A phase 1 dose escalation study of continuous intravenous L-citrulline during sickle cell pain crisis or acute chest syndrome

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Study Drug: **IV L-citrulline**

Drug supplier: **Asklepion**

Clinical Phase: **Phase I**

Indication: **Sickle Cell Disease**

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1.0 General Information

1.1 Contact Information

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2.0 Study Objectives

2.1 Primary Objectives

2.1.1 To characterize the pharmacokinetic profile of continuous IV L-citrulline in patients > 6 years old during a sickle cell pain crisis or acute chest syndrome.

2.1.2 To evaluate the safety profile of continuous IV L-citrulline in patients >6 years during a sickle cell pain crisis or acute chest syndrome

2.2 Secondary Objectives

2.2.1 To determine the effect of continuous IV L-citrulline on NO and NO metabolites in individuals with sickle cell disease experiencing a sickle cell pain crisis or acute chest syndrome

3 Hypotheses

3.1 Continuous IV L-citrulline will be well tolerated, without significant adverse effects in patients with sickle cell disease during a sickle cell pain crisis or acute chest syndrome

3.2 Continuous IV L-citrulline will increase NO and NO metabolites in patients with sickle cell disease receiving IV L-citrulline.

4 Study Overview

4.1 Description of Design of Study

This study is a single center, prospective, open label phase 1 trial for subjects admitted for sickle cell pain crisis or acute chest syndrome. A total of 18 participants will be

recruited during their hospitalization at the University of Mississippi Medical Center (UMMC).

5 Study Population

5.2 Inclusion criteria:

5.2.1 Sickle cell disease genotypes (HbSS, HbS/β°-thalassemia, HbS/β^+-thalassemia, HbSC)

5.2.2 Patients with sickle cell disease aged 6 to 50 years old

5.2.3 Presence of sickle cell pain crisis defined by the presence of pain requiring hospitalization and parental opioid therapy

5.2.4 Presence of acute chest syndrome defined by the presence of a new CXR infiltrate and any one of the following respiratory symptoms of fever, shortness of breath, wheezing, chest pain, cough or new onset hypoxia.

5.3 Exclusion criteria

5.3.1 Presence of any other complication related to sickle cell disease requiring hospitalization such as splenic sequestration, hepatic sequestration, stroke, avascular necrosis of the hip/shoulder, acute priapism, etc.

5.3.2 Severe anemia (hemoglobin < 5g/dL)

5.3.3 History of red blood cell transfusion within the last 30 days

5.3.4 Systemic steroid therapy within the last 48 hours

5.3.5 Pregnant (as confirmed by a negative urine pregnancy test) or lactating female

5.3.6 Alanine/aspartate transferase >2x upper limit of normal laboratory range for age.

5.3.7 Subject has the following serum creatinine:

- 5.3.7.1 Age 6 to 13 years > 0.9 mg/dL
- 5.3.7.2 Age 14-17 years 1.0 mg/dL
- 5.3.7.3 Age 18 years >1.5mg/dL

5.3.8 Patients with an inability to give consent will be excluded

6 Study Conduct

6.2 Procedures - Whether participants participate in this study or not, they will still receive the standard of care for treatment of their sickle cell pain crisis or acute chest syndrome.

6.2.1 Participant Enrollment and Screening

Prior to enrollment, the investigator will:

1. Determine initial eligibility prior to performing any study-specific procedures.

2. Obtain signed informed consent from the patient participant before any study-specific procedures are performed.

3. Review patient eligibility.

4. Assign the potential participant a unique enrollment number, beginning with 005. If a participant withdraws from participation in the study, then his/her enrollment code cannot be reused.

Once the consent form is signed and the participant is enrolled into the study, the investigator will:

5. Collect demographics, medical history and concomitant medications.

6. Obtain vital signs (weight, height, blood pressure, heart rate, temperature, respiratory rate) and complete a physical examination.

7. Obtain a blood sample for clinical chemistry, liver function tests and hematology assessments (if standard of care labs are obtained within 48, those labs can be used for screening).

