Chronobiology and Chronopharmacology to Prevent Sickle Cell Nephropathy Feasibility Trial

Study Protocol & Statistical Analysis Plan

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INTRODUCTION AND OBJECTIVES

Chronic Kidney Disease and End Stage Renal Disease in Sickle Cell Disease

In adults with sickle cell disease (SCD), ~ 40% of patients have chronic kidney disease which may be associated with hypertension and albuminuria.[1] In this SCD patient population, 12% of patients progress to renal failure and 15-30% of deaths in SCD are related to kidney disease.[2,3] The treatment for a patient that has renal failure is dialysis, often as a bridge to renal transplantation. Dialysis records suggest that 0.1-0.5% of those patients initiated on dialysis for end stage renal disease (ESRD) have SCD and these patients were are nearly 7 years younger than the average dialysis at the time of initiation.[4-6] The one year mortality rate for dialysis patients with SCD may be three times higher than patients with ESRD but without SCD and the mean survival time after initiating dialysis is only 4 years.[6,7] Renal transplantation is a viable option for sickle cell patients on dialysis and may improve survival.[4,5,8] However, this patient population is less likely to be offered or receive renal transplantation which may be due in part to lower survival of grafts or patients with SCD as compared to other diseases with ESRD. [8,9] The known progression to and poor survival of SCD patients with chronic kidney disease mandates early identification of patients at risk and therapies that may prevent progression.

Sickle Cell Disease and Potential Biomarkers of Chronic Kidney Disease

Toddlers with SCD may initially develop hyperfiltration which progressively declines during adolescence and young adulthood and indicates progression to chronic kidney disease.[10,11] A cross-sectional study of adolescent SCD patients identified in-clinic systolic BP as a risk for worsening glomerular filtration rate.[12] Pediatric patients with sickle cell disease also develop microalbuminuria (microalbumin/creatinine >30mcg/mg) and proteinuria (>300mcg/mg) which may proceed kidney disease. Several studies have evaluated the presence of albuminuria pediatric sickle cell disease. (Table)

Author	Sample size	Prevalence	Correlations
McKie[13]	191	37/191 (19.4%)	Lower Hb, Age
McBurney[14]	142	Overall: 19% 7-14yrs: 18/75 (24%) 15+: 9/31 (29%)	Lower Hb, Age
Gurkan[15]	40 (33 HbSS)	MiA- 6/40 (15%) MA- 2/40 (5%) No MiA <12yrs	LDH and MiA (not correlated with HbSS alone)
Becton[16]	90	14/90 (16%)	Lower Hb, Increasing BP
McPherson[17]	261	60/261 (23%)	Lower Hb, Age
Egberue[18]	69	14/69 (20.3%) >9yrs: 23%	Age
Alvarez[19]	165 (SS and SC)	46/165 (28%) 40 HbSS. 8/46 had MA	MA vs. MiA: Lower Hb, Higher Retic, Lower GFR

Dharnidharka[20]	102	MiA (>20mg/g Cr) Overall: 26.5% 10-18yrs:46%	Age
Lebensburger[21]	144	32/144 (22%)	Low Hb
Mawanda[22]	305	86/305 (28.2%)	Low Hb, Age, more transfusions
Aygun[12]	85	15.9%	Blood Pressure, Low WBC and ANC

The novel biomarkers Kim-1 and NAG are higher in SCD patients with albuminuria.[23,24] Cystatin C has been negatively correlated with hemoglobin and positively correlated with age, B2M and NAG.[25]

Abnormal Ambulatory Blood Pressure in Pediatrics is a Risk Factor for Chronic Kidney Disease:

Hypertension, based on in-clinic BP, in SCD patients has been associated with albuminuria and hyperfiltration.[12,16,18,26-28] Additional SCD studies have associated in-clinic hypertension as a risk factor chronic kidney disease and renal failure.[9,29,30] In non-SCD pediatric populations, 24 hour ambulatory blood pressure is more accurate than clinic BP in defining secondary hypertension and abnormal 24 hr ABPM has been strongly linked to progressive renal disease.[31-35] In the large pediatric study Chronic Kidney Disease in Children (CKiD), an association was identified between abnormal ABPM and progression of proteinuria and renal function decline.[36] Despite the recent emphasis on utilizing 24 hr ABPM in clinical trials for other diseases, in SCD, the roles of hypertension defined by ABPM as a risk factor for kidney injury or intensive antihypertensive therapy to prevent the devastating complications of CKD has not been explored.

Selection of Angiotensin II Antagonist Therapy to Correct Abnormal Ambulatory Blood Pressure.

Despite the high prevalence of hypertension in SCD and increased morbidity and mortality from cardiovascular disease, there are currently no randomized clinical trials in SCD to demonstrate 1) the appropriate selection of an antihypertensive medication, or 2) dosing of that medication in the pediatric setting. Angiotensin Converting Enzyme Inhibitors and Angiotensin II Antagonists both may reduce proteinuria and abnormal blood pressure in SCD patients. The rationale for selecting losartan in this feasibility trial is that unlike ACE Inhibitors, Angiotensin II Antagonists do not accumulate bradykinin which may contribute to nocturnal hypertension; losartan, unlike other Angiotensin II Antagonists, has uricosuric effect which may be important as uric acid may be associated with abnormal circadian BP and uricosuric medications may lower blood pressure (Table 4).[37-41] Of great interest, an ambulatory blood pressure clinical trial comparing an Angiotensin II Antagonist (Losartan) to an ACE Inhibitor (quinapril) demonstrated that losartan preferentially decreased nocturnal hypertension.[42] The findings of a reduction in nocturnal hypertension by Angiotensin II Antagonists was replicated in additional studies and independent of time the drug was administered. [43,44]

