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Protocol and Statistical Analysis Plan

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Study Title: The safety and efficacy of macitentan for treatment of pulmonary arterial hypertension in sickle cell disease

Study Objectives: 1) To conduct a pilot study to assess the safety of macitentan in patients with pulmonary hypertension of sickle cell disease
2) To begin to assess the efficacy of macitentan for treatment of pulmonary hypertension of sickle cell disease

Background and Rationale: Sickle cell disease (SCD) affects 250,000 births per year worldwide, with 70-80,000 patients currently residing in the US. Although classically thought of as a genetic hemoglobinopathy, most of the clinical complications are vascular in etiology and pulmonary manifestations are the primary cause of morbidity and mortality. Pulmonary hypertension (PH), one such pulmonary complication, occurs in 6-10.5% of SCD adults and is associated with a 60% four-year survival [1-4]. No specific therapy for PH in SCD exists representing an area of intense clinical need in this field.

Clinical trials of pulmonary vasodilator medications in PH of SCD have been problematic. There have been no randomized placebo controlled trials of any traditional pulmonary arterial hypertension (PAH) medication completed in this population to date [5, 6]. Three randomized placebo-controlled trials have been undertaken previously. Two compared treatment with bosentan to placebo in SCD patients with right heart catheterization (RHC)-defined elevated pulmonary vascular resistance (PVR) with a normal pulmonary capillary wedge pressure (PCWP) (the ASSET-1 trial) or pulmonary venous hypertension (PVH) with a PVR $\geq$ 100 dynes·sec/cm^5 (the ASSET-2 trial) [5]. After the randomization of only 14 subjects in ASSET-1 and 12 patients in ASSET-2, the trials were prematurely terminated due to slow patient enrollment. Although very few patients were enrolled, there were no apparent toxicity issues. The third trial, Walk-PHaSST (Pulmonary Hypertension and Sickle Cell Disease with Sildenafil Therapy) [6], compared the safety and efficacy of sildenafil to placebo in SCD patients with a TRV ≥2.7m/s. After 74 (of a targeted 132) subjects were enrolled, the study was prematurely discontinued due to an increase in serious adverse events in the sildenafil group, primarily hospitalization for pain.

There are a number of possible explanations for these failed trials:
1) The hemodynamics of PH in SCD reflect a spectrum of abnormalities. Approximately 40-50% of PH in SCD patients have hemodynamics similar to other forms of PAH; a mean pulmonary arterial pressure $\geq$ 25 mmHg, normal left-sided filling pressures (PCWP or left ventricular end diastolic pressure < 15 mmHg) and an elevated PVR [1, 3]. But at least 50% of PH in SCD patients have at least some degree of PVH usually

due to diastolic dysfunction of the left ventricle [7]. How an elevated PVR is defined in PH of SCD is controversial. While typically in other forms of PAH, it is defined as 3 Wood units or 240 dynes·sec/cm^5, this is reflective of a normal PVR of 120-160 dynes·sec/cm^5. In SCD, the anemia-induced elevations in cardiac output observed in these patients produce a baseline PVR of 60-100 dynes·sec/cm^5 suggesting that a PVR of 160 dynes·sec/cm^5 or 2 Wood units may be a more appropriate value [8].

2) SCD is considered to be a rare disease in the US according to the NIH. As PAH of SCD probably only occurs in 2-4% of HbSS adults, many centers in the US will only have a few (<10) eligible patients for enrollment even under the best circumstances. SCD patients often have co-morbidities limiting their participation in clinical trials, which often decreases this number even further.

3) The epidemiology of PH in SCD has been evolving over the past 10-15 years. Numerous studies demonstrated an elevated pulmonary artery systolic pressure (PASP) by echocardiography reflected by an elevated tricuspid regurgitant jet velocity (TRV) was present in 1/3 of HbSS and 10-28% of HbSC adults[9-11]. However, an elevated TRV only has approximately a 25% positive predictive value for PH in SCD [1]. The need for a right heart catheterization to confirm a diagnosis of PH in SCD has only been gaining clinical acceptance over the past few years and when the prior clinical trials were conducted, this was not a standard part of the PH workup in these patients.

Given the serious limitations of the randomized trials, our clinical guidelines committee decided that its judgments regarding whether targeted PAH therapy is indicated in SCD patients with an elevated PVR and normal PCWP should be informed by indirect evidence from Group 1 PAH populations and our own clinical experience. In Group 1 PAH patients, it has been well-established by meta-analyses of randomized trials that targeted PAH therapy consistently improves exercise capacity, functional status, symptoms, cardiopulmonary hemodynamics and outcome [12-14]. This indirect evidence is supported by four case series in which SCD patients with RHC-confirmed pre-capillary PH received targeted PAH therapy with bosentan, sildenafil, and/or epoprostenol. Targeted PAH therapy was associated with improvement in exercise capacity, with the six minute walk distance increasing 41 to 144 m beyond baseline [15-18]. There were also improvements in the mean PAP, PVR, and cardiac index, although these parameters were measured in only a few patients [18]. The magnitude of the benefits was greatest among symptomatic patients. The most common adverse effects were headache (15%) and peripheral edema (21%); transaminase elevation was reported in 14% of patients during endothelin receptor antagonist therapy [15-18]. Based upon these results and the increased morbidity associated with sildenafil use, we are weakly recommending a trial of either a prostanoid or an endothelin receptor antagonist for select patients with SCD who have a RHC-confirmed marked elevation of their PVR, normal PCWP, and related symptoms [8].

