Montelukast Trial in Sickle Cell Anemia

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Background and Significance

SCD is an autosomal recessive disorder that affects one of every 400 African-American newborns in the United States[1]. The basis for SCD is a point mutation in the sixth codon of the β-globin gene. Under hypoxic conditions, the resulting hemoglobin S polymerizes inducing rigid, dense and deformed erythrocytes. In a multi-cellular process, sickle erythrocytes interact with non-sickle erythrocytes, leukocytes, platelets and endothelial cells causing recurrent microvascular occlusion, tissue ischemia and ultimately end-organ damage. Chronic vasculopathy is complicated by acute vaso-occlusive episodes, which are the pathogenic basis for the two most common morbidities in SCD, pain[2] and acute chest syndrome (ACS)[3] episodes. Hydroxyurea is the only FDA-approved drug for preventing vaso-occlusive episodes and has become standard medical care for most adolescents and adults with SCD.

The largest study examining the relationship between pain, ACS and asthma was performed in a cohort of 291 children identified from the Cooperative Study of Sickle Cell Disease (CSSCD)[4]. Of these children, 49 (16.8%) had a diagnosis of asthma noted in the record. Children with asthma had twice as many episodes of pain (1.39 episodes per patient-year versus 0.47 episodes per patient-year, $p<0.001$) and twice as many episodes of ACS (0.39 v. 0.20 events per patient-year, $p<0.001$) when compared to children without asthma.

In a separate study of 1,963 children and adults with SCD enrolled in the CSSCD, those with asthma and SCD died at younger ages when compared to individuals with SCD without asthma. The median survival for individuals with asthma was 52.5 years in comparison to 64.3 years in individuals without asthma. After controlling for previously identified risk factors for death[5], individuals with asthma had a more than 2-fold increase in risk of death (Hazard Ratio: 2.36 by Cox regression, 95% CI 1.21 to 4.62, $p=0.01$). Taken together, these data indicate that asthma is a significant cause of acute vaso-occlusive episodes and premature mortality. Since asthma worsens the course of SCD, examining mechanisms that are important to asthma pathogenesis may provide therapeutic targets for individuals with SCD.

Inhibition of the leukotriene pathway is an effective strategy for prevention of asthma symptoms, another pro-inflammatory disease. Leukotrienes are a family of lipid mediators that cause bronchoconstriction and are involved in inflammatory responses. Two types of leukotrienes exist: 1) CysLTs – leukotrienes C_4 (LTC_4), D_4 (LTD_4), and E_4 (LTE_4),-that are peptide-conjugated lipids and prominent products of activated eosinophils, basophils, mast cells and macrophages and 2) leukotriene B_4 (LTB_4), a leukocyte chemoattractant and activator. CysLTs bind to receptors on vascular endothelial cells and bronchial smooth muscle. In the vasculature, CysLTs mediate vasoconstriction [6], upregulation of cell adhesion molecules[7] and increased vascular permeability[8]. In the airway, CysLTs promote bronchoconstriction, airway remodeling, increased mucous production and smooth muscle proliferation [8-10].

Levels of CysLTs correlate with asthma severity[11], asthma exacerbations[12], allergen challenge [13,14] and exercise-induced bronchoconstriction[15].

LTB_4 is a 5-lipoxygenase metabolite of arachidonic acid in neutrophils that acts as a chemoattractant and enhances neutrophil adhesion to endothelium. In a cross-sectional study, Setty et al. assessed plasma levels of this metabolite in controls (n = 9) and in individuals with SCD both in basal "steady state" (n = 37) and during episodes of pain (n = 10) and ACS (n = 5)[16]. LTB_4 levels were markedly increased in patients with SCD in basal steady state (P <.003) compared with those in controls. Levels were further increased during pain (P <.04) and ACS (P <.0001) episodes. Taken together, these data suggest that the study of leukotriene pathogenesis and perhaps leukotriene receptor inhibition may dampen the anti-inflammatory state and lessen the impact of the co-morbid conditions associated with SCD.

Inhibition of leukotriene activity is an anti-inflammatory target for asthma. Therapeutic benefit of the leukotriene receptor antagonist montelukast is well documented. Montelukast is associated with an increased exercise-induced bronchoprotection[17], reduced asthma exacerbations[18] and has no evidence of tolerance with prolonged use[19]. Further, montelukast has been well tolerated with relatively few reported toxicities[20]. In contrast, the 5-lipooxygenase inhibitor, zileuton, has been associated with hepatotoxicity, limiting the utility of this drug[21].

Inhibiting the leukotriene pathway may attenuate vaso-occlusion by two potential mechanisms. First, blocking the actions of leukotrienes may decrease vascular inflammation by decreasing leukocyte migration and the expression of cell adhesion molecules on vascular endothelium. Second, inhibiting CysLTs may improve airway mechanics leading to better oxygen delivery to the microvasculature. Importantly, reducing vascular inflammation and improving airway mechanics are not mutually exclusive mechanisms and, if we show a benefit to montelukast therapy, both may contribute to clinical improvement.

2. Study Objectives

2.1 Primary Objective: To determine whether montelukast versus placebo added to hydroxyurea will improve markers of vaso-occlusion/tissue injury in adolescents and adults with SCD.

2.2 Secondary Objectives:

1) To determine if montelukast versus placebo added to hydroxyurea will improve lung function in adolescents and adults with SCD.

2) To determine if montelukast versus placebo added to hydroxyurea will improve blood flow in adolescents and adults with SCD.

