Hydroxyurea therapy: Optimizing Access in Pediatric Populations Everywhere (HOPE18)

IND # 141719

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Protocol Summary

Protocol MNEMONIC and Title: HOPE18 - Hydroxyurea therapy: Optimizing Access in Pediatric Populations Everywhere
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Brief Overview: This trial is an open label, single center assessment of the pharmacokinetics of two formulations of hydroxyurea (HU) designed to (1) determine the pharmacokinetic profile of a liquid formulation in infants and to (2) determine the bioavailability of "sprinkles", a novel method of administration for older children. The study aims to generate data to facilitate FDA approval for HU in children and potentially validate a new mode of administration ("sprinkles") that will optimize access and adherence for children in the US and globally.
Intervention: Participants will receive either a single dose of oral liquid formulation of HU (20 mg/kg/day) followed by PK sampling or HU sprinkle formulation and capsules (Droxia® 200 mg) administered on 2 separate occasions.
Brief Outline of Treatment Plan: HOPE18 will be an open label, 2-arm study of HU disposition in 48 children with SCD. In Arm 1, n=18 infants ages 9 months to 2 years will be administered an extemporaneous oral liquid formulation of HU on a single occasion followed by PK sampling. The dose administered will be ~20 mg/kg/day or the infant's usual daily dose. In Arm 2, n=30 children who range in age from 2 to 18 years will be administered HU, both a sprinkle formulation and capsules (Droxia® 200 mg), on two separate occasions separated by at least 1 day but no more than 30 days in a randomized, crossover fashion. The doses of HU on each occasion will be rounded to the nearest 200 mg and will not exceed 35 mg/kg or 2000 mg. We hypothesize that the PK profile of the sprinkle formulation will not differ significantly from the PK profile of Droxia® capsules in children and adolescents ages ≥2 - 18 years of age.
Study Design: The HOPE18 trial is designed as a randomized, open-label, cross-over study, to assess HU bioavailability using a liquid formulation of HU and to assess the relative bioavailability of HU capsules to "sprinkles" as a stable, reliable and convenient non-liquid formulation that will increase HU availability globally.
Sample Size: 48 participants
Data Management: Data management and statistical analysis will be provided locally by the Hematology Division and Biostatistics Department at St. Jude Children's Research Hospital.
Human Subjects: risks to participants are related to hydroxyurea; however, since participants will receive only single dose HU or two doses HU on separate occasions at 20 mg/kg, the risks are extremely unlikely and thus not anticipated. Adverse events will be monitored, reported and treated appropriately.

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1.0 OBJECTIVES

1.1. Primary Objective

1. Define the pharmacokinetics of liquid-formulated HU in infants (9 months to <2 years)
2. Assess the relative bioavailability of HU "sprinkles" compared to capsules in children and adolescents (≥2 to 18 years).

1.2. Secondary Objective

Compare PK parameters in infants versus older children on this study and those from our previous "Pharmacokinetics and Bioavailability of a Liquid Formulation of Hydroxyurea in Pediatric Patients with Sickle Cell Anemia" (NCT01506544) trial.

1.3. Exploratory Objectives

Capture information regarding the taste of HU sprinkles using palatability questionnaire.

2.0 BACKGROUND AND RATIONALE

2.1. Background

Sickle Cell Disease (SCD)

Every year, over 300,000 infants are born with either SCD or one of its variants with most births occurring in mid- to low-income countries[1;2]. A classic example of recessive Mendelian inheritance, SCD is caused by a HBB missense mutation (p.Glu6Val) and results in production of hemoglobin S (HbS). Deoxygenated HbS forms stiff polymers, leading to microvascular occlusion and chronic hemolytic anemia. Clinically, persons with SCD can experience a wide spectrum of debilitating problems including severe pain crises, acute chest syndrome, splenic sequestration, cholelithiasis, priapism, and stroke. SCD is associated with frequent acute events, chronic progressive organ damage, and early mortality[3;4].

Hydroxyurea Therapy for children with SCD

Hydroxyurea (HU) is a FDA approved medication for adults and children older than 2 years of age, however based on the landmark BABY HUG trial[5], current NIH guidelines recommend that HU be offered to most children with SCD, beginning at 9 months of age[6]. HU works in part by inducing fetal hemoglobin (HbF) expression[7-9], but other benefits exist. For example, HU increases total hemoglobin concentration (Hb) and red cell mean corpuscular volume (MCV), and decreases the number of circulating white blood cells (WBC) and reticulocytes. All of these are beneficial effects because they reduce vaso-occlusion and increase blood flow, which ameliorates the clinical sequelae of SCD[7-11].

Over the past several decades, a number of long-term studies have reported the benefits of hydroxyurea in preventing complications and reducing mortality in older children with SCA[12-15]. The HUG-KIDS phase I/II prospective trial was designed to identify the maximum tolerated dose (MTD) for hydroxyurea in children and treat them at that dose for one year. Eligible children 5 to 15 years old were initiated hydroxyurea at 15 mg/kg/day with escalation by 5 mg/kg/day every 8 weeks to MTD, defined as the dose 2.5 mg/kg below which 2 successive hematologic toxicities occurred or a maximal dose of 30 mg/kg, and was sustained without toxicity for 8 weeks. The mean (±SD) MTD observed was 25.6 (±6.2). Children treated with hydroxyurea at MTD showed significant hematologic responses similar to those observed in adults and treatment was well-tolerated without clinical AEs[16].

The first pilot trial in infants with SCD (HUSOFT) demonstrated that hydroxyurea therapy was feasible, well-tolerated, and it had hematologic efficacy[17]. The long-term efficacy and safety of hydroxyurea for infants were subsequently reported in the HUSOFT extension study in patients receiving an escalated dose of hydroxyurea to MTD[18]. Infants receiving continuous hydroxyurea at MTD for a total of 15 years exhibited normal growth and development into adolescence/young adulthood, displayed sustained hematologic efficacy and experienced very few vaso-occlusive and transfusion events[19].

