The Effect of Voxelotor on Exercise Capacity of Youths with Sickle Cell Anemia

Short Title: Voxelotor SCA Exercise Study

Protocol Number: ESR-C006

National Clinical Trial (NCT) Identified Number: <Number, if available>

Principal Investigator: Elizabeth Yang

Funded by: Global Blood Therapeutics (GBT)

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5 June 2020

Summary of Changes from Previous Version:

Affected Section(s)	Summary of Revisions Made	Rationale

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STATEMENT OF COMPLIANCE

This pilot study will be conducted in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP), applicable US Code of Federal Regulations (CFR). As the Sponsor-Investigator, the PI will assure that no deviation from, or changes to the protocol, will take place without prior agreement from the investigational drug sponsor Global Blood Therapeutics, and documented approval from the IRB, except where necessary to eliminate an immediate hazard(s) to the study participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form will be obtained before any participant is enrolled. Any amendment to the protocol will be reviewed and approved by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved.

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:

The Effect of Voxelotor on Exercise Capacity of Youths with Sickle Cell Anemia

Study Description:

This study is a pilot, open-label, single-arm study to evaluate the effect of voxelotor on exercise capacity, as measured by cardiopulmonary exercise testing (CPET) in patients 12 years of age and older with sickle cell anemia (SCA). Voxelotor was recently approved for the treatment of SCA in patients 12 years and older. We hypothesize that exercise capacity will be improved by voxelotor treatment in sickle cell patients whether they are on Hydroxyurea or not. This study will assess exercise capacity by cardiopulmonary exercise testing (CPET) before and after 8 weeks of voxelotor therapy.

Objectives:

Primary Objective: To evaluate the effect of voxelotor on peak oxygen consumption (VO2) in adolescents with SCA as assessed by change in CPET from baseline.

Secondary Objective: To correlate peak VO2 with biochemical markers, including hemoglobin, reticulocyte count, bilirubin, lactate dehydrogenase, haptoglobin, % Hgb F expressing cells, P50 oxygen dissociation, point of sickling (POS), and dense cells.

Exploratory Objective: To evaluate the effect of voxelotor on HRQOL as assessed by patient-reported outcome (PGIC) and clinician-reported outcome (CGIC) at end of treatment study visit

Endpoints:

Primary endpoint: Change in Peak VO2 from baseline

Secondary endpoint: Hemoglobin and biochemical markers of sickling and hemolysis

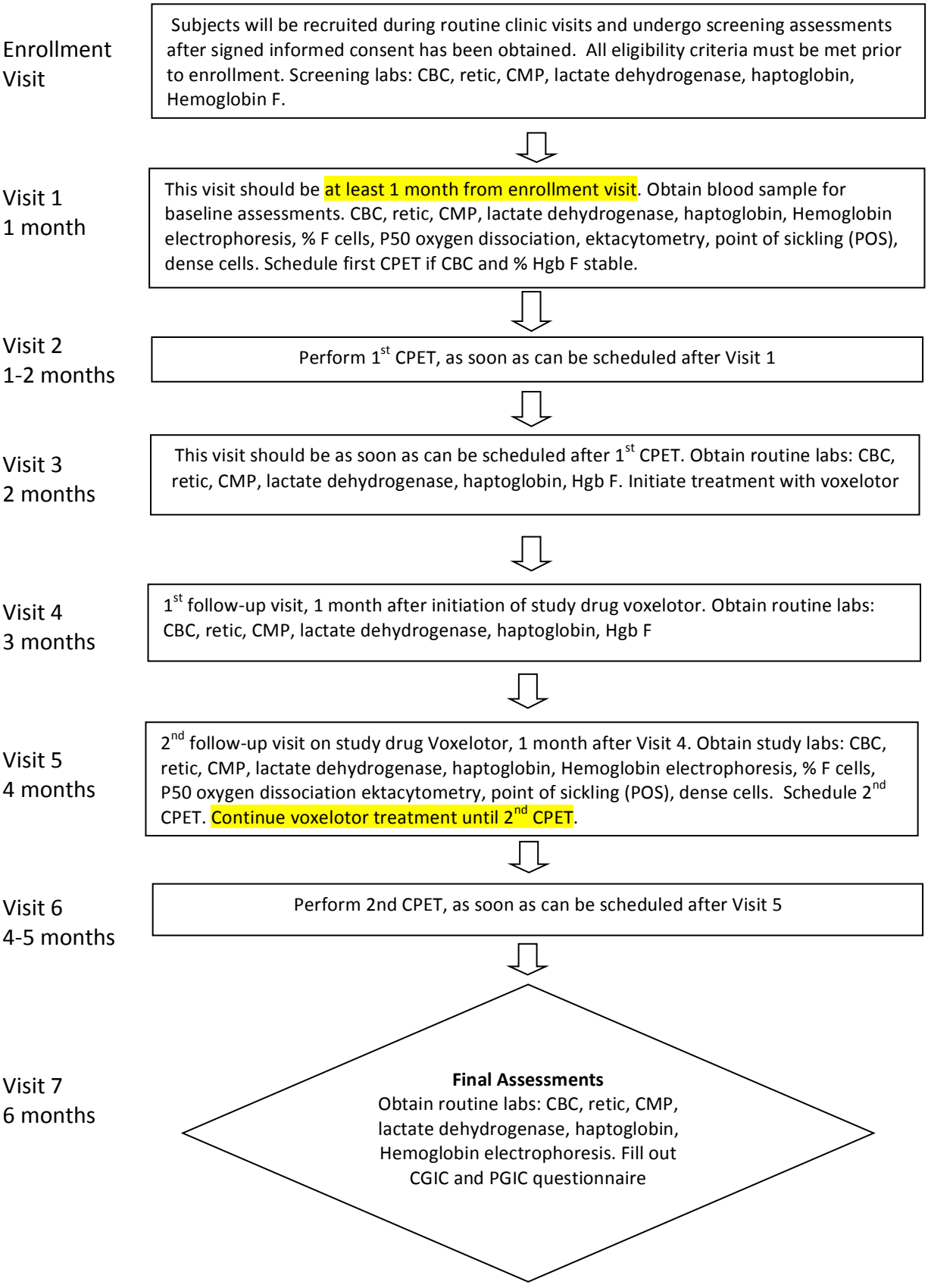
Exploratory endpoint: Clinician and Patient Global Impression of Change assessment (CGIC and PGIC)

