CLINICAL STUDY PROTOCOL
GBT440-039

Study Number	**GBT440-039**
Study Title	A Phase 4, Multicenter, Open-label Study to Evaluate the Treatment Effect of Voxelotor on Physical Activity in Adolescents and Adults with Sickle Cell Disease
Study Drug	Voxelotor
IND Number	121,691
Sponsor	Global Blood Therapeutics, Inc. 181 Oyster Point Blvd South San Francisco, CA 94080 United States of America
Study Director	PPD , PharmD, MBA Senior Medical Science Director, Medical Evidence, Medical Affairs Global Blood Therapeutics, Inc. 181 Oyster Point Blvd South San Francisco, CA 94080 United States of America Telephone: PPD (office); PPD (mobile) Email: PPD
Protocol Amendment 2	28 April 2021
Protocol Amendment 1	18 May 2020
Original Protocol	29 January 2020

CONFIDENTIALITY STATEMENT

The information in this study protocol is strictly confidential and is available for review to investigators, study center personnel, the ethics committee and the health authorities. It will not be disclosed to third parties without written authorization from the Sponsor, except to obtain informed consent from persons receiving the study treatment. Once the protocol is signed, its terms are binding for all parties.

STATEMENT OF APPROVAL AND COMPLIANCE

A Phase 4, Multicenter, Open-label Study to Evaluate the Treatment Effect of Voxelotor on Physical Activity in Adolescents and Adults with Sickle Cell Disease

SPONSOR APPROVAL

The signature of the Sponsor representative below represents that the above-referenced clinical trial is being conducted under United States (US) Food and Drug Administration (FDA) Investigational New Drug (IND) Number 121691 GBT440 for the treatment of sickle cell disease. This IND application is held by Global Blood Therapeutics (GBT). The protocol is being conducted in accordance with International Council on Harmonisation (ICH) Good Clinical Practice (GCP) and all applicable federal, state and local regulations governing the conduct of this research, including the Department of Health and Human Services 45 Code of Federal Regulations (CFR) Part 46, FDA 21 CFR Parts 50, 54, 56, 312 and 812. GBT will provide the investigator with all information including safety information pertinent to the conduct of the study.

Sponsor Representative (Signature):	PPD
Name:	PPD
Date:	29-Apr-2021 | 05:11 PDT
Title:	Senior Medical Science Director

INVESTIGATOR APPROVAL

The signature of the investigator below constitutes approval of this protocol as written and reflects the investigator's commitment to conduct the study in accordance with the protocol, the applicable laws and regulations and in compliance with ICH GCP guidelines and the Declaration of Helsinki. All data obtained during the study will be provided to GBT. GBT requires that any presentation or publication of study data by an investigator be reviewed by GBT, before release.

Principal Investigator (Print):	
Signature:	
Date:	

TABLE OF CONTENTS

CLINICAL STUDY PROTOCOL GBT440-039 1
STATEMENT OF APPROVAL AND COMPLIANCE 2
TABLE OF CONTENTS 3
LIST OF TABLES 5
LIST OF FIGURES 5
SYNOPSIS 6
LIST OF ABBREVIATIONS AND DEFINITION OF TERMS 11
1. INTRODUCTION 13
1.1. Disease Background 13
1.2. Voxelotor 15
1.3. Summary of Relevant Nonclinical Data and Clinical Data 15
1.4. Rationale for the Study 16
1.5. Dose Rationale 17
2. STUDY OBJECTIVES 17
2.1. Safety 17
3. INVESTIGATIONAL PLAN 17
3.1. Study Design 17
3.2. Duration of Study Participation and Duration of the Study 19
3.3. Stopping Rules 19
4. SELECTION OF STUDY POPULATION 20
4.1. Inclusion Criteria 20
4.2. Exclusion Criteria 21
5. TREATMENTS ADMINISTERED 22
5.1. Treatment Regimen 22
5.2. Dose Frequency 22
5.3. Dose Modification 22
5.4. Physical Description 23
5.5. Formulation 23
5.6. Packaging and Labeling 23
5.7. Study Drug Supply 24
5.8. Storage and Handling Procedure 24

5.9. Drug Accountability and Retention 24
5.10. Treatment of Overdose 24
5.11. Concomitant Medications 25
5.12. Fertility/Contraceptive Requirements 26
5.13. Assessment of Treatment Compliance 28
6. STUDY PROCEDURES AND EVALUATIONS 28
6.1. Informed Consent/Assent 28
6.2. Unique Participant Number 28
6.3. Demographics and Medical History 28
6.4. Physical Examination 29
6.5. Vital Signs 29
6.6. Actigraphy Assessments 29
6.7. Nocturnal Pulse Oximetry 29
6.8. Patient-Reported Outcomes 29
6.9. Clinical Global Impression of Change (CGIC) 30
6.10. Adverse Events and Concomitant Medications 30
6.11. Laboratory Assessments 30
7. ADVERSE AND SERIOUS ADVERSE EVENTS 31
7.1. Adverse Events 32
7.2. Adverse Event Reporting 34
7.3. Serious Adverse Events and Requirements for Immediate Reporting 35
7.4. Reporting Pregnancy 36
7.5. Reporting Overdose 36
8. DATA ANALYSIS AND STATISTICAL PLANS 37
8.1. Endpoints 37
8.2. Sample Size 37
8.3. Populations for Analysis 37
8.4. Analyses 37
9. REGULATORY, ETHICAL AND LEGAL OBLIGATIONS 38
9.1. Ethical Conduct of the Study 38
9.2. Good Clinical Practice 38
9.3. Written Informed Consent and Assent 38
9.4. Institutional Review Board and Regulatory Approval 39

9.5. Essential Documentation Requirements 39
9.6. Confidentiality 39
9.7. Regulatory, Ethical, and Legal Obligations 40
9.8. Study Documentation and Data Storage 40
10. DATA HANDLING AND RECORDKEEPING 40
10.1. Inspection of Records 40
10.2. Retention of Records 41
10.3. Disclosure of Information 41
11. INSURANCE AND FINANCIAL DISCLOSURE 42
12. PUBLICATION POLICY 42
13. ADMINISTRATIVE OBLIGATIONS 42
13.1. Source Data 42
13.2. Data Collection 43
13.3. Monitoring 43
13.4. Quality Control, Quality Assurance and Regulatory Inspections 43
14. REFERENCES 44
APPENDIX 1. SCHEDULE OF ASSESSMENTS 47

LIST OF TABLES

Table 1: Dose Modification Guidelines for Study Drug–Related Adverse Events 23
Table 2: Sensitive CYP3A4 Substrates with a Narrow Therapeutic Range 25
Table 3: Examples of Strong CYP3A4 Inhibitors 26
Table 4: Examples of Moderate and Strong CYP3A4 Inducers 26
Table 5: Clinical Laboratory Tests 31
Table 6: Grading for Adverse Events not Covered in the NCI CTCAE 33

LIST OF FIGURES

Figure 1: Study Schematic 49

SYNOPSIS

Title	A Phase 4, Multicenter, Open-label Study to Evaluate the Treatment Effect of Voxelotor on Physical Activity in Adolescents and Adults with Sickle Cell Disease
Short Title	Actigraphy Improvement with Voxelotor (ActIVe) Study
Protocol Number	GBT440-039
Sponsor	Global Blood Therapeutics, Inc. 181 Oyster Point Blvd South San Francisco, CA 94080 United States of America
Study Drug	Voxelotor, 1500 mg administered orally (three 500 mg tablets)
Study Description	This study is a Phase 4 multicenter, open-label, single-arm study to evaluate the effect of voxelotor on daily physical activity and sleep quality, as measured by actigraphy in participants with sickle cell disease (SCD) and chronic moderate anemia. Actigraphy assessments will be performed using wrist-worn tri-axial accelerometry device.
Objectives	The objectives of this study are to explore the effect of voxelotor on the below and are considered exploratory: • Change in physical activity as measured by actigraphy in adolescent and adult participants with SCD and chronic moderate anemia • Change in sleep quality as measured by overnight actigraphy • Change in peripheral oxygen saturation (SpO_2) as measured by overnight monitoring • Change in hemoglobin (Hb) response, as defined by > 1 g/dL increase from baseline • Patient-reported outcome (PRO) measures of physical activity, fatigue, sleep quality, pain interference, depression, anxiety, and overall function (Patient-Reported Outcome Measurement Information System [PROMIS®], PROMIS Pediatric Profile-37 v2.0/PROMIS-43 V2.1 and Patient Global Impression of Change [PGIC]) • Clinician global impression of change (CGIC) • Safety and tolerability of voxelotor

Study Design	The study is divided into a Screening Period, a Run-in Period, an Open-label Treatment Period and a Follow-up Period. Participant safety and tolerability will be monitored during the study using standard measures, including physical examinations, vital signs (including temperature, blood pressure, pulse rate, respiratory rate, and SpO_2, clinical laboratory tests, and adverse event [AE] monitoring). **Screening Period (up to 4 weeks in duration):** During this period, participants will sign the informed consent form (ICF), after which they will complete the screening assessments as detailed in the Schedule of Assessments (SOA). **Run-in Period (2 weeks in duration):** During this period, participants will enter a 2-week Run-in Period (Day 14 to Day -1) during which baseline actigraphy measures of physical activity and sleep quality, overnight pulse oximetry assessments of oxygen saturation, and PRO assessments will be collected before initiating treatment with voxelotor. **Treatment Period (24 weeks in duration):** After completion of the 14-day Run-in Period, participants will enter the open-label Treatment Period and receive voxelotor 1500 mg once daily for 24 weeks. Repeat actigraphy assessments of physical activity and sleep quality, and overnight pulse oximetry will be performed during the Treatment Period (Weeks 10 to 12 and Weeks 22 to 24). PRO and CGIC assessments will be completed at scheduled study visits. The open-label Treatment Period is considered the continuous 24 weeks of voxelotor treatment from date of first dose (Day 1). **Follow-up Period (4 weeks in duration):** Immediately following the 24-week Treatment Period, participants will enter a 4-week Follow-up Period.
Dose	During the open-label Treatment Period, all participants will receive 1500 mg of voxelotor once daily (administered as three 500 mg tablets) for 24 weeks
Number of Participants	Approximately 50 eligible participants will initiate treatment in this study.
Number of Centers	The study will be conducted at approximately 10 clinical sites in the United States (US).
Duration of Study Participation	The total duration of the study will be approximately 34 weeks.

