soon as possible. The information collected before you decided to stop taking part may still be used in the study and shared with others.

If you stop, you should tell the study staff and follow the instructions they give you. If you leave the study, you will still have the same services and care you normally would have.

11. Can I be taken out of the study without my consent?

You may be taken out of the study without your consent for these reasons:

- The researcher decides that continuing in the study would be harmful
- A treatment is needed that is not allowed on this study
- You miss so many appointments that the data cannot be used in the study
- Your condition gets worse
- New information is learned that a better treatment is available, or that the study is not in your best interest
- The study sponsor (St. Jude) decides to end the study.

12. Will I be paid for my time or expenses?

Yes. If you are in Arm 1, you will have 4 visits to the St. Jude outpatient Hematology clinic receiving $25 for each visit. If you are in Arm 2, you will have 5 visits receiving $20 for each visit. You could receive a total of up to $100 for completing all visits. This is to reimburse you for your time and expenses in taking part in the study. We will record your Social Security number and address before you are paid.

13. How will new findings related to this study be shared with me?

We will share new findings related to this study during study visits that might change your mind about staying in the study.

14. How will I find out the results of this study?

The researcher will give you information about the overall results of this study. St. Jude researchers share information with people in studies in many ways, including:

- articles on *www.stjude.org*
- in newsletters
- in medical or scientific journals
- in the media

Published research results will only describe groups of people who took part in the study. Information that points out a single person will not be in research journals or other reports.

Results from the trial will be submitted for publication in medical journals and presented at the scientific meetings. We will not identify you in any text printed about this study. You personal information will not be in any text published about this study. All identifiable patient information will be removed prior to sharing any research information.

15. Who will see my research records and medical information?

We will keep your medical records private to the degree allowed by law. Federal privacy regulations provide safeguards for privacy, security, and authorized access. Except when required by law, you will not be identified by name, social security number, address, telephone number, or any other direct personal identifier in study records disclosed outside of St. Jude. St. Jude may give your health data, without identifiers, to other researchers or use it for other approved research projects not listed in this form. St. Jude, Dr. Estepp and his staff will comply with any and all laws regarding the privacy of such information. There are no plans to pay you for the use or transfer of this information.

Government agencies oversee research studies involving people. Your medical records may be reviewed by such agencies if you takes part in this research study. It may be necessary to check parts of your medical record to be sure that the study data are correct and complete. Such a check might be done by the following groups:

1) Representatives from St. Jude Children's Research Hospital, the HOPE18 Data Coordinating Center

2) A federal agency such as the Food and Drug Administration (FDA) or the National Heart, Lung, and Blood Institute

3) St. Jude Institutional Review Board (IRB), a committee which reviews the ethics of research studies

No information other than what is needed for the study is recorded. Every effort is made to protect your privacy.

SUMMARY OF RESEARCH AND PRIVACY RIGHTS

The following statement describes your rights as a research participant in this study:

1) You may refuse to be in this research study or stop at any time. This decision will not affect your care or your relationship with your doctor or St. Jude. If available, you may receive routine medical care at St. Jude Children's Research Hospital.

2) If you have insurance, TennCare or Medicaid, or other health care coverage such as an employer-sponsored benefit plan, they will be billed for many of the services we provide. However, we do not bill patients or their families for the cost of medical care not covered by their health plans. This includes research costs.

3) Your samples and information may be used to develop a new product or medical test, which may be sold. If this happens, you will not receive any payments for these new products.

4) If you have any questions about this study or if you are injured as a result of this study, contact Dr. Estepp, at 901-595-3300 immediately. If you are injured from being in this research study, St. Jude will provide reasonable and necessary care for that injury. If you need more care than St. Jude can provide, we will help you find medical care somewhere else. It is not the hospital's policy to provide payment if you are injured from being in this study; however, you are not giving up any of your rights by signing this consent form.

5) A description of this clinical trial will be available on http://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.

6) A decision to take part in this research means that you agree to let the research team use and share with other researchers your health information also called protected health information (PHI) for the study explained above. This information will be kept indefinitely. You have the right to see, copy, and ask for changes to your protected health information that will be used or given out. However, research information may not be seen until the end of the study.

7) When you first registered at St. Jude, you received a copy of the St. Jude Notice of Privacy Practices. It tells how your PHI may be used or given to someone outside the hospital. You have the right to read the Notice of Privacy Practices before you sign this form. It may have changed since you first registered at St. Jude. You can find it at the bottom of every page on the St. Jude Internet website: *www.stjude.org*.

8) Federal agencies such as the Food and Drug Administration (FDA), the Office of Human Research Protections (OHRP), the National Institutes of Health (NIH), and St. Jude Children's Research Hospital Institutional Review Board (IRB), your insurance company or other health benefits plan (if charges are billed to these plans), as well as other regulatory agencies, committees, or persons involved in overseeing research studies may review your research and medical record.