Study Population:

1.1.1.1.1.1 Patients seen in the Pediatric Sickle Cell Program in Northern Virginia (Fairfax, VA) who have a genetically severe forms of sickle cell disease (including Hgb SS, Hgb Sbeta^{0}thalassemia, or Hgb SC^{Harlem}) and are age 12 or older.

Phase:	This is a single-center, open-label, single-arm longitudinal interventional pilot study.
Description of Sites/Facilities Enrolling Participants:	The outpatient sickle cell clinic of Pediatric Specialists of Virginia located in the Schar Cancer Institute on Inova Hospital Campus in Fairfax, VA. This pilot study aims to enroll 10 patients.
Description of Study Intervention:	During the open-label treatment period, all participants will receive voxelotor at a fixed dose of 1500mg (administered as three 500mg tablets) orally once daily for 8 weeks
Study Duration:	12 months
Participant Duration:	6 months

1.2 SCHEMA


Enrollment Visit
Subjects will be recruited during routine clinic visits and undergo screening assessments after signed informed consent has been obtained. All eligibility criteria must be met prior to enrollment. Screening labs: CBC, retic, CMP, lactate dehydrogenase, haptoglobin, Hemoglobin F.
Visit 1
1 month
This visit should be at least 1 month from enrollment visit. Obtain blood sample for baseline assessments. CBC, retic, CMP, lactate dehydrogenase, haptoglobin, Hemoglobin electrophoresis, % F cells, P50 oxygen dissociation, ektacytometry, point of sickling (POS), dense cells. Schedule first CPET if CBC and % Hgb F stable.
Visit 2
1-2 months
Perform 1st CPET, as soon as can be scheduled after Visit 1
Visit 3
2 months
This visit should be as soon as can be scheduled after 1st CPET. Obtain routine labs: CBC, retic, CMP, lactate dehydrogenase, haptoglobin, Hgb F. Initiate treatment with voxelotor
Visit 4
3 months
1st follow-up visit, 1 month after initiation of study drug voxelotor. Obtain routine labs: CBC, retic, CMP, lactate dehydrogenase, haptoglobin, Hgb F
Visit 5
4 months
2nd follow-up visit on study drug Voxelotor, 1 month after Visit 4. Obtain study labs: CBC, retic, CMP, lactate dehydrogenase, haptoglobin, Hemoglobin electrophoresis, % F cells, P50 oxygen dissociation ektacytometry, point of sickling (POS), dense cells. Schedule 2nd CPET. Continue voxelotor treatment until 2nd CPET.
Visit 6
4-5 months
Perform 2nd CPET, as soon as can be scheduled after Visit 5
Visit 7
6 months
Final Assessments
Obtain routine labs: CBC, retic, CMP, lactate dehydrogenase, haptoglobin, Hemoglobin electrophoresis. Fill out CGIC and PGIC questionnaire

1.3 SCHEDULE OF ACTIVITIES (SOA)

Procedures	Screening/ Enrollment Day -60	Study Visit 1 Day -30 +/- 7 days	Study Visit 2 Day – 29 to -1	Study Visit 3 Day 1 +/- 14 days	Study Visit 4 Day 30 +/- 7 days	Study Visit 5 Day 60 +/- 7 days	Study Visit 6 Day 60-89	Final Study Visit 7 Day 90 +/- 14 days
Informed consent	x							
Demographics	x							
Medical history	x							
Dispense voxelotor[d]				x	x	x[d]		
Concomitant Medication review	x	x		x	x	x		x
Physical exam	x	x		x	x	x		x
Vital signs, Ht, Wt	x	x	x	x	x	x	x	x
Performance status	x					x		x
Routine labs [a]	x	x		x	x	x		x
Study labs [b]		x				x		
Pregnancy test [c]	x			x	x	x		
Adverse event review and evaluation	x			x	x	x		x
Schedule CPET		x				x		
CPET			x				x	
CGI, PGI assessments								x
Data collection and entry	x	x		x	x	x		x

[a] Routine labs: CBC diff, retic, CMP, LDH, haptoglobin, Hemoglobin F or hemoglobin electrophoresis

[b] Study labs: Send to UCSF Dr. Frans Kuypers lab: % F cells, P50 oxygen dissociation, ektacytometry, point of sickling (POS), dense cells.

[c] Pregnancy test: All menstruating female participants

[d] Participants will be treated with voxelotor for at least 8 weeks before the 2nd CPET, which will be scheduled as close to the date following 8 weeks of treatment with voxelotor. Participants will continue voxelotor until the 2nd CPET is completed.