Study Population	**Inclusion Criteria:** Participants who meet all the following criteria will be eligible for enrollment in this study: 1. Male or female participants with sickle cell anemia (SCA) (sickle hemoglobin with two sickle cell genes [HbSS] or sickle hemoglobin (S) and one beta thalassemia gene [HbS β0] thal genotype) 2. Between 12 to 55 years of age (inclusive) 3. Screening Hb level ≤ 8.0 g/dL 4. Treatment with hydroxyurea (HU) therapy on study is permitted if the participant has been on a stable dose for at least 90 days before enrollment with no dose modifications planned or anticipated by the investigator 5. Treatment with glutamine is permitted 6. Treatment with erythropoiesis-stimulating agents (ESAs) is permitted if the participant has been on a stable dose for at least 12 weeks before enrollment with no dose modifications planned or anticipated by the investigator 7. Female participants of child-bearing potential must use highly effective methods of contraception to 30 days after the last dose of study drug. Male participants must use barrier methods of contraception to 30 days after the last dose of study drug 8. Females of child-bearing potential and postmenopausal females are required to have a negative pregnancy test before the administration of study drug 9. Written informed consent and/or parental/guardian consent and participant assent per Institutional Review Board (IRB) policy and requirements, consistent with International Council on Harmonisation (ICH) guidelines **Exclusion Criteria:** Participants meeting any of the following exclusion criteria will not be eligible for study enrollment: 1. Red blood cell (RBC) transfusion within 3 months before initiation of study drug 2. Planned initiation of regularly scheduled RBC transfusion therapy (also termed chronic, prophylactic, or preventive transfusion) during the study 3. Hospitalization for vaso-occlusive crisis (VOC) or acute chest syndrome (ACS) within 30 days prior to informed consent/assent. 4. More than 10 VOCs requiring hospitalization, emergency department or clinic visit within the past 12 months 5. Planned elective surgery within the next 6 months 6. Physical inactivity attributable to clinically significant musculoskeletal, cardiovascular, or respiratory comorbidities 7. Anemia due to bone marrow failure (eg, myelodysplasia) 8. Absolute reticulocyte count (ARC) < 100×10^9/L 9. Screening alanine aminotransferase (ALT) > 4 × upper limit of normal (ULN) 10. Severe renal dysfunction (estimated glomerular filtration rate < 30 mL/min/1.73 m^2 by Schwartz formula) or is on chronic dialysis

	11. Known active hepatitis A, B, or C or known to be human immunodeficiency virus (HIV)-positive. 12. Females who are breast-feeding or pregnant 13. Major surgery within 8 weeks before enrollment. Participants must have completely recovered from any previous surgery before enrollment 14. History of hematopoietic stem cell transplant or gene therapy 15. Received an investigational drug within 30 days or 5-half-lives, whichever is longer, prior to consent, or is currently participating in another trial of an investigational or marketed drug (or medical device) 16. Use of concomitant medications (eg, crizanlizumab) that confound the ability to interpret data from the study 17. Medical, psychological, or behavioral condition that, in the opinion of the investigator, would confound or interfere with evaluation of safety and/or efficacy of the study drug, prevent compliance with the study protocol; preclude informed consent; or, render the participant unable/unlikely to comply with the study procedures 18. Use of herbal medications (eg, St. John's Wort), sensitive cytochrome P450 (CYP) 3A4 substrates with a narrow therapeutic index, strong CYP3A4 inhibitors, fluconazole, or moderate or strong CYP3A4 inducers 19. Symptomatic coronavirus disease of 2019 (COVID-19) infection
Concomitant Medications and Restrictions	The following concomitant medications are **allowed**: • HU (stable dose for at least 3 months before signing the ICF and with no dose modifications planned or anticipated and no sign of hematological toxicity) • Glutamine • ESAs (stable dose for at least 4 weeks with no dose modifications planned or anticipated by the investigator) The following concomitant medications are **prohibited**: • Sensitive CYP3A4 substrates with a narrow therapeutic range • Strong CYP3A4 inhibitors or fluconazole • Moderate and strong CYP3A4 inducers • Crizanlizumab (Adakveo®) • Other experimental SCD therapy
Study Endpoints	All endpoints in this study are exploratory and include: • Change in total daily physical activity (expressed in counts per minute) from baseline to Week 10-12 and to Week 22-24 • Categorical change from baseline in total daily physical activity as: light (LPA), moderate (MPA), and vigorous (VPA) physical activity from baseline to Week 12 and Week 24 • Change in total nocturnal sleep time from baseline to Week 10-12 and to Week 22-24

	• Change in wake time after sleep onset from baseline to Week 10-12 and to Week 22-24 • Change in sleep efficiency from baseline to Week 10-12 and to Week 22-24 • Change in mean overnight SpO_2 (%) and median number of overnight SpO_2 dips > 3% per hour from baseline to Week 2 and to Week 12 and to Week 22-24 • Proportion of participants with a > 1 g/dL increase in Hb from baseline to Week 10-12 and to Week 22-24 • Change in PRO measures (PROMIS Pediatric Profile-37 v2.0/PROMIS-43 V2.1) • PGIC score at Week 24 • CGIC score at Week 24

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Description
ACS	acute chest syndrome
AE	adverse event
ALT	alanine aminotransferase
ARC	absolute reticulocyte count
AST	aspartate aminotransferase
CFR	(United States) Code of Federal Regulations
CGIC	Clinician Global Impression of Change
COVID-19	coronavirus disease of 2019
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
eCRF	electronic case report form
EDC	electronic data capture
EOS	end of study
ESA	erythropoiesis-stimulating agents
GBT	Global Blood Therapeutics
GCP	Good Clinical Practice
Hb	hemoglobin
HbF	fetal hemoglobin
HbS	sickle hemoglobin
HbS β^0 thal	sickle cell disease due to inheritance of one sickle hemoglobin (S) allele and one beta zero thalassemia (β^0 thal) allele
HbSS	sickle cell disease due to inheritance of two sickle hemoglobin (S) alleles
HU	Hydroxyurea
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council on Harmonisation
IND	Investigational New Drug
IID	Inactive Ingredient Database
IRB	Institutional Review Board
NCI	National Cancer Institute
oxyHb	oxyhemoglobin

Abbreviation	Description
PD	pharmacodynamic(s)
PE	physical examination
PGIC	Patient Global Impression of Change
PRO	patient-reported outcome(s)
PROMIS	Patient-Reported Outcomes Measurement Information System
QOL	quality of life
RBC	red blood cell
RSI	Reference Safety Information
SAE	serious adverse event
SCA	sickle cell anemia
SCD	sickle cell disease
SOA	schedule of assessments
SpO_2	peripheral oxygen saturation
SUSAR	suspected unexpected serious adverse reactions
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
US(A)	United States (of America)
VOC	vaso-occlusive crisis

1. INTRODUCTION

1.1. Disease Background

Sickle cell disease (SCD) is an inherited blood disorder caused by a point mutation in the βglobin gene resulting in the formation of sickle hemoglobin (HbS). The disease is marked by the pathophysiologic features of hemolytic anemia, microvascular occlusion, and progressive end-organ damage, with a clinical course characterized by life-long disability and early death.[1, 2] In addition to unpredictable and recurrent vaso-occlusive pain episodes, hemolytic anemia directly damages blood vessels, resulting in a systemic vasculopathy that leads to progressive tissue and organ injury.[3, 4] Cumulative injury to multiple organ systems from repeated episodes of red blood cell (RBC) sickling, vaso-occlusion, and chronic hemolytic anemia detrimentally affects patients' quality of life (QOL) and overall functioning.[5]

1.1.1. Impact of Anemia on Physical Activity and Sleep Quality in Sickle Cell Disease

Moderate-to-severe anemia is a common feature of SCD. In individuals with the more severe form (sickle hemoglobin with two sickle cell genes [HbSS] or sickle hemoglobin (S) and one beta thalassemia gene [HbS/β^0] thalassemia), referred to as sickle cell anemia (SCA), average hemoglobin (Hb) concentrations range from 6 to 8 g/dL.[6]

Anemia is a well-established risk factor for cerebrovascular, cardiopulmonary, and renal complications in SCD.[2, 7, 8, 9, 10] Chronic anemia in SCD and other hemolytic disorders is also associated with lower physical activity levels and symptoms of fatigue, shortness of breath, sleep disturbance, and reduced QOL.[11, 12, 13, 14] Similar associations of anemia with impaired physical functioning and limited daily activities have been reported in adults with renal failure.[7]

Impaired exercise performance and overall diminution of activity have been observed in both adults and adolescent patients with SCD.[15] Exercise limitation may be related to the anemia directly or to chronic complications such as pulmonary vascular disease, congestive heart failure, and chronic parenchymal lung disease.[16, 17, 11] Chronically low Hb levels are associated with decreased aerobic capacity and exercise performance in individuals with beta thalassemia.[18] Pre-transfusion Hb level and functional status are the leading indications for RBC transfusion in these patient populations.

There is growing evidence that SCD pathophysiology is associated with Hb oxygen desaturation at rest and during exercise.[19] Approximately 50% of children with SCA have mild or moderate oxygen desaturation at rest that is independently associated with hemolysis. Exercise-induced Hb oxygen desaturation is observed in 34% of children with SCA. Low Hb oxygen saturation is associated with severity of anemia and markers of hemolysis.[20]

Sleep disordered breathing and nocturnal oxygen desaturation events are common in SCD with a reported prevalence of 69% in children and adolescents and 50% in adults.[21, 22,23] Nocturnal hypoxemia is also associated with reduced exercise capacity, poor sleep quality, diminished self-reported QOL and is a risk factor for stroke, cardiopulmonary complications, and death.[23, 24, 25] In individuals with SCD, lower baseline oxygen saturation significantly correlates with anemia and worsening neurocognitive performance.[26, 27] Hydroxyurea and blood transfusions are therapies used to improve oxygen saturation and alleviate associated complications.[28]

1.1.2. Relationship Between Anemia and Fatigue

Although pain is the most frequent symptom reported by individuals living with SCD, fatigue is an increasingly recognized symptom that interferes with the ability to carry out daily activities.[29] Adolescents with SCD report lower levels of general, sleep/rest, cognitive, and total fatigue compared to healthy peers,[30] and young adults with SCD report significantly lower levels of vitality (energy) than the general population.[14]

Despite the known pathophysiologic effects of chronic hemolytic anemia on tissue oxygenation, there has been little research examining the association between anemia and fatigue in SCD. Anemia is a significant contributor to fatigue in diseases such as cancer[31, 32] and chronic kidney disease.[33] In patients receiving transfusion for anemia related to other causes, an average increase in Hb of 1 g/dL was associated with a significant reduction in fatigue.[34]

In a recent study examining biologic and behavioral correlates of fatigue in adolescents with SCD, lower Hb levels were associated with higher scores on Patient Reported Outcomes Measurement Information System (PROMIS®) measures of fatigue and sleep interference.[35] Moreover, fatigue interfered with mood and daily activities such as school, work, and exercise. The relationship between anemia, physical activity, sleep quality, and fatigue symptoms in the SCD population suggests that therapeutic interventions to improve anemia may be an effective strategy to impact these outcomes.

1.1.3. Actigraphy Measures of Physical Activity

Actigraphy makes use of wearable digital movement sensors, such as accelerometers, for continuous activity monitoring to capture objective real-world data that correlates to patient functional abilities and health outcomes. As an accepted methodology for tracking activity levels, time spent in moderate and vigorous physical activity, step counts, and energy expenditure, actigraphy is being increasingly utilized to identify clinically meaningful activity parameters and has even been incorporated as a primary endpoint in clinical trials for cardiopulmonary indications.

A recent cross-sectional study using actigraphy to evaluate physical activity in SCD found that children and adolescents with SCD took fewer steps, spent significantly less time in moderate-to-vigorous daily activity, and burned fewer calories compared with healthy controls.[36] Moreover, among the participants in this study, the time spent in vigorous physical activity was significantly lower in those with a Hb level less than 8 g/dL compared to those with higher Hb levels.

The specific impact of chronic anemia on physical activity, sleep patterns, and QOL in SCD merits further investigation. Therapeutic agents with the potential to improve daily activity, sleep, and overall well-being in children and adults with SCD are needed. Voxelotor, an inhibitor of HbS polymerization, has recently been approved for the treatment of anemia in SCD.[37] This exploratory study aims to evaluate the therapeutic potential of voxelotor to improve physical activity levels, sleep quality, and other patient-reported QOL measures, by targeting anemia.

1.2. Voxelotor

Voxelotor (previously GBT440) is a HbS polymerization inhibitor that binds to HbS with a 1:1 stoichiometry and exhibits preferential partitioning to RBCs. Voxelotor binds covalently and reversibly to the N-terminal valine of the Hb α chain and allosterically increases HbS-oxygen (O_2) affinity,[38] stabilizing the oxyhemoglobin (oxyHb) state and inhibiting polymerization.[39] The voxelotor binding site is distant from heme pockets and it can therefore increase O_2 affinity without sterically blocking the release of O_2.