Rationale for Evaluating Safety of Using an Intensive BP Treatment Strategy

Current standard of care in our institution is to place pediatric patients on an antihypertensive medication with a goal of reducing BP to <95th percentile based on NHLBI BP Tables for Children and Adolescent. A recent meta-analysis of 11 trials identified intensive blood pressure therapy (BP<50th or 75th percentile) as compared to standard therapy reduced adverse outcomes, most effectively in patients with concomitant proteinuria. [45] Pediatric non-SCD trials using intensive anti-hypertensive therapy guided by 24 hr ABPM resulted in decrease progression to CKD.[46,47] In a large non-SCD pediatric randomized trial of intensive vs. standard therapy for control of 24 hours blood pressure with an ACE Inhibitor, intensive BP control improved renal outcomes and the greatest impact was seen in patients with glomerulopathies.[46] As most SCD patients without renal disease have low BP relative to the black population, a target of 95 percentile BP may be physiologically hypertensive in SCD and intensive BP may be more appropriate. As no prospective anti-hypertensive trials focused on adolescent patients with SCD, it is vital to first conduct a feasibility trial to determine the safety and tolerability of standard and intensive dosing strategies

1.1 AIMS OF THE TRIAL

1.1.a Primary Objectives

To identify participants at risk for developing progressive kidney disease and to target therapeutic approaches that prevents progressive kidney disease. The primary endpoint is to conduct a randomized feasibility trial of losartan among participants with abnormal ambulatory blood pressure. We expect that 30% of participants in a pediatric hypertension cohort (n=60) will have abnormal ambulatory blood pressure and abnormal clinic blood pressure. Of these sixty participants, we estimate that 40 participants will accept enrollment in the feasibility trial.

1.1.b Secondary Objectives

Objective 1: To determine the acceptability of enrollment and retention in a randomized feasibility trial of losartan

Objective 2: To determine the safety of losartan at two different dosing strategies

Objective 3: To complete the necessary preparations for a definitive phase III trial including preparing a manual of operations, case report forms, and sample size calculations

2.0 STUDY OVERVIEW AND DESIGN

2.1 Study Overview.

2.1.a Cohort Study (X130312027) already approved cohort study being conducted)

A five year prospective cohort study will be conducted among participants with HbSS or SB0 thalsassemia ages 5-22 years of age. The study will evaluate standard of care labs and medical history (including type of sickle cell therapy) to determine the incidence of hypertension and markers of progressive kidney injury. Annually, participants will undergo research evaluations using 24 hour ambulatory blood pressure monitoring and analysis of urine samples for biomarkers of kidney injury. Participants with abnormal nocturnal blood pressure dipping will be eligible for this feasibility trial.

2.2 Randomized Feasibility Trial-

A randomized feasibility trial of losartan for the correction of abnormal nocturnal blood pressure dipping in adolescent patients with HbSS or SB0 thalsassemia 11-22 years of age who have documented hypertensive blood pressure in clinic will be conducted. Participants will be randomized to losartan at doses to maintain clinic BP either <95th percentile (standard dosing strategy) or <75th percentile (intensive dosing strategy). The study will be analyzed using intention to treat for outcomes which will begin immediately after randomization to losartan. Participants will be followed monthly as standard of care with additional research procedures of performing ambulatory blood pressure monitoring at baseline, 3 months, and 6 months and urine/blood biomarkers of kidney injury at baseline, 3 months and 6 months. We propose to identify 60 eligible participants of which 40 will participate in the randomized feasibility trial. The parents/legal guardians of these children will have a one hour educational session on hypertension and kidney disease in sickle cell disease. The parents/legal guardians will be offered the opportunity to discuss hypertension and kidney disease with a Pediatric Nephrologist prior to participation in the trial.

2.2.a. Eligibility for the Feasibility Trial

Inclusion Criteria for Pediatric Cohort (Separate IRB approved study-X130312027))

1. Participant must have sickle cell anemia (hemoglobin SS) or sickle β°-thalassemia (hemoglobin Sβ°) as confirmed at the local institution by hemoglobin analysis.
2. Participant must be 5 to 22 years of age (i.e., must not have attained their 23rd birthday).
3. Informed consent in accordance with the institutional policies (institutional IRB approval) and Federal guidelines (approved by the United States Department of Health and Human Services) must be signed by the participant's legally authorized guardian acknowledging written consent to join the study.

2.2.b. Inclusion Criteria for Feasibility Trial Screening

1. Enrolled in Pediatric Cohort Study
2. History of abnormal clinic blood pressure (3 abnormal blood pressure readings (systolic or diastolic) in last 4 visits) as defined by NHLBI Blood Pressure Tables for age and height.
3. History of 1) abnormal nocturnal blood pressure dipping as defined by <10% dip (daytime-nightime systolic or diastolic blood pressure/daytime blood pressure x 100) or 2) abnormal nocturnal load defined by >25% sleep BP >95th percentile.
4. Informed consent in accordance with the institutional policies (institutional IRB approval) and Federal guidelines (approved by the United States Department of Health and Human Services) must be signed by the participant's legally authorized guardian acknowledging written consent to join the study

2.2.c. Exclusion Criteria for Feasibility Trial Screening

1. Participant with history of angioedema to prior ARB or ACE inhibitor
2. Participants with moderate to severe renal impairment (GFR <60mL/min/1.73m2)
3. Co-administration of another hypertensive medication
4. History of known bilateral renal artery stenosis, unilateral renal artery stenosis to a solitary kidney
5. Hyperkalemia at time of screening (K>6 mmol/L- non-hemolyzed sample)
6. Pregnancy
7. Current use of lithium, digitalis, warfarin

2.2.d. Inclusion Criteria for Feasibility Trial Randomization

1. Repeat ABPM demonstrating abnormal blood pressure dipping (systolic or diastolic dipping <10%) or abnormal nocturnal load
2. Complete a Survey of Barriers and Facilitators to Enrollment in a Pediatric SCD Hypertension Trial

2.3 BASELINE EVALUATION AND FOLLOW-UP

2.3.a Baseline Evaluations

1. Screening
    a. Eligible participants will undergo repeat 24 hour ABPM to confirm abnormal nocturnal dipping prior to randomization.
    b. Participants, and if participants is a minor, parents/guardians, with abnormal 24 hour ABPM will be educated about hypertension, kidney disease in SCD. Participants will also be offered consult with Pediatric Nephrologist prior to randomization.