2 INTRODUCTION

2.1 STUDY RATIONALE

The beta globin mutation in sickle cell disease leads to production of sickle hemoglobin (HbS) that in the deoxygenated state polymerizes and results in sickling and hemolysis of red blood cells. Studies have shown that children and adults with sickle cell anemia (SCA) exhibit decreased cardiopulmonary fitness. While multiple factors influence exercise capacity, anemia is directly related to oxygen-carrying capacity and is one factor that affects cardiopulmonary fitness. Low exercise capacity in SCA is partly due to low hemoglobin. Voxelotor is a recently approved therapy for SCA, shown to decrease hemolysis and increase hemoglobin in untreated as well as Hydroxyurea-treated SCA patients. Increasing hemoglobin is expected to increase oxygen carrying capacity, therefore, treatment with voxelotor is expected to improve exercise capacity.

2.2 BACKGROUND

Why do we need to know about exercise tolerance in SCA?

Physical activity has been significantly limiting for patients with sickle cell anemia. Whereas people with sickle cell trait (SCT) engage in high intensity athletics and military training, individuals with sickle cell anemia (SCA) have not participated, either due to patients' own inability to tolerate exercise or restrictions placed upon them by others, or a combination of factors[1,2]. In the era of hydroxyurea, lifestyles for many SCA patients have improved. In our own pediatric sickle cell program, which has a high hydroxyurea usage rate, many children are described by their parents as being as active as other children, and some teenagers participate in team sports and even try out for varsity sports, including football. As sickle cell providers, we are often asked by school athletic departments to sign sports clearance forms and list specific restrictions for the student with sickle cell disease. While organizations such as NCAA provide general guidelines for SCT, no published specific guidelines exist for SCA[3,4]. What is known about SCT, i.e., increased risk of exertional rhabdomyolysis, is not directly applicable to SCA, which presents distinct challenges, not the least of which appears to be limited physical ability. Yet, regular exercise has been shown to improve health in chronic illnesses, including sickle cell disease[1, 5-9]. Increasingly, demonstration that exercise is beneficial in SCA is prompting SCA healthcare providers to encourage their patients to be physically active. Given SCA youths' desire to be athletic and the advocacy for physical exercise in SCA, understanding the exercise capacity in SCA is increasingly necessary.

How is exercise capacity measured?

Cardiopulmonary exercise testing, or CPET, is the commonly accepted benchmark of aerobic capacity[10, 11]. While a subject is performing a standardized exercise protocol with incremental ramping, either on a bicycle or a treadmill, and breathing through a non-rebreathing mouthpiece, expired air is analyzed via breath-by-breath sampling. Fractions of oxygen, carbon dioxide, air volume and flow are measured to calculate oxygen uptake (VO2), carbon dioxide output (VCO2) and minute ventilation, all in real-time. The peak VO2 (VO2 max) is the maximal ability of the subject to take in and utilize oxygen, which is the functional aerobic exercise capacity. Peak VO2 is determined by the cardiovascular, pulmonary, musculoskeletal, as well as the hematologic system. CPET is most commonly done in adults, but is also utilized in children, particularly in those with cystic fibrosis and congenital heart disease, as well as in adolescents with sickle cell disease[12].

What is known about exercise testing in SCA?

Although reports are limited, exercise in SCA has been investigated, and the field is growing. Experience in these investigations, including GBT's phase 1/2 voxelotor study, has reassured that maximal exercise testing is safe in SCA and does not induce pain or other sickle cell crisis[1, 8, 13, 14, 24]. Studies have shown that children and adults with SCA exhibit decreased cardiopulmonary fitness, most informatively demonstrated through cardiopulmonary exercise testing (CPET) and peak oxygen consumption. Peak VO2 in adolescents and adults with SCA in ergometric bicycle CPET was as much as 30% lower than controls, even after adjusting for BMI and hemoglobin[15, 16, 17]. A study of more than 200 adults with SCA using a standard Balke treadmill exercise test found lower exercise capacity among participants than the general African American population, with lower exercise capacity associating with lower hemoglobin[14,18]. SCA is a systemic disease affecting all organs, and decreased peak VO2 is likely multi-factorial. Anemia directly affects oxygen-carrying capacity, and low hemoglobin would be expected to compromise aerobic activity. Indeed, CPET before and after transfusion both in patients with chronic anemia conditions and in pre-surgical patients with anemia showed ~10% difference in

peak VO2[19, 20]. Thus, low hemoglobin in SCA is likely one factor contributing to decreased exercise capacity, and increasing hemoglobin in SCA might improve VO2 max.

Can medical therapy improve exercise capacity of sickle cell patients?

Our clinical experience suggests that physical ability is improved in young patients treated with Hydroxyurea, but this has not been documented. Voxelotor can further raise hemoglobin in untreated patients as well as patients already on Hydroxyurea[21]. Our patient population includes a cohort of teenagers eligible for treatment with voxelotor, and although most are on Hydroxyurea, not all respond with significant increases in hemoglobin. While an exercise study in 1997 found Hydroxyurea treatment correlated with better exercise performance[22], more recently published exercise studies in SCA have not compared patients treated with and without Hydroxyurea. Regardless, one would expect that peak VO2 would improve with voxelotor due to its positive effect on hemoglobin, as well as indirect effects of decreased sickling and hemolysis. In GBT's phase 1/2 voxelotor study, CPET was done in 12 adult sickle cell patients to address the concern that the higher O2 affinity of drug-modified hemoglobin could negatively impact oxygen consumption. No significant change, either positive or negative, was observed in VO2 max and ventilatory threshold, but the voxelotor doses used in that study were below GBT's currently recommended dose [24]. Thus, the question of whether voxelotor treatment, at the currently recommended dose, could improve exercise capacity is unanswered.