Between October, 2003 and September, 2009, BABY HUG[6] investigators from thirteen medical centers randomized very young (9-18 months) children with SCA to receive either placebo or hydroxyurea (20 mg/kg/day) and followed subjects for two years. The primary endpoints were splenic function (qualitative uptake of ^{99m}Tc spleen scan) and renal function (glomerular filtration rate by ^{99m}Tc-DTPA clearance). Secondary endpoints included hematologic parameters, biomarkers of splenic and renal function, transcranial Doppler (TCD) ultrasonography and growth. Of primary importance and contrary to some investigators' concerns[20], hydroxyurea was found to be safe in this young cohort. Expectedly, mild to moderate myelosuppression occurred more frequently in those on hydroxyurea, but no episode was associated with an invasive bacterial infection. Severe anemia and thrombocytopenia occurred infrequently and were not associated with hydroxyurea therapy. No renal or hepatic toxicities were observed despite monitoring of bilirubin and creatinine[21]. Importantly, hydroxyurea did not adversely alter growth velocity[22]. Children treated with hydroxyurea had a normal clinical response to pneumococcal polysaccharide vaccines and a normal immune state[23]. Children did not suffer from an increased frequency or a delayed incidence of splenic sequestration, and importantly, hydroxyurea did not appear to be mutagenic[24].

Hydroxyurea Pharmacokinetics (PK) and Bioavailability

Despite the safety and efficacy profiles for HU, limited data exists regarding the PK of HU, particularly for children under 2 years of age. Through a multicenter, prospective, open-label trial of 39 children (> 2 years to 17 years of age) with SCD, we compared: 1) bioavailability of the liquid formulation of HU administered in BABY HUG to capsules; and 2) HU PK profiles in younger and older children. Liquid and capsule formulations were bioequivalent; Younger and older children had similar PK profiles for every parameter tested[10] (Table 1). Furthermore, we demonstrated that that the weight-normalized apparent clearance (CL/F/BW and CL/F/BW^0.75) of HU versus age supported the current weight-based dosing scheme, and that age-based dosing is not required in children greater than 2 years old[6;11;25]. These studies provided definitive evidence that for children with SCD who are ≥2 years old, a weight-normalized HU dosing strategy results in consistent drug exposure independent of age. However, it is imperative to determine whether similar strategies apply to infants (≥9 months to 2 years), by examining the PK of liquid-formulated HU in this age group.

Table 1. PK parameters of a liquid HU formulation in children

Parameters, mean (SD)	Toddlers; n=17	Older Children; n=22
Age (y)	4.5 (1.7)	12.0 (3.6)
Dose (mg/kg)	22.7 (3.0)	21.7 (6.4)
C_{max} (μg/mL)	37.4 (9.3)	34.0 (8.7)
T_{max} (hr)	0.57 (0.34)	0.74 (0.5)
AUC_{INF} (μg·hr/mL)	104.5 (18.8)	111.9 (29.4)
$t_{½}$ (hr)	1.96 (0.18)	2.3 (0.5)
Cl/F/BW (L/hr/kg)	0.23 (0.03)	0.21 (0.04)

C_{max}, maximum observed plasma concentration; T_{max}, time to maximum plasma concentration; AUC_{INF}, area under the concentration versus time curve calculated using the log-linear trapezoidal method from time 0 extrapolated to time infinity; Cl/F/BW, clearance normalized for body weight. Parameters compared with a paired two-tailed t-test and none were significantly different.

We have previously shown that a liquid formulation of HU was bioequivalent to a proprietary capsule (Droxia® 200mg) for children 2-18 years of age (Table 2). Capsules are the only FDA-approved formulation; however, most young children cannot swallow capsules. Liquid HU formulations are not standardized and require specialized compounding pharmacies, which are not available in many countries and in some US regions. Moreover, liquid formulations are unstable, particularly in hot, humid regions where SCD is most prevalent. Thus, new HU formulations with associated PK studies must be developed to optimize delivery of this proven beneficial medication to infants/very young children in the US and worldwide. To extend these results and increase HU availability in regions where liquid formulations are not available or unstable, there is a need to develop a stable, reliable and convenient non-liquid HU formulation and to assess its bioavailability in children with SCD.

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Table 2[10]. Assessment of HU bioavailability via FDA guidelines

Parameters (units)	Geometric LS mean		Ratio (%)	90% Confidence limits	
	Capsule	Liquid		Lower	Upper
C_{max} (μg/mL)	32.3	33.1	**102.4**	91.8	114.2
AUC_{last} (μg·hr/mL)	100.3	98.6	**98.3**	94.5	102.3
AUC_{INF} (μg·hr/mL)	113.3	110.1	**97.2**	93.4	101.1

C_{max}, maximum observed plasma concentration; AUC_{last} (μg·hr/mL) indicates area under the concentration versus time curve calculated using the log-linear trapezoidal method from time 0 to the last quantifiable concentration; AUC_{INF} (μg·hr/mL) indicates area under the concentration versus time curve calculated using the log-linear trapezoidal method from time 0 extrapolated to time infinity LS indicates least-square.

2.2. Rationale

HU is the only FDA approved medication for adults with SCD and is frequently used "off-label" in children. Based on the landmark BABY HUG trial, current NIH guidelines recommend that HU be offered to most children with SCD, beginning at 9 months of age. Insufficient PK data for HU in children under 2 years of age and the lack of a pediatric-friendly formulation impede the universal access and administration of HU to young SCD patients. The HOPE18 trial addresses these gaps as follows:

1) Insufficient PK data exist for HU in children less than 2 years of age. PK data generated by the BABY HUG study from infants is limited due to a suboptimal PK sampling time point[10]. Nevertheless, experts provided a "strong recommendation based on high quality evidence" to begin this medication in most 9 month old patients with SCD. Currently, the only FDA-approved HU formulations are capsules, which infants and young children cannot swallow. Now we must generate high quality PK parameters for drug absorption, metabolism, distribution and excretion in infants which may differ from those observed in older children[26].