9) Information about you that may be given out includes your complete medical records, including details about diagnosis, illness, treatment, and information that may be recorded about past diagnosis or treatment and information taken as a part of this research study as explained in this informed consent.

10) After your records are given to or used by others, St. Jude Children's Research Hospital cannot promise that information will not be given out again. Also, the information given out may no longer be protected by federal privacy laws.

11) St. Jude uses reasonable safeguards and means to protect your private information. However, St. Jude cannot guarantee the security and confidentiality of e-mail, text messages, fax communications or mail.

12) Researchers and study staff are required by law to report suspected child abuse, threat of harm to self or others, and certain diseases that spread from person to person.

13) Your permission to use and give out your protected health information will end when you turn 18 years of age. At that time, we may contact you for your permission to continue using it.

14) You may take back permission for your records to be used or given out at any time, for any reason, except when that information has already been given out or used for the study based on your permission. To take back your permission, please fill out a form called a Revocation of Release of Authorization. You may ask for this form by calling the St. Jude Privacy Officer at 901-595-6141. You must mail the form or hand it to:

    HIPAA Privacy Officer
    St. Jude Children's Research Hospital
    262 Danny Thomas Place, Mail Stop 280
    Memphis, TN 38105

15) You can get more details about your rights as a research participant by calling the St. Jude Institutional Review Board at 901-595-4357 or the Research Participant Advocate at 901-595-4644. If you are outside of the Memphis area, please call toll-free 1-866-583-3472 (1-866-JUDE IRB).

16) The St. Jude Research Participant Advocate is an individual who is not part of the research study team and is available to you to discuss problems, concerns, and questions. The Advocate can help you obtain information and can relay any input you may have concerning the research to the research study team. You can reach the Advocate by calling 901-595-4644, or if you are outside of the Memphis area, call toll free at 1-866-583-3472 (1-866-JUDE-IRB).

17) You will be given a copy of this signed consent form.

PARENT/GUARDIAN STATEMENT (Required for participants younger than 18 years):
I have read this document or it was read to me. I have been encouraged to ask questions and all my questions have been answered. I give permission for my child to be in this research study.

_____	_____	_____	AM/PM
Parent/Legal Guardian Signature	Date	Time	(circle one)
_____	_____	_____	AM/PM
Parent/Legal Guardian Signature	Date	Time	(circle one)

ASSENT DISCUSSION (Required for participants 7–13 years old)

☐ The research was explained to the minor participant in age-appropriate terms and the minor verbally agreed to take part in the study.

☐ Minor declined to take part in the study. The minor declined for the following reason(s):

_____

☐ An assent discussion was not initiated with the minor for the following reason(s):
- ☐ Minor is under 7 years of age.
- ☐ Minor is incapacitated.
- ☐ Minor refused to take part in the discussion.
- ☐ Other_____

RESEARCH PARTICIPANT STATEMENT (7-13 years old and Adult Participants 18 years and older):
I have read this document or it was read to me. I have been encouraged to ask questions and all my questions were answered. I agree to take part in this research study.

_____	_____	_____	AM/PM
Research Participant Signature	Date	Time	(circle one)

RESEARCH PARTICIPANT STATEMENT (14–17 years old and Adult Participants 18 years and older):
I have read this document or it was read to me. I have been encouraged to ask questions and all my questions were answered. I agree to take part in this research study.

_____	_____	_____	AM/PM
Research Participant Signature	Date	Time	(circle one)

RESEARCHER/DESIGNEE STATEMENT: I have explained the research to the participant and his/her parent(s) or legal guardian(s). The research participant and parent(s)/guardian(s) were encouraged to ask questions and all questions were answered to their satisfaction. A copy of this form has been given to the participant or his/her representative.

_____	_____	_____ AM/PM
Researcher/Designee Signature	Date	Time (circle one)

_____
Print Name

RESEARCH PARTICIPANT ADVOCATE STATEMENT: I observed the informed consent process. The research study, intervention/observation, risks, benefits, and alternatives were presented to the research participant's parents and/or legal guardians. They were encouraged to ask questions, and research team members answered all their questions. The parents and/or legal guardians indicated that they: 1) understood the information presented; and 2) voluntarily consented /agreed to take part in the research.

_____	_____	_____ AM/PM
Research Participant Advocate	Date	Time (circle one)

_____
Print Name

_____	_____	_____ AM/PM
Interpreter (if needed)	Date	Time (circle one)

_____
Print Name

Please scan and email the consent form to the Clinical Trial Operations Office (CTO): ProtocolEligibilityOffice@STJUDE.ORG