8. Collect a urine sample in females of childbearing potential for a urine pregnancy test.

9. The study drug will be administered within 72 hours of admission to the hospital for the sickle cell pain crisis or acute chest syndrome

6.2.2 Initiation of Investigational Product

Once the eligibility of the participant is confirmed, the investigator will:

1. Establish intravenous access for drug infusion and blood sample collection.

2. Apply a blood pressure cuff for continuous cardiopulmonary monitor

3. Collect about 2 teaspoon of blood immediately prior to the drug infusion for a baseline level of citrulline (trough level), and for NO and NO metabolites.

4. Administer intravenous citrulline at a bolus dose of 20 mg/kg over 5 minutes and then continuous at a rate of 7 mg/kg/hour for the next 23 hours.

5. Collect about 2 teaspoon of blood at each of the following time-points: 10 minutes (peak level), 30 minutes, 1 hour, 2 hours, 3 hours, 4 hours, 6 hours, 8 hours, 12 hours, 24 hours and 48 hours after start of the IV citrulline infusion.

6. Vital signs will be collected prior to each blood collection.

7. Monitor the participant for any adverse events.

6.2.3 24 hour Post-Infusion Follow-Up

At the end of 24 hours (+/- 3 hours) hours from start of infusion, the investigator will:

1. Perform a physical examination.

2. Evaluate the participant for any adverse events.

3. Obtain blood sample for complete count, liver and renal function tests (if standard of care labs are performed, then those laboratory results will be used).

At the end of 48 hours (+/- 3 hours) hours from start of infusion, the investigator will:

1. Perform a physical examination.

2. Evaluate the participant for any adverse events.

3. Obtain blood sample for complete count, liver and renal function tests (if standard of care labs are performed, then those laboratory results will be used).

6.2.4 15 Day Post-Infusion Follow-Up

The following assessment will be completed 15 days (+/- 3 days) following the discontinuation of IV citrulline. This assessment may be completed via telephone contact with the subject and will not require an office visit.

1. Adverse event reporting.

6.2.5 30 Day Post-Infusion Follow-Up

The following assessment will be completed 30 days (+/- 3 days) following the discontinuation of IV citrulline.

2. Adverse event reporting.

3. Obtain blood samples for complete blood count, liver and renal function tests

6.3 Administration of Investigational Product

6.3.1 Administration Regimens

This study will include 2 cohorts each consisting of 7 participants for a total of 14 study participants. The second cohort will receive an escalated or reduced dose of the continuous study medication until a target peak goal citrulline concentration of 100 µmol/L is achieved. Each cohort will receive a single IV dose of L-citrulline administered as a single bolus infusion over a 5 minute period and then a continuous infusion for 23 hours.

Cohort 1 will receive 20 mg/kg of study medication and then a continuous rate of 7 mg/kg/hour for 23 hours. After pharmacokinetic data and safety profile (toxicity) is analyzed for cohort 1, the dosage for cohort 2 will change as follows:

1. Higher continuous dose: IV citrulline 20 mg/kg bolus infusion followed by 9 mg/kg/hour for 23 hours OR

2. Lower continuous dose: IV citrulline 20 mg/kg bolus infusion followed by 5 mg/kg/hour for 23 hours

7.2.2. Study Drug Accountability, Storage and Mode of Administration

The manufacturer of citrulline will supply the study drug in sufficient quantities to complete the study. The study drug will be stored at ambient room temperature. The pharmacist will be asked to maintain a temperature log to document storage temperature conditions. The pharmacist will prepare and label all study drugs, and all labeling will meet standard requirements. L-citrulline will be supplied from the pharmacy as open label vials, and administered as a 50 mg/mL (5%) isotonic solution, with distilled water as a suspending agent.

6.4 Data Collection at Enrollment and Follow-up

For this study, participant data will be collected by paper source documents. Every effort should be made to collect all required data, including blood samples and to complete all assessments required for each visit as detailed in the study plan.