3. Study Population

3.1 Enrollment Inclusion Criteria:

1) Diagnosis of HbSS, or HbSβ-thalassemia^0, confirmed by hemoglobin analysis
2) Males and females age 16 years to 70 years old
3) Greater than 2 episodes of pain in the last 12 months
4) On a stable dose of hydroxyurea for at least 2 months and a stable hemoglobin

3.2 Enrollment Exclusion Criteria:

1) Judged not likely to be study compliant by his/her hematologist
2) History of adverse reaction to montelukast or any of the components of montelukast
3) Have used medications known to interact with montelukast such as rifampin, phenobarbital, and gemfibrozil within 4 weeks of enrollment
4) Currently being treated with a leukotriene antagonist (montelukast or zileuton) or have used montelukast/zileuton within the last 60 days
5) Chronic blood transfusion therapy defined as regularly scheduled transfusions.
6) Hemoglobin A greater than15% on hemoglobin analysis
7) Individuals with a current physician diagnosis of asthma (within last 12 months) or requires continuous supplemental oxygen, or predicted or current use of asthma medications (inhaled corticosteroids, but participants taking bronchodilators will be allowed to participate).
8) Current participation in another therapeutic trial for SCD
9) Known current pregnancy
10) Known history of HIV
11) Serum creatinine greater than 3 times the site's upper limit of normal

4. Trial Enrollment

4.1 Selection of Subjects

Subjects will be recruited in Nashville and Milwaukee. The newly created Vanderbilt - Meharry Center for Excellence for SCD, currently follows about 50 pediatric patients between 16 to 21 years of age and 150 adult patients between 21 to 70 years of age. The Center Director, M. DeBaun, also has a collaborative relationship with Tennessee Oncology, and they actively follow 180 adults with SCD in the Middle Tennessee region and have agreed to refer patients for participation in this feasibility trial. The Froedtert Hospital Adult Sickle Cell Clinic in Milwaukee currently serves approximately 75 children (≥

16 years) and 200 adults with HbSS/HbSβ-thalassemia^0 between 21 to 70 years of age.

Clinical manifestations of sickle cell disease change with the age of the patient and as a result the subject's age is taken into consideration for study participation. In regards to painful vaso-occlusive crises, the incidence rate increases with age and contributing factors to vaso-occlusive crises may be different at age extremes. We chose to exclude very young and older patients with SCD from our study to reduce the potential confounding effects of age.

Currently there are few other trials available to this patient population and many of these individuals are currently on hydroxyurea. In our experience >50% of adult patients with HbSS/HbS β-thalassemia^0 will have ≥ 3 pain episodes per year (including those that did not result in healthcare utilization). We recognize that this is a higher rate of pain than has been previously reported in the literature, however, the clinic populations in the academic medical centers at Nashville and Milwaukee provide care for individuals with more severe disease compared to community-based centers. For this phase II study, we conservatively estimate the dropout rate at 20%. However, we will use an intent-to-treat analysis and so have 50 for the primary outcome, but 63 for all analyses. Additionally, we will conservatively estimate that four patients will need to be approached for each one that participates (4:1 ratio). Therefore, we will plan to screen 252 eligible patients and consent 63 individuals in order to accrue 50 study subjects. Based on data from Washington University in St. Louis, 35% of adults with HbSS/Sβ-thalassemia^0 were prescribed hydroxyurea. Assuming similar rates of hydroxyurea administration in Milwaukee and Nashville and that all adults prescribed hydroxyurea will have >2 pain episodes per year, approximately 271 adolescents and adults with SCD will be available for screening. Decreasing the entry criteria to ≥ 2 pain episodes per year will further increase the number of potentially eligible patients. Randomization will occur after the 2 week lead-in period. Randomization will be done using the software BREEZE and will occur in blocks of 10 to allow for any potential seasonal differences. Individuals who complete 70% of diary days in the lead-in period will be eligible for randomization. Patients will be recruited in clinic with direct contact by the study physicians and/or study personnel. Patients may also be contacted with a phone call prior to scheduled visits to inform them of the study.

Definitions

Baseline: The subject is well, reporting no more than baseline pain and at least 30 days from a hospitalization or emergency department visit for any reason.

Pain: An episode of acute pain with no cause other than a vaso-occlusive event lasting at least 24 hours that requires the administration of oral or parenteral opioids in a medical facility or by the patient[25].

4.2 Study Design

For this double blind placebo controlled phase II trial a total of 63 subjects will be recruited from the Sickle Cell Clinics at two national sites; Vanderbilt University in Nashville, Tennessee and Froedtert Hospital in Milwaukee. A 20% subject dropout rate is expected therefore it is anticipated approximately 50 subjects will complete the study.

We are investigating montelukast as an adjuvant therapy with hydroxyurea. Individuals with asthma will be excluded from this study because the benefit of montelukast for the treatment of asthma is well established[22-24]. Although the best therapy for individuals with SCD and asthma is not known, the present study is designed to evaluate the effect of montelukast on chronic vasculopathy and not on asthma-related morbidity.

Study subjects will be randomized to receive either:

- Oral montelukast therapy taken daily for eight weeks with current hydroxyurea regiment

OR

- Oral placebo taken daily for eight weeks with current hydroxyurea regiment

After informed consent is obtained, subjects will begin the study activities. Subjects, family members, health personnel, study investigators and team members will be blinded to treatment allocation. The study pharmacy/pharmacy staff will be unblinded to treatment allocation. The DSMB with be unblended at the time of DSMB reporting by the biostatistician. Unblinding would only occur in cases of adverse events where unblinding is essential for subject safety and will be at the discretion of the principal investigator or DSMB. Subjects whose treatment is unblinded would be taken off study drug and would be discontinued from the study.

5. Intervention

5.1 Study Drug Formulation

Montelukast 10 mg and matching placebo capsules will be supplied by the Vanderbilt University Medical Center Investigational Drug Service Pharmacy. Please see appendix 3.