2. Randomization
    a. Participants will have overnight urine collected for biomarker analysis. Participants can be consented to allow additional urine to be stored for future urine studies of kidney injury.

b. Participants will have standard of care labs obtained including CBC with diff, CMP with LDH and uric acid, urine for microalbumin/creatinine ratio, Cystatin c
c. Participants can be consented to Buccal Cell collection

2.3.b Follow-up

1. Monthly evaluations (6 months total from randomization)
    a. Participants will have monthly clinic visits
    b. Obtain vital signs
    c. Obtain standard of care labs: including CBC, CMP
    d. Complete assessment of potential side effects of losartan
    e. Complete assessment of adherence
2. Three months from randomization
    a. Obtain overnight urine specimens for urine biomarkers including standard evaluation of microalbumin/creatinine ratio and experimental evaluation of biomarkers
    b. Obtain cystatin C
    c. Buccal Cell Collection
    d. Repeat 24 hour ABPM
3. Six months from randomization
    a. Obtain overnight urine specimens for urine biomarkers including standard evaluation of microalbumin/creatinine ratio and experimental evaluation of biomarkers
    b. Obtain cystatin C
    c. Buccal Cell collection
    d. Repeat 24 hour ABPM

Table XX: Baseline and monthly evaluations

Test	Entry	1 mo	2 mo	3 mo	4 mo	5 mo	6 mo
Vital Signs, Hx and PE	X	X	X	X	X	X	X
CBC with diff	X	X	X	X	X	X	X
CMP	X	X	X	X	X	X	X
Adherence Measures		X	X	X	X	X	X
Ferritin	X			X			X
Cystatin C	X			X			X
Uric Acid	X			X			X
Urine Microalbumin/Creatinine	X			X			X
Overnight Urine Collection	X			X			X
24 hr ABPM	X			X			X
Urine and blood biomarkers	X			X			X
Pregancy Test	X	X	X	X	X	X	X
Enrollment Survey	X						
Buccal Cell collection	X			X			X

3. UNDERSTANDING ENROLLMENT

All participants approached to participate in the feasibility trial have consented to the cohort study, but will be asked to complete a survey to identify barriers/facilitators to enrollment in a drug trial. Quantitative surveys questions will include Likert questions to determine barriers/facilitators to participation in this trial using two direction intensity scale (strongly agree, agree, disagree, and strongly disagree. The questionnaire will be piloted among adolescent SCD patients not eligible for the feasibility trial.

4. BLOOD PRESSURE MONITORING

4.1. CLINIC BLOOD PRESSURE MONITORING

Participants will have standard of care blood pressure monitoring in clinic. Participants will have blood pressure obtained in a sitting position. Blood pressure cuffs will be selected by study member or clinic nurse and applied to the participant's non-dominant arm. The cuff bladder should cover at least two thirds of the upper arm and the bladder should encircle 80% to 100% of the circumference of the arm. Blood pressure should be measured twice in a controlled environment after 3-5 minutes of sitting.

4.2. AMBULATORY BLOOD PRESSURE MONITORING

SpaceLabs 90217 monitors will be used to perform 24 hour ABPM. Participants and parents/guardians will be educated on how to operate the monitor including how to stop a reading if there is excessive discomfort, what to expect when a reading is obtained, and need to keep the arm still during BP readings. Participants will be educated that BP will be recorded every 20 minutes during the day and every 30 minutes from 10PM to 6 AM. If the monitor is removed, the device should be removed immediately after a recording and reapplied as soon as possible. Participants should immediately contact the study team if apparent allergic reaction or extreme uncomfortable pressure. Finally, participants will be educated to keep a log book of activity during the day including activities that may influence BP. At minimum, the log should record sleep and wake times.

Blood pressure cuffs will be selected by study member and applied to the participant's non-dominant arm. The cuff bladder should cover at least two thirds of the upper arm and the bladder should encircle 80% to 100% of the circumference of the arm. The study member will allow the ABPM to inflate two times prior to leaving the clinic. Participants will receive a pre-addressed stamped FedEx box to return the diary and monitor to study team. Participants who do not complete ABPM will participate in an interview to determine the barriers to completing the ABPM and facilitators that would enhance adherence.

4.3. ABPM INTERPRETATION

To be considered an acceptable procedure, the following readings must be recorded: 1) A minimum of 1 reading per hour including during sleep and 2) total of 40 readings during the period.

Values outside the following range will be discarded

1) SBP 60-220 mm Hg

2) DBP 35-120 mm Hg
3) Heart rate: 40-180 BPM
4) Pulse pressure 40-120 mm Hg

The following calculations will be recorded

1) Mean Ambulatory SBP and DBP for the entire 24 hour period, awake period, and sleep period
2) Dipping will be calculated as ((Mean Awake BP- Mean Sleep BP)/Mean Awake BP) x 100. Normal Dipping will be defined as >10% dipping. Reverse Dipping will be defined as mean sleep BP that is higher than mean Awake BP.
3) BP Load is the percentage of systolic and diastolic BP readings above the 95th percentile for the 24 hour, awake, and sleep periods as defined by the 2014 Statement from the American Heart Association- Update: Ambulatory Blood Pressure Monitoring in Children and Adolescents.
4) BP index will be calculated as the mean BP/normative data for 95th BP for the 24 hour, awake, and sleep periods.

5.1. URINE BIOMARKERS

Urine will be collected by the patient on any urine overnight and first urine in the morning into a sterile container provided by the study coordinator. Urine will be collected at 0, 3, and 6 months. The urine will be centrifuged and aliquoted into 10 microcontainers within one hour. Five microcontainers will be sent immediately to the UAB lab of Dr. Jennifer Pollock and David Pollock. Five microcontainers will be stored at -80 degrees Celsius at the Children's of Alabama Lab. Two of the frozen microcontainers from each participant will be sent to the UAB-UCSD O'Brien Center for Acute Kidney Injury Research, Bioanalytical Core at 3-6 month by Fed Ex Overnight shipping on dry ice to UCSD on Mon or Tues (once every 3 months). Dr. Satish Rao at UCSD will analyze urine for Kidney Injury Marker-1 (KIM-1), Neutrophil gelatinase-associated lipocalin (NGAL), and Beta-2-microglobulin. One urine sample microcontainer tube per patient will be sent to Dr. John Moore's lab at UAB to be analyzed for cystatin-C, urine albumin/creatinine.