This study aims to determine whether changes in peak VO2 can be detected in youths with SCA after treatment with voxelotor.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

Physical risk
Voxelotor: The most common adverse reactions reported with incidence > 10% are headache, diarrhea, abdominal pain, nausea, fatigue, rash, and pyrexia. No significant toxicities requiring medical intervention have been reported. If a subject complains of intolerable side effects, voxelotor will be stopped and the subject will come off study. Voxelotor binds to hemoglobin. When the drug is stopped, voxelotor-modified hemoglobin will degrade, and no long-term risk is expected.

CPET: Aggravation of SCA symptoms during exercise testing is unlikely, because exercise testing is stopped when participants complain of fatigue or discomfort. Studies of exercise testing in patients with sickle cell disease have been published, including GBT's phase 1/2 voxelotor study, and no adverse events, such as pain crisis, have been reported. [, 8, 13, 14-17, 24]

Venipuncture: The risks of drawing blood from a vein include fainting, local pain, bruising, swelling, or rarely an infection at the needle site. Patients routinely have blood draws as part of regular sickle cell care, and this study will take blood from the same venipuncture as routine care blood draws, no extra venipunctures are required. In the event of adverse effects to the subjects, necessary medical or professional intervention will be instituted immediately. Approximately 5 cc (1 teaspoon) of blood will be drawn for study labs on 2 occasions in the study.

Psychological risk

Voxelotor treatment: Most patients are already taking the medication for sickle cell disease. Adding another oral medication to be taken at the same time as the existing medication is unlikely to induce an adverse psychological effect.

CPET: Patients may experience potential anxiety, stress, and uncomfortable emotions if CPET results are not as they expected. As we do not know what the expected peak VO2 will be for our patient population, we have no expected results for peak VO2 and will not be communicating any expectations to our patients that might be anxiety-provoking. CPET will be explained to patients and patients will be prepared for CPET by the exercise physiologist to reduce apprehension and anxiety. A pediatric psychologist is part of the sickle cell care team and is available to provide counseling, if needed.

Venipuncture: Blood draw is part of routine sickle cell care. This study will obtain blood from the same venipuncture used for routine blood work, therefor will post no additional psychological effect.

Economic risk
Patients and/or their parents will be compensated for participation and their travel costs to the exercise lab will be covered by the study, therefore there is no economic risk.

Legal risk
There is no legal risk.

Social risk
Privacy will be maintained. There is no foreseeable social risk.

2.3.2 KNOWN POTENTIAL BENEFITS

Immediate direct benefits of study participation to the patients include free access to the newly FDA approved medication voxelotor, rise in hemoglobin and improved oxygen carrying capacity, as well as free exercise testing that can provide information for personal physical activity guidelines.

Long-range benefits include fewer complications of sickle cell disease and potentially improved lifestyle.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

Voxelotor has proven benefit in sickle cell disease without toxicity. CPET has been shown to be safe for sickle cell patients. The risk of minor adverse reactions to voxelotor is significantly outweighed by the benefit of higher hemoglobin, decreased sickling, and fewer sickle cell complications. The information gained from this study about exercise capacity, which is a functional outcome of the new medication (rather than just a blood test result), greatly outweighs the inconvenience of trips to the exercise lab.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
Compare peak VO2 from sequential CPETs performed on SCA patients before and during voxelotor therapy	Change in Peak VO2 from baseline to Week 8 (voxelotor)	The gold standard for exercise capacity is peak VO2.
Secondary		
Correlate peak VO2 with biochemical markers, including hemoglobin, reticulocyte count, bilirubin, lactate dehydrogenase, haptoglobin, hemoglobin F, % F cells, P50 oxygen dissociation, point of sickling.	Correlation of peak VO2 with biochemical markers of sickling and hemolysis	These are established measurements of the biochemical effects of sickling and hemolysis. They will show whether improved exercise capacity is a direct or indirect effect of voxelotor's biochemical activity.
Tertiary/Exploratory		
HRQOL assessment	Clinician Global Impression of Change and Patient Global Impression of Change assessments (CGIC and PGIC)	The small number of patients on this pilot study may limit CPET quantitative results from reaching statistical significance. Whether or not peak VO2 changes significantly on voxelotor, whether voxelotor has the potential to offer overall clinical improvement and better quality of life can be assessed.

4 STUDY DESIGN

4.1 OVERALL DESIGN

Hypothesis: Voxelotor improves exercise capacity in SCA patients.

Study type: single-center, open-label, single-arm longitudinal interventional pilot study

Methods: Patients with genetically severe forms of sickle cell disease age 12 or older will be enrolled from the PSV sickle cell clinic in Northern Virginia. A baseline CPET will be performed. Voxelotor will be initiated, and a second CPET will be performed. The CPET after the study intervention (voxelotor) will be compared to the baseline CPET. Each patient will be his/her own control.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

The phenotype of sickle cell anemia is variable, depending on genetic modifiers, such as baseline fetal hemoglobin level, and response to the existing sickle cell therapy Hydroxyurea. The baseline hemoglobin in sickle cell anemia patients vary; individuals' physical activity also vary, whether they have sickle cell disease or not, and CPET results would likely show significant inter-subject variability across the sickle cell population. To answer the question whether voxelotor increases exercise capacity for individual patients taking the drug, inter-subject variability can be eliminated by comparing each subject to him/herself. In addition, fewer subjects will be needed in a longitudinal design than if subjects were divided into a study group and a control group. Therefore, we chose a longitudinal design, in which each participant's CPET after voxelotor is compared to the same participant's CPET before initiation of voxelotor.