5.1.1 Packaging

Montelukast and placebo will be supplied by Froedtert Hospital Investigational Drug Service for the Froedtert Hospital Adult Sickle Cell Clinic. The Vanderbilt-Meharry Center for Excellence in Sickle Cell Disease will be supplied by Vanderbilt University Medical Center Investigational Drug Service Pharmacy. Each bottle will contain 30 tablets of montelukast 10 mg capsules or placebo.

5.1.2 Storage

Store montelukast and placebo at room temperature, 25˚C (77˚F). Excursions permitted to 15-30˚C (59-86˚F). Subjects will be instructed to keep the medication in the original container, tightly closed, and out of the reach of children.

5.1.3 Administration

Montelukast 10 mg or placebo will be taken once daily at approximately the same time every day, with or without food. Subjects will continue to take montelukast or placebo daily for 8 weeks. Each subject will receive 2 bottles of montelukast or placebo. One bottle dispensed on day 0 and one bottle dispensed at week 4. Hospitalizations for pain or ACS are expected outcomes in SCD trial. Montelukast/Placebo will not be stopped for hospitalizations unless a causal relationship is suspected by the PI. If the subject is hospitalized or records an acute pain episode within two weeks of completion of study drug the final lab measurements will be delayed for an additional four weeks and subject will continue to take the study drug for the additional two weeks.

5.1.4 Compliance Monitoring

The study coordinator will inventory the subject's usage of montelukast or placebo during study visits at weeks 4, 7 and 8. The study coordinator will attempt to contact the subject by phone daily Monday through Friday to remind and encourage subjects to take study drug and complete the diary.

5.1.5 Drug Accountability and Ordering

Drug accountability logs will be maintained for all study drugs. At a minimum, these logs must contain quantity of drug received and dispensed, date received and dispensed, subject number, expiration date, dose, quantity returned, balance forward, and initials of individual dispensing the study drug. Used medication vials can be discarded according to institutional standards.

Fax completed order form to Froedtert Hospital Investigational Drug Service, [redacted] for the Froedtert Hospital Adult Sickle Cell Clinic. Contact the Vanderbilt University Medical Center Investigational Drug Service Pharmacy at [redacted] for the Vanderbilt-Meharry Center for Excellence in Sickle Cell Disease. Allow 5 business days for shipment.

5.1.6 Prohibited Concomitant Medications

Concomitant use of rifampin, phenobarbital, or gemfibrozil should be avoided during the study.

The use of a leukotriene inhibitor or any other investigational agent is prohibited during the treatment period of this study.

At each clinic visit after screening, the investigator will ask the patient whether any medications (other than study drug), including over-the-counter medications, were taken since the previous visit.

5.2 Montelukast Diary

The research coordinator will pre-fill the subject's opioid medications and medication amounts into the diary.

Study subjects will be asked to complete the following daily:

- List the date and day of the week
- Rate their maximum daily pain score on a scale of 0-9 (0 is no pain and 9 is greatest pain)
- Complete the questions on how pain has affected their general activity
- Record daily opioid use

5.3 Pulmonary Function Test

Spirometry, diffusion capacity of carbon monoxide (DLCO), and lung volumes will be tested with according to American Thoracic Society criteria[26,27]. We will also obtain pre- and post-bronchodilator measurements (Albuterol, 4 puffs from a metered dose inhaler administered by an aerochamber). A calibrated spirometer will be used. While seated, the subject will be encouraged to perform between 5 and 8 maneuvers to obtain 3 acceptable tracings. Up to five maneuvers will be repeated after inhalation of an Albuterol inhaler. The adequacy of the blows will be judged using the following Epidemiologic

Standardization Criteria: a minimum duration of 6 seconds, back extrapolated volume < 5%, FVC within 5% or 200cc (whichever is less), and assessment by the technician as to the adequacy of the effort. For lung volumes, patients will be tested with body plethysmography. To ensure American Thoracic Society criteria are met across the two participating sites for spirometry, test results will be over-read by a single pulmonologist.

5.4 Blood Measurements

Blood samples for inflammatory markers will be collected at the following study time points:

- Pre-randomization
- Randomization
- Week 4
- Week 8

Whole blood samples will be collected in a 5mL light blue top citrate tube. Samples will be centrifuged at 1500 *g* for 15 minutes. Plasma will be aliquoted into four eppendorf tubes (about 600μL each) and immediately frozen at –80°C as per a routine coagulation reference sample. Samples will be batched and stored frozen at -80°C until shipped. Samples will be shipped on dry ice overnight by Fed-X to the laboratory of Dr. Nancy Wandersee, Sickle Cell Disease Laboratory, [redacted] Milwaukee, Wisconsin, 53226 for testing.

IL-1β, IL-6, TNFα and IFN-γ will be measured with the human-specific Bio-Plex cytokine assay kit. To determine plasma levels of the human-specific soluble VCAM-1, soluble E-selectin, and soluble P-selectin, ELISA kits DVC00, BBE2B, and BBE6, will be used respectively,

5.5 Urine Analysis

A urine specimen will be collected at the following study time point:

- Pre-randomization
- Randomization
- Week 8

Subject will provide a clean catch urine sample by standard methods of urine collection that are non-invasive and do not require catheterization. A maximum of 4 ml of urine will be saved and processed within 2 hours of collection. Urine will be centrifuged to remove particulates. Urine specimen

will be aliquoted and frozen at -80°C. Samples will be batched and stored frozen at -80°C until shipped. Samples will be shipped on dry ice overnight by Fed-X to the laboratory of Dr. Nancy Wandersee, Sickle Cell Disease Laboratory, [redacted] Milwaukee, Wisconsin, 53226for testing.