2) Universal access to HU therapy within the US and globally requires the development of a non-liquid formulation. Young children cannot swallow capsules and few patients (in the US or globally) have access to a liquid formulation. Liquid formulations are costly and must be prepared in a specialized compounding pharmacy. Additionally, liquid HU is more sensitive to heat degradation and has limited long-term stability after compounding compared to powder[27]. All of these limitations restrict the use of HU for young children in underdeveloped countries and in some regions of the US. One potential answer could be to open capsules and "sprinkle" the contents on food prior to administration. This is a common approach in pediatrics and is often done without determining how the process impacts drug stability or bioavailability. It is established that manipulating capsule formulations

may change drug absorption characteristics, destabilize the drug, cause local irritant effects, and/or result in a preparation with an unacceptable taste, all of which can alter drug exposure with significant clinical repercussions[28, 29, 30]. Prior to utilizing or endorsing HU "sprinkles" in children with SCD on a global scale, it is imperative that the PK of this formulation be determined in the relevant age group.

In summary, HU is effective and for many people, the best or only therapy available, yet many treatment barriers hamper its universal application. The HOPE18 trial will address fundamental and critical knowledge gaps regarding HU availability by defining the PK of liquid HU in infants, and defining parameters for the use of HU "sprinkles" in children. The information gained could be game changing by supporting FDA approval in pediatric SCD and increasing drug availability for a vast number of young patients.

2.3. Background and Rationale for Exploratory Studies

Palatability is an important aspect of patient acceptability of an oral pediatric medicine and for the success of a drug and treatment outcomes. One of our aims in this study is to determine bioavailability of HU capsules Droxia® to HU sprinkles in order to develop a pediatric-friendly formulation to allow for universal access to HU therapy globally. We propose to develop a palatability questionnaire to gather data related to taste. We will adapt the facial hedonic scale, a commonly used scale for palatability.

3.0 RESEARCH PARTICIPANT ELIGIBILITY CRITERIA AND STUDY ENROLLMENT

3.1. Inclusion Criteria

Participants will be eligible for this study if only if **all** of the following inclusion criteria apply:

1. Laboratory (i.e. electrophoretic, chromatographic or DNA) confirmation of HbSS or HbSβ^0thalassemia.
2. Participants may or may not be currently receiving HU. If participants are taking HU, then their most recent dose must be ≥24 hours prior to the start of the study.
3. Participant is in the "well" state (defined by ≥ 2 weeks since the last SCD-related complication).
4. Clinical evidence of normal gastrointestinal function and structure.
5. No clinical evidence of hepatic compromise, including transaminases < 3 times the upper limit of normal.
6. Estimated glomerular filtration rate (Schwartz equation) > 70 ml/min/1.73m^2.
7. Body mass index (BMI) ≥5th and ≤95th percentile as per CDC growth charts.

In addition:

For the Pharmacokinetic Study (Arm 1):

1. Age ≥ 9 months and < 2 years.
2. Able to consume a minimum of 30 ml of water following ingestion of the study article.

For the Bioavailability Study (Arm 2):

1. Age ≥ 2 years and ≤ 18 years.
2. Weight of ≥ 10 kg
3. Females of child-bearing potential must have a negative pregnancy test prior to dosing and be willing to practice appropriate contraceptive measures, including abstinence, from the time of the initial pregnancy testing through the remainder of the study (30 days after last administration of investigational agents).
4. Males of child-bearing potential must be willing to practice appropriate contraceptive measures, including abstinence, during study participation (30 days after last administration of investigational agents).
5. Able to ingest both sprinkles and capsule study articles and consume a minimum of 30 ml of water following ingestion of each agent.

3.2. Exclusion Criteria

1. Chronic transfusion therapy, or transfused within 3 months of study participation.
2. Known renal impairment (creatinine >1.5x the upper limit of normal for age). See Appendix II for reference ranges.
3. Known hepatic impairment or Grade 2 or higher transaminases and bilirubin levels. See Appendix II for reference ranges. Known malignancy.
4. Diagnoses other than sickle cell anemia or sickle beta-zero thalassemia (i.e., other sickle cell variants or sickle/ hereditary persistence of fetal hemoglobin).
5. Blood count parameters as follows: hemoglobin <6.0 gm/dL, absolute reticulocyte count <80,000/mm^3, absolute neutrophil count <1000/mm^3, or platelet count <80,000/mm^3.
6. The participant has used opiates, H2 blockers, proton pump inhibitors, antacids, other GI motility agents or any other medication that, in the opinion of the investigator, will interfere with the study procedures or affect the interpretation of the results of the study for 3 days prior to the first dose of study.
7. Participants taking antiretroviral drugs (including didanosine and stavudine) due to increased risk of toxicity with concomitant use.
8. Participation in another clinical intervention trial utilizing an IND/IDE agent, but can participate in HUGKISS since same drug agent.

3.3. Research Participant Recruitment and Screening

Universal newborn screening data will be utilized to identify potentially eligible children. In light of the recent NIH/NHLBI treatment guidelines for SCD recommending that HU therapy be offered to all infants at 9 months of age and our team's experience

with the HUG KISS trial, we will approach all available eligible participants. The local PI and/or study coordinator will discuss the trial objectively with the families of eligible patients until enrollment goals are met.

3.4 Enrollment on Study at St. Jude

A member of the study team will confirm potential participant eligibility as defined in Sections 3.1 and 3.2, and complete the "Participant Eligibility Checklist." The completed checklist will be scanned and emailed to the Central Protocol and Data Monitoring Office (CPDMO): [redacted]. Eligibility will be reviewed and entered into the PPM system. A research participant-specific consent form will be generated when applicable. The protocol and consent document will be delivered to the area designated on the checklist. The entire signed informed consent must be scanned and emailed to the CPDMO to complete the enrollment process.

The CPDMO is staffed 7:30 am-5:00 pm CST, Monday through Friday. A staff member is on call Saturday, Sunday, and holidays from 8:00 am to 5:00 pm. Enrollments may be requested during weekends or holidays by calling the CPDMO on call cell phone [redacted] or referencing the "On Call Schedule on the intranet).