Clinical information obtained as part of standard clinical care before the informed consent is signed may be used as part of the screening and evaluation process.

The investigator will ensure the data are recorded on the CRFs as specified in the study protocol. He will ensure the accuracy, completeness, and timeliness of the data recorded.

7 Blood Sample Processing

7.2 Citrulline Pharmacokinetic and NOx metabolite sampling

Plasma sampling for PK studies and NOx metabolites will be collected. As noted above, baseline PK and NOx testing will be performed just prior to giving the bolus (trough levels), 10 minutes after the bolus (peak level), and then 30 minutes, 1 hour, 2 hours, 3 hours, 4 hours, 6 hours, 8 hours, 12 hours and 24 hours after the bolus infusion.

7.3 Collection and Processing of Blood Samples

Ten ml of venous blood will be collected in collection tubes containing citrate or EDTA. Samples will be kept on ice and processed within 3 hours after collection. Specimens will be centrifuged at 2000 rpm for 5 min and plasma collected and stored at –80ºC. Samples will be shipped by overnight courier to Marshall Summar MD, Center for Genetic Medicine Research at the Children's National Medical Center for amino acid testing, and Paresh Ray, PhD at Jackson State University for nitric oxide testing.

8.3 Amino Acid Analysis

Briefly, deproteinated plasma samples will be subjected to cation exchange chromatography using a 4-component pH and ionic strength graded lithium citrate buffer system on a Beckmann 7300 amino acid analyzer (Beckmann, Palo Alto, CA). Arginine and citrulline will be the main focus as measurable products of urea cycle function, but will measure all urea cycle intermediates. In addition, the level of total essential amino acids (TEEA) to control for overall nutrition and metabolic state will be calculated. Analysis of amino acids will be completed as previously described.

8.4 Nitric Oxide Assay

NO will be measured by chemiluminescence using a Sievers 280 nitric oxide analyzer (NOA). Samples are mixed one part sample with two parts of cold ethanol at 0^0C for 30 minutes. Following centrifugation at 14000 RPM for 5 min, samples are injected into the NOA. This method relies on catalytic reduction of NOx by exposure to warm vanadium hydrochloride. Liberated NO is driven by nitrogen gas into an ozone chamber. Light released by NO/O3- interaction is captured by a photomultiplier tube and relayed to an analytical software program. A standard curve using sodium nitrite is required.

8.5 Pharmacokinetic analysis

Data obtained for each patient will be fit to a single-compartment pharmacokinetic model. The appearance of citrulline in plasma is described by a zero-order process (rate of citrulline appearance, R_{app}) to account for endogenous production, whereas the removal of citrulline is determined by a first-order process (constant of citrulline removal, k_{rem}). It is assumed that the values of all parameters will remain constant for each patient during the course of plasma sampling. Origin (OriginLab Corporation, Northhampton, MA) will be used to solve for the pharmacokinetic parameters using a weighted, least squares procedure to obtain simultaneous values for R_{app}, C_o (plasma concentration at time zero), k_{rem}, and AUC (area under the curve).The volume of distribution (V_d) will be calculated from the total dose/C_o and the half-life from 0.693/k_{rem}. Clearance will be calculated from k_{rem} multiplied by the V_d.

8 Safety Assessments

Safety assessments will be collected as part of this bolus and continuous dose infusion, pharmacokinetic study. Safety will be assessed throughout the infusion in all subjects, and monitored through 30 days after the end of the infusion. Subject safety will be assessed by monitoring adverse events (see section 10 for full detail), clinical laboratory tests, vital signs and physical examinations.

8.2 Clinical Parameters

- Vital Signs

Vital signs (temperature, respiratory rate, blood pressure and heart rate) will be collected prior to the initiation of study drug and prior to each blood sample collection at 10 minutes, 30 minutes, 1 hour, 2 hours, 3 hours, 4 hours, 6 hours, 8, 12 hours and 24 hours after the infusion.