Urine leukotriene E_4 levels will be quantified by liquid chromatography-mass spectrometry. Samples will be analyzed by using LC-ESI-MS (Agilent 1100 LC/MSD, SL model). For quantitative measurements, the *m/z* = 440 will be used for LTE_4 and the m/z = 445 is used for $[^2H_5]$-LTE_4 (the internal standard, at retention time of 13.38 min), respectively. The detection limit is 5 pg of LTE_4. The standard curves will be constructed over the range of 5 pg to 2500 pg of LTE_4 per injection. The concentrations of LTE_4 in the samples will be calculated by comparing the ratios of peak areas LTE_4:$[^2H_5]$-LTE_4 to the standard curves.

5.6 Six-Minute Walk

The six-minute walk test will be performed in accordance with a modified version of the American Thoracic Society Six-Minute Walk Guidelines as listed in Appendix One. Subjects will be asked to walk at a brisk pace for 6 minutes along a marked 30 meter path. Subjects will be asked to assess their fatigue level and shortness of breath using the Borg scale in Appendix Two prior to the 6 minute-walk and immediately after completion of the 6 minute-walk.

5.7 Unblinding

Investigators will remain blind to treatment assignment until the entire study is complete. Only research pharmacist (and designated pharmacy staff) at each study site, the DSMB and the designated study statistician at Medical College of Wisconsin should be aware of the treatment that is assigned to each subject. However, concerns regarding serious toxicity or safety may arise, prompting unblinding to become necessary.

If an investigator at a participating institution deems it necessary to unblind, it must be submitted in writing to the Principal Investigator, Michael DeBaun, MD, MPH with the reason. Requests for unblinding should also be submitted to the Study Coordinator. If the PI agrees, the request will be forwarded to the study statistician by e-mail. The treatment assignment is then relayed to the Study Coordinator who communicates with the site. It will be the responsibility of each institution to withdraw the participant from the study and complete a Date Off Treatment/Off Study Form with the date the patient is unblinded as the date off-treatment.

If a participant needs to be unblinded for urgent clinical care, the investigator or the site monitor physician at the participating institution may withdraw the participant from the study and the PI can find out the participant's treatment assignment from the respective pharmacy. The investigator must notify the Principal Investigator, Michael DeBaun, MD, MPH, in writing within one week of the unblinding and withdrawal of the subject from the study.

5.8 Discontinuation Criteria

Subjects may be removed from the study, or treatment stopped by the Investigator for any of the following reasons:

1. Occurrence of CTCAE Criteria of grade 3 or higher that are deemed attributable to the drug per the opinion of the PI.
2. . Subject makes the decision to withdraw.
3. . PI decides to withdraw the subject due to noncompliance.
4. Withdrawal by the PI or subject because of treatment side effects or complications.
5. The subject's study treatment is unblinded.

6. Study Procedures

6.1 Pre-randomization (two weeks prior to randomization, plus or minus 3 days)

- Collection of subject's demographics
- Subject is instructed on how to complete Montelukast diary and is given written directions for diary. Instruct subject to bring diary to all clinic visits
- Education for Montelukast diary reviewed
- Montelukast diary pain section completed daily by subject with first entry completed in clinic with study staff
- Urine pregnancy test will be performed on women of child bearing age
- CBC with differential that include:
  - ✓ White blood cell count
  - ✓ Hemoglobin
  - ✓ Hematocrit
  - ✓ Mean corpuscular volume (MCV)
  - ✓ Platelet count

- ✓ Eosinophil count
- Blood Chemistry
  - ✓ Creatinine
- Laboratory blood measures that include:
  - ✓ Reticulocyte count
  - ✓ Lactate dehydrogenase (LDH)
- Lab Sample for the following inflammatory mediators sent to Dr. Wandersee's Lab:
  - ✓ sVCAM-1
  - ✓ sP-selectin
  - ✓ IL-1β, IL-6
  - ✓ TNFα
  - ✓ IFN-γ
- Urine specimen collected for send out analysis of LTE_4
- Study staff determines eligibility status by completing Eligibility Study form
- If eligible subject is randomized by:
  - ✓ Study staff sends eligibility form to pharmacy with assigned unique study ID number
  - ✓ Pharmacy will be supplied with study drug kits for both treatment arms and will assign study drug kit to subject
  - ✓ Pharmacist will be unblinded to study treatment assignment Pharmacist will confirm randomization by returning signed Eligibility form to study staff to confirm randomization

6.1.1 Randomization Criteria

After the consent is signed study subjects will record a daily pain score, and daily opioid use, in the Montelukast diary during the pre-randomization period. If the subject completes 70% of the Montelukast diary entries during the pre-randomization period and also meets study eligibility criteria then the subject will be considered eligible for randomization.

6.1.2 Hospitalization during Pre-randomization

If the subject is hospitalized for a pain crisis prior to randomization then study participation is discontinued. Two weeks after the pain crisis resolves subjects may be re-screened and restart the study if eligibility criteria are met. If greater than 30 days has passed since the date the consent was signed the individual will be re-consented.