4.3 JUSTIFICATION FOR DOSE

The dose of 1500 mg daily for voxelotor is the standard approved dose, as a result of dose comparison studies completed and published by GBT.

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed all phases of the study including 2 CPETs and the last visit shown in the Schedule of Activities (SoA), Section 1.3.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

Subjects will be recruited from the Pediatric Specialists of Virginia Sickle Cell Program.

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Provision of signed and dated informed consent form
2. Stated willingness to comply with all study procedures and availability for the duration of the study
3. Male or female, age $\geq$ 12 years
4. In good general health as evidenced by medical history and diagnosed with a genetically severe form of sickle cell anemia (Hgb SS, Hgb S beta 0 thalassemia, Hgb SC^{Harlem}, and others)

5. Patients who are on Hydroxyurea need to be on a stable dose for at least 3 months without anticipated change in dosing until the study is completed.
6. Ability to take oral medication and willingness to adhere to daily voxelotor and 2 CPETs at scheduled intervals.
7. For females of reproductive potential who are sexually active: use of highly effective contraception for at least 1 month prior to screening and agreement to use such a method during study participation and for an additional 30 days after the end of study.
8. For males of reproductive potential: use of condoms or other methods to ensure effective contraception with partner

5.2 EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Patients on chronic transfusions or who received a transfusion within last 8 weeks
2. Patients who had hospitalization for vaso-occlusive crisis or acute chest syndrome within 30 days prior to informed consent/assent.
3. Patients who have screening alanine aminotransferase (ALT) > 4X upper limit of normal
4. Patients who suffer from physical inactivity attributable to clinically significant musculoskeletal, cardiovascular, or respiratory comorbidities
5. Patients already taking commercially available voxelotor
6. Prior hypersensitivity to voxelotor or excipients.
7. Pregnant patients

5.3 LIFESTYLE CONSIDERATIONS

During this study, participants are asked to:

- Refrain from using herbal medications (e.g. St. John's Wort), or medications that are sensitive cytochrome CYP3A4 substrates or CYP3A4 modulators, such as fluconazole.

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical trial but are not entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this trial (screen failure) because Hydroxyurea dose or hemoglobin had not been stable for 3 months may be rescreened. Rescreened participants should be assigned the same participant number as for the initial screening.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

- Target study sample size is 10 patients with any mix of male or female gender
- Anticipated accrual rate is 2-3 a month
- Participants will be recruited when they come to the PSV sickle cell clinic in Northern Virginia
- Potential participants will be identified by preview of patients scheduled for upcoming clinics. Potential participants will be pre-screened through electronic medical record. They will be approached during their clinic visit
- Recruitment flyer will be emailed and mailed to potential participants. It will also be handed to patients and families when they come to clinic.
- The study requires 5-6 months of participation, CRA will keep in constant contact with participants by telephone. $150 plus the cost of a meal will be offered as compensation for completion of each CPET, to be paid to the participant, with parental consent if the participant is < age 18.
- Transportation to and from the exercise lab will be covered by the study
- A full CPET report that can be used for personal exercise and sports guidelines will be provided to each participant.
- This study population are patients with sickle cell anemia, who are all in minority groups historically under-represented. Our patient population includes African-Americans, Africans, Hispanics, and Middle Easterners.
- This is a pediatric study, therefore, the vulnerable population of minors are included by definition.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

No text is to be entered in this section; rather it should be included under the relevant subheadings below.

6.1.1 STUDY INTERVENTION DESCRIPTION

The study intervention is voxelotor, taken orally. It will be used for the approved indication of sickle cell anemia. This is a single-arm study. There is no control intervention.

6.1.2 DOSING AND ADMINISTRATION

Participants will be instructed to take voxelotor 1500mg consisting of three 500mg-tablets once daily for at least 8 weeks. It can be taken with Hydroxyurea. If a participant misses a dose, the participant should resume normal dosing next day (i.e., the dose on the day after a day of a missed dose should not be increased or decreased). Voxelotor will be dispensed from the sickle cell clinic in bottles with 90 tablets each for a 30-day supply.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

No text is to be entered in this section; rather it should be included under the relevant subheadings below.

6.2.1 ACQUISITION AND ACCOUNTABILITY

Voxelotor tablets will be supplied in high-density polyethylene bottles with induction-sealed polypropylene child-resistant caps. Packaged and labeled drug product (voxelotor) will be supplied by GBT and shipped to the clinical site. Study drug will be dispensed at Visit 3 in bottles of 90 tablets. The PSV pharmacist will receive the bottles, which will be stored in a temperature controlled locked med room. The PI will dispense the drug. The study coordinator or PI will pick up/sign pharmacy log and dispense study drug to participant with instructions during the study visit.

The participants will bring the medicine bottle back to clinic each month. Unused pills will be counted and recorded. Dates of receipt, dispense, return, lot numbers, and pill counts will all be recorded in a log.

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

Voxelotor comes in 500mg tablets that are film-coated, light yellow to yellow, oval shaped, biconvex, debossed with “GBT 500” on one side. It is packaged in bottles of 90 tablets with child-resistant closure.

6.2.3 PRODUCT STORAGE AND STABILITY

Voxelotor will be stored at controlled room temperature between 15 °C and 25°C (59°F to 77°F) in a secure, temperature-controlled storage area of the investigational site’s clinic medication room which is a secure, locked environment with restricted access. No special procedures for the safe handling of voxelotor are required.