5.2. ADDRESSING NOVEL BIOMARKERS

Participants can consent to use of urine for future evaluations of kidney disease or hypertension. Two remaining microcontainers will be kept in a research freezer. During the course of the study, the principal investigator may be able to analyze the urine samples for novel biomarkers of hypertension or kidney injury.

5.3 BLOOD BIOMARKERS

Uric acid will be processed and analyzed by Children's of Alabama laboratory. 10mL of whole blood will be collected in EDTA tubes and sent to the UAB laboratory of Drs. Jennifer and David Pollock for analysis to include: thiobarbituric acid reactive substances, endothelin, aldosterone, BNP, and renin.

5.4. BUCCAL CELL SWABS

Participants will have buccal cell swab testing performed at three times during the study (entry, 3 mo, and 6mo). The goal of the buccal swab testing is to determine if abnormal nocturnal blood pressure in sickle cell disease is related to abnormal circadian rhythms. In animal models, an abnormal circadian rhythm is associated with hypertension. The swabs will be collected at multiple time points (6AM, 10AM, 6PM, 10PM) to determine the circadian rhythms in this patient population.

Participants will be given 3 bags: one with buccal swabs, one with labeled tubes, and an empty bag to place the tubes containing the swab tips after each collection. Holding the handle end of the swab, participants will scrape the swab collection tip firmly against the inside of the cheek 6 times (about 10 seconds). After taking the sample, the participant will eject the tip by pushing down the plunger at the end of the handle into the tube labelled for that time. Ensure the lid on the tube is tight. Place the tube into a bag and refrigerate the bag.

6. LOSARTAN DOSING AND MONITORING

Prior to randomization, participants will need to have 1) three documented blood pressure recordings (in last 4 visits) documenting a systolic or diastolic blood pressure that is >95th percentile for age, gender, and height as defined by NHBLI BP tables and 2) two 24 hour ABPM recordings documenting abnormal nocturnal blood pressure dipping.

6.1.Initial Dose: All participants will be initiated on 25 mg of losartan at their initial monthly visit.

6.2.Randomization scheme.

This trial will use block randomization with 6 participants per block. The blocks will be put in sealed envelopes and seven blocks out of 10 possible blocks will be selected by the pharmacist. Participants assigned A will receive intensive dosing of losartan (titrate

to keep BP <75th percentile) and B will receive standard dosing of losartan (titrate to keep BP <95th percentile).

6.3. Losartan dosing

Participants will have their dose increased by the study team based on blood pressure response at monthly clinic visits to a max of 1.4mg/kg/day or 100mg/day. Dosing will be rounded to the closest 25 mg tablet. The study coordinator and PI will review the mean BP obtained by aneroid technique during the clinic visit and compared to either the 75th or 95th percentile normative data for systolic and diastolic BP by age, height, and gender. A dose can be increased for either a systolic or diastolic BP that is greater than the randomized target BP goal). Participants that miss a dose should not take an extra dose, rather the participant should resume their usual schedule. Losartan should be stored at room temperature, kept in a tightly closed container, and protected from light.

7. Safety Reporting and Adverse Events

All patients will have standard of care monthly clinic visits while on losartan. Side effects and adverse events will be recorded by study coordinator at each clinic visit. Participants will have monthly complete metabolic profiles for monitoring of potassium, liver function tests. Participants will be asked about symptoms of hypotension.

Hyperkalemia: Participants will have potassium monitored monthly. Potassium > 6 mEq/L will be repeated and if abnormal, the dose of losartan will be decreased. If participants are still >95th percentile blood pressure when hyperkalemia, a diuretic will be added as standard of care.

Liver function tests: Participants baseline AST and ALT will be recorded and compared to monthly AST and ALT levels. If AST/ALT is greater than three times the upper limit of normal, losartan will be stopped

Symptomatic hypotension: Participants will be asked about symptoms of hypotension prior to enrollment and at each visit including feeling lightheaded or dizzy. Participants will be asked to call the study PI to notify them of symptoms and take a blood pressure at home.

Allergic reaction: Participants will be asked to call the study PI if they develop swelling of the face, lips, throat, and/or tongue. Participants will be asked to describe any new rashes.

Musculoskeletal: Participants will be asked to describe any muscle pain, muscle tenderness, or dark urine.

Additional AEs will be documented based on participant interview and voluntary disclosure of additional toxicities. AEs will be scored using the Common Toxicity Criteria for Adverse Events 4.0.

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

Reporting of Events

Serious safety events will be reported to the DSMB and IRB which will make recommendations to the study PI. Unexpected SAE will be reported to the DSMB and IRB within 7 calendar days if fatal or life-threatening, and within 15 calendar days if not. All SAE will be provided to the DSMB quarterly. All AE (serious and non-serious) will be reported to the DSMB every six months.

Expected Adverse Events in Children with Sickle Cell Disease

- Acute chest syndrome
- Aplastic crisis
- Anemia
- Bacteremia
- Cholelithiasis, cholecystitis, biliary tract obstruction
- Dehydration
- Fever
- Gastroenteritis
- Headache
- Hematuria
- Hyposthenuira
- Hyperbilirubinemia
- Leukocytosis
- Nocturia
- Obstructive sleep apnea
- Osteomeylitis
- Otitis media
- Pain
- Pharyngitis
- Pneumonia
- Priapism
- Splenic sequestration
- Upper respiratory tract infections
- Urinary tract infections
- Tachycardia

Tachypnea
Thrombocytosis

Serious adverse event (SAE)
Results in death
Life-threatening (participant at risk of death at the time of the event)
Requires or prolongs hospitalization (unless an expected event).
Causes persistent or significant disability.
Results in a congenital anomaly.
Other medical events (in the opinion of the investigator) that may put the participant at risk or require intervention to prevent a serious AE.