6.2 Randomization and Procedures (Day 0)

- Montelukast diary reviewed by study staff for compliance in order to determine if eligible to be randomized

After confirmation of randomization the following procedures will be performed:

- Urine pregnancy test will be performed on all women of child bearing age
- Physical examination
- Collection of medical history
- Montelukast questionnaire completed
- Concomitant medications reviewed by study staff
- All laboratory blood measurements including inflammatory mediators for Pre-randomization are repeated
- Urine specimen collected for send out analysis of LTE_4
- Pulmonary function test
- Six minute walk
- 4 week supply of montelukast or placebo dispensed to subject
- Subject takes and records first dose of montelukast or placebo, records daily pain score, opioid usage, in Montelukast Diary in clinic to demonstrate understanding of diary usage
- The first dose of montelukast or placebo is to be taken one hour (but no longer than 90 minutes) prior to the pulmonary function test
- Subject instructed to bring diary and study drug to each visit

6.3 Week 4 (post day of randomization plus or minus 3 days)

- Study staff monitors Montelukast diary and inventories study drug for compliance
- Assessment for toxicities by physician/ nurse practitioner
- Physical examination
- Collection of medical history
- All laboratory blood measurements including inflammatory mediators for pre-randomization are repeated (see pre-randomization)
- Urine pregnancy test will be performed on all women of child bearing age
- Concomitant medications reviewed by study staff
- 4 week supply of montelukast/placebo dispensed to subject
- Subject continues recording daily pain, opioid usage, and records receipt of study medication in Montelukast Diary

6.4 Week 7 (post day of randomization plus or minus 3 days)

- Study Staff monitors Montelukast diary and inventories study drug for compliance

- Subject continues recording daily pain, opioid usage, and records receipt of study medication in Montelukast Diary
- Concomitant medications reviewed by study staff
- Collection of medical history

6.5 End of Active Study Visit Week 8 (post day of randomization plus or minus 3 days)

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- Study coordinator collects Montelukast diary and study drug container from subject
- Assessment for study toxicities
- Physical examination
- Collection of medical history
- All laboratory blood measurements including inflammatory mediators for pre-randomization are repeated (see pre-randomization)
- Urine pregnancy test will be performed on all women of child bearing age
- Pulmonary function test
- Six minute walk
- Urine specimen collected for send out analysis of LTE_4

6.6 Post-study Follow up Period (weeks 9-12 plus or minus 3 days)

- Subjects will be contacted by phone weekly (plus or minus 3 days) for 4 weeks following the conclusion of montelukast or placebo therapy to assess for any potential toxicities related to study drug

6.7 Hospitalizations during active drug treatment

In the event that a subject is hospitalized for a sickle cell pain crisis prior to the end of the 8-week treatment period, the study endpoint will be extended for 2 additional weeks, post-inpatient discharge, during which time the study subject will continue to take montelukast/placebo. In this case, all aforementioned tests to be performed at weeks 7 and 8 will be rescheduled to weeks 9 and 10, respectively.

7. Subject Remuneration

For their time and efforts in study activities, research subjects will receive $50 for each of the following patient visits:

- Pre-randomization
- Day of randomization visit

- Study week 4 visit
- Study week 7 visit
- End of active study week 8 visit

A total of $250.00 will be paid to subjects completing all study visits.

7.1 Potential benefits to subjects

There may be no direct benefit to subjects for taking part in the study; however, it may benefit others with SCD. Novel therapies for the prevention of pain episodes in adults with SCD are desperately needed. Hydroxyurea therapy was a major advance for the treatment of SCD-related morbidity; however, many adults continue to suffer repeated episodes of pain despite hydroxyurea therapy. Abundant pre-clinical and clinical data suggests that CysLT contribute to the pathogenesis of painful episodes and preliminary data suggesting that montelukast may be an effective preventative therapy. This phase II trial may lead to a larger, multi-center, phase III trial if montelukast has some efficacy for improving markers of vaso-occlusion.

Table 1. Study Schedule of Procedures

Procedure	Pre-Rand./ Week -2	Randomization (Day 0)	Daily	Week 4	Week 7†	Week 8†
Montelukast Diary	X	X	X	X	X	X
Urine pregnancy test will be performed on women of child bearing age	X	X		X		X
Six Minute Walk		X				X
Physical Examination		X		X		X
Documentation-medical history, medications, transfusions, & clinical data		X		X	X	X
Montelukast Questionnaire		X				
Blood draw- routine labs,* blood chemistry & inflammatory mediators**	X	X		X		X
Urine analysis of LTE_4	X	X				X
Pulmonary Function Test		X				X
Coordinator calls subject & records (Mon-Fri) administration of study drug		X††	X	X	X	X
Subject records opioid use in montelukast diary		X	X			
Coordinator inventories drug usage and monitors diary compliance		X		X	X	X
Montelukast/Placebo dispensed to subject		X		X		

*CBC, Reticulocyte count, eosinophil count, LDH

** sVCAM-1, sP-selectin, IL-1β, IL-6, TNFα and IFN-γ

† delayed by 2 weeks, post-discharge, if hospitalized for sickle cell pain crisis

†† **First montelukast/placebo dose to be taken and recorded in clinic**

Follow-up procedures Subjects will be contacted by phone weekly (plus or minus 3 days) for 4 weeks following the conclusion of montelukast or placebo therapy to assess for potential toxicities

8. Human Subjects Protection

8.1 Informed Consent:

Subjects are required to sign an informed consent prior to screening, and before undergoing any study procedures or assessments, in accordance with ICH E6; 4.8, "Informed Consent of Trial Subjects." When substantial modifications are made to the informed consent, the IRB may require that all subjects currently enrolled in the study will be re-consented; ICH E6; 4.8 guidelines would still apply.

Subjects will be provided with a copy of the signed informed consent form used in the study, procedures, and assessments. Subjects will also be provided with the contact telephone numbers of the investigator and qualified personnel who can assist with their questions and concerns.

8.2 Protected Health Information

Protected health information that will be collected as part of this study includes name, date of birth and dates for hospitalization. This information will be stored for 10 years beyond the completion of the study. After blood is used for study testing it will be discarded.