3.4. 3.5 Procedures for Identifying and Randomizing Research Participants

Older children (n=30 children; ≥2 to 18 years) will participate in a randomized crossover study designed to determine the relative bioavailability of opening HU capsules and mixing them with food (sprinkles) compared to the standard clinically utilized formulation for age (unmanipulated capsules). Participants will be randomized in a 1:1 ratio to receive 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. Assignment to treatment groups will be determined by a computer-generated random sequence housed within the Department of Biostatistics (see section 9.2).

4.0 DESIGN AND METHODS

4.1. Design and Study Overview

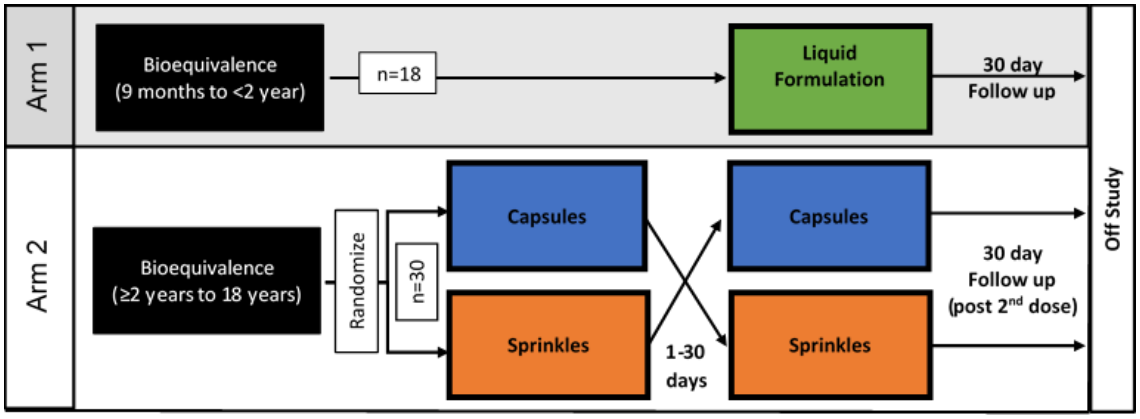
This trial will be an open label, 2-arm study of HU disposition in 48 children with SCD.

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

In Arm 2, n=30 children who range in age from 2 to 18 years will be administered 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. The doses of HU on each occasion will be rounded to the nearest 200 mg and will not exceed 35 mg/kg or 2000 mg (Figure 1)(Appendix 1).

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

Figure 1: Study Design



4.2. Study Interventions

Two different formulations of hydroxyurea will be used in this study: a liquid formulation and capsules.

Purchased hydroxyurea, USP will be hand filled into amber wide-mouth bottles with poly-seal-lined caps at KP Pharmaceutical Technology, Inc. (Bloomington, IN) a cGMP compliant facility. Due to limited stability of liquid formulations, clinical trial material will be reconstituted on site within the St. Jude Investigational Pharmacy with Syrpalta® (without color) and purified water to achieve a final liquid concentration of 100 mg/mL. We have performed microbial examination and stability testing on HU liquid formulation (100 mg/ml) stored at room temperature for 6-weeks. All samples meet USP release testing and specifications listed under the currently approved IND (#132032) for HUGKISS protocol. A single dose of this preparation will be dispensed to a participant and any remainder of the study drug will be stored and destroyed in a manner consistent with St. Jude Children's Research Hospital Pharmaceutical Services standard operating procedures.

Purity (95-105%) of Hydroxyurea, USP validated by GC-MS.
Source: Spectrum Pharmacy Products (New Brunswick, NJ)

Capsules (Droxia® 200 mg) will be purchased commercially and supplied to the St. Jude Children's Research Hospital Investigational Pharmacy without modification or disturbance of the commercially obtained bottles. Following USP795 and USP800, the capsule(s) will be opened by pharmacist/pharmacy technician and contents mixed in 10 mL of sterile water in a powder containment hood and transferred to participant in a labeled, child-resistant bottle. The diluted hydroxyurea will be mixed with 2 ounces of rice cereal or pudding by the participant/caregiver or clinic nurse if assistance is needed. The bottle will be rinsed with additional 10 mL of water and mixed with the rice cereal or pudding. It will be administered as soon as possible (ideally within 15 minutes and no

later than 1 hour after mixing). PK sampling will occur in clinic at predefined time points. Participant's dosing will be rounded to the nearest 200 mg of hydroxyurea and will only be administered in increments of an entire capsule.

4.3. Study Measures

The main study measures are pharmacokinetic parameters for 1) HU liquid formulation in infants (9 months to <2 years) and 2) HU "sprinkles" compared to capsules in children and adolescents (≥2 to 18 years).

HU levels will be determined via validated gas chromatography-mass spectrometry (GC-MS). This technique is linear from 0.1–100 µg/mL of HU and has an intra- and inter-assay coefficient of variation of <10% across concentrations spanning the range of linearity[31].

5.0 REQUIRED EVALUATIONS, TESTS, AND OBSERVATIONS

5.1. Pre-Study Evaluations

Eligibility screening (ES) and baseline evaluations (BE) will be performed prior to administration of the study drug. Eligibility screening may be performed the same time as baseline evaluations. A new hemoglobin identification only needs to be performed at eligibility screening if a previous result is not already available in the subject's medical record (Table 3). Collection of hydroxyurea dosing history including dose and time of administration for at least 2 days prior to study doses for participants taking hydroxyurea prior to enrollment.

5.2. Evaluations during Therapy

Participants on the study will receive the following evaluations as detailed in Table 3.