Potential Risks

Losartan: This medication is FDA approved to treat hypertension. The FDA warnings include fetal toxicity (Pregnancy Category D) and Hypotension-Volume Depleted Patients. Female participants will have monthly pregnancy tests performed and educated to stop Losartan immediately if pregnant. Participants will be excluded if they are on a medication that leads to volume depletion (diuretics) and educated about volume depletion. Precautions for losartan include 1)hypersensitivity (Angioedema)- participants will be educated on angioedema and immediately removed for life threatening events, 2) impaired hepatic function- participants will have monthly liver function tests, 3) impaired renal function in patients whose renal function depends on the renin-angiotensin-aldosterone system (i.e. CHF), 4) electrolyte imbalance- participants will have monthly electrolyte levels.

Alternative treatments: The alternative to participation in this trial is to have usual care, with an anti-hypertensive medication.

Adequacy of protection against risks

Phlebotomy: Blood draws will be performed by trained personnel with expertise in pediatric phlebotomy and follow hospital standards for phlebotomy. All blood obtained during this trial will be collected at the same time as standard of care labs to minimize extra risk of an additional blood draw.

Urine samples: Obtaining participant urine samples will follow hospital standards for urine collection and occur in a private setting

History and physical exam: Participants will undergo a monthly history and physical by an experienced sickle cell practitioner.

Participant confidentiality: To protect confidentiality, every participant will be assigned a study identification number that is unique. The link between participant name and study ID will be kept on a locked, password protected computer that is separate from the locked, password

protected computer used to enter participant information. All study forms will be entered using the study ID number. Data will be retrieved using the study ID number.

Data Safety and Monitoring Board

We will identify investigators (at least 4 members to include a pediatric hypertension expert, sickle cell expert, patient representative, and biostatistician) to participate in an independent DSMB to monitor study safety and minimize research associated risk. Incidence of adverse events during the 6 month period will be analyzed during all mentoring meetings and independently by the DSMB. The percentage and 95% confidence intervals for serious adverse events and adverse events will be recorded and sent to DSMB every 3 months. The DSMB will evaluate excessive SAEs overall or in any one group and consider either: 1) reducing the dose of losartan or 2) closing the study and offering an alternative hypertensive medication. Patients will be withdrawn from the trial if they experience angioedema, recurrent symptomatic hypotension despite dose reduction, hyperkalemia, or recurrent symptomatic hypoglycemia.

8. ADHERENCE TO LOSARTAN

8.1. Methods for Monitoring Adherence:

Participants will complete a modified Morisky Scale of Adherence and ask open ended questions about adherence (qualitative measure of adherence). Participants will be given a pill bottle of losartan dispensed by a study pharmacist with the number of dispensed pills recorded (1-5 extra pills dispensed each month) by the study monitor (quantitative measure of adherence). Participants will return the pill bottles at each visit and the remaining pills will be counted to determine quantitative adherence to losartan. The study coordinator will place a reminder phone call to participants prior to their clinic appointment. Adherence will be defined as taking at least 80% of losartan doses (23 doses/4 weeks).

8.2 Strategies to Promote Adherence:

To evaluate the success of common strategies that promote adherence to losartan during the feasibility trial, all participants will be provided with a monthly study calendar that includes: dose/tablet number taken or missed dose, and side effects experienced that day. Participants will be asked to complete and return the calendar. Participants who do not return the calendar will be provided a stamped envelope to mail the calendar back to the study coordinator. For patients that miss >20% doses (6 missed doses/4 wks), structured qualitative interviews will be conducted to identify individual barriers to adherence.

8.3. Procedures for Missed appointments

If a participant misses an appointment, the study team will immediately contact the participant using the most recently provided telephone number. The study team will identify and record the cause for the missed appointment. The study team will attempt to reschedule the appointment

as soon as possible. All attempts to contact the participant and discussions with participant will be recorded in the patient record.

9. SAMPLE SIZE AND STATISTICAL ANALYSIS

9.1 Sample Size

An endpoint for this feasibility trial is to determine the effect size needed to appropriately power a definitive trial of losartan to correct nocturnal dipping, rather than efficacy of losartan. Data will be collected to understand the acceptance rate, rate of recruitment, and the drop-out rate. In preliminary fashion this feasibility trial will identify the difference in nocturnal BP improvement between the two treatment arms, and within group standard deviation of BP. The feasibility trial will evaluate the change in nocturnal dipping % from baseline in all participants and among participants receiving two different dosing strategies (intensive losartan therapy (BP <75th percentile) as compared to standard dosing (BP <95th percentile)). Sample size analysis for repeated measures and adjustments to sample size to compensate for non-adherence will occur.

The feasibility trial will enroll 40 participants with hypertension (clinic and ABPM). It is expected that 30% of the 200 cohort participants will meet eligibility criteria. Of these 60 cohort participants, we expect that 40 participants will enroll in the feasibility trial. We expect a dropout rate of <10% to ensure that the feasibility trial has > 30 participants, an accepted participant size for feasibility trials.

9.2. Analysis:

Objective 1: To demonstrate in a feasibility trial the optimal dose of losartan and effect size necessary to conduct a trial of losartan in participants with abnormal nocturnal dipping.

Objective 2: Demonstrate the Acceptability of and Barriers to Enrollment into a Feasibility Trial of Losartan**.**

Objective 3: Demonstrate and Promote Adherence to Study Medication during Feasibility Trial

Objective 4: Demonstrate Adherence to Study Procedures and Retention in the Clinical Trial.

Analysis for Objective 1: The feasibility trial will evaluate two dosing strategies of losartan. The DSMB will be instrumental in evaluating safety of losartan during the course of the trial. At the end of the trial, the two dosing strategies for losartan will be directly compared using student's t-test. The effect size necessary to conduct a definitive trial will be obtained through identifying the acceptance rate (objective 2), adherence/dropout rate (objective 3 and 4). The correction of abnormal nocturnal dipping will be evaluated using

continuous data. To properly power a definitive trial, this feasibility trial will document the standard deviation/variability in BP among participants, the estimated difference in nocturnal blood pressure at baseline and exit.