8.3 Confidentiality

Loss of confidentiality is always a potential risk when collecting protected health information. Research records will remain confidential. Subject's records will be available to the study staff and to each site's IRB and for audit purposes. Only authorized personnel will have access to the protected health information and research records. In order that confidentiality can be maintained, the PI/study staff will keep records in locked cabinets/room and results of tests will be coded to prevent association with volunteers' names. All electronic data will be entered into a secured, website data management system that requires training and is password protested. Identifying information will not be included on laboratory samples, faxes, or correspondence. Laboratory samples will be shipped with only unique study numbers that will be linked to a key kept by the site PI.

All study team members are trained in HIPAA privacy regulations and other applicable site privacy policies. No information will be released, nor will participation in the research be acknowledged, to any party except where compulsory according to law or intuitional policy. The results of the research

study may be published, but volunteers' names or identities will not be revealed.

9. Adverse Event Monitoring

9.1 Definitions

Adverse Event (AE) **–** Any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in research, whether or not considered related to the subject's participation in research. Pain episodes documented in the diary will not be reported as adverse events.

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

- Results in death;
- Is life-threatening (places subject at immediate risk of death from the event as it occurs);
- Requires inpatient hospitalization;
- Results in a persistent significant/incapacity;
- Results in a congenital anomaly/birth defect; or
- Any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent on the other outcomes listed in this definition

Note that seriousness and severity are separate concepts. The term "severe" refers to the intensity of a specific event; a severe event may be of minor medical significance (e.g., a severe leg cramp). The term "serious" is based on an outcome or action criteria that are usually associated with events that pose a threat to the patient's life or functioning. An event that is mild in severity is serious if it leads to one of the outcomes defined above.

Grade 4 and 5 events will always be considered Serious Adverse Events. Many Grade 3 and some Grade 1 and 2 events may meet the definition of a Serious Adverse Event.

Unexpected Adverse Event- Any adverse event occurring in one or more subjects in a research protocol, the nature, the severity, or frequency of which is not consistent with either:

- The known of foreseeable risk of adverse events associated with the procedures involved in the research that are described in;

- the protocol related documents or the current IRB-approved informed consent document and;
- other relevant sources of information, such as a product labeling or package insert or;

- The expected natural progression of any underlying disease, disorder, or condition of the subject(s) experiencing the adverse event and the subject's predisposing risk factor profile for the adverse event.

Unanticipated problem involving risks to subjects or others (UP) - Any incident, experience or outcome that meets all the following criteria:

- Unexpected (in terms of nature, severity, or frequency) given:
  - The research procedures that are described in the protocol related-documents, such the IRB-approved research protocol and the informed consent form document and,
  - The characteristics of the subject population being studied;
- Related or possible related to the subject participation in research; and
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) related to the research than was previously known or recognized.

Grading of Adverse Events – Events will be graded by using the Common Terminology Criteria for Adverse Events (CTCAE) Criteria version 4.0.

Attribution – the determination and documentation of whether an adverse event is related to a medical procedure.

Attribution Categories:

1. Not Related –Event clearly related to other factors (e.g., clinical state, other therapies; concomitant drugs)
2. Possible Related – Sequence of event is compatible with study drug, device, or procedure, but could have been produced by other factors
3. Probably Related - Sequence of event is compatible with study drug, or procedure and cannot be explained by other factors without much doubt
4. Definitely Related - Sequence of event is compatible with study drug, or procedure and beyond doubt cannot be explained by other factors

9.2 Study Staff

Information on all adverse events, whether reported by the subject, directly observed, or detected by physical examination, laboratory test or other means, will be collected, recorded, followed, and reported as described in the following sections.

The PI will monitor and review adverse events monthly or more often as needed.

9.3 Timeline for Reporting of Adverse events, Serious Adverse Events, Unexpected Adverse Events and Unanticipated Problems

All serious adverse events, all unexpected adverse events, and all unanticipated problems will be reported to the DSMB within 24 hours of learning of the event's occurrence/or within 24 hours of the business day by phone, email, or SAE form regardless of attribution to the study drug.

9.4 Reporting Events to Local Institutional Review Boards

All serious adverse events will be reported to the institutional review board (IRB). Each site will comply with their institution's standard operating procedures for reporting adverse events. Subjects will be instructed to report any adverse event(s) during the study and post-study .The investigator will notify the IRB and any other applicable regulatory agency of any unanticipated death or adverse event occurring after a participant has discontinued or terminated study participation that may reasonably be related to the study.

9.5 Data Safety Monitoring Board (DSMB)

The principal investigator will appoint three outside physicians and one local biostatistician from the MCW site with research experience as members of the DSMB group. They will monitor accruing data in order to confirm that the patients in the trial are being cared for safely. The DSMB will be responsible for:

1) Reviewing and analyzing the progress of the study;
2) Approving amendments to the trial protocol, if warranted;
3) Monitoring the safety of the study treatments and diagnostic procedures;
4) Ensuring data quality;

5) Reviewing interim analyses and recommending early stopping or continuation of the trial; and
6) Reviewing recruitment and event rates.
7) Provide a summary of their findings in a written report

The DSMB will meet every 6 months by phone, or in person, or more often if warranted to review serious adverse events.

Local Data Safety Monitoring Plan -The local principal investigator and/or members of the research team will monitor the study for inclusion/exclusion criteria, accrual/withdrawal rates, and breech of confidentially annually prior to submission to the IRB. Any adverse events will be reviewed immediately with the Principal Investigator and will be reported to the local respective IRB per site IRB regulations. All study events will be summarized once a year for the IRB, during annual continuing review progress report.

9.6 Potential Risks to Volunteer

Likely:

Blood Sampling: Venipuncture can cause pain and discomfort at the needle puncture site.

Spirometry: Breathing out hard and fast can cause coughing, mild chest discomfort or lightheadedness.

Albuterol: CNS stimulation can cause restlessness, irritability, and nervousness

Less Likely:

Blood Sampling: Venipuncture can cause, bruising, fainting or local infection at the needle site.

Montelukast: Upper respiratory infection, fever, headache, pharyngitis, cough, abdominal pain, diarrhea, otitis media, influenza, rhinorrhea, sinusitis

Albuterol: Hypertension, tremor, Insomnia, headache, muscle cramps, irritation of the oropharynx (hoarseness).

Rare:

Blood Sampling: In rare circumstances venipuncture can cause blood clots, peripheral nerve injury or an arterial puncture.

In addition to the above possible risks, there is always the risk of developing previously unknown side effects.

Montelukast: Neuropsychiatric events including:

- Aggression
- Hostility
- Anxiousness
- Disorientation
- Insomnia
- Depression
- Restlessness
- Irritability
- Dream abnormalities
- Somnambulism
- Hallucinations
- Suicidal thinking
- Behavior changes
- Tremor
- Death

Albuterol:

- Paradoxical bronchospasm
- Hypersensitivity reaction (including urticaria, angioedema, rash)
- Hypokalemia
- Arrhythmias/ Angina
- fast, pounding, or irregular heartbeat
- chest pain

10. Data

10.1 Data Management

The data gathered will be entered into REDCap data system with each ID having a unique identifier for each participant. REDCap is a secure, web-based application for building and managing online databases. All data will be de-identified and samples will only have a unique identifier that will link the unique identifier with the patient's name.

The REDCap clinical database will be maintained by the Department of Quantitative Health Sciences, at the Children's Research Institute under the direction of Pippa Simpson, PhD.

10.2 Data Collection

Research information, including consent forms and Montelukast Daily Diary will be maintained secure as described in the Confidentiality section 8.3.

Each participant will be identified with a unique identifier number in REDCap. This unique identifier will be linked to the same unique identifier for a biological specimen sample stored in Dr. Nancy Wandersee's SCD Lab.

11. Statistical Considerations

11.1 Description of Endpoints:

11.1.1 Primary Endpoint: Our primary endpoint is a 30% reduction in sVCAM. The study will conclude 8 weeks after initiation of montelukast or placebo treatment, at which time markers of vaso-occlusion/tissue injury will be compared to baseline in individuals with SCD.

11.1.2 Secondary Endpoints:

1) Other inflammatory markers (sP-selectin, sE-selectin, IL-1β, IL-6, TNFα, IFN-γ and LTE_4)
2) Daily pain score
3) Proportion of pain free days to days with pain
4) Opioid use, as reported in the diary
5) Pulmonary function as measured by FEV_1.
6) Six-minute walk

11.2 Statistical Analysis

Summary statistics such as mean, median, standard deviation, range and correlation and plots will be used to examine distributions and interrelationships. Where necessary, for parametric assumption, we will employ appropriate transformations with justifications. For example, the log of some of the biomarkers data may be used since cytokine growth tends to be multiplicative. We will model relationships using regression trees and regression models (linear and non linear). We will use random effects model to investigate changes over time, where patient is random. Initially we will use an auto correlation structure for the variance covariance matrix but will explore other structures. In models covariates such as group, age, gender, WBC, hemoglobin, % fetal hemoglobin and interactions of group with other covariates will be used. Statistical software will be employed for data analysis: SAS version 9.13, Salford System CART for trees, and SPSS Version 18.0. We plan to accrue 25 participants in each arm. From preliminary data, the mean sVCAM level is 353 ng/ml with a standard deviation of 104 ng/ml. If we have similar variability in the proposed study, we will be able to detect a change of ≥ 62 ng/ml (or 18%) with 80% power. Our primary outcome measure is based on a 30% reduction, which would be ~106 ng/ml reduction. The study was designed with 25 in each group in order to explore all three aims and potential confounders. The 95% confidence interval for detecting a 30% difference is between 204 ng/ml and 290 ng/ml (or an 18-42% reduction in sVCAM). Importantly, the lower limit of the 95% confidence interval (18%) is still, in our opinion, a clinically relevant reduction in sVCAM. Thus, if we detect a 30% or larger difference in sVCAM in this study, we will be assured that, based on the 95% confidence interval, these data are clinically important[28].

11.3 Follow-up and Record Retention

The current proposal involves on-going data collection for the duration of the study at each site. The records will be maintained per site policy.

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Appendix One

Six Minute Walk

Location

The 6MWT should be performed indoors, along a long, flat, straight, enclosed corridor with a hard surface that is seldom traveled. The walking course must be 30 meters in length. A 100-ft hallway is required. The length of the corridor should be marked every 3 meters. The turnaround points should be marked with a cone. A starting line, which marks the beginning and end of each 60-m lap, should be marked on the floor using brightly colored tape.

Required Equipment

1. Countdown timer or stopwatch
2. Two small cones to mark the turnaround points
3. A chair that can be easily moved along the walking course
4. Worksheets on a clipboard
5. Meter tape measure and colored tape

Subject Preparation

1. Comfortable clothing should be worn.
2. Appropriate shoes for walking should be worn.
3. Subjects should use their usual walking aids during the test (cane, walker, etc.).
4. Subjects should not have exercised vigorously within 2 hours of beginning the test.

Measurements

1. A "warm-up" period before the test should not be performed.
2. The subject should sit at rest in a chair, located near the starting position, for at least 10 minutes before the test starts. During this time, check for contraindications, measure pulse and blood pressure, and make sure that clothing and shoes are appropriate. Complete the first portion of the worksheet.
3. Have the subject stand and rate their baseline dyspnea and overall fatigue using the Borg scale.
4. Set the timer to 6 minutes. Assemble all necessary equipment (timer, clipboard, Borg Scale, worksheet) and move to the starting point.
5. Instruct the subject as follows:

"The object of this test is to walk as far as possible for 6 minutes. You will walk back and forth in this hallway. Six minutes is a long time to walk, so you will be exerting yourself. You will probably get out of breath or become exhausted. You are permitted to slow

down, to stop, and to rest as necessary. You may lean against the wall while resting, but resume walking as soon as you are able.

You will be walking back and forth around the cones. You should pivot briskly around the cones and continue back the other way without hesitation. Now I'm going to show you. Please watch the way I turn without hesitation."

Demonstrate by walking one lap yourself. Walk and pivot around a cone briskly.

Remember that the object is to walk AS FAR AS POSSIBLE for 6 minutes, but don't run or jog.

Start now or whenever you are ready.

1. Position the subject at the starting line. You should also stand near the starting line during the test. Do not walk with the subject. As soon as the subject starts to walk, start the timer.
2. Do not talk to anyone during the walk. Use an even tone of voice when using the standard phrases of encouragement. Watch the subject. Do not get distracted and lose count of the laps. Each time the participant returns to the starting line, count the lap on the worksheet. Let the participant see you do it.

After the first minute, tell the subject the following (in even tones): "You are doing well. You have 5 minutes to go."

When the timer shows 4 minutes remaining, tell the subject the following: "Keep up the good work. You have 4 minutes to go."

When the timer shows 3 minutes remaining, tell the subject the following: "You are doing well. You are halfway done."

When the timer shows 2 minutes remaining, tell the subject the following: "Keep up the good work. You have only 2 minutes left."

When the timer shows only 1 minute remaining, tell the subject: "You are doing well. You have only 1 minute to go."

Do not use other words of encouragement (or body language to speed up).

If the subject stops walking during the test and needs a rest, say this: "You can lean against the wall if you would like; then continue walking whenever you feel able." Do not stop the timer. If the subject stops before the 6 minutes are up and refuses to continue

(or you decide that they should not continue), wheel the chair over for the subject to sit on, discontinue the walk, and note on the worksheet the distance, the time stopped, and the reason for stopping prematurely.

When the timer is 15 seconds from completion, say this: "In a moment I'm going to tell you to stop. When I do, just stop right where you are and I will come to you."

When the timer rings (or buzzes), say: "Stop!" Walk over to the subject. Consider taking the chair if they look exhausted. Mark the spot where they stopped by placing a bean bag or a piece of tape on the floor.

1. Post-test: Record the post walk Borg dyspnea and fatigue levels and ask this: "What, if anything, kept you from walking farther?"
2. If using a pulse oximeter, measure SpO_2 and pulse rate from the oximeter and then remove the sensor.
3. Record the number of laps from the counter (or tick marks on the worksheet).
4. Record the additional distance covered (the number of meters in the final partial lap) using the markers on the wall as distance guides. Calculate the total distance walked, rounding to the nearest meter, and record it on the worksheet.
5. Congratulate the subject on the good effort and offer a drink of water.

Appendix Two

Borg Scale

At the beginning of the of the 6-minute exercise show the scale to the subject and ask the subject this: “please grade your level of shortness of breath using this scale” Then ask this: Please grade your level of fatigue using this scale. Document the grade chosen.

At the end of the walk, remind the subject of the breathing number they chose before the walk and ask the subject to grade their breathing level again. Then ask the subject to grade their level of fatigue, after reminding them of their grade before the walk. Document the grade chosen.

One to Ten BORG SCALE	
0	Nothing at all
1	Very slight
2	Slight (light)
3	Moderate
4	Somewhat severe
5	Severe (heavy)
6	
7	VERY Severe
8	
9	
10	Very, very severe (maximal)

Appendix Three

MONTELUKAST 10 MG CAPSULES
SIZE "1" IRB# 130794

Ingredients:	Montelukast 10 mg tablets	# 90
	Microcrystalline cellulose	to cover
Yield	90 capsules	
Starting Materials:	Capsule machine	Capsule cleaning towel
	Size "1" dark green caps	

Compounding:

1. Don appropriate attire for compounding.
2. Fill capsule machine with empty capsules, remove tops.
3. Cut one tablet into two halves (if necessary) and place in each empty capsule.
4. Obtain verification from a pharmacist.
5. Cover with microcrystalline, replace tops and clean capsules.
6. Package and label appropriately.
7. Log in Investigational Drug Accountability Record.

References: USP795

Expiration Date: 6 months

Storage: Room Temperature

Auxiliary Labels: Investigational Use Only

Sample Labels:

Vanderbilt Investigational Drug Service
Montelukast 10 mg caps # 90
Lot# IDS 0000 Exp: xx/xx/xx xx/xx
IRB # 130794 Dr. DeBaun

PLACEBO FOR MONTELUKAST 10 MG CAPSULES
SIZE "1" IRB# 130794

Ingredients:	Microcrystalline cellulose	to fill
Yield	**100 capsules**	
Starting Materials:	Capsule machine Size "1" dark green caps	Capsule cleaning towel

Compounding:

1. Don appropriate attire for compounding.
2. Fill capsule machine with empty capsules, remove tops.
3. Fill each capsule with microcrystalline.
4. Replace tops and clean capsules.
6. Package and label appropriately.
7. Log in Investigational Drug Accountability Record.

References: USP795

Expiration Date: 6 months

Storage: Room Temperature

Auxiliary Labels: Investigational Use Only

Sample Labels:

Vanderbilt Investigational Drug Service
Placebo for Montelukast 10 mg caps # 90
Lot# IDS 0000 Exp: xx/xx/xx xx/xx
IRB # 130794 Dr. DeBaun