Table 3. Schedule of Evaluations

Evaluation	ES[1]	BE	Day 1	Day 2-30[2]	Off Study
	-4 to 0	0	within 30 days of enrollment		± 4 weeks
Informed Consent	X				
Weight, height & vital signs	X	X	X	X	X
History, physical exam	X	X	X	X	X
Prior/concomitant medications	X	X	X	X	X
Adverse events	X	X	X	X	X
Hemoglobin identification[3]	X				
Pregnancy Test		X		X	
CBC with WBC count		X		X	
Reticulocyte count		X		X	
Hydroxyurea Dose			X	X	
Pharmacokinetic Sampling Pre dose			X		
Pharmacokinetic Sampling Post dose			X	X	

Palatability Questionnaire[4]			X		

ES, eligibility screening; BE, baseline evaluation which should be performed prior to administration of study drug.[1]Eligibility screening may be performed the same time as baseline evaluations. [2]Assessments on Day 2-30 will only occur for children enrolled on Arm 2 of the HOPE18 trial. This is a single visit that could occur any day between 2-30 days after the first dose. [3]A new hemoglobin identification only needs to be performed at eligibility screening if a previous result is not already available in the subject's medical record. [4] Only completed by participants on Arm 2 of the HOPE18 trial.

Pharmacokinetic Blood Sampling. Blood sampling for HU levels will occur via an indwelling peripheral vein catheter at pre-dose, then 10 min, 15 min, 30 min, 45 min, and 1, 1.5, 2, 4, 6, and 8 hours after a directly observed dose of HU. At each time point, 1 ml whole blood will be collected into heparinized tubes, inverted a minimum of 8-10 times, held on ice, centrifuged at 750 x g for 10 minutes at 4°C, plasma will then be stored at -80°C within 30 minutes of sample collection. Batches of 50 frozen samples will be shipped to Children's Mercy Hospital (Kansas City, MO) for HU level determination via validated gas chromatography-mass spectrometry (GC-MS). Participants will be allowed clear liquids from the approved list as desired up to 1 hour before and then one hour after Hydroxyurea administration. Participants can then eat an age appropriate meal 2 hour after dosing. (Estepp 2016) See Table below:

Table 4. PK Blood collection log

Day	Scheduled time point	PK collection number	Sample volume (mL)
1	Pre-dose (±3 min)	1	1
1	Post-dose 10 min (±3 min)	2	1
1	Post-dose 15 min (±3 min)	3	1
1	Post-dose 30 min (±3 min)	4	1
1	Post-dose 45 min (±5 min)	5	1
1	Post-dose 1 hour (±5 min)	6	1
1	Post-dose 1.5 hour (±5 min)	7	1
1	Post-dose 2 hour (±10 min)	8	1
1	Post-dose 4 hour (±10 min)	9	1
1	Post-dose 6 hour (±10 min)	10	1
1	Post-dose 8 hour (±10 min)	11	1
2-30*	Pre-dose (±3 min)	12	1
2-30*	Post-dose 10 min (±3 min)	13	1
2-30*	Post-dose 15 min (±3 min)	14	1
2-30*	Post-dose 30 min (±3 min)	15	1
2-30*	Post-dose 45 min (±5 min)	16	1
2-30*	Post-dose 1 hour (±5 min)	17	1
2-30*	Post-dose 1.5 hour (±5 min)	18	1
2-30*	Post-dose 2 hour (±10 min)	19	1
2-30*	Post-dose 4 hour (±10 min)	20	1
2-30*	Post-dose 6 hour (±10 min)	21	1
2-30*	Post-dose 8 hour (±10 min)	22	1

*Arm 2 only

Table 5. 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.

5.3. Follow-up on Study

Participants in both arms of the study will be followed up 30 days from their hydroxyurea dose and will receive baseline labs, CBCs, Reticulocyte counts, toxicity discussions and adverse events collection. The follow-up visit will be scheduled to coincide with a routine clinical visit.

6.0 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF-STUDY CRITERIA

6.1. Off-study criteria

1. Initiation of chronic blood transfusion therapy
2. Stroke
3. Death
4. Lost to follow-up
5. Request of the Patient/Parent
6. Discretion of the Study PI, such as the following
   a. The researcher decides that continuing in the study would be harmful
   b. A treatment is needed that is not allowed on this study
   c. The participant misses so many appointments that the data cannot be used in the study
   d. New information is learned that a better treatment is available, or that the study is not in the participant's best interest
   e. Study evaluations are complete

7.0 SAFETY AND ADVERSE EVENT REPORTING REQUIREMENTS

7.1. Reporting Adverse Experiences and Deaths to St. Jude IRB

The Common Terminology Criteria for Adverse Events (CTCAE) version 5 will be used to grade adverse events. Only "unanticipated problems involving risks to participants or others" referred to hereafter as "unanticipated problems" are required to be reported to the SJCRH IRB promptly, but in no event later than 10 working days after the investigator first learns of the unanticipated problem. Regardless of whether the event is internal or external (for example, an IND safety report by the sponsor pursuant to 21 CFR 312.32), only AEs that constitute unanticipated problems are reportable to the SJCRH IRB. As further described in the definition of unanticipated problem, this includes any event that in the PI's opinion was:

- Unexpected (in terms of nature, severity, or frequency) given (1) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document, as well as other relevant information available about the research; (2) the observed rate of occurrence (compared to a credible baseline for comparison); and (3) the characteristics of the subject population being studied; and
- Related or possibly related to participation in the research; and
- Serious; or if not serious suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Unrelated, expected deaths do not require reporting to the IRB. Though death is "serious," the event must meet the other two requirements of "related or possibly related" and "unexpected/unanticipated" to be considered reportable.

Deaths meeting reporting requirements are to be reported immediately to the local IRB and sponsor (SJCRH), but in no event later than 48 hours after the investigator first learns of the death.

The following definitions apply with respect to reporting adverse experiences:

Serious Adverse Event (SAE): Any AE temporally associated with the subject's participation in research that meets any of the following criteria:

- Results in death;
- Is life-threatening (places the subject at immediate risk of death from the event as it occurred);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in a persistent or significant disability/incapacity;
- Results in a congenital anomaly/birth defect; or

- Any other AE that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition (examples of such events include: any substantial disruption of the ability to conduct normal life functions, allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse), a congenital anomaly/birth defect, secondary or concurrent cancer, medication overdose, or is any medical event which requires treatment to prevent any of the medical outcomes previously listed.