Analysis for Objective 2: The acceptance rate will be defined by the percent of participants enrolled divided by the number of patients approached for enrollment. The acceptability of the trial will be defined by evaluating barriers or facilitators to enrolling in this feasibility trial. Dichotomous dependent variables will be created for participants that enroll or do not enroll in the study. Independent variables will reflect (ordinal) responses provided during the survey. Bivariate relationships will be tested using chi-square or Fischer's exact tests and/or logistic regression. The mentorship team will review the identified barriers and facilitators to enrollment and develop strategies to enhance enrollment in future BP trials. For example, if mistrust is a barrier, a future strategy enrollment may include peer-delivered video testimonials.

Analysis for Objective 3. Dr. Muntner will mentor Dr. Lebensburger in the analysis of medication adherence during a clinical trial. Specifically, the adherence rates will be reviewed for each individual participant and for all participants over time to determine feasibility of losartan adherence over the six month trial. In addition, the effect of adherence interventions (calendar, phone calls) on losartan will be reviewed as well as participant reasons stated for good/poor adherence. The mentoring team will review adherence reports and work to develop an intervention plan for enhanced adherence during the planned definitive trial.

Analysis for Objective 4: To effectively design a multicenter trial, it is vital to understand the rate and barriers to trial retention and feasibility of repeated ABPM prior to conducting a SCD hypertension trial. The retention rate will be recorded and re-evaluated against the initial Likert surveys to identify variables that may suggest future drop-out. The completion of ABPM at baseline, 3 months, and 6 months will be recorded, including days to return ABPM device. Dr. Feig will mentor Dr. Lebensburger in analyzing the barriers in a hypertension trial.

10. Consent/Assent Form

The parent/legal guardian and participant will be given consent forms (and assent if participant is <14.0 yrs.) to read and sign prior to the participant's entry into the screening and randomization phases, if eligible. The consent and assent forms will be reviewed and approved by the IRB for content and general readability. The forms will provide participants and parents with an overview of the study objectives, a detailed description of all study procedures/evaluations, study medication side effects. The forms will be given to participant, participant's parent/legal guardian by an approved study team member. The forms will be signed by the participant and parent/guardian as well as study team member and witness.

11. Payment and Remuneration

The participating families will receive $25 for each 24 ABPM performed

Costs

The following will be paid for by the study: Shipping costs for ABPM and urine biomarker, ABPM analysis, urine biomarker analysis, and Losartan

12. Inclusion of Women and Minorities

The study should include a similar number of males and females, based on the sex of participants with HbSS and SB0 thalassemia seen at the Pediatric Hematology clinic. We expect that most of our participants will be of African descent, given the ethnic distribution of SCD in the United States. We will invite participants of other ethnic backgrounds to participate, if they meet the eligibility requirements for the study.

13. Inclusion of Children

We plan to enroll only children and adolescent patients with SCD ages ≥ 5 and < 23 years of age with hypertension.

CONSENT FORM

TITLE OF RESEARCH:	Chronobiology and Chronopharmacology to Prevent Sickle Cell Nephropathy
IRB PROTOCOL NO.:	IRB-141107009
INVESTIGATOR:	Jeffrey Lebensburger DO
SPONSOR:	National Institutes of Health (NIH)
SUPPORT PROVIDED BY:	American Society of Hematology (ASH)

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

Purpose of the Research

We are asking you to take part in a research study. This research study will test how well a medicine to lower blood pressure helps young adults with sickle cell disease. Losartan is a medication approved by the US Food and Drug Administration (FDA) to treat children and adults with high blood pressure. If patients with high blood pressure are not treated, they may develop health problems including heart attacks, strokes, and kidney problems. You are being asked to join this clinical trial since you have high blood pressure. We could treat you with this same blood pressure medicine not on a clinical trial. We would like you to participate in this 6 month trial so we can learn how losartan may protect your kidneys. We would also like to know the right dose of losartan for you. Finally, we would like to learn more about how sickle cell disease may hurt your kidneys or cause high blood pressure. After 6 months, we will

continue to treat your high blood pressure but will do so not on a trial. This study will enroll 60 participants from UAB.

Explanation of Procedures

We will perform one more 24 hour blood pressure test to make sure you have high blood pressure. High blood pressure means that your blood pressure is greater than 95 % of adolescents/young adults your age (95th percentile). If you have high blood pressure, we will prescribe you an approved blood pressure medicine called Losartan. The first dose will be administered in clinic to make sure no side effects occur. The usual way to treat blood pressure is to get your blood pressure lower than the 95th percentile. In other diseases, patients may do better if their blood pressure is not greater than than 75% of adolescents/young adults (75th percentile).

If you enter the study, you will be randomly picked (like the flip of a coin) to receive either strategy (lower less than the 95th percentile or 75th percentile). The major goal of this study is to determine the safest and most effective way to treat high blood pressure in patients with sickle cell disease.

When we start a blood pressure medication, we ask that you come to clinic every 4 weeks for the first 6 months to determine if the medicine is helping you or causing side effects. At each visit you will be asked if you have had any bad reactions and how you are feeling on the medicine. If your blood pressure during these clinic visits is in the normal blood pressure range, we will keep you on the same dose. If your blood pressure is still too high, we will increase your dose. We will also perform some blood and urine tests to make sure you are doing well on the medicine and how sickle cell may hurt your kidneys or cause high blood pressure. Some of these tests will be done for research and others are normal tests while on a blood pressure medication. For females, we must check if you are pregnant at each visit.

The research tests on urine and blood will help us learn if the blood pressure medication is helping your kidneys. The best way to study urine is to collect your urine overnight. We will give you a urine container to collect your urine the night before three of your visits. You will then bring your urine to clinic. We may not be able to run these tests on the urine the day that you come to clinic so we will ask your permission to store your urine and blood in a research freezer. We will only use your urine or blood to evaluate the role of high blood pressure in sickle cell disease. Finally, we would like to learn about how your body handles sodium. To do this test, we would ask you, on three different visits, to brush your cheek with a swab up to six times over 2 days.

We would also like to learn how you feel about participating in a research study. We would like to ask you to answer a few questions about what you like and don't like about this trial. If you enter this research study, we would also ask you questions each month about how often you take your medicine.