The FDA approval of macitentan for treatment of PAH represents a unique opportunity for study of the use of this medication in SCD. Endothelin-1 has long been established as an important mediator of vasoconstriction in SCD [19, 20] and more recent studies

have implicated a role for this molecule in mouse models of PH in SCD [21]. PH and an elevated TRV are both independent risk factors for mortality in SCD [1, 2, 9, 22] and, as the median age of death of SCD patients is in the 5th decade irrespective of a PH diagnosis, the possibility of therapeutically altering this outcome is of key importance in this disease. With the upcoming publication of the American Thoracic Society sponsored clinical guidelines for the diagnosis and treatment of PH in SCD (additionally endorsed by the Pulmonary Hypertension Association and the American College of Chest Physicians), this makes the timing for re-addressing the possibility of a clinical trial of a PAH therapy in this population perfect. We propose to utilize the information gathered from the trials which proceeded it to specifically design a clinical trial using macitentan to treat the SCD patients most likely to respond to this therapy; those with PAH-like hemodynamics without co-existent left-sided heart disease.

Hypotheses: 1) Macitentan will be safe for treatment in patients with PAH of sickle cell disease
2) Macitentan will improve hemodynamics, exercise capacity and quality of life in patients with pre-capillary pulmonary hypertension of sickle cell disease
3) Long-term use of macitentan will improve survival in patients with sickle cell disease and pulmonary hypertension

Specific Aims:
1- To assess safety and efficacy of macitentan for PAH of SCD
2- To generate pilot data on the feasibility of a clinical trial of macitentan for treatment of pulmonary hypertension in sickle cell disease
3- To begin to assess the efficacy of macitentan for PAH of SCD

Study Design: To conduct a 16 week prospective open-labelled Phase II clinical trial of macitentan in SCD patients with hemodynamics consistent with pulmonary arterial hypertension.

We plan to enroll 10 patients in this study. All enrolled patients will be treated with 10 mg macitentan daily for the entire treatment period.

The study is comprised of the three consecutive periods:

Screening Period/Baseline Studies: This period will be up to 30 days in duration, commencing with the first screening visit and completing with the start of study medication.

Treatment Period: This will begin at Visit 2, the baseline visit and will continue until the end of 16 weeks of therapy or earlier in the case of premature stoppage of treatment. During this period, there will be a safety assessment at the first visit followed by visits to assess safety and efficacy at weeks 4, 8, 12 and 16.

Post-Treatment Study Period: This will last 30 days after the completion of the treatment period and will allow for additional assessment of medication safety.

Inclusion Criteria:

1) A diagnosis of sickle cell disease (HbSS, HbSC, HbS- $\beta^{+ \text{ or } 0}$) confirmed by hemoglobin electrophoresis

2) Provision of informed consent

3) Suspicion of Pulmonary Hypertension by echocardiography within the last 6 months (RVSP $\geq$ 40mmHg or a TRV $\geq$ 3.0 m/sec) or diagnosis of Pulmonary Hypertension by cardiac catheterization within the last 12 months (mean PAP ≥25 mmHg at rest). Left ventricular ejection fraction $\geq$ 50%.

3) Right heart catheterization which demonstrates the following:
a) mPAP $\geq$ 25 mmHg
b) PAOP or LVEDP < 15 mmHg
c) PVR $\geq$ 160 dynes-sec/cm^5 or 2 Wood Units

3) Age $\geq$ 18 years

4) NYHA Class II or III by symptoms

5) Six minute walk distance (6MWD) $\geq$ 150 meters and $\leq$ 450 meters

6) A woman of child-bearing potential is eligible only if the following applies:

a) Negative pre-treatment serum pregnancy test and agreement to monthly tests
b) Use of two highly effective methods of contraception if not truly abstinent with a male partner OR permanent female sterilization has been performed.
7) May be on background therapy or may be treatment naïve.

Exclusion Criteria:

1) Current pregnancy or lactation

2) Any one of the following medical conditions:

a) Stroke within the last 6 weeks
b) New diagnosis of pulmonary embolism within the last 3 months
c) Clinically significant laboratory abnormalities, including, but not limited to: Positive Hepatitis B surface antigen or Hepatitis C antibody, Positive HIV test, Serum alanine aminotransferase (ALT) greater than or equal to 2.0 x ULN, Serum creatinine greater than or equal to 2.5mg/dL (or calculated creatinine clearance less than or equal to 30mL/min).
d) Hospitalization within the prior 4 weeks for a vasoocclusive crisis or acute chest syndrome

e) Any unstable (acute or chronic) condition that in the opinion of the investigator will prevent completion of the study

3) Evidence of diastolic dysfunction of the left ventricle as defined by a mPAP ≥ 25 mmHg and PCWP or LVEDP > 15 mmHg by right heart catheterization with a normal left ventricular ejection fraction by echocardiogram or MUGA.