Unexpected AE:

- Any AE for which the specificity or severity is not consistent with the protocol-related documents, including the applicable investigator brochure, IRB approved consent form, IND or Investigational Device Exemption (IDE) application, or other relevant sources of information, such as product labeling and package inserts; or if it does appear in such documents, an event in which the specificity, severity or duration is not consistent with the risk information included therein; or
- The observed rate of occurrence is a clinically significant increase in the expected rate (based on a credible baseline rate for comparison); or
- The occurrence is not consistent with the expected natural progression of any underlying disease, disorder, or condition of the subject(s) experiencing the AE and the subject's predisposing risk factor profile for the AE.

Internal Events: Events experienced by a research participant enrolled at a site under the jurisdiction of SJCRH IRB for either multicenter or single-center research projects.

External Events: Events experienced by participants enrolled at a site external to the jurisdiction of the SJCRH IRB or in a study for which SJCRH is not the coordinating center or the IRB of record.

Unanticipated Problem Involving Risks to Subjects or Others: An unanticipated problem involving risks to subjects or others is an event which was not expected to occur and which increases the degree of risk posed to research participants. Such events, in general, meet all of the following criteria:

- Unexpected;
- Related or possibly related to participation in the research; and
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized. An unanticipated problem involving risk to subjects or others may exist even when actual harm does not occur to any participant.

Consistent with FDA and OHRP guidance on reporting unanticipated problems and AEs to IRBs, the SJCRH IRB does not require the submission of external events, for example IND safety reports, nor is a summary of such events/reports required; however, if an

event giving rise to an IND safety or other external event report constitutes an "unanticipated problem involving risks to subjects or others" it must be reported in accordance with this policy. In general, to be reportable external events need to have implications for the conduct of the study (for example, requiring a significant and usually safety-related change in the protocol and/or informed consent form).

Although some AEs will qualify as unanticipated problems involving risks to subjects or others, some will not; and there may be other unanticipated problems that go beyond the definitions of serious and/or unexpected AEs. Examples of unanticipated problems involving risks to subjects or others include:

- The theft of a research computer containing confidential subject information (breach of confidentiality); and
- The contamination of a study drug. Unanticipated problems generally will warrant consideration of substantive changes in the research protocol or informed consent process/document or other corrective actions in order to protect the safety, welfare, or rights of subjects or others.

7.2. Reporting to the Federal Agencies

Study coordinator will assist PI with protocol submissions for review by federal or institutional committees as applicable.

8.0 DATA COLLECTION, STUDY MONITORING, AND CONFIDENTIALITY

8.1. Data Collection

Data will be captured during each study visit (Table 3). The Clinical Trials Group within the Department of Hematology at SJCRH will assist in creating and managing a secure HOPE18 database. All data entered will have verifiable source documents in the medical record, which will be made available for review at site monitoring and audit visits. Study staff will complete a Manual of Operations (MOO) for the study and will complete data entry as outlined in the MOO. The protocol coordinator will monitor database entries for protocol and regulatory compliance.

8.2. Study Monitoring

High Risk 3 (HR-3) – Phase II, Phase III or Pilot Therapeutic Studies with an IND or IDE

This study is considered high risk (HR-3) for monitoring purposes. Protocol and regulatory compliance, including essential regulatory documentation, will be assessed as well as the accuracy and completeness of all data points relating to the primary and secondary objectives semi-annually. If the study design has strata, accrual will be

tracked continuously. The first two enrollees will be monitored and 15 % of the study enrollees thereafter, semi-annually.
The PI and study team are responsible for protocol and regulatory compliance, and for data accuracy and completeness. The study team will meet at appropriate intervals to review case histories or quality summaries on participants and retain copies of the minutes which are signed by the PI.

The Eligibility Coordinators in the Central Protocol and Data Monitoring Office (CPDMO) will verify informed consent documentation and eligibility status on 100% of St. Jude participants within 5 working days of enrollment completion.

The Clinical Research Monitor (CRM) will verify informed consent documentation and eligibility status of all non-St. Jude participants and perform a quality verification of select St. Jude participants during routine monitoring intervals (every 6 months). Overall study conduct, compliance with primary and secondary objectives, age of majority consenting, safety assessments and reporting, and the timeliness and accuracy of database entries are monitored routinely.

Study documents routinely monitored on selected participants include medical records, database entries, study worksheets, and case report forms. Study documents are monitored for participant status, demographics, staging, subgroup assignment, treatments, investigational drug accountability, evaluations, responses, participant protocol status, off-study and off-therapy criteria, and for all other specifics as detailed in a separate study-specific monitoring plan. The study-specific monitoring plan may be revised over time, to adapt monitoring frequency and/ or intensity to a changing environment when appropriate (for example: new safety signals; positive history of compliance; all participants are in long term follow-up; or the enrollment period has ended).

The recording and reporting of Adverse Events, Serious Adverse Events (SAEs), and Unanticipated Problems (UPs) to include type, grade, attribution, duration, timeliness and appropriateness will be reviewed by the Monitor/ CRM. The CRM will generate a formal report which is shared with the Principal Investigator (PI), study team and the Internal Monitoring Committee (IMC).

Continuing reviews by the Internal Review Board (IRB) and Clinical Trials- Scientific Review Committee (CT-SRC) will occur at least annually. In addition, unanticipated problems are reviewed in a timely manner by the IRB.

St. Jude affiliates and domestic collaborating study sites will be monitored on-site by a representative of St. Jude as needed. International collaborators will be monitored by a Contract Research Organization (CRO), or other mechanism according to the study specific monitoring plan.

8.3. Confidentiality

Blood samples sent for PK analysis will be de-identified and replaced with unique study codes. The list containing the study number and the medical record number will be maintained in a locked file and will be retained indefinitely. Samples will be stored and batched in the St. Jude Biorepository by trained personnel used to handling human specimens and with strict procedures for protecting participant confidentiality. Samples sent for PK analysis to Children's Mercy Hospital (Kansas City, MO) will be sent in a de-identified manner.