6.2.4 PREPARATION

Voxelotor is a tablet ready to be swallowed. There is no drug preparation.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Not applicable. There is no randomization.

6.4 STUDY INTERVENTION COMPLIANCE

Each bottle of voxelotor contains 90 tablets. The dose is 3 tablets a day. Each bottle lasts 30 days. Participants will be scheduled for clinic visits no longer than 30 days apart. Participants will be given a bottle of voxelotor at a clinic visit and will be asked to bring back the bottle with left over pills in it. Compliance will be determined by pill counting. The number of pills remaining will be counted and subtracted from 90 to get the number of pills taken, which can be divided by 3 to get the number of days the drug was taken. The difference between the number of days drug was taken and the number of days between the clinic visits is the number of days drug was missed.

6.5 CONCOMITANT THERAPY

All concomitant medications will be recorded each time a subject comes to clinic. Hydroxyurea is permitted as a concomitant medication but hydroxyurea dose change during the study is not permitted.

Participants will be asked always to check with the PI or clinical study staff before taking a new medication. Medications that are Inducers or inhibitors of cytochrome CYP3A4 may affect voxelotor metabolism, and participants will be told to avoid these medications.

6.5.1 RESCUE MEDICINE

Not-applicable

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

If a participant discontinues voxelotor before completing the 2nd CPET but is willing to resume treatment on study, then the participant must take voxelotor continuously for at least 1 month before performing the 2nd CPET. If the participant discontinues voxelotor and is unwilling to resume treatment per the study protocol, then the participant will be discontinued from the study. Only routine clinical laboratory monitoring blood work results will be collected at the time of treatment discontinuation, not study labs.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request.
An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Pregnancy
- Significant study intervention non-compliance
- If any clinical adverse event (AE), such as hypersensitivity to the study drug, laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- Participant unable to perform CPET
- Participant unexpectedly moves to another location not within travel distance of the exercise lab and is unable to complete the 2nd CPET before moving

The reason for participant discontinuation or withdrawal from the study will be recorded on the Case Report Form (CRF). Subjects who sign the informed consent form and subsequently withdraw, or are withdrawn or discontinued from the study, will be replaced.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to return for both of the study visits before study drug initiation and both of the study visits after initiation of study drug, or if he or she fails to show for scheduled CPETs and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit within 1-2 weeks and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant, including at least 3 telephone calls using all available phone numbers for the patient and the emergency contact, 3 emails, letters to the participant and to the participant's pediatrician or PCP. These contact attempts will be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

Efficacy of study drug will be assessed as follows:

- CPET (cardiopulmonary exercise test) is non-invasive and will be performed using a motorized treadmill (Trackmaster Model TMX428, Full Vision, Inc.). Participants will have their nose clipped and breathe through a mouthpiece with a nonbreathing valve. Breath by breath gas exchange data will be collected and analyzed using a VMax Encore 29C metabolic cart (CareFusion Corp, San Diego, CA). The participants will have EKG leads and pulse oximetry monitoring while running on a treadmill that increases in incline incrementally to induce peak physical effort according to a modified Bruce protocol based on patient age, size, and exercise ability. A peak exercise response will be defined as a respiratory exchange ratio of greater than 1.1 or to patient's volitional fatigue. The patient exercises for 8-12 minutes. Approximately 1.5 hour will be allotted for the entire CPET visit, which will include checking in, explanation of the procedure, preparation and setup for the test, the exercise test itself, and post-test debriefing. This exercise test will be done twice by each participant: once before and once after starting the study drug. The CPET report will be provided to the participant.

- During exercise the following will be measured and recorded:
- · 12-Lead ECG
- · Pulse oximetry
- · Blood Pressure
- · Peak HR
- · Peak VO2 (ml/kg/min)

- · Peak VO2 (L/min)
- · Respiratory Exchange Ratio (RER)
- · O2 Pulse
- · VE/VO2
- · VE/VCO2
- · VO2/HR
- · VAT (ventilatory anaerobic threshold)
- · Percent VO2 at VAT

- Blood will be drawn for study labs once before the study drug and once after. Study labs will be performed by the research laboratory of Dr. Frans Kuypers at UCSF. Blood samples will be sent by FEDEX overnight.

- Blood work as part of regular standard of care will continue to be done during the study.

- The "Patient Global Impression of Change" and the "Clinician Global Impression of Change" single-question surveys will be completed by the participant and the clinician, respectively, at the final study visit.

8.2 SAFETY AND OTHER ASSESSMENTS

Screening and enrollment can occur in the same visit. Screening consists of physical exam and vital signs to ensure general good health of the patient, as well as reviewing labs and medication dose to ensure that the hemoglobin and Hydroxyurea dose have been stable for 3 months. The study procedure CPET will be explained to potential participants in detail at the screening/enrollment visit.

All visits will include physical examination, vital sign, standard of care labs, and assessment of adverse events, which will be entered into CRFs.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS (AE)

Adverse event means any untoward medical occurrence associated with the use of voxelotor or performance of exercise testing, whether or not considered intervention-related (21 CFR 312.32 (a)).

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An AE or suspected AE is considered "serious" if it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or any event that may jeopardize the

participant or require medical or surgical intervention. An AE for this study may be a hypersensitivity reaction in the form of bronchospasm requiring intensive treatment in the emergency room or clinic or result in hospitalization.

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT.

8.3.3.1 SEVERITY OF EVENT

For adverse events (AEs), guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment.
-

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION

All adverse events (AEs) will be assessed for relationship to study intervention as the following:

Related – The AE is known to occur with voxelotor, such as diarrhea, nausea, abdominal pain, and there is a reasonable possibility that voxelotor caused the AE, or there is a temporal relationship between voxelotor and the event.