After the 6 months, the study will be over. We will continue to follow you and treat your blood pressure at regular visits.

Standard Tests while on a blood pressure Medicine

Test	Entry	1 mo	2 mo	3 mo	4 mo	5 mo	6 mo
Vital Signs, Hx and PE	X	X	X	X	X	X	X
CBC with diff	X	X	X	X	X	X	X
CMP	X	X	X	X	X	X	X
Ferritin	X			X			X
Cystatin C	X			X			X
Urine Microalbumin/Creatinine	X			X			X
Evaluate your Adherence	X	X	X	X	X	X	X
Pregancy Test	X	X	X	X	X	X	X

Research Tests if you consent

Test	Entry	1 mo	2 mo	3 mo	4 mo	5 mo	6 mo
Uric Acid from collected blood	X			X			X
Urine and blood biomarkers	X			X			X
Overnight Urine Collection	X			X			X
24 hr Blood pressure	X			X			X
Buccal Cell Collection	X			X			X
Enrollment Survey	X						

Risks and Discomforts

This blood pressure medicine (Losartan) is FDA approved to treat high blood pressure in children. You may have some side effects from taking this drug. The main side effect of Losartan is cough or a drop in blood pressure that you can feel.

Losartan may alter potassium levels in the body. We will check your potassium level monthly while on losartan. If your potassium goes up, we can lower the dose or stop the medicine. Precautions for losartan include: allergic reactions (cough or swelling), muscle cramping, dizziness, abdominal or chest pain, nausea, headache, sore throat, diarrhea, poor sleep, sinus disorders. There may also be risks that are unknown at this time. You will be given more information if other risks are found.

You will be assigned to a treatment group by chance. You will be either assigned to a group that lowers blood pressure to below the 95th percentile which may not be as effective in lowering blood pressure. However, we have not proven that a higher dose of blood pressure medicine is better in sickle cell disease. You may be assigned to the group that lowers blood

pressure to the 75th percentile. This may require a higher dose of losartan. This higher dose may cause you to have more side effects from the medicine.

Information for Women of Childbearing Potential and/or Men Capable of Fathering a Child

Losartan should not be taken if you are pregnant. We will ask you not to become pregnant for the next 6 months. We will check a pregnancy test at each visit. If you are pregnant or become pregnant, there may be risks to the fetus. This risk is highest during the 2nd or 3rd trimester. You must take a pregnancy test before the start of the study and at each visit to make sure you are not pregnant. You must agree to an effective form of birth control when taking losartan. Effective birth control includes avoiding sexual activity that could cause you to become pregnant, birth control pills, patch, IUD, condom, sponge, or diaphragm with spermicide.

Benefits

You may not benefit directly from taking part in this study. However, this study may help us better understand how to treat high blood pressure in the future.

Alternatives

There are other drugs that are used to treat high blood pressure in children. The investigator or research staff will discuss these other drugs with you.

Confidentiality

Information obtained about you for this study will be kept confidential to the extent allowed by law. However, research information that identifies you may be shared with the UAB Institutional Review Board (IRB) and others who are responsible for ensuring compliance with laws and regulations related to research, including people on behalf of the NIH, ASH, and the Office for Human Research Protections (OHRP). The information from the research may be published for scientific purposes; however, your identity will not be given out.

If any part of this study takes place at Children's of Alabama, this consent document will be placed in your file at that facility. The document will become part of your medical record chart. Information relating to this study, including your name, medical record number, date of birth and social security number, may be shared with the billing offices of Children's of Alabama and its billing agents so that the costs for clinical services can be appropriately paid for by either the study account or by the patient/patient's insurance. Monitors, auditors, the Institutional Review Board for Human Use, and regulatory authorities will be granted direct access to your original medical records for verification of trial procedures and/or data without violating confidentiality.

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

Voluntary Participation and Withdrawal

Whether or not you take part in this study is your choice. There will be no penalty if you decide not to be in the study. If you decide not to be in the study, you will not lose any benefits. You are free to withdraw from this study at any time. Your choice to leave the study will not affect your relationship with this institution.

We may remove your from this study without your consent. The study doctor may decide it is not in the best interest of your health.

Cost of Participation

There will be no additional cost to you for taking part in this study. Since you require a medicine for high blood pressure, the cost of coming to the clinic, having your blood pressure checked and labs checked will be billed to you and/or your insurance company in the usual manner. We will pay for all of the research tests. The medicine (Losartan) will be provided to you at no cost during the 6-month study period. After the 6-month study period, the study will no longer pay for losartan.

Payment for Participation in Research

You will be paid $25 for each 24 hour ambulatory blood pressure performed. You will have three of these tests performed during the study. If you complete the entire study, you will receive a total of $75 for blood pressure tests.

You will be paid $25 for each overnight urine collection performed. You will have three of these tests performed during the study. If you complete the entire study, you will receive a total of $75 for urine tests.

You will be paid $25 for each day you swab your cheeks. You will have three of these tests performed during the study. If you complete the entire study, you will receive a total of $75 for cheek swabs.

If you complete all of these tests, you will receive in total $225

Payment for Research-Related Injuries

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

Significant New Findings

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

Questions

If you have any questions, concerns, or complaints about the research or a research-related injury including available treatments, you may contact Dr. Jeffrey Lebensburger. He will be glad to answer any of your questions. Dr. Lebensburger's number is 205-638-9285.

If you have questions about your rights as a research participant, or concerns or complaints about the research, you may contact the UAB Office of the IRB (OIRB) at (205) 934-3789 or toll free at 1-855-860-3789. Regular hours for the OIRB are 8:00 a.m. to 5:00 p.m. CT, Monday through Friday. You may also call this number in the event the research staff cannot be reached or you wish to talk to someone else.

Legal Rights

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

Storage of Specimens for Future Use

In the future, we may have a better test to learn about the problems of high blood pressure in patients with sickle cell disease. As part of this study, we would like to store some extra blood and urine for future research. Dr. Lebensburger will decide if the blood or urine is used for a new test. Dr. Jeffrey Lebensburger or by an IRB approved researcher may run the test. The urine and blood will be stored in a research freezer using a study ID. Only Dr. Lebensburger will be able to identify you from this study ID. Results of future research may not be given to you. You do not have to agree to allow your blood and urine specimens to be stored in order to be part of this study.

