CLINICAL STUDY PROTOCOL

Study Number	GBT440-044
Study Title	A Phase 3b, Randomized, Double-blind, Placebo-controlled, Multicenter Study to Evaluate the Treatment Effect of Voxelotor on Neurocognitive Function in Pediatric Participants 8 to < 18 Years of Age with Sickle Cell Disease
Short Title	Voxelotor Neurocognitive Function Study
Investigational Product	Voxelotor (GBT440)
IND Number	121691
Sponsor	Global Blood Therapeutics, Inc. 181 Oyster Point Blvd South San Francisco, CA 94080 United States of America
PPD	PPD Telephone: PPD email: PPD
Original Protocol **Amendment 1**	28 April 2021 10 December 2021 Version 2.0

CONFIDENTIAL

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/assent from persons receiving the study treatment. Once the protocol is signed, its