A primary and obligatory event in the molecular pathogenesis of SCD is the polymerization of deoxygenated HbS. Because oxyHb is a potent inhibitor of HbS polymerization, increasing the proportion of oxyHb in all RBCs with voxelotor can reduce HbS polymerization, decrease RBC membrane damage and destruction, and potentially achieve long-term disease modification. This principle is supported by the finding that in patients with in patients with coinherited HbS and hereditary persistence of fetal hemoglobin (HbS/HPFH), the dilution of HbS by 20% to 30% fetal hemoglobin (HbF) in all RBCs is sufficient to inhibit HbS polymerization, preventing RBC damage and SCD clinical sequelae. This suggests that pharmacologically maintaining approximately 20% to 30% of Hb in the nonpolymerizing oxygenated state in all RBCs may be an effective approach for the treatment of SCD. This therapeutic effect was demonstrated in the pivotal Phase 3 study (GBT440-031) where 1500 mg of voxelotor, achieving Hb modification of 20-30%, administered daily orally for 24 weeks showed a significant and clinically meaningful increase in Hb and decrease in hemolysis.[37]

Voxelotor was approved for use in the United States (US) under the tradename Oxbryta® by the Food and Drug Administration (FDA) and is indicated for the treatment of SCD in adults and pediatric patients 12 years of age and older.

Voxelotor continues to be evaluated in ongoing clinical studies exploring the safety, tolerability, pharmacokinetics, pharmacodynamics (PD), and treatment response in pediatric and adult participants with SCD as well as in clinical pharmacology studies in healthy adult participants.

1.3. Summary of Relevant Nonclinical Data and Clinical Data

1.3.1. Nonclinical Data

Primary PD studies of voxelotor consisted of in vitro and in vivo studies to characterize (a) voxelotor binding and affinity for Hb, (b) the effect of voxelotor on HbS modification using purified Hb, washed RBCs, and whole blood, and (c) the efficacy of voxelotor in vivo in a mouse model of SCD. These in vitro assays of increasing complexity included measuring HbO_2 via hemoximetry, quantifying stabilization of the oxyhemoglobin state conformation, delaying HbS polymerization at low oxygen tension, preventing in vitro sickling induced by a low oxygen environment, decreasing viscosity, and improving deformability of RBCs in blood from patients with SCD. In addition, these studies show that voxelotor-modified Hb retains the Bohr Effect, which is the ability to augment oxygen delivery in metabolically active (low pH) tissues.

Collectively, these studies demonstrate that voxelotor potently increases HbO_2 affinity with high specificity of binding to Hb; stabilizes the oxygenated or relaxed-state conformation of Hb; prevents HbS polymerization and RBC sickling in vitro; and improves sickle blood viscosity, and deformability in vitro. In addition, voxelotor increases HbS-oxygen affinity and RBC lifespan, while decreasing ex vivo sickling and reticulocyte count in a SCD mouse model.

Additional information regarding nonclinical pharmacology (including safety pharmacology and metabolism) and toxicology is provided in the most current version of the Investigator's Brochure (IB) for voxelotor.

1.3.2. Clinical Data

Global Blood Therapeutics' (GBT's) clinical development program for voxelotor and the results of clinical studies in participants with SCD are detailed in the current version of the IB.

1.3.2.1. Summary of the Known and Potential Risks and Benefits of Voxelotor

Voxelotor is well tolerated in adult and pediatric participants 4 years of age and older with SCD. Adverse events, primarily associated with underlying disease and gastrointestinal events, were generally low-grade in severity, were managed by dose reduction and/or symptomatic treatment, and seldom resulted in discontinuation of therapy. Identified risks, which include the ADRs of diarrhea, abdominal pain, nausea, rash, and drug hypersensitivity, were low grade in severity and clinically manageable.

In the pivotal Phase 3 study, Study GBT440-031, voxelotor was shown to significantly increase Hb, improve anemia, and reduce clinical measures of hemolysis in adult and pediatric participants 12 years of age and older with SCD.

There have been no major safety findings arising from the ongoing studies or any pattern of adverse events (AEs) that would raise concerns or alter the benefit-risk profile of voxelotor. Clinical data to date support further development of voxelotor in adult and pediatric SCD populations.

In conclusion, voxelotor has a favorable benefit-risk profile based on clinical data from studies enrolling participants 4 years of age and older with SCD. Overall, by inhibiting HbS polymerization voxelotor has the potential to alter the clinical course of the disease by improving anemia and hemolysis in SCD disease.

1.4. Rationale for the Study

Sickle cell disease is a chronic debilitating disease characterized by vaso-occlusive episodes, hemolytic anemia, and progressive vascular injury to multiple organ systems.[22] Chronic anemia is associated with decreased physical activity, poor sleep quality, cognitive impairment, fatigue and reduced QOL in patients with SCD. Given the negative impact of anemia on physical activity, sleep, and QOL in SCD and other hemolytic disorders, treatment of anemia represents a rational approach to improve measures of daily functioning. Voxelotor has been well tolerated in adult and pediatric participants aged ≥ 4 years and has shown rapid, significant, and sustained improvement in Hb and hemolysis measures over that achieved from standard-of-care therapy including HU;[37] therefore, exploration of the effect of voxelotor in participants who may have the greatest potential to benefit from a disease-modifying therapy is warranted. Actigraphy provides an objective measure of physical function and has been successfully used in prospective interventional studies to assess the impact of pharmacologic treatments on physical activity, sleep, and QOL measures. The rationale for this study is based on the potential for voxelotor, through its effects on anemia and hemolysis, to improve measures of daily functioning, as assessed by actigraphy in participants with SCD and moderate anemia.

1.5. Dose Rationale

Voxelotor is indicated for the treatment of SCD in adults and pediatric patients 12 years of age and older. This indication was approved under accelerated approval based on increase in Hb. The approved dose of 1500 mg taken orally once daily is supported by results of the pivotal Phase 3 Study GBT440-031 in adults and adolescents with SCD demonstrating: (1) a statistically significant and clinically meaningful increase in mean Hb level of 1.1 g/dL and reductions in clinical markers of hemolysis observed with voxelotor 1500 mg compared to placebo and which were more robust than those observed with voxelotor 900 mg; (2) a favorable safety profile with absence of concerning exposure-related safety findings[37]; 3) the efficacy of the 1500 mg dose in adolescents is supported by similar improvements Hb and hemolysis measures observed in the Phase 2a Study GBT440-007[40]; 4) exposure-response analyses using data from both Study GBT440-031 and Study GBT440-007 demonstrating dose-dependent treatment effects of voxelotor on Hb and hemolysis measures; and 5) the majority of adult and adolescent participants receiving voxelotor 1500 mg in the GBT440-031 study achieved the intended therapeutic target of 20% to 30% mean % Hb occupancy.

2. STUDY OBJECTIVES

The objectives of this study are to evaluate the effect of voxelotor on the outcomes listed below and are considered exploratory:

- Change in daily physical activity as measured by actigraphy in adolescent and adult participants with SCD and chronic moderate anemia
- Change in sleep quality as measured by overnight actigraphy monitoring
- Change in peripheral oxygen saturation (SpO_2) as measured by overnight SpO_2 monitoring
- Change in Hb response, as defined by > 1 g/dL increase from baseline
- Change in nocturnal oxygen saturation as assessed by overnight pulse oximetry
- Patient-reported outcome (PRO) measures of physical activity, fatigue, sleep quality, pain interference, depression, anxiety, and overall function (PROMIS), and Patient Global Impression of Change (PGIC)
- Clinician global impression of change (CGIC)

2.1. Safety

The safety and tolerability of voxelotor will be evaluated.

3. INVESTIGATIONAL PLAN

3.1. Study Design

This study is a Phase 4, multicenter, open-label, single-arm study to evaluate the effect of voxelotor on daily physical activity, measured by actigraphy, in participants with SCD and

chronic moderate anemia. The study is composed of a 28-day Screening Period, a 14-day Run-in Period, a 24-week Treatment Period, and a 28-day (4-week) Follow-up Period after last dose.

This study will be conducted at approximately 10 clinical trial sites in the US. The overall study design is illustrated in the Study Schematic provided in Figure 1.

Screening Period (28 days prior to Run-in)

After signed informed consent and/or assent form has been provided, all eligibility criteria are met, and screening assessments have been completed, participants (12 to 55 years of age [inclusive]) will enter the Run-in Period.

Run-in Period (14 days)

During the Run-in Period, participants will be given a wrist-worn actigraphy device (eg, tri-axial accelerometer) to be worn continuously throughout the Run-in and Treatment Periods. Baseline measurements of physical activity, sleep parameters, and nocturnal oxygen saturations (SpO_2) will be established during the Run-in Period.

Participants will also be given a home pulse oximeter to record continuous overnight oxygen saturation during a scheduled overnight evaluation to establish baseline nocturnal SpO_2. Additionally, QOL PRO assessments for measures of fatigue, sleep interference, pain (PROMIS), and depression (Patient Healthy Questionnaire-9 [PHQ-9]) will be completed during the Run-in Period.

Treatment Period (24 weeks)

Participants will be given a wrist-worn actigraphy device (eg, tri-axial accelerometer) to be worn continuously throughout the Run-in and Treatment Periods. During the Treatment Period, actigraphy assessments of physical activity and sleep quality, and overnight pulse oximetry assessments will be performed at scheduled time points. PRO and CGIC will be assessed at scheduled study visits. The open-label Treatment Period is considered the continuous 24 weeks of voxelotor treatment from date of first dose (ie, Day 1).

Follow-up Period (28 days)

Safety assessments including the collection of AE data, vital sign measurements, physical examinations, and laboratory evaluations will be collected at scheduled study visits.

3.1.1. Study Treatment

Dosage and treatment administration are described in Section 5.

3.1.2. Study Assessments

Study procedures and assessments are described in Section 6. The timing of the scheduled procedures and assessments are provided in Appendix 1.

Safety will be assessed during the study using standard measures, including AE monitoring, clinical laboratory tests, vital sign measurements, physical examinations (PEs), and concomitant medication use. SCD-related complications will also be monitored.

3.1.3. Study Endpoints

Study endpoints are described in Section 8.1.

3.1.4. COVID-19 Risk Evaluation and Action Plan

The Sponsor, or designee, will determine a risk-evaluation plan and implement an action plan considering the need to reduce unnecessary contacts in the context of the coronavirus disease of 2019 (COVID-19) pandemic or other epidemiological emergency. Site visits may be replaced by enhanced centralized monitoring or local visits may be postponed. These methods will be described in a monitoring plan by the Sponsor, or designee.

3.2. Duration of Study Participation and Duration of the Study

Participation is expected to last up to 34 weeks, including a 4-week Screening Period, a 2-week Run-in Period, a 24-week Treatment Period and a 4-week Follow-up Period.

The study will end when the last participant's last visit occurs.

3.3. Stopping Rules

3.3.1. Early Discontinuation of the Study

The Sponsor has the right to terminate the study at any time. Reasons for terminating the study may include, but are not limited to, the incidence or severity of TEAEs in this or other studies indicating a potential health hazard to participants.

In any instance of early termination of the study, the Sponsor will notify, in writing, the investigators, regulatory authorities, and Institutional Review Boards (IRBs) and will specify the reason(s) for termination.

3.3.2. Discontinuation of Individual Participants

3.3.2.1. Withdrawal of Consent

Participants and/or their caregiver/legal representative will be informed that participation is voluntary and that they may withdraw from study at any time and for any reason. Any participant who requests to be withdrawn or whose caregiver/legal guardian requests withdrawal will be withdrawn from the study by the investigator.

3.3.2.2. Discontinuation of Study Treatment

Participants may be discontinued from study treatment for any of the following reasons:

- Participant is lost to follow-up.

  Every effort should be made for the participant to return to the clinic to complete the scheduled study visits. If the participant fails to return for the scheduled study visit, a documented effort must be made to determine the reason. If the participant cannot be reached by telephone after 2 attempts, a certified letter will be sent to the participant (or participant's legally authorized representative, if appropriate) requesting the participant to contact the investigator. This information will be recorded in the study

records. Only after the documented efforts are conducted and the participant is still unresponsive will the participant be considered lost to follow-up.

- Adverse event(s)
- Discretion of the investigator
- Discretion of the Sponsor
- Pregnancy

The participant should return to the investigational site for an End of Study (EOS) visit approximately 28 days after the last dose of study treatment as indicated in Appendix 1.

4. SELECTION OF STUDY POPULATION

Eligibility will be based on assessments performed prior to receiving study drug on Day 1 in this study.