Not Related – There is not a reasonable possibility that voxelotor caused the event, there is no temporal relationship between voxelotor and event onset, or an alternate etiology has been established.

OR

Definitely Related – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to taking voxelotor and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study intervention (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.

Probably Related – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after taking voxelotor, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.

Potentially Related – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after taking voxelotor). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.

Unlikely to be related – A clinical event, including an abnormal laboratory test result, whose temporal relationship to voxelotor makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after taking voxelotor) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).

Not Related – The AE is completely independent of voxelotor, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

8.3.3.3 EXPECTEDNESS

The PI will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for voxelotor in Section 2.3.1.

Expected AEs include: headache, diarrhea, abdominal pain, nausea, fatigue, rash, pyrexia

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

Example text provided as a guide, customize as needed:

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by the study PI.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate study database form. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The study coordinator will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.3.5 ADVERSE EVENT REPORTING

AEs will be reported to the GBT Medical Affairs Research Program at regular intervals as required by GBT. SAEs will be reported to GBT Pharmacovigilance or Designee and to the IRB within 24 hours after the investigator learns of the event. GBT or Sponsor-Investigator will be responsible for notifying the FDA of any unexpected fatal or life-threatening suspected SAE as soon as possible, but in no case later than 7 calendar days after GBT's initial receipt of the information.

Expected AEs will be recorded in CRFs.

8.3.6 SERIOUS ADVERSE EVENT REPORTING

The study principal investigator will immediately report to GBT Pharmacovigilance or Designee any serious adverse event, whether or not considered study intervention related, including those listed in the protocol or investigator brochure and must include an assessment of whether there is a reasonable possibility that the study intervention caused the event within 24 hours of finding out about the event. Study endpoints that are serious adverse events (e.g., all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the study intervention and the event (e.g., death from anaphylaxis). In that case, the investigator must immediately report the event to GBT Pharmacovigilance or Designee.

All serious adverse events (SAEs) will be followed until satisfactory resolution or until the PI deems the event to be chronic or the participant is stable. Other supporting documentation of the event may be requested by GBT and should be provided as soon as possible.

GBT Pharmacovigilance or Designee will be responsible for notifying the Food and Drug Administration (FDA) of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible, but in no case later than 7 calendar days after the initial receipt of the information from the study principal investigator. In addition, GBT Pharmacovigilance or Designee must notify FDA and all participating investigators in an Investigational New Drug (IND) safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after GBT Pharmacovigilance or Designee determines that the information qualifies for reporting.

8.3.7 REPORTING EVENTS TO PARTICIPANTS

Not applicable

8.3.8 EVENTS OF SPECIAL INTEREST

Not applicable

8.3.9 REPORTING OF PREGNANCY

In the event of pregnancy that occurs during study, the pregnancy will be reported to GBT Pharmacovigilance or Designee and the decision for the participant to continue on study or not will depend on the specific situation and will be discussed with GBT Pharmacovigilance or Designee.

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

Since the study intervention is a FDA-approved commercially available medication and CPET is a standardized orderable test, unanticipated problems would not involve risks but rather might be:

- Inability to enroll the expected number of patients, in which case, the possibility of extending the study until 10 patients are enrolled will be discussed with GBT.
- Subject unexpectedly moves away to a location such that travel to the exercise lab is not feasible and can no longer complete the study, in which case, the option of enrolling another subject to maintain the total number of evaluable subjects at 10 will be discussed with the sponsor

8.4.2 UNANTICIPATED PROBLEM REPORTING

The investigator will report unanticipated problems (UPs) to the reviewing Institutional Review Board (IRB) and to the principal investigator (PI). The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are serious adverse events (SAEs) will be reported to the IRB and to GBT Pharmacovigilance or Designee within 24 hours of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB and to GBT Pharmacovigilance or Designee within 10 days of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and the Office for Human Research Protections (OHRP) within 10 days of the IRB's receipt of the report of the problem from the investigator.]

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

Not applicable

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

- Primary Efficacy Endpoint(s): Peak VO2 in the CPET on voxelotor is higher than peak VO2 in baseline CPET.
- Secondary Efficacy Endpoint(s): Higher peak VO2 is correlated with improved biochemical markers of sickling and hemolysis.

Paired t-test will be used to evaluate results, as patients are their own controls.

9.2 SAMPLE SIZE DETERMINATION

This is a pilot study of 10 patients to define the magnitude of change. Power cannot be calculated at this time.

9.3 POPULATIONS FOR ANALYSES

There will be one dataset for this pilot study of 10 patients.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

Peak VO2 is measured as ml/kg/min or L/min and statistics will be presented as percent change between the peak VO2 on voxelotor and baseline peak VO2. As the primary objective of this study is to obtain clinical and laboratory information to justify a larger clinical efficacy trial of voxelotor in SCA patients, the results of this study will first be analyzed descriptively.

9.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

The primary endpoint is peak VO2, which is a quantitative measurement from the CPET instrument. There will be a single measurement as a baseline and another single measurement after the study drug for each participant. Paired t-test will be used to compare the 2 peak VO2s.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

The secondary endpoint is a group of biochemical tests, each with a different scale and different unit of measure. For each biochemical test, there will be a baseline measurement and a measurement after the study drug for each participant. Appropriate statistical comparison will be used for each biochemical measurement.

9.4.4 SAFETY ANALYSES

AEs will be coded by MedDRA terminology. Each AE will be counted once for a given participant. Severity, relationship to study drug, expectedness, dates, outcome, and duration of AEs will be reported.