- Physical Examination

  A complete physical examination will be performed during the screening period. If the drug infusion occurs on a different day than the screening procedures are performed, then an abbreviated physical examination will be completed prior to the drug infusion. A follow up complete physical examination will be performed at 24 hours after the end of the infusion.

8.3 Laboratory Parameters

Laboratory parameters will be evaluated at screening and then at 24 hours at completion of infusion and then at 30 days after the infusion to include the following:

- Complete Blood Count (white blood cell count, hemoglobin, MCV, platelet count)
- Renal Function (Sodium, potassium, blood urea nitrogen (BUN), HCO3, Creatinine)
- Liver Function (Alkaline phosphatase, aspartate transferase, alanine transferase, and total bilirubin).

9 Adverse/Serious Adverse Events

9.2 Adverse Event (AE) Definition

An adverse event (AE) is any untoward medical occurrence in a subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. AE may be reported by the subject, discovered by investigator questioning, or detected through physical examination, laboratory test, or other means.

At each evaluation, subject will be interviewed to elicit potential adverse reactions from the drug. The occurrence of an AE will be based on changes in the subject's physical examination, laboratory results, and/or signs and symptoms. All AEs (except Grade 1 and 2 laboratory abnormalities that do not require an intervention), regardless of causal relationship, will be recorded in the case reporting form (CRF) and source documentation. The Investigator will determine the intensity of any AE according to the NCI Common Terminology Criteria for

Adverse Events (CTCAE) Version 4.03 (see http://ctep.info.nih.gov) and their causal relationship.

In this phase 1 trial, a participant with at least a grade 2 level of toxicity will be considered as dose-limiting for IV citrulline, and will be used as the stopping rule for testing further cohorts of participants.

10.2 Adverse Event Reporting

AE will be monitored and reported on a CRF that includes the description of the event, onset date, stop date, and outcome. The subjects will be instructed to inform the study personnel or clinical staff of any AEs experienced during the trial. In addition, subject safety will be assessed by monitoring clinical laboratory tests, vital signs and physical examinations. Any subject who has an AE will be evaluated by the investigator and will be treated accordingly. The investigator or designated study physicians will review each event and assess its relationship to the drug treatment (unrelated, possibly related, or probably related) based on the following definitions:

10.2.1. Serious Adverse Events (SAEs)

An AE or suspected AE is considered serious if, in the view the Investigator, it results in any of the following outcome

1. Death;

2. A life-threatening adverse event;

3. Inpatient hospitalization or prolongation of existing hospitalization, excluding hospitalization for VOC required for inclusion into the study;

4. A persistent or significant disability/incapacity;

5. Congenital anomaly/birth defect; or

6. Other events that, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

10.2.2. Unexpected Adverse Event

An AE is considered unexpected if it is not described in the Investigator's Brochure or if it is of greater frequency and/or severity than mentioned in the Investigator's Brochure. Unexpected, as used in this definition, refers to an adverse drug event that has not been previously observed rather than from the

perspective of such event not being anticipated from the pharmacological properties of the pharmaceutical product.

10.2.3. Relationship

The Investigator will assess the relationship of the event (not-related, unlikely-related, possibly related, probably related, or definitely related). The relationship of an adverse event will be assessed using the following definitions:

Not Related: Evidence exists that the adverse event definitely has an etiology other than the investigational agent, such as a pre-existing condition or underlying disease, a concurrent illness, or concomitant medication, and does not meet any of the criteria above.

Unlikely: The causality of the AE is supported by enough evidence to reasonably suggest that the event could more likely be attributed to something other than the investigational product such as the underlying disease or an intercurrent illness or injury.

Possibly Related: A temporal relationship exists between the event's onset and investigational agent administration. Although the event may appear unlikely to be related to the investigational agent, a relationship cannot be ruled out with certainty, and/or the event cannot be readily explained by the subject's clinical state or concomitant treatment.