A participant will be enrolled after signing the informed consent form (ICF) or the assent form for this study. Informed consent/assent must be properly executed prior to the performance of any protocol-required assessments or procedures.

4.1. Inclusion Criteria

Participants who meet all of the following inclusion criteria will be eligible for study enrollment:

1. Male or female with SCA (HbSS or [HbS β^0]thal genotype)
2. Age 12 to 55 years, inclusive
3. Hb ≤ 8.0 g/dL during screening
4. Treatment with HU therapy on study is permitted if the participant has been on a stable dose for at least 90 days before enrollment with no dose modifications planned or anticipated by the investigator
5. Treatment with glutamine is permitted
6. Treatment with erythropoiesis-stimulating agents (ESAs) is permitted if the participant has been on a stable dose for at least 12 weeks before enrollment with no dose modifications planned or anticipated by the investigator
7. Female participants of child-bearing potential must use highly effective methods of contraception to 30 days after the last dose of study drug. Male participants must use barrier methods of contraception to 30 days after the last dose of study drug.
8. Females of child-bearing potential and postmenopausal females are required to have a negative pregnancy test before the administration of study drug
9. Written informed consent and participant assent per IRB policy and requirements, consistent with International Council and Harmonisation (ICH) guidelines

4.2. Exclusion Criteria

Participants meeting any of the following exclusion criteria will not be eligible for study enrollment:

1. RBC transfusion within 3 months before initiation of study drug
2. Planned initiation of regularly scheduled RBC transfusion therapy (also termed chronic, prophylactic, or preventive transfusion) during the study
3. Hospitalization for VOC or acute chest syndrome (ACS) within 30 days prior to informed consent/assent.
4. More than 10 VOCs requiring hospitalization, emergency department or clinic visit within the past 12 months
5. Planned elective surgery within the next 6 months
6. Physical inactivity attributable to clinically significant musculoskeletal, cardiovascular, or respiratory comorbidities
7. Anemia due to bone marrow failure (eg, myelodysplasia)
8. Absolute reticulocyte count (ARC) $< 100 \times 10^9$/L
9. Screening alanine aminotransferase (ALT) > 4 × upper limit of normal (ULN)
10. Severe renal dysfunction (estimated glomerular filtration rate < 30 mL/min/1.73 m^2 by Schwartz formula) or is on chronic dialysis
11. Known active hepatitis A, B, or C or who are known to be human immunodeficiency virus (HIV) positive.
12. Females who are breast-feeding or pregnant
13. Major surgery within 8 weeks before enrollment. Participants must have completely recovered from any previous surgery before enrollment
14. History of hematopoietic stem cell transplant or gene therapy
15. Received an investigational drug within 30 days or 5-half-lives, whichever is longer, prior to consent, or is currently participating in another trial of an investigational or marketed drug (or medical device)
16. Use of concomitant medications (eg, crizanlizumab) that confound the ability to interpret data from the study
17. Medical, psychological, or behavioral condition that, in the opinion of the investigator, would confound or interfere with evaluation of safety and/or efficacy of the study drug, prevent compliance with the study protocol, preclude informed consent, or render the participant unable/unlikely to comply with the study procedures
18. Use of herbal medications (eg, St. John's Wort), sensitive cytochrome P450 (CYP) 3A4 substrates with a narrow therapeutic index, strong CYP3A4 inhibitors, or fluconazole
19. Symptomatic COVID-19 infection

5. TREATMENTS ADMINISTERED

5.1. Treatment Regimen

Participants will be instructed to take 1500 mg of voxelotor (three 500 mg tablets) orally once daily for 24 weeks (168 days).

Instructions for administration of voxelotor tablets:

- Details regarding oral administration of the voxelotor tablets are provided in the Pharmacy Manual (provided separately).
- For younger participants, voxelotor administration should be supervised by a parent or guardian. Detailed instructions will be provided to participants and their caregivers/legal guardians prior to the first dose of study drug.

Treatment compliance will be based on comparison of the dispensed versus returned study drug.

At assigned visits, participants will be supplied a sufficient quantity of voxelotor to ensure continuous dosing through to the next dispensing visit. All study drug packaging must be returned at designated visits, regardless of whether it is empty or contains unused study drug.

5.2. Dose Frequency

Participants will receive a 1500 mg dose of voxelotor as three 500 mg tablets administered orally, once daily. If a participant misses a dose, the participant should resume normal dosing the next day (ie, the dose on the day after a day of a missed dose should not be increased or decreased).

5.3. Dose Modification

Participants should adhere to their assigned dose level. However, dose modification may be considered if warranted as outlined in Table 1.

All instances of study drug modification (dose reduction, interruption, or discontinuation) should be documented in the participants' medical record and recorded in the electronic case report form (eCRF). If the condition/event leading to the dose modification has resolved, the original dose level should be resumed, unless in the judgment of the investigator this cannot be done safely.

Table 1: Dose Modification Guidelines for Study Drug–Related Adverse Events

Dose Reduction	
Event	**Recommended Action**
Grade ≥ 2 (NCI grading scale) AE deemed considered related to study drug by the Investigator AND Precludes continued dosing at the current dose level due to safety concern or lack of tolerability (in the Investigator's judgment)	**Study drug:** May be reduced by one (1) tablet. If, in the opinion of the Investigator, a Grade 2 AE has resolved to ≤ Grade 1, participant may resume study drug at the original dose. If, in the opinion of the Investigator, the AE poses a significant safety concern such that a dose hold is considered, the Investigator should contact the Medical Monitor.
Dose Interruption (Hold)	
Event	**Recommended Action**
Grade ≥ 3 (NCI grading scale) AE deemed considered related to study drug by the Investigator AND Precludes continued dosing at the current or at a reduced dose level due to safety concern or lack of tolerability in the Investigator's judgment	**Study drug:** Hold dose until ≤ Grade 2, then resume study drug at original dose. If, in the opinion of the Investigator, dosing should be resumed at a lower dose, contact the Medical Monitor for further discussion. If the AE recurs or worsens, reduce dose by one tablet. Maximum dose hold is 5 continuous days. If, in the opinion of the Investigator, a longer dose hold is clinically needed, the Medical Monitor should be contacted for discussion.
Drug Discontinuation	
Event	**Recommended Action**
Grade ≥ 3 study drug-related AE that, at the discretion of the Investigator, warrants discontinuation of study drug (eg, has not improved or resolved after dose hold).	**Study drug:** Discontinue study drug. If the Investigator considers that the participant would benefit from continuing treatment, the Medical Monitor should be contacted.

Abbreviations: AE, adverse event; SAE, serious adverse event.

5.4. Physical Description

Voxelotor is a synthetic small molecule bearing the chemical name 2-hydroxy-6-((2-(1-isopropyl-1H-pyrazol-5-yl) pyridin-3-yl) methoxy) benzaldehyde. The chemical formula is $C_{19}H_{19}N_3O_3$ and the molecular weight is 337.4 g/mol.

5.5. Formulation

Voxelotor (500 mg) tablets contain voxelotor drug substance along with several formulation excipients. All excipients used for the formulation are listed in the US FDA Inactive Ingredient Database (IID) or are pharmaceutical excipient mixtures entirely composed of FDA IID listed components.

5.6. Packaging and Labeling

Voxelotor tablets will be supplied to clinical sites in high-density polyethylene bottles with induction-sealed polypropylene child-resistant caps. Additional details are provided in the Pharmacy Manual.

5.7. Study Drug Supply

The Sponsor or its representative will supply the packaged and labeled drug product to the clinical sites. Study drug will be dispensed at the Day 1 visit and at the Week 12 visit. Participants will receive a 3-month (90-day) supply of study drug at each dispensation visit. Additional details are provided in the Pharmacy Manual.

5.8. Storage and Handling Procedure

All study drug will be stored at controlled room temperature between 15°C to 25°C (59°F to 77°F) in the storage area of the investigational site pharmacy, which must be a secure, temperature-controlled, locked environment with restricted access.

No special procedures are required for the safe handling of the study drug. The Sponsor (or its representatives) will be permitted (upon request) to audit the supplies, storage, dispensing procedures, and records.

5.9. Drug Accountability and Retention

In accordance with Good Clinical Practice (GCP), the investigational site will account for all supplies of the study drug. Details of receipt, storage, assembly, and return will be recorded. The lot numbers for the study drug will be provided to the site by the supplier/manufacturer as soon as they are available.

The investigator (or designee) will maintain an accurate record of the receipt of the study drug as shipped by the Sponsor (or designee), including the date received and storage conditions/location. In addition, an accurate drug disposition record will be kept, specifying amount dispensed to each participant, the date of dispensation, the date of return, the number of tablets returned, and destruction records. A copy of this record will be returned to the Sponsor when the contents and condition of the study drug shipment have been verified.

Current dispensing records will also be maintained, including the date and amount of study drug dispensed and the participant receiving the drug. This drug accountability record will be available for inspection at any time.

All unused supplies of voxelotor will either be destroyed by the investigational site or returned to the Sponsor's designated location throughout and at the end of the study in accordance with instruction by the Sponsor.

Additional details are provided in the Pharmacy Manual (provided separately).

5.10. Treatment of Overdose

Based on the mechanism of action of voxelotor, an extreme overdose might decrease oxygen delivery to tissues. Transfusion, exchange transfusion, and/or hyperbaric oxygen therapy may be administered in the event of a medical emergency due to a suspected voxelotor overdose.

Guidelines for reporting a suspected treatment overdose are provided in Section 7.5.

5.11. Concomitant Medications

A concomitant medication is defined as any prescription or over-the-counter preparation, including vitamins and supplements.

In the interests of participant safety and acceptable standards of medical care, the investigator will be permitted to prescribe treatment(s) at his/her discretion. For all participants who initiate treatment, all administered concomitant medications from signing the informed consent until 28 days after the participant's last dose of study drug, must be recorded in the participants' eCRF (medication, dose, treatment duration, and indication).

Penicillin prophylaxis and vaccinations (including the COVID-19 vaccine) are allowed in accordance with standard of care.

All reported prior and concomitant medications will be coded using the current version of the World Health Organization Drug Dictionary.

5.11.1. Restrictions Regarding Usage of Concomitant Medications

Concurrent treatment with HU is allowed if the dose and regimen have been stable for at least 3 months prior to signing the ICF and with no anticipated need for dose adjustments during the study and no sign of hematological toxicity. Concurrent treatment with ESAs is allowed if the dose and regimen have been stable for at least 4 weeks with no dose modifications planned or anticipated by the investigator.

5.11.1.1. Prohibited Concomitant Medications

Any experimental SCD therapy is not allowed during the entire study period. Any medication which is not approved for the indication of SCD and is not suggested in the current guidelines for the treatment of SCD is considered "experimental." Additionally, concomitant medications (eg, crizanlizumab) that confound the ability to interpret data from the study are prohibited.

Voxelotor is a moderate CYP3A4 inhibitor and should be not be coadministered with sensitive CYP3A4 substrates with a narrow therapeutic index (refer to Table 2 for examples).

Table 2: Sensitive CYP3A4 Substrates with a Narrow Therapeutic Range

Sensitive CYP3A4 Substrates with Narrow Therapeutic Range
Alfentanil, sirolimus, and tacrolimus

Abbreviation: CYP, cytochrome P450.
Please note: This is not an exhaustive list. Substrates with a "narrow therapeutic range" refers to drugs whose exposure-response relationship indicates that small increases in their exposure levels by the concomitant use of CYP inhibitors may lead to serious safety concerns. Adapted from: FDA DRAFT Guidance for Industry: Drug Interactions Studies-Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations. February 2012.

Avoid coadministration of strong CYP3A4 inhibitors (refer to Table 3 for examples) or fluconazole with voxelotor. If coadministration is unavoidable, the Sponsor's Medical Monitor should be contacted.