At any time, you can have your blood or urine removed from storage. Please contact Dr. Jeffrey Lebensburger at the University of Alabama at Birmingham at 205-638-9285. Once you contact Dr.

Lebensburger, and if your samples have not already been used, they will be destroyed. If you do not make such a request, your specimens will be stored until used.

Initial your choice below:

___ I agree to allow my samples to be kept and used for future research high blood pressure and kidney disease in sickle cell.

___ I do not agree to allow my samples to be kept and used for future research.

Signatures

You are making a decision whether or not to have your child participate in this study. Your signature indicates that you have read (or been read) the information provided above and decided to allow your child to participate.

You will receive a copy of this signed consent form.

_____

Signature of Participant (14 years of age and older) Date

_____

Signature of Parent or Legally Authorized Representative (for participants less than 14) Date

_____

Signature of Person Obtaining Consent Date

Waiver of Assent

The assent of _____ (name of child/minor) was waived because of:

Age _____ Maturity _____ Psychological state of the child _____

University of Alabama at Birmingham
AUTHORIZATION FOR USE/DISCLOSURE OF

PROTECTED HEALTH INFORMATION (PHI) FOR RESEARCH

Participant Name: _____
Research Protocol: Chronobiology and Chronopharmacology to Prevent Sickle Cell Kidney Disease

UAB IRB Protocol Number: IRB-141107009
Principal Investigator: Jeffrey D. Lebensburger, D.O.
Sponsor: The National Institutes of Health (NIH)/ American Society of Hematology (ASH)

What is the purpose of this form? You are being asked to sign this form so that UAB may use and release your protected health information for research. Participation in research is voluntary. If you choose to participate in the research, you must sign this form so that your protected health information may be used for the research.

Why do the researchers want my protected health information? The researchers want to use your protected health information as part of the research protocol listed above and as described to you in the informed consent.

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

Who will disclose, use and/or receive my protected health information? All Individuals/entities listed in the informed consent documents, including but not limited to, the physicians, nurses and staff and others performing services related to the research (whether at UAB or elsewhere); other operating units of UAB, HSF, UAB Highlands, Children's of Alabama, Eye Foundation Hospital, and the Jefferson County Department of Health, as necessary for their operations; the IRB and its staff; the sponsor of the research and its employees and agents, including any CRO; and any outside regulatory agencies, such as the Food and Drug Administration, providing oversight or performing other legal and/or regulatory functions for which access to participant information is required.

How will my protected health information be protected once it is given to others? Your protected health information that is given to the study sponsor will remain private to the extent possible, even though the study sponsor is not required to follow the federal privacy laws. However, once your information is given to other

organizations that are not required to follow federal privacy laws, we cannot assure that the information will remain protected.

How long will this Authorization last? Your authorization for the uses and disclosures described in this Authorization does not have an expiration date.

Can I cancel this Authorization? You may cancel this Authorization at any time by notifying the Principal Investigator, in writing, referencing the research protocol and IRB Protocol Number. If you cancel this Authorization, the study doctor and staff will not use any new health information for research. However, researchers may continue to use the protected health information that was provided before you cancelled your authorization.

Can I see my protected health information? You have a right to request to see your protected health information. However, to ensure the scientific integrity of the research, you will not be able to review the research information until after the research protocol has been completed.

Signature of participant: _____ Date: _____

or participant's legally authorized representative: _____ Date: _____

Printed Name of participant's representative: _____

Relationship to the participant: _____

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ADHERENCE QUESTIONNAIRE

1. Do you sometimes forget to take losartan?	□Yes □No
2. People sometimes miss taking their medication for reasons other than forgetting. Thinking over the past two weeks, were there any days when you did not give your child his/her losartan?	□Yes □No
3. Have you ever cut back or stopped giving your losartan without telling your doctor because you felt worse	□Yes □No
4. When you travel or leave home, do you sometimes forget to bring along your losartan?	□Yes □No
5. Did you take your losartan yesterday?	□Yes □No
6. When you feel like your blood pressure is under control, do you sometimes stop taking losartan?	□Yes □No
7. Taking a medicine every day is a real inconvenience for some people. Do you ever feel hassled about sticking to your blood pressure treatment plan?	□Yes □No
8. How often do you have difficulty remembering to take all of your medicine?	□Never/Rarely □Once in a while □Sometime □Usually □All the time
9. How many doses have you missed since the last visit?	_____

ENROLLMENT SURVEY

I/My child will enroll in this clinical trial	□Yes □No
You may have reasons to enroll or not enroll in this trial Please read the next 5 sentences and circle how much you agree with each reason	
I want to help doctors learn how to treat MY (my child's) blood pressure	Strongly Agree Agree Neutral Disagree Strongly Disagree
I want to help doctors learn how to treat blood pressure for ALL children with sickle cell disease	Strongly Agree Agree Neutral Disagree Strongly Disagree
I want to make sure my (my child's) blood pressure is closely monitored	Strongly Agree Agree Neutral Disagree Strongly Disagree
I want to make sure my (my child's) blood pressure improves at night	Strongly Agree Agree Neutral Disagree Strongly Disagree
I want to prevent future problems with my (my child's) kidneys	Strongly Agree Agree Neutral Disagree Strongly Disagree
You may have reasons not enroll in this trial Please read the next 5 sentences and circle how much you agree with each reason	
I do not want (my child) to be in a clinical trial	Strongly Agree Agree Neutral Disagree Strongly Disagree
I do not want (my child) to take a blood pressure medicine	Strongly Agree Agree Neutral Disagree Strongly Disagree
I do not want (my child) to take this medicine (losartan)	Strongly Agree Agree Neutral Disagree Strongly Disagree
I do not have the time to come to clinic each month	Strongly Agree Agree Neutral Disagree Strongly Disagree
I do not want (my child) to do the blood pressure cuff three more times	Strongly Agree Agree Neutral Disagree Strongly Disagree