9.0 STATISTICAL CONSIDERATIONS

9.1. Anticipated Completion Dates

Anticipated Primary Completion Date: 06/30/2020
Anticipated Study Completion Date: 06/30/2022

9.2. Study Design and Sample Size Justification

This is a prospective, open-label, trial composed of 2 arms. Arm 1 is to define the pharmacokinetics of liquid-formulated HU in infants (9 months to <2 years). Arm 2 is to assess the relative bioavailability of HU "sprinkles" compared to capsules in children and adolescents (≥2 to 18 years). In arm 1, n = 18 infants ages 9 months to 2 years will be administered an extemporaneous oral liquid formulation of HU on a single occasion followed by PK sampling. In arm 2, n = 30 children who range in age from 2 to 18 years will be administered 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. All infants in arm 1 will receive one dose of liquid HU and will be followed up to 30 days post HU to monitor any potential adverse toxicities per FDA safety mandate. All older patients in arm 2 with two doses of HU will be followed up to 30 days post second dose of HU to monitor any potential adverse toxicities per FDA safety mandate. The patients enrolled on arm 1 can be enrolled on arm 2 later on. Thus, in total, a maximum of 48 patients will be needed to answer the primary and secondary objectives of this HOPE18 study. On our current ongoing frontline HUGKISS study, there were 6 patients aged 9 months to 24 months enrolled at St. Jude in the last three months (The first patient was enrolled on study on June 19, 2017). Based on this accrual rate of about 2 patients each month, we are able to enroll 18 patients in arm 1 within approximately one year. As of today, 244 children with sickle cell disease aged 5-18 years are receiving hydroxyurea therapy as per best clinical practices as St. Jude Children's Research Hospital. We anticipate an accrual rate of 2 patients each month, which would allow for completion of enrollment of arm 2 (n=30) within approximately 15 months.

Statistical planning for primary and secondary objectives is based on PK data that we generated from the multicenter, HU PK trial[11], in compliance with published FDA guidance on the determination of bioequivalence (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070244.pdf). From this study, 22 individuals aged from 2 to 17 years were randomized to liquid and capsule based on a cross-over design. The mean ± SD are AUC_{inf} (Mean±SD: 114.1±29.4), AUC_{last} (Mean±SD: 101.7±24.7), and C_{max} (Mean±SD: 33.8±8.3) based on 44 samples (22 individuals), respectively.

In arm 1, children (n = 18; ages 9 months to <2 years) with SCD being treated with HU will participate in Arm 2 of the HOPE18 trial. A comparison of PK parameters in infants versus older children from the HOPE18 Arm 2 and from our previous "Pharmacokinetics and Bioavailability of a Liquid Formulation of Hydroxyurea in Pediatric Patients with Sickle Cell Anemia" (NCT01506544) trial[11] will be performed. Assuming all samples are independent and SDs are the same between two groups, this comparison in 18 infants compared to 74 older children (30 patients from HOPE18 trial and 44 patients from HU PK trial) will provide 82.9%, 87% and 86.3% power with a significance level 0.05 to detect a 20% difference in AUC_{inf}, AUC_{last}, or C_{max} using two-sample t-test with two-sided test, respectively.

In arm 2, older children (n = 30 children; ≥2 to 18 years) will participate in a randomized crossover study designed to determine the relative bioavailability of opening HU capsules and mixing them with food (sprinkles) compared to the standard clinically utilized formulation for age (unmanipulated capsules). Bioequivalence studies between treatment and control groups will be performed in 30 individuals. These tests are based on a 2-sided ratio of means in a 2x2 crossover design with continuous response variable, and they assume equivalence limits (upper and lower) of 0.8 and 1.2. By randomizing 30 individuals to the test article versus the standard of care with an allocation ratio of 1, we will have 82.4%, 85.9% and 82.4% power with a significance level of 0.05 for AUC_{inf} (mean = 114.1), AUC_{last} (mean = 101.7) , and C_{max} (mean = 33.8) with a root mean square error of the log ratio of 0.25 using two-sample t-test with two-sided test, respectively (for example for AUC_{inf}: the coefficient of variation (CV) is 29.4/114.1 = 0.258; thus, the mean square error (MSE) is equal to log(1+0.258^2) = 0.064; so, the square root of MSE is 0.25) using two-sample t-test with two-sided test, respectively. In addition, point estimates (PEs) for AUC_{inf}, AUC_{last}, and C_{max} are 97.2, 98.3, and 102.4 (NCT01506544)[11]. Per Diletti E, Hauschke D, and VW Steinijans method, (Int J Cli Pharmacol Ther Toxicol 29, 1-8, 1991), the sample size to reach 80% power with a significance level of 0.05 to detect a CV of 0.25 with PEs ranging from 97.2 to 102.4 would be 28 which is slightly smaller than 30.

Randomization: In arm 2, eligible patients will be consented and randomized in a 1:1 ratio in an open label fashion based on a 2×2 cross-over design to receive either Capsule-Sprinkle or Sprinkle-Capsule. Randomization will be performed by CRA based on the registration identifiers, using the randomization program developed by the Department of Biostatistics. Once a patient is randomized, all related randomization information will be frozen in the Biostatistics randomization database and cannot be changed.

9.3. Statistical Analysis

9.3.1 Primary Objective

Define the pharmacokinetics of liquid-formulated HU in infants (9 months to <2 years)

Summary statistics including mean, SD, median and range will be reported for all pharmacokinetics parameters including C_{max}, T_{max}, AUC_{last}, $AUC_{infinity}$, Mean Residence Time (MRT), CL/F/BW, λ_z, and $t_{1/2}$. Here all these pharmacokinetics parameters are summary statistics calculated from all pharmacokinetics samples as below.
C_{max}: The maximum concentration observed after dosing.
T_{max}: The time of maximum observed concentration (C_{max}) relative to time of dosing.
AUC_{last}: The area under the concentration-time curve from time of dosing of the drug to the time of the last measurable concentration or when concentrations were Below the Limit of Quantitation (BLQ) were calculated using either the linear (concentration before C_{max}) or log trapezoidal rule (concentrations after C_{max}).
$AUC_{infinity}$: The AUC extrapolated from the last measured concentration (C_{last}) to time infinity using the formula $AUC_{last} + C_{last} / \lambda_z$
MRT: Mean Residence Time as generated by WinNonlin (AUMC/AUC).
CL/F: Apparent clearance calculated from Dose/ AUCINF
CL/F/BW: Apparent clearance normalized for Body Weight (BW)
λ_z: (Elimination slope): The first-order linear slope associated with the terminal (log-linear) portion of the curve and estimated via linear regression of log concentrations vs. time.
$t_{½}$: Terminal elimination half-life obtained from: $t_{½} = \ln(2)/ \lambda_z$.