Table 3: Examples of Strong CYP3A4 Inhibitors

CYP Enzyme	Strong Inhibitors
CYP3A4	Boceprevir, ceritinib, clarithromycin, cobicistat, conivaptan, danoprevir/ritonavir, elvitegravir/ritonavir, grapefruit juice, idelalisib, indinavir/ritonavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, mifepristone, nefazodone, nelfinavir, posaconazole, ribociclib, ritonavir, saquinavir/ritonavir, telaprevir, telithromycin, tipranavir/ritonavir, troleandomycin, Viekira Pak, voriconazole

Abbreviation: CYP, cytochrome P450.
Please note: this is not an exhaustive list. For an updated list, refer to the following link: https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#table 3-2.

Since CYP3A4 is a primary CYP responsible for the metabolism of voxelotor, concomitant use of moderate or strong inducers of CYP3A4 with voxelotor is not allowed (refer to Table 4 for examples).

Table 4: Examples of Moderate and Strong CYP3A4 Inducers

CYP3A4 Inducer	Examples
Moderate	Ritonavir, St. John's wort, semagacestat, efavirenz, tipranavir/ritonavir, dabrafenib, lesinurad, bosentan, genistein, thioridazine, rifabutin, lorlatinib, nafcillin, talviraline, lopinavir, daclatasvir/asunaprevir/beclabuvir, modafinil, etravirine, elagolix, lersivirine, telotristat ethyl
Strong	Rifampin, mitotane, avasimbe, rifapentine, apalutamide, ivosidenib, phenytoin, carabamazepine, enzalutamide, St. John's wort extract, lumacaftor, phenobarbital

Abbreviation: CYP, cytochrome P450.
Please note: this is not an exhaustive list. For an updated list, refer to the following link: https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#table3-3.

5.12. Fertility/Contraceptive Requirements

All female participants of child-bearing potential should avoid pregnancy and all sexually active male participants should avoid fathering a child.

5.12.1. Instructions for Female Participants of Child-Bearing Potential

For female participants of child-bearing potential who are sexually active, pregnancy should be avoided by either abstinence from sex/sexual intercourse or the use of highly effective means of contraception for the duration of the study, and for a total period of 30 days after the participant has taken her last dose of voxelotor. Highly effective means of contraception are listed below in Section 5.12.4 and pregnancy reporting requirements are outlined in Section 7.4. Female participants who become pregnant during the study will be withdrawn from the study.

5.12.2. Female Participants of Non-Child-Bearing Potential

Female participants of non-child-bearing potential are defined as either (1) those who have not started their menarche; or (2) bilateral oophorectomy/hysterectomy/postmenopausal females being amenorrhoeic for greater than 2 years with an appropriate clinical profile, eg, age appropriate, history of vasomotor symptoms.

5.12.3. Instructions for Male Participants Capable of Fathering a Child

There is no information about effects that voxelotor could have on the development of the fetus in humans. Therefore, it is important that the partners of male participants do not become pregnant during the study and for a total period of 30 days after the male participant has taken the last dose of voxelotor.

As a precaution, all male participants who are sexually active should avoid fathering a child by either true abstinence or the use of barrier methods of contraception.

5.12.4. Acceptable Forms of Contraception

Highly effective methods of birth control are defined as those which result in a low failure rate (ie, less than 1% per year) when used consistently and correctly. Effective methods of birth control are as follows:

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Intravaginal
  - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Injectable
  - Implantable
- Hormonal contraception must be supplemented with a barrier method (preferably a male condom)
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomized partner: Note that a vasectomized partner is a highly effective birth control method provided that the partner is the sole sexual partner of the woman of child-bearing potential trial participant and that the vasectomized partner has received medical assessment of the surgical success.
- Sexual abstinence: Sexual abstinence is considered a highly effective method only if the participant is refraining from heterosexual intercourse during the entire period of

risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the participant.

For male participants with female partners capable of reproduction:

- Barrier methods of contraception: Condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository. The use of barrier contraceptives should always be supplemented with the use of a spermicide.

5.13. Assessment of Treatment Compliance

Drug disposition records will be maintained, specifying the amount of study drug dispensed to each participant and the date of dispensation. This record will be available for Sponsor review at any time. Compliance will be determined by returned tablet/packet count.

6. STUDY PROCEDURES AND EVALUATIONS

6.1. Informed Consent/Assent

A signed and dated ICF and/or assent form will be obtained before any protocol-specified screening procedures are performed.

For pediatric participants, consent should be obtained from at least one parent (or both if it is required per clinical site policy) or the participant's legal representative. Care will be taken to avoid coercion of this vulnerable population of parents of children with SCD.

Evaluations obtained as part of routine medical care and performed during the Screening Period may be used in place of the study-specific evaluations, provided they meet the time windows described below. Participants will acknowledge and agree to the possible use of this information for the study by giving informed consent.

The Screening Period for a participant commences at the point at which the participant undergoes the first study-specific screening assessment and must be completed within 28 days after signing the ICF. Details of the assessments to be performed during the Screening Period are provided on the Schedule of Study Assessments (SOA) (Appendix 1).

6.2. Unique Participant Number

Upon execution of informed consent/assent, all participants will be given a unique participant number. This participant number will be used to identify the participant throughout the study and must be used on all study documentation related to that participant.

6.3. Demographics and Medical History

Demographic and baseline characteristics of sex, race, ethnicity, age, weight, and height of the participant will be collected at time of screening.

Clinically significant medical history (as determined by the investigator) will be recorded at the time of the screening.

Medical history includes clinically significant disease manifestations, comorbid conditions, surgeries, and all medications used by participant within 30 days prior to screening.

6.4. Physical Examination

The PE will be a complete PE according to the standard at the site for this age group at screening and an abbreviated, symptom-directed examination at the scheduled study visits.

- A complete PE should include, at a minimum, the following: height, weight, general appearance, examination of head, eyes, ears, nose, and throat, skin, cardiovascular and respiratory systems, abdominal examination, neurological, musculoskeletal, and symptom-directed examination
- An abbreviated PE should include the following: general appearance; examination of eyes (including presence of scleral icterus), skin, cardiovascular system, and respiratory system; abdominal examination; and a symptom-directed examination.

The physical examination will be completed at the time points indicated in the Schedule of Assessments (SOA) (Appendix 1).

6.5. Vital Signs

Vital signs (temperature, blood pressure, heart rate, respiratory rate, SpO_2 [pulse oximetry], and body temperature) will be measured at the time points indicated in the SOA (Appendix 1). Blood pressure and heart rate measurements will be performed after the participant has rested comfortably for at least 5 minutes in the supine or sitting position, as age appropriate and feasible. If the first vital sign measurement is outside of the normal range and deemed clinically significant, the measurement will be repeated within 5 minutes.

6.6. Actigraphy Assessments

Actigraphy assessments of physical activity and sleep quality will be performed per the SOA (Appendix 1. Actigraphy assessments will be performed using a wrist-worn actigraphy device (eg, tri-axial accelerometer) that will be provided to the participant and will be worn continuously throughout the Run-in and Treatment Periods.

6.7. Nocturnal Pulse Oximetry

Nocturnal oxygen saturation will be assessed using a wearable home pulse oximeter to record continuous overnight oxygen saturation during sleep at a scheduled two-night evaluation; procedures will be performed according to standard protocols which will be provided in a manual to each site.

Refer to the SOA in Appendix 1 for details of when these measures will be conducted throughout the study.

6.8. Patient-Reported Outcomes

Patient-reported outcomes will be evaluated using the National Institute of Health Patient Reported Outcome Measurement Information System (PROMIS) short forms and the PGIC

survey provided by the Sponsor. The following assessments will be used to collect QOL measures:

- PROMIS Pediatric Profile-37 v2.0 (for pediatric participants)
- PROMIS-43 V2.1 (for adult participants)
- PGIC

PRO assessments will be self-administered by study participants at scheduled study visits, as specified in the SOA.

6.9. Clinical Global Impression of Change (CGIC)

The investigator's assessment of a participant's overall health condition will be measured using the CGIC assessment, which is a 7-point scale used to assess how much the participant's SCD has improved or worsened relative to baseline.

Refer to the SOA in Appendix 1 for details of when these measures will be conducted throughout the study.

6.10. Adverse Events and Concomitant Medications

AEs and concomitant medications will be recorded throughout the study. See Section 7.2.1 for details regarding AE reporting period for this study. AEs and serious adverse events (SAEs) will be recorded from the time the study participant signs the ICF/assent form until 28 days after the last dose of study drug (EOS). See Section 7 for details regarding the definitions of and reporting requirements for AEs and SAEs.

6.11. Laboratory Assessments

It is the responsibility of the investigator to assess the clinical significance of all abnormal clinical laboratory values, as defined by the list of normal values on file for the local clinical laboratory. All clinically significant laboratory value abnormalities are to be recorded as AEs.

For the purpose of this study, a clinically significant laboratory value will be any abnormal result that, in the judgment of the investigator, is an unexpected or unexplained laboratory value or if medical intervention or corrective action (transfusion, hydration, initiation of antibiotics, or other concomitant medication) is required. Any abnormal values that persist should be followed at the discretion of the investigator.

Additional and repeat laboratory safety testing for the evaluation of abnormal results and/or AEs during the study may be performed at the discretion of the investigator or upon request of the Sponsor. Repeat laboratory testing of abnormal potentially clinically significant or clinically significant results for the screening evaluation of the participant may be repeated once at the discretion of the investigator.

All laboratory safety testing will be performed by the local laboratory. The clinical laboratory tests that will be performed are listed in Table 5. Refer to Appendix 1 (SOA), for all time points.

Table 5: Clinical Laboratory Tests

Hematology	Serum Chemistry	Urine	Other
• Hematocrit • Hemoglobin • %HbF (Screening only) • MCV • MCH • MCHC • Platelet count • RBC count • RDW • Reticulocyte count (percent) • Reticulocyte count (absolute) • WBC count with differential (basophils, eosinophils, neutrophils, monocytes, lymphocytes)	• Albumin • Alkaline phosphatase • ALT • AST • Bicarbonate • Bilirubin (total, direct, and indirect) • BUN • Calcium • Chloride • Creatinine • Glucose • LDH • Phosphorus • Potassium • Serum erythropoietin • Sodium • Total protein	• pH • Specific gravity • Blood • Glucose • Protein • Ketones • Bilirubin • Urobilinogen • Nitrite • Leukocytes • Microscopic examination of sediment, if clinically indicated	• Pregnancy test [a]

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; HbF, fetal hemoglobin; LDH, lactate dehydrogenase; MCH, mean cell hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; RBC, red blood cell; RDW, RBC distribution width; WBC, white blood cell.

[a] Pregnancy tests will be performed for female participants who are postmenarche, including those who are postmenopausal. A serum β-human chorionic gonadotropin pregnancy test will be performed at screening and urine pregnancy tests will be performed prior to the first dose of study drug and at other times during the study.

7. ADVERSE AND SERIOUS ADVERSE EVENTS

Safety assessments will consist of AE and SAE monitoring, protocol-specified hematology and serum chemistry tests, abbreviated PEs, protocol-specified vital sign measurements, and the results from other protocol-specified tests that are deemed critical to the safety evaluation of voxelotor.

The determination, evaluation, reporting, and follow-up of AEs will be performed, as outlined in this section. At each visit, the study participant or participant caregiver will be asked about any new or ongoing AE since the previous visit. Assessments of AEs will occur at each study visit. See Section 7.2 for details regarding the required time periods for AE reporting.

Clinically significant changes from study baseline in physical examination findings, weight, vital signs, and clinical laboratory test results will be recorded as AEs or SAEs, as appropriate.

7.1. Adverse Events

7.1.1. Definition of Adverse Events

An AE is defined as any untoward medical occurrence in a participant administered a pharmaceutical product during the course of a clinical investigation. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational product, whether or not thought to be related to the investigational product. In addition to new events, any increase in the severity or frequency of a pre-existing condition that occurs after the participant signs the ICF for participation is considered an AE. This includes any side effect, injury, toxicity, or sensitivity reaction.