9.4.5 BASELINE DESCRIPTIVE STATISTICS

Not applicable. There will only be one group.

9.4.6 PLANNED INTERIM ANALYSES

Not applicable

9.4.7 SUB-GROUP ANALYSES

Not applicable

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

Individual participant data will be listed by measure and time point.

9.4.9 EXPLORATORY ANALYSES

There are no exploratory analyses.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study intervention. The following consent materials are submitted with this protocol: sample consent and assent form, voxelotor information sheet.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

For subjects age < 18, the parent or legal guardian will sign the consent and the subject will sign the assent.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigator, and GBT Medical Affairs Research Program and the IRB. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and GBT Medical Affairs Research Program and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the IRB and/or Food and Drug Administration (FDA).

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators and the study team. This confidentiality covers the clinical information relating to participants. Therefore, the

study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the Principal Investigator.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the Principal Investigator, representatives of the Institutional Review Board (IRB), regulatory agencies or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies and requirements.

Study participant research data, which are for purposes of statistical analysis and scientific reporting, will be stored in a local secure database. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management system used will be secured and password protected. At the end of the study, all study data will be de-identified and archived.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

Data collected for this study will be analyzed and stored in a password-protected file on the site server. After the study is completed, the de-identified, archived data will be held by the sponsor investigator. Permission for GBT to access data will be included in the informed consent.

No biological specimens will be retained and no genetic material will be collected in this study.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Provide the name and contact information of the Principal Investigator and the Medical Monitor.

Principal Investigator
Elizabeth Yang, MD, PhD
Pediatric Specialists of Virginia
8081 Innovation Park Dr. Fairfax, VA 22031
571-472-1717
eyang@psvcare.org

The Medical Monitor will be the PI and the IRB, if necessary

The study team will consist of:
Principal Investigator – Elizabeth Yang, MD, PhD

Co-Investigators – Jared Hershenson, MD, Laura Caldarera, MA, RCEP, Ana Cortez, DO, Frans Kuypers, PhD
Clinical Research Assistants
Pharmacist

10.1.6 SAFETY OVERSIGHT

The study intervention is taking an oral, commercially available, FDA-approved drug and the study measurement is doing exercise studies, which is minimal risk. No DSMB is required.

10.1.7 CLINICAL MONITORING

This study is minimal risk, monitoring by PI and IRB is sufficient. No CMP is necessary.

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

The clinical site will perform internal quality management of study conduct, data collection, documentation and completion. The PI will check the quality and accuracy of data entry. The exercise lab is a certified exercise lab and will conduct its own quality control. The research lab conducts quality control on all its instrumentation and lab protocols.

Summarized data will be provided to GBT in study progress reports.

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the study team under the supervision of the principal investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents will be completed in a neat, legible manner to ensure accurate interpretation of data.

Hardcopies of the study visit worksheets will be provided for use when necessary as source document worksheets for recording data for each participant enrolled in the study. Data will be recorded in password-protected database accessible only by PI and the study personnel. Any source document on paper will be stored in locked cabinet in the Clinical Research Associate's office.

Clinical data (including adverse events (AEs), concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered a database designed for this study. The data system includes password protection. Clinical data will be entered directly from the source documents.

10.1.9.2 STUDY RECORDS RETENTION

Study documents will be retained for 3 years or as required by the IRB after completion of the study. No records will be destroyed without the written consent of the Sponsor-Investigator, if applicable. It is the responsibility of the investigator to determine when these documents no longer need to be retained.

10.1.10 PROTOCOL DEVIATIONS

Examples of protocol deviations in this study include:

- Noncompliance with voxelotor
- Starting the study drug before baseline CPET
- Failure to send study labs

Protocol deviations will be reported to the Sponsor-Investigator and a decision will be made whether to discontinue the subject from study, if the data from the subject will become uninterpretable.

10.1.11 PUBLICATION AND DATA SHARING POLICY

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

Any final peer-reviewed journal manuscripts that arise from this study will be submitted to the digital archive PubMed Central upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Data from this study may be requested from other researchers x years after the completion of the primary endpoint by contacting the study Principal Investigator.

10.1.12 CONFLICT OF INTEREST POLICY

All study team members will disclose conflicts of interest, which will be managed in ways that prevents interference with proper conduct of the study.

10.2 ADDITIONAL CONSIDERATIONS

10.3 ABBREVIATIONS

The list below includes abbreviations utilized in this template. However, this list should be customized for each protocol (i.e., abbreviations not used should be removed and new abbreviations used should be added to this list).

AE	Adverse Event
ANCOVA	Analysis of Covariance
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
DRE	Disease-Related Event
EC	Ethics Committee
eCRF	Electronic Case Report Forms
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FFR	Federal Financial Report
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GWAS	Genome-Wide Association Studies
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ISO	International Organization for Standardization
ITT	Intention-To-Treat
LSMEANS	Least-squares Means
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
MSDS	Material Safety Data Sheet
NCT	National Clinical Trial
NIH	National Institutes of Health
NIH IC	NIH Institute or Center
OHRP	Office for Human Research Protections
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMC	Safety Monitoring Committee

SOA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
UP	Unanticipated Problem
US	United States

10.4 PROTOCOL AMENDMENT HISTORY

The table below is intended to capture changes of IRB-approved versions of the protocol, including a description of the change and rationale. A Summary of Changes table for the current amendment is located in the Protocol Title Page.

Version	Date	Description of Change	Brief Rationale

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