Probably Related: A temporal relationship exists between the event's onset and investigational agent administration, and the event appears with some degree of certainty to be related to investigational agent, based on the investigational agent's known therapeutic and pharmacologic actions. The event cannot be readily explained by the subject's clinical state or concomitant treatment. If the investigational agent is discontinued or the dose is reduced the event abates or resolves.

Definitely Related: Strong evidence exists that the investigational agent caused the adverse event. There is a temporal relationship between the event's onset and investigational agent administration, and strong therapeutic and pharmacologic evidence that the investigational agent caused the event. The subject's clinical state and concomitant treatment have been ruled out as causes. If the investigational agent is discontinued or the dose is reduced the event abates or resolves, but it reappears upon rechallenge.

10.2.4. Severity of Adverse Events

Severity or intensity of adverse events will be graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 4.03, and reported as indicated on the CRF.

10.3. Serious Adverse Event Reporting

10.3.1. Time-Frame for Reporting

Under 21 CFR 312.32(c), the Principal Investigator will notify the FDA within 7 calendar days an event that meets all three definitions of a suspected adverse reaction, serious adverse reaction and unexpected adverse reaction via a secure e-mail account with the FDA. The Principal Investigator will evaluate the available information and decide whether there is a reasonable possibility that the drug causes the adverse event, and therefore, that the event meets the definition of *suspected* adverse reaction. In addition, the investigator will identify in each IND safety report all IND safety reports previously submitted to the FDA concerning a similar suspected adverse reaction in light of previous, similar reports of any other relevant information. As per 21 CFR part 312, the investigator will conduct ongoing safety evaluations, including a periodic review and analyses of the entire safety database, not only for IND safety reporting purposes, but also to update investigator brochures, protocols, and consent forms with new safety information.

10.3.2 Follow-Up of Adverse Events

Any SAE or AE assessed as possibly, probably, or definitely related after last dose of study treatment will be followed until either resolution of the event or determination by the Investigator that the event has become stable or irreversible. This follow-up guidance also applies to possibly, probably, or definitely related SAE that occur 7 days after the last dose of study drug administration. The status of all other continuing AEs will be documented as of 7 days after last dose of IV citrulline. Follow-up data concerning reported SAE must also be reported to the FDA.

10.3.3. Regulatory Reporting

Reporting of SAEs by the Investigator to the IRB will be done in accordance with the standard operating procedures and policies of the IRB. Adequate documentation will be maintained showing that the IRB was properly notified.

11. Safety Monitoring Plan

A Data Safety Monitoring Board (DSMB) will be comprised of 3 University of Mississippi Medical Center physicians who are not related to the study. Every third patient will be reviewed by the DSMB to ensure the safety of the study participants.

12. Data Handling and Record Keeping

In compliance with ICH guidelines, the investigator will maintain copies of all source documents that support data collected from each patient and all study documents as specified in ICH Section 8, Essential Documents for the Conduct of a Clinical Trial. The investigator will take measures to prevent accidental or premature destruction of these documents.

All data containing protected health information will be collected and stored in a locked cabinet located in the Children's Cancer Clinic. In addition, all electronic data in for the form of Microsoft excel spreadsheet, word documents etc. will be stored in a password protected encrypted computer. The study coordinator will file all the material. Any information that is shared with other study personnel via e-mail will be de-identified in order to protect the participants' health information.

13. Institutional Review Board (IRB)/Ethics

The protocol complies with the principles of the Declaration of Helsinki, 1964. In addition, the protocol complies with the laws and regulations of the state of Mississippi.

The collection and processing of personal data from patients enrolled in the this study will be limited to that data which is necessary to investigate the efficacy, safety, quality, and utility of the investigational study medicine used in this study.

The data will be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations.

Only approval by the Institutional Review Board (IRB), explicit consent for the enrollment in this research study, and processing of personal data will be obtained from the participating patient before collection of data.

The patient has the right to request through the investigator access to his/her personal data and the right to request rectification of any data that is not correct or complete. Reasonable steps should be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

Data will be kept confidential and if published in a scientific journal, will be done without identification of the individual patients.

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