A suspected adverse reaction is any AE for which there is a reasonable possibility that the drug caused the AE. For the purposes of expedited safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the AE. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug.

Life-threatening AE or life-threatening suspected adverse reaction is an AE or suspected adverse reaction that, in the view of either the investigator or Sponsor, places the study participant at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

An AE or suspected adverse reaction is considered to be "unexpected" if it is not listed in the Reference Safety Information (RSI) section of the current IB or is not listed at the specificity or severity that has been observed.

An SAE or serious suspected adverse reaction is an AE or suspected adverse reaction that, at any dose, in the view of the either the investigator or Sponsor, results in any of the following outcomes:

- Death
- A life-threatening AE
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant incapacity or disability (substantial disruption of the ability to conduct normal life functions)
- A congenital anomaly/birth defect
- Important medical events that may not result in death, be immediately life-threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the study participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

NOTE: Hospitalization planned prior to study enrollment (eg, for elective surgeries) is not considered to be an SAE. Any complications arising from a planned hospitalization may be considered an AE and should be reported, as applicable. Hospitalizations that occur for pre-existing conditions that are scheduled after study enrollment are considered SAEs.

The investigator will assess each AE for seriousness, severity, and relationship to the study drug.

7.1.2. Severity of Adverse Events

Whenever possible, the severity of all AEs will be graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 5.

For AEs not adequately addressed in the NCI CTCAE, Version 5, the criteria presented in Table 6 should be used.

Table 6: Grading for Adverse Events not Covered in the NCI CTCAE

Severity	Description
Grade 1 – mild	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2 – moderate	Minimal, local or noninvasive intervention indicated; limited age-appropriate instrumental ADL
Grade 3 – severe	Medically significant but not immediately life threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL
Grade 4 – life threatening	Life-threatening consequences; urgent intervention indicated
Grade 5 – fatal	Death

Abbreviations: ADL, activities of daily living; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events.

To make sure that there is no confusion or misunderstanding between the terms "serious" and "severe," which are not synonymous, the following note of clarification is provided. The term "severe" is often used to describe the intensity (severity) of a specific event (ie, mild, moderate, or severe); the event itself, however, may be of relatively minor medical significance (eg, severe headache). This is not the same as "serious," which is based on the study participant/event outcome or action criteria associated with events that pose a threat to a participant's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

7.1.3. Relationship to Study Drug

The relationship of an AE to the study drug should be determined by the investigator according to the following definitions:

- NOT RELATED: Evidence exists that the AE has an etiology other than the study drug and/or the temporal relationship of the AE/SAE to study drug administration makes the relationship unlikely. If an SAE is not considered to be related to the study drug, then an alternative explanation should be provided.
- RELATED: A temporal relationship exists between the event onset and the administration of the study drug and makes a causal relationship possible or probable. It cannot be readily explained by the participant's clinical state or concomitant therapies and may appear, with some degree of certainty, to be related based on the known therapeutic and pharmacologic actions of the drug. Good clinical judgment should be used for determining causal assessment.

7.1.4. Unexpected Adverse Reactions

An AE is "unexpected" if its nature and severity are not consistent with the information about the study drug provided in the RSI in the voxelotor IB.

7.2. Adverse Event Reporting

7.2.1. General

All AEs will be recorded from the time the study participant signs the ICF/assent form until 28 days after the last dose of study drug (EOS). All SAEs, regardless of causal attribution, must be reported within 24 hours of SAE awareness in the SAE eCRF via the electronic data capture (EDC) system. The investigator is responsible for evaluating all AEs, obtaining supporting documents, and ensuring that documentation of the event is complete. Details of each reported AE must include at a minimum severity, relationship to study treatment, duration, and outcome. All AEs (both serious and nonserious) must be followed until they are resolved or stabilized, or until reasonable attempts to determine resolution of the event are exhausted.

Any participant who experiences an AE may be discontinued from study drug at any time, at the discretion of the investigator. The Sponsor and the Contract Research Organization (CRO) Medical Monitors must be notified of the study participant discontinuation.

7.2.2. Diagnosis Versus Signs and Symptoms

If known, a diagnosis should be recorded in the eCRF rather than individual signs and symptoms (eg, record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded separately in the eCRF. If a diagnosis is subsequently established, it should be reported as follow-up information.

7.2.3. Abnormal Laboratory Values

Only clinically significant laboratory abnormalities will be recorded in the AE eCRF (eg, abnormalities that have clinical sequelae, require study drug dose modification, discontinuation of study treatment, more frequent follow-up assessments, or further diagnostic investigation). If the clinically significant laboratory abnormality is a sign of a disease or syndrome (eg, alkaline phosphatase and bilirubin 5 × the ULN associated with cholecystitis), only the diagnosis (eg, cholecystitis) needs to be recorded on the eCRF.

If the clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the eCRF. If the laboratory abnormality can be characterized by a precise clinical term, the clinical term should be recorded. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia".

Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded in the AE eCRF, unless the severity, seriousness, or etiology changes.

7.2.4. Worsening of Sickle Cell Disease

SCD-related AEs that are common complications associated with the study participant's SCD may not be considered to be related to voxelotor unless judged by the investigator to have worsened in severity and/or frequency or changed in nature during the study. SCD-related AEs include the following: SCA with crisis, ACS, pneumonia, priapism, and osteonecrosis.[14] These events will be recorded on the AE eCRF.

Vaso-occlusive Crisis

VOC is defined as a composite of acute painful crisis and/or ACS. To allow for an assessment of VOC events, while minimizing variability in reporting and assessment, additional data will be collected for SCD-related AEs (eg, acute painful crisis, ACS events).

7.3. Serious Adverse Events and Requirements for Immediate Reporting

All SAEs, regardless of causal attribution, must be reported by the investigator (or designee) or site personnel within 24 hours of SAE awareness. The SAE will be reported by completing the AE CRF via the EDC system.

The Sponsor or designee may request additional source documentation pertaining to the SAE from the investigational site. Follow-up reports must be submitted within 24 hours of awareness, and participant identifier information (eg, name, medical record number) must be redacted in the hospital discharge summaries, autopsy reports, and/or death certificates.

Follow-up SAE information must be submitted within 24 hours of awareness as additional information becomes available. All SAEs regardless of causal attribution must be followed to resolution or stabilization, or until reasonable attempts to determine resolution of the SAE are performed.

7.3.1. Reporting Suspected Unexpected Serious Adverse Reactions and Urgent Safety Issues

The Sponsor or designee is responsible for reporting suspected unexpected serious adverse reactions (SUSARs) to regulatory agencies, competent authorities, IRBs, and investigators as per local laws and regulations. Fatal and life-threatening SUSARs will be submitted no later than 7 calendar days of the Sponsor's or designee's first knowledge of the event and follow-up information submitted within an additional 8 calendar days, or as otherwise required per local laws and regulations. All other SUSARs will be submitted within 15 calendar days of the Sponsor's or designee's first knowledge of the event. The investigator is responsible for notifying the local IRBs of all SAEs that occur at his or her site, as required by local regulations or IRB policies, if this responsibility resides with the site.

Investigators are required to report any urgent safety matters to the Sponsor or designee within 24 hours of awareness. The Sponsor or designee will inform regulatory authorities, IRBs, and investigators, as applicable, of any events (eg, change to the safety profile of voxelotor, major safety findings that may place study participants at risk) that may occur during the clinical trial that do not fall within the definition of a SUSAR but may adversely affect the safety of study participants.

7.4. Reporting Pregnancy

If a participant becomes pregnant while taking study drug, the study drug will be immediately discontinued and the pregnancy must be reported to the Sponsor or designee within 24 hours of awareness. The investigator will discuss the risks and concerns of study drug exposure to a developing fetus and counsel the participant and/or pregnant partner (or ensure such counselling is provided).

Reported pregnancy of a participant or a participant's partner, while participating in this study, will be monitored for the full duration of the pregnancy and/or followed through a definitive outcome (ie, birth, spontaneous or elective abortion).

An uncomplicated pregnancy will not be considered an AE or SAE. Pregnancy complications such as spontaneous abortion/miscarriage and congenital anomalies are considered SAEs and must be reported as described in Section 7.3. Note that an elective abortion is not considered an SAE. Pregnancy and pregnancy outcomes must be reported on a Pregnancy Notification Form or Pregnancy Outcome Form, respectively, and sent to the Sponsor or designee within 24 hours of the investigational site personnel learning of the pregnancy or pregnancy outcome.

The child born to a female participant or partner of a male participant exposed to study drug will be followed for 3 months after delivery. The outcome of any pregnancy and the presence or absence of any congenital abnormality will be recorded in the Pregnancy Outcome Form and reported to the Sponsor or designee. Any congenital abnormalities in the offspring will be reported as an SAE and must be reported as described in Section 7.3.

Information regarding pregnancy testing is provided in Section 6.11. Females of non-child-bearing potential are defined in Section 5.12.2. Highly effective means of contraception are listed in Section 5.12.4.

7.5. Reporting Overdose

If a participant takes more than the protocol-defined dose of study drug in a day and experiences a study drug-related AE, this will be reported as an overdose (AEs must be recorded in the AE eCRF) and a protocol deviation. However, if the participant did not experience any AEs, this will only be reported as a protocol deviation.

The investigator will discuss the risks and concerns of study drug exposure with the participant. Participants are to be instructed to contact their investigational site immediately if an overdose of study drug is suspected. An overdose with associated AEs must be reported within 24 hours of the investigator, designee, or site personnel learning of the overdose and reported to the Study Director/Medical Monitor. An overdose must be followed until any adverse effects are resolved or stabilized or until reasonable attempts to determine resolution of the event are exhausted.

8. DATA ANALYSIS AND STATISTICAL PLANS

8.1. Endpoints

All endpoints in this study are exploratory and include:

- Change in total daily physical activity (expressed in counts per minute) from baseline to Week 10-12 and to Week 22-24
- Categorical change from baseline in total daily physical activity as: light (LPA), moderate (MPA), and vigorous (VPA) physical activity from baseline to Week 10-12 and Week 22-24
- Change in total nocturnal sleep time from baseline to Week 10-12 and to Week 22-24
- Change in wake time after sleep onset from baseline to Week 10-12 and to Week 22-24
- Change in sleep efficiency from baseline to Week 10-12 and to Week 22-24
- Proportion of participants with a > 1 g/dL increase in Hb from baseline from baseline to Week 10-12 and to Week 22-24
- Change in mean overnight SpO_2 (%) and median number of overnight SpO_2 dips > 3% per hour from baseline to Week 12 and to Week 24
- Change in PRO measures (PROMIS Pediatric Profile-37 v2.0/PROMIS-43 V2.1)
- PGIC score at Week 24
- CGIC score at Week 24

8.2. Sample Size

Approximately 50 participants who are 12 through 55 years of age (inclusive) with SCD and chronic moderate anemia will be enrolled and treated with voxelotor in this study.

8.3. Populations for Analysis

All participants who receive at least 1 dose of study treatment will be included in the safety population. This is the analysis population used to summarize all efficacy and safety data.

8.4. Analyses

Demographic and baseline characteristics, efficacy, PRO, and safety parameters will be summarized using descriptive statistics and presented in select individual listings.

8.4.1. Efficacy

Actigraphy assessments will be averaged over the 14-day period during the Run-in Period, Weeks 10 to 12, and Weeks 22 to 24.

Change in actigraphy, SpO_2, and PRO endpoints will be summarized for observed values and changes from baseline using appropriate descriptive statistics.

Hemoglobin response, defined as an increase in Hb of > 1 g/dL compared with baseline, will be summarized.

8.4.2. Safety

TEAEs, defined as an event that occurs on or after Day 1 of treatment with study drug or the worsening of a pre-existing condition on or after Day 1 of study treatment, will be classified according to the Medical Dictionary for Regulatory Activities. The incidence of TEAEs will be tabulated by System Organ Class, Preferred Term, severity, and relatedness to study treatment as assessed by the investigator.

Clinical laboratory results and vital sign measurements, over time, will be descriptively summarized at each visit for observed values and changes from baseline.