Assess the relative bioavailability of HU "sprinkles" compared to capsules in children and adolescents (≥2 to 18 years).

Summary statistics similar to the first objective will be reported for "sprinkles" and capsules and will be compared using two-sample t-test or Wilcoxon rank sum test depending on the normality of the data at a significance level of 0.05 per study design above. Logarithmic transformation will be applied if data do not follow normal. Mixed effects linear model (e.g., SAS PROC MIXED) will also be used as a secondary analysis to account for the repeated measurements that yield period and carryover effects and to model the various sources of intra-patient and inter-patient variability.

9.3.2 Secondary Objective

Compare PK parameters in infants versus older children on this study and those from our previous "Pharmacokinetics and Bioavailability of a Liquid Formulation of Hydroxyurea in Pediatric Patients with Sickle Cell Anemia" (NCT01506544) trial.

We will compare PK parameters as listed in first primary objective in two groups: infants versus older children. The older children will include children on arm 2 on this study and those from our previous "Pharmacokinetics and Bioavailability of a Liquid Formulation of Hydroxyurea in Pediatric Patients with Sickle Cell Anemia" (NCT01506544) trial. Statistical analysis methods are similar to those for the second primary objective. In detail, summary statistics will be reported for the infants and older children and will be compared using two sample t-test or Wilcoxon rank sum test depending on the normality of the data. Logarithmic transformation will be applied if data do not follow normal. Due to the repeated measurements in the older children, mixed effects linear model (e.g., SAS PROC MIXED) will also be used to account for the repeated measurements. Depending on the conclusion from the second primary objective after the study is completed, appropriate statistical models will be used to compare PK parameters in infants versus the older children. For example, after the study is completed, if the second primary objective shows the relative bioavailability of HU "sprinkles" versus capsules in children and adolescents and no yield period and carryover effect, then we will not include yield period, treatment and sequences in the model as a covariate. Otherwise, if the second primary objective does not show the relative bioavailability, we will compare the infants with the older children with Sprinkles on this study and with capsules and liquid on this study and NCT01506544, separately.

9.3.3 Exploratory Objective

Capture information regarding the taste of HU sprinkles using palatability questionnaire.

Descriptive statistics will be reported.

10.0 OBTAINING INFORMED CONSENT

10.1. Informed Consent Prior to Research Interventions

This trial will be designed and implemented with great concern for the welfare of subjects. Subjects will be recruited from the Hematology clinic. Because this study will involve the participation of minors, the child's guardian will be approached during regular clinic visits and invited to have his/her child participate in the HOPE18 pilot study. If a child is eligible, the family will be informed about the study, and detailed information about the trial will be given, including the risks and benefits of study participation. An informed consent session will take place in which patients and guardians will have the opportunity to ask questions regarding participation in the study, and to learn the risks and benefits of participation. After detailed discussion of the protocol, they will be given a copy of the informed consent document for review. Participation will be completely voluntary and parents may withdraw their child from the study at any time. Families will receive $100 payment for participation over the course of the study other than the costs of medical care performed as part of the study and modest reimbursement for parking, food, and travel. Subjects and families will be informed of any information that becomes available during the trial that might impact their continued participation.

10.2. Consent at Age of Majority

The age of majority in the state of Tennessee is 18 years old. Research participants will be consented at the next clinic visit after their 18th birthday.

10.3. Consent When English is Not the Primary Language

When English is not the patient, parent, or legally authorized representative's primary language, the Social Work department will determine the need for an interpreter. This information documented in the participant's medical record. Either a certified interpreter or the telephone interpreter's service will be used to translate the consent information. The process for obtaining an interpreter and for the appropriate use of an interpreter is outlined on the Interpreter Services, OHSP, and CPDMO websites.

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12.0 APPENDIX I

Dosing for Hydroxyurea Naïve

kg	Dose Administered in Clinic
10-14.9	200
15.0-24.9	400
25.0-34.9	600
35.0-44.9	800
45.0-54.9	1000
55.0-64.9	1200
65.0-74.9	1400
75.0-84.9	1600
85.0-94.9	1800
95.0-100.0	2000

Dosing for Chronic Hydroxyurea Therapy

Daily Dose	Dose Administered in Clinic
150-299.9	200
300-499.9	400
500-699.9	600
700-899.9	800
900-1099.9	1000
1100-1299.9	1200
1300-1499.9	1400
1500-1699.9	1600
1700-1899.9	1800
1900-2000	2000

13.0 APPENDIX II

Reference Ranges

Serum Creatinine

Male

Age	mg/dL
0-30d	0.22-0.48
31d-1y	0.13-0.34
2-3y	0.17-0.45
4-6y	0.22-0.53
7-9y	0.26-0.66
10-12y	0.30-0.80
13-15y	0.41-1.05
>15y	0.55-1.33

Female

Age	mg/dL
0-30d	0.22-0.48
31d-1y	0.13-0.34
2-3y	0.17-0.45
4-6y	0.22-0.53
7-9y	0.26-0.66
10-12y	0.30-0.80
13-15y	0.41-1.05
>12y	0.40-1.01

ALT- Alanine aminotransferase

Range
<41 U/L

AST- Aspartate aminotransferase

Age	U/L
0-3y	<61
4-6y	<51
>6y	<41