4) Left ventricular ejection fraction < 50% of significant ischemic, valvular or constrictive heart disease

5) Acute or chronic impairment (other than dyspnea) limiting the ability to comply with study requirements (particularly the 6MWT) e.g. symptomatic hip osteonecrosis

6) Active therapy with an IV prostacyclin

7) Subjects who are taking other investigational medications at the time of the study

8) Clinically significant psychiatric, addictive (defined by DSM-IV criteria), neurologic disease or condition that, in the opinion of the Investigator, would compromise his/her ability to give informed consent, participate fully in this study, or prevent adherence to the requirements of the study protocol.

Efficiency Parameters:

Primary:
1. Assess the rate of adverse and serious adverse events in SCD patients taking macitentan

Secondary:
1. Assess the change in the following hemodynamic parameters, by RHC, from baseline after 16 weeks of 10 mg daily of macitentan:
- Right atrial pressure (RAP)
- Right ventricular pressure (RVP)
- Systolic pulmonary artery pressure (SPAP)
- Diastolic pulmonary artery pressure (PADP)
- Cardiac output (CO)
- Cardiac index (CI)
- Systemic vascular resistance (SVR)
- Right ventricular function assessed by pressure-volume loop measurements

2. Assess the change from baseline in 6MWT after 16 weeks of 10 mg daily macitentan

3. Assess the change from baseline of Borg Dyspnea Index (BDI) and NYHA/WHO functional classification after 16 weeks of 10 mg daily macitentan

4. Assess the change from baseline in cardiac biomarkers (e.g., BNP, NT-pro-BNP) after 16 weeks of 10 mg daily macitentan

Screening Period: After obtaining informed consent, the patient will undergo the screening protocol which includes assessment of baseline demographics (sex, age, race, ethnicity, height, and body weight), as well as an assessment of why the female patients are not of child-bearing potential as appropriate. The following data will be obtained:

1) Medical history- To include:
a) SCD related complications (stroke, AVN, priapism, lower extremity ulcers etc.)
b) Frequency of vasoocclusive crises and hospitalizations
c) Frequency of blood transfusions
d) History and frequency of acute chest syndrome
e) History of thromboembolic disease
f) History of congestive heart failure
g) History of asthma
h) History of systemic hypertension
i) History of proteinuria
j) History of chronic kidney disease
k) Echocardiogram and any data from previous echos over past 12 months
l) Pulmonary function data from the prior 12 months

2) Concomitant Medication Use – All medications will be recorded. Hydroxyurea use will be assessed in all subjects.

3) Physical Examination and Vital Signs

4) 12 lead electrocardiogram

5) Laboratory Testing: Complete blood counts, blood chemistries including BUN and creatinine, liver function testing, markers of hemolysis (lactate dehydrogenase, total and indirect bilirubin, AST, reticulocyte counts), urinalysis, urine pregnancy test and NT-pro-BNP levels.

6) WHO Functional Class

7) 6 minute walk test and Borg Dyspnea Score

8) SF-36 questionnaire

9) Right Heart Catheterization (can be done up to 12 weeks prior to initiation of study medication).

Baseline Visit (Day 1):

1) Medical History

2) Concomitant Medication Usage

3) Physical Examination and Vital Signs

4) Laboratory and Pregnancy Testing

5) WHO functional class

6) 6 minute walk test and Borg Dyspnea Score

7) SF-36 questionnaire

Week 4 visit:

1) Physical Examination and Vital Signs

2) Laboratory and Pregnancy Testing

3) Assessment of Adverse Events

Week 8 Visit:

1) Medical History

2) Concomitant Medication Usage

3) Physical Examination and Vital Signs

4) Laboratory and Pregnancy Testing

5) WHO functional class

6) 6 minute walk test and Borg Dyspnea Score

7) SF-36 questionnaire

8) Assessment of Adverse Events

Week 12:

1) Physical Examination and Vital Signs

2) Laboratory and Pregnancy Testing

3) Assessment of Adverse Events

Week 16:

1) Medical History

2) Concomitant Medication Usage

3) Physical Examination and Vital Signs

4) Laboratory and Pregnancy Testing

5) WHO functional class

6) 6 minute walk test and Borg Dyspnea Score

7) SF-36 questionnaire

8) Assessment of Adverse Events

9) 12 lead electrocardiogram

10) Right heart catheterization

11) Echocardiogram

Post-Treatment Follow-Up Visit:

1) Assessment of Adverse Events

Statistical Analysis Plan

T tests will be completed among the hemodynamic parameters for each subject and for the means of each hemodynamic value for the group. T tests will also be utilized to compare the frequency and volume of AE's and/or SAE's reported by our subjects.