9. REGULATORY, ETHICAL AND LEGAL OBLIGATIONS

9.1. Ethical Conduct of the Study

The investigator will ensure that this study is conducted in full conformity with the current revision of the 1964 Declaration of Helsinki.

The investigator is generally not to deviate from the protocol. In medical emergencies, the investigator will use medical judgment and will remove the participant from immediate hazard. The investigator will immediately notify the Sponsor and IRB regarding the nature of the emergency and the course of action taken. The investigator is to notify the Sponsor of any inadvertent protocol deviations upon discovery and is to document the deviations appropriately in the study files or in the eCRFs. The Sponsor assumes no responsibility or liability for any unapproved deviations. Major changes in the protocol initiated by the Sponsor will be provided as an amendment and will be approved by the IRB prior to implementation (refer to Section 9.4).

9.2. Good Clinical Practice

The study will be conducted according to the protocol; guidelines established by ICH GCP in clinical studies; and US regulations (21 Code of Federal Regulations [CFR] Parts 50, 54, 56, and 312).

9.3. Written Informed Consent and Assent

Each individual will be provided with oral and written information describing the nature, purpose, and duration of the study; participation/termination conditions; and risks and benefits. It is the investigator's responsibility to obtain written informed consent/assent from the participant after adequate explanation of the objectives, methods, anticipated benefits, and potential risks of the study and before any study procedures are commenced.

Prior to initiation of any study-related procedures, participants (and/or their parent or legal guardian for participants under 18 years of age) will sign and date the ICF to participate in the study. Participants under 18 years of age (and their parent or legal guardian) will review the ICF and sign a child assent form, according to local institution/IRB guidelines. The parent or legal guardian for participants under 18 years of age will also sign and date an authorization form

required under the Health Insurance Portability and Accountability Act, if applicable, that authorizes the use and disclosure of the participant's protected health information. Participants who initially sign the assent form and subsequently legally become an adult while actively participating in the study (before the EOS visit) should be re-consented using the adult ICF soon after their status changes.

Participants unable to sign the ICF may participate in the study if a legal representative or witness provides the consent (in accordance with the procedures of ICH GCP and local regulations) and the participant confirms his/her interest in study participation. The participant will be informed that he/she can freely withdraw consent and stop participation in the study at any time with no prejudice to further treatment. It is the participant's responsibility to communicate this decision to the investigator.

In the event of a pregnancy in the female partner of a male participant, a pregnancy consent form will be provided to allow the follow-up of the pregnancy.

The participant should be given a copy of the ICF in their native language. The informed consent process should be recorded in the source documentation. The original copy of the signed and dated informed consent must be retained in the institution's records and is subject to inspection by representatives of the Sponsor, or representatives from regulatory agencies.

9.4. Institutional Review Board and Regulatory Approval

The investigator must inform, and obtain approval from, the IRB for the conduct of the study at named sites, for the protocol, the participant ICF, and any other written information that will be provided to the participants and any advertisements that will be used. Written approval must be obtained prior to recruitment of participants into the study and shipment of study drug.

Proposed amendments to the protocol and documents must be discussed with the Sponsor and CRO, and then submitted to the IRB for approval as well as submitted to regulatory authorities for approval prior to implementation. Amendments that are intended to eliminate an apparent immediate hazard to participants may be implemented prior to receiving Sponsor or IRB approval. However, in this case, approval must be obtained as soon as possible after implementation.

The investigator will be responsible for ensuring that an annual update is sent to the IRB to facilitate their continuing review of the study (if needed) and that the IRB is informed about the end of the study. Copies of the update, subsequent approvals, and final letter must be sent to the Sponsor. The investigator will inform the IRB of any reportable AEs.

9.5. Essential Documentation Requirements

The Sponsor or Sponsor's representative will collect from the investigational site the required essential regulatory documents per ICH guidance prior to voxelotor shipment to the site.

9.6. Confidentiality

The investigator must ensure that the participant's privacy is maintained. In the eCRF or other documents submitted to the Sponsor, participants will be identified by a participant study number

only. Documents that are not submitted to the Sponsor (eg, signed ICF) should be kept in a strictly confidential file by the investigator.

The investigator shall permit authorized representatives of the Sponsor, regulatory agencies, and IRBs to review the portion of the participant's medical record that is directly related to the study. As part of the required content of informed consent, the participant must be informed that his/her records will be reviewed in this manner.

9.7. Regulatory, Ethical, and Legal Obligations

The study will comply with General Data Protection Regulation (GDPR) 2018 and applicable local data protection regulations. Data collected will be pseudonymized.

The processing of the personal data of participants will be minimized by making use of a unique participant number only in study documents and electronic database(s).

All study documents will be stored securely and only accessible by study staff and authorized personnel. The study staff will safeguard the privacy of participants' personal data. The participant information sheet/ICF for the study will inform the participant of their rights and provide appropriate contact details of the Data Protection Officer.

9.8. Study Documentation and Data Storage

The investigator must retain a comprehensive and centralized filing system of all study-related documentation that is suitable for inspection by the Sponsor and representatives of regulatory authorities.

The investigator must retain essential documents as detailed in Section 10.2. Participant files and other source data (including copies of protocols, original reports of test results, study drug dispensing logs, correspondence, records of informed consent, and other documents pertaining to the conduct of the study) must be kept for the maximum period of time permitted by the institution. Documents should be stored in such a way that they can be accessed/data retrieved at a later date. Consideration should be given to security and environmental risks.

No study document will be destroyed without prior written agreement between the Sponsor and the investigator. Should the investigator wish to assign the study records to another party or move them to another location, written agreement must be obtained from the Sponsor.

10. DATA HANDLING AND RECORDKEEPING

10.1. Inspection of Records

GBT will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, participant charts, study source documents, and other records relative to study conduct.

The investigator agrees to maintain a Regulatory Binder in a current, organized fashion; this Binder will contain documentation supportive of the protocol- and GCP-compliance of the study. The contents of the Binder will be organized according to the standards of ICH E6, Section 8

(Essential Documents). The investigator agrees to make this Binder accessible to the monitor, auditor, and representatives of regulatory agencies and the IRB.

10.2. Retention of Records

The investigator will maintain adequate records, including participants' medical records, laboratory reports, signed consent forms, drug accountability records, safety reports, information regarding participants who discontinued the protocol, and any other pertinent data. All study records must be retained for at least 2 years after the last approval of a marketing application in the US or an ICH region and until (1) there are no pending or contemplated marketing applications in the US or an ICH region or (2) at least 2 years have elapsed since the formal discontinuation of clinical development of the study drug. The investigator/institution should retain participant identifiers for at least 15 years after the completion or discontinuation of study. Study participant files and other resource data must be kept for the maximum period of time permitted by the hospital, institution but not less than 15 years. These documents should be retained for a longer period, if required by the applicable regulatory requirements or by the Sponsor. GBT must be notified with retention should the investigator/institution become unable to continue with the maintenance of study participant files for the full 15 years. All study records must be stored in a secure and safe facility.

The investigators must retain protocols, amendments, IRB approvals, copies of Form FDA 1572, signed and dated consent forms, medical records, eCRFs, drug accountability records, all correspondence, and any other documents pertaining to the conduct of the study.

If the investigator moves, withdraws from an investigation or retires, the responsibility for maintaining the records may be transferred to another person who will accept responsibility. Notice of transfer must be made to and agreed by the Sponsor. The investigator must notify the Sponsor immediately in the event of accidental loss or destruction of any protocol records.

10.3. Disclosure of Information

Participants' medical information obtained as a result of this study is considered confidential, and disclosure to third parties, other than those noted in this protocol, is prohibited. Subject to any applicable authorization(s), all reports and communications relating to participants in this study will identify participants only by initials and number. Medical information resulting from a participant's participation in this study may be given to the participant's personal physician, other authorized parties, or to the appropriate medical personnel responsible for the participant's participation in this clinical study. Data generated in this study will be available for inspection on request by the FDA or other government regulatory agency auditors; the Sponsor, the Sponsor's Medical Monitor (or designee), and their designated representatives; the IRB; and other authorized parties. All information concerning the study drug and the Sponsor's operations (such as patent applications, formulas, manufacturing processes, basic scientific data, or other information supplied by the Sponsor and not previously published) are considered confidential and shall remain the sole property of the Sponsor. The investigator agrees to use this information only in conducting this study and not to use it for other purposes without the Sponsor's prior written consent. The information developed in this clinical study will be used by the Sponsor in the clinical development of voxelotor and therefore, may be disclosed by the Sponsor as required, to authorized parties (including its corporate partners for the study drug, if any, and

their designated representatives), other clinical investigators, pharmaceutical companies, the FDA, and other government agencies. Any information, inventions, discoveries (whether patentable or not), innovations, suggestions, ideas, and reports made or developed by the investigator(s) as a result of conducting this study shall be promptly disclosed to the Sponsor and shall be the sole property of the Sponsor. The investigator agrees, upon the Sponsor's request and at the Sponsor's expense, to execute such documents and to take such other actions as the Sponsor deems necessary or appropriate to obtain patents in the Sponsor's name covering any of the foregoing.

11. INSURANCE AND FINANCIAL DISCLOSURE

The Sponsor has subscribed to an insurance policy covering, in its terms and provisions, its legal liability for injuries caused to participating persons and arising out of this research performed strictly in accordance with the scientific protocol as well as with applicable law and professional standards.

Financial Disclosure statements will be handled in a separate agreement apart from the protocol, kept on file and submitted as applicable with any subsequent license application.

12. PUBLICATION POLICY

It is intended to publish the results of the study once all participants have completed the study and the study has been analyzed.

The investigator or the Sponsor may not submit for publication or present the results of this study without allowing each of the other parties to review and comment on the pre-publication manuscript, as defined in the site's clinical trial agreement.

The investigator may not submit any of the results of the study for publication without the prior consent of the Sponsor.

13. ADMINISTRATIVE OBLIGATIONS

13.1. Source Data

Original documents, data, records (eg, clinic records, laboratory notes, memoranda, participant diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, X-rays, participant files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial) and all relevant sections of the participant's medical records and all other data collection made specific to this trial constitute source documents.

The completed eCRF is not a source document. The investigator/institution will permit trial--related monitoring, audits, IRB review and regulatory inspection by providing direct access to source documents.

13.2. Data Collection

All participant data relating to the study will be recorded on electronic CRFs unless transmitted to the Sponsor or designee electronically (eg, actigraphy data).

The investigator will be responsible for maintaining accurate and adequate case records (source documents) from which data will be transcribed (or if EDC, source data, transferred) to eCRFs designed to record data pertinent to this study. All relevant observations and data related to the study will be recorded. This will include medical and medication history, PEs, a checklist of inclusion and exclusion criteria, study drug administration, a record of sample collection, clinical assessments, AEs and final evaluation. The clinical site Clinical Research Associate will review all eCRFs and compare data to that contained in clinic notes and participants' source documents/medical records.

Data collected regarding each participant will be entered into the eCRF in a timely manner (generally within 5 business days of data capture). The investigator will be responsible for the timeliness, completeness, and accuracy of the documentation entered into the eCRFs.

13.3. Monitoring

It is understood that monitors, and any authorized personnel contracted to Sponsor may contact and visit the investigator, and that they will be allowed to inspect the various records of the trial on request (original source records and other pertinent trial data), provided that participant confidentiality is maintained, and that the inspection is conducted in accordance with local regulations.

It is the monitor's responsibility to inspect the eCRFs at regular intervals throughout the trial to verify adherence to the protocol, the completeness, accuracy and consistency of the data, and adherence to GCP regulations and guidelines.

The investigator agrees to cooperate with the monitor to ensure that any problems detected during the course of these monitoring visits are resolved.

13.4. Quality Control, Quality Assurance and Regulatory Inspections

Quality Control will be performed according to Sponsor and CRO internal procedures. A Quality Assurance representative of the Sponsor and/or CRO may audit the study. In addition, the investigative site may be inspected by a representative of a regulatory authority. The investigator commits to making all necessary data/documents and key personnel available to support the inspection or audit.

14. REFERENCES

1. Gladwin MT, Barst RJ, Gibbs JSR, et al. Risk factors for death in 632 patients with sickle cell disease in the United States and United Kingdom. PLoS ONE. 2014;9(7):e99489. doi:10.1371/journal.pone.0099489.
2. Nouraie M, Lee JS, Zhang Y, et al. The relationship between the severity of hemolysis, clinical manifestations and risk of death in 415 patients with sickle cell anemia in the US and Europe. Haematologica. 2013;98(3):464-72.
3. Kato GJ, Gladwin MT, Steinberg MH. Deconstructing sickle cell disease: reappraisal of the role of hemolysis in the development of clinical subphenotypes. Blood Rev. 2007;21:37-47.
4. Kato GJ, McGowan V, Machado RF, et al. Lactate dehydrogenase as a biomarker of hemolysis-associated nitric oxide resistance, priapism, leg ulceration, pulmonary hypertension, and death in patients with sickle cell disease. Blood. 2006;107:2279-85.
5. Swanson ME, Grosse SD, Kulkami R. Disability among individuals with sickle cell disease: literature review from a public health perspective. Am J Prev Med. 2011;41(6S4):S390-S397.
6. Brown AK, Sleeper LA, Miller ST, et al. Reference values and hematologic changes from birth to 5 years in patients with sickle cell disease. Arch Pediatr Adolesc Med. 1994;148(8):796-804.
7. Powars DR, Elliott-Mills DD, Chan L, et al. Chronic renal failure in sickle cell disease: risk factors, clinical course, and mortality. Ann Intern Med. 1991;115:614-20.
8. Hijmans CT, Grootenhuis MA, Oosterlaan J, et al. Neurocognitive deficits in children with sickle cell disease are associated with the severity of anemia. Pediatr Blood Cancer. 2011;57:297-302.
9. Bernaudin F, Verlhac S, Fréard F, et al. Multicenter prospective study of children with sickle cell disease: radiographic and psychometric correlation. J Child Neurol. 2000;15:333-43.
10. Kral MC, Brown RT, Connelly M, et al. Radiographic predictors of neurocognitive functioning in pediatric sickle cell disease. J Child Neurol. 2006;21:37-44.
11. Liem RI, Nevin MA, Prestridge A, et al. Functional capacity in children and young adults with sickle cell disease undergoing evaluation for cardiopulmonary disease. Am J Hematol. 2009;84:645-649.
12. Liem RI, Reddy M, Pilligra SA, et al. Reduced fitness and abnormal cardiopulmonary responses to maximal exercise testing in children and young adults with sickle cell anemia. Physiol Rep. 2015;3(4):e12338. doi: 10.14814/phy2.12338.
13. Badawy SM, Thompson AA, Lai J-S, et al. Health-related quality of life and adherence to hydroxyurea in adolescents and young adults with sickle cell disease. Pediatr Blood Cancer. 2016;64(6). doi: 10.1002/pbc.26369.

14. Dampier C, LeBeau P, Rhee S, et al. Health-related quality of life in adults with sickle cell disease (SCD): a report from the Comprehensive Sickle Cell Centers Clinical Trial Consortium. Am J Hematol. 2011 Feb;86(2):203-5. doi: 10.1002/ajh.21905.

15. Badawy SM, Payne AB, Rodeghier MJ, Liem RI. Exercise capacity and clinical outcomes in adults followed in the Cooperative Study of Sickle Cell Disease (CSSCD). Eur J Haematol. 2018 October;101(4):532-541. doi:10.1111/ejh.13140.

16. Woodson RD, Wilks RE, Lenfant C. Effect of acute and established anemia on O_2 transport at rest, submaximal and maximal work. J Appl Physiol Respir Environ Exerc Physiol. 1978 Jan;44(1):36-43.

17. Callahan LA, Woods KF, Mensah GA, et al. Cardiopulmonary responses to exercise in women with sickle cell anemia. Am J Respir Crit Care Med. 2002;165:1309-16.

18. Marinov BI, Terziyski KV, Sapunarova KG, Kostianev SS. Exercise performance in children with severe beta thalassemia before and after transfusion. Folia Med (Plovdiv). 2008;50(4):48-54.

19. Waltz X, Romana M, Lalanne-Mistrih ML, et al. Hematologic and hemorheological determinants of resting and exercise-induced hemoglobin oxygen desaturation in children with sickle cell disease. Haematologica. 2013;98(7):1039-44.

20. Rackoff WR, Kunkel N, Silber JH, et al. Pulse oximetry and factors associated with hemoglobin oxygen desaturation in children with sickle cell disease. Blood. 1993 Jun 15;81(12);3422-7.

21. LeBourgeois MK, Giannotti F, Cortesi F, et al. The relationship between reported sleep quality and sleep hygiene in Italian and American adolescents. Pediatrics. 2005 Jan;115(1 Suppl):257-65.

22. Kato GJ, Piel FB, Reid CD, et al. Sickle cell disease. Nature Rev Dis Primers. 2018 Mar 15;4:18010. doi: 10.1038/nrdp.2018.10.

23. Samuels C. Sleep, recovery, and performance: the new frontier in high-performance athletics. Neurol Clin. 2008 Feb;26(1):169-80.

24. Whitesell PL, Owoyemi O, Oneal P, et al. Sleep disordered breathing and nocturnal hypoxemia in young adults with sickle cell disease. Sleep Med. 2016 June;22:47-9.

25. Kaleyias J, Cruz M, Goraya JS, et al. Spectrum of polysomnographic abnormalities in children with epilepsy. Pediatr Neurol. 2008 Sep;3:170-76.

26. Hill CM, Hogan AM, Omugha N, et al. Increased cerebral blood flow velocity in children with mild sleep-disordered breathing: a possible association with abnormal neuropsychological function. Pediatrics. 2006;118(4):e1100-8.

27. Hollocks MJ, Kok TB, Kirkham FJ, et al. Nocturnal oxygen desaturation and disordered sleep as a potential factor in executive dysfunction in sickle cell anemia. J Int Neuropsychol Soc. 2012 Jan;18(1):168-73.

28. Pashankar F, Manwani D, Lee MT, Green NS. Hydroxyurea improves oxygen saturation in children with sickle cell disease. J Pediatr Hematol Oncol. 2015 Apr;37(3):242-43.

29. While AE, Mullen J. Living with sickle cell disease: the perspective of young people. Br J Nurs. 2004;13(6):320-5.

30. Dampier C, Lieff S, LeBeau P, et al. Health-related quality of life in children with sickle cell disease: a report from the Comprehensive Sickle Cell Centers Clinical Trial Consortium. Pediatr Blood Cancer. 2010 Sep;55(3):485-94. doi: 10.1002/pbc.22497.

31. Cella D, Lai J-S, Chang C-H, et al. Fatigue in cancer patients compared with fatigue in the general United States population. Cancer. 2002;94(2):528-38.

32. Yeh C-H, Chiang Y-C, Lin L, et al. Clinical factors associated with fatigue over time in paediatric oncology patients receiving chemotherapy. Brit J Cancer. 2008;99:23-9.

33. Lasch KF, Evans CJ, Schatell D. A qualitative analysis of patient-reported symptoms of anemia. Nephrol Nurs J. 2009;36(6):621-4,631-2; quiz 633.

34. Prochaska MT, Newcomb R, Jiang D, Meltzer DO. The effect of red blood cell transfusion on fatigue in hospitalized patients with anaemia. Vox Sang. 2018 Oct;113(7):669-77.

35. Ameringer S, Elswick RK, Smith W. Fatigue in adolescents and young adults with sickle cell disease: biological and behavioral correlates and health-related quality of life. J Pediatr Oncol Nurs. 2014;31(1):6-17.

36. Melo HN, Stoots SJM, Pool MA, et al. Objectively measured physical activity levels and sedentary time in children and adolescents with sickle cell anemia. PLoS One. 2018;13(12):e208916.

37. Vichinsky E, Hoppe CC, Ataga KI, et al. A phase 3 randomized trial of voxelotor in sickle cell disease. N Engl J Med. 2019;381(6):509-19.

38. Eaton WA, Henry ER, Hofrichter J, Mozzarelli A. Is cooperative oxygen binding by hemoglobin really understood? Nat Struct Biol. 1999 Apr;6(4):351-8.

39. Oksenberg D, Dufu K, Patel MP, et al. GBT440 increases haemoglobin oxygen affinity, reduces sickling and prolongs RBC half-life in a murine model of sickle cell disease. Br J Haematol; 2016;175:141-53.

40. Brown C, Hoppe C, Inati A, et al. Efficacy and safety of 1500 mg voxelotor in a phase 2a study (GBT440-007) in adolescents with sickle cell disease. Blood. 2018;132(Suppl 1): 509.

APPENDIX 1. SCHEDULE OF ASSESSMENTS

Period	Screening	Run-in	Open-label Treatment				Follow-up
Week	Week -6	Week -2	Week 1	Week 2	Week 12	Week 24	Week 28
Visit Day	*Day -42*	*Day -14*	*Day 1*	*Day 14*	*Day 84*	*Day 168*	*Day 196*
Visit Window			(±3 days)	(±3 days)	(±3 days)	(±3 days)	(±3 days)
Informed consent/assent	X						
Inclusion/exclusion [a]	X						
Medical history	X						
Physical examination [b]	X		X		X	X	X
Body weight	X		X		X	X	
Height	X						
Vital signs [c]	X		X		X	X	X
Serum pregnancy test [d]	X						
Urine pregnancy test [e]			X		X	X	X
Hematology, serum chemistry, liver function, urinalysis [f]	X		X	X	X	X	
CGIC/PGIC assessments				X	X	X	X
PRO assessments		X [g]		X	X	X	
Measure nocturnal SpO_2 [h]		X		X	X	X	
Dispense actigraphy device		X					
Return actigraphy device						X	
Dispense study drug			X		X		
Collect study drug					X	X	
Concomitant medications	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CGIC, Clinician Global Impression of Change; Hb, hemoglobin; HbF, fetal hemoglobin; LDH, lactate dehydrogenase; MCH, mean cell hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; PGIC, Patient Global Impression of Change; PRO, patient-reported outcome; RBC, red blood cell; RDW, red blood cell distribution width; SpO_2, peripheral oxygen saturation; WBC, white blood cell.

[a] All screening evaluations must be completed and reviewed before the Run-in Visit to confirm all eligibility criteria are met before dosing.

[b] Physical examinations after the Screening Period may be abbreviated, focusing on abnormalities identified on the screening examination and as related to adverse events.

[c] Vital signs (heart rate, blood pressure, respiratory rate, SpO_2 [pulse oximetry], and body temperature) will be measured after a participant has rested for at least 5 minutes in the supine or sitting position. Pulse oximetry, on room air, will be performed with vital signs.

[d] Females of child-bearing potential and postmenopausal females will have a serum pregnancy test at screening.
[e] Urine pregnancy tests will be performed at scheduled visits for females of child-bearing potential and postmenopausal females. If a urine pregnancy test is positive the result must be confirmed with a serum pregnancy test.
[f] Hematology assessments will include %HbF (screening only), WBC (with differential), RBC count, Hb, hematocrit, RDW, MCH, MCHC, MCV, platelet count, reticulocyte percentage, and absolute reticulocyte count. Serum chemistry will include sodium, potassium, bicarbonate, chloride, calcium, phosphorus, BUN, creatinine, glucose, bilirubin (total, direct, and indirect), total protein, albumin, ALT, alkaline phosphatase, AST, LDH, and serum erythropoietin.
[g] PRO assessments to be completed during Run-in Period prior to start of treatment on Day 1.
[h] Nocturnal SpO_2 device will be dispensed at Week -2 (Run-in Period) and at Weeks 2, 12, and 24. Measurements will be performed for 2 consecutive nights and the device should be returned within 48 hours after the measurements have been performed.

Figure 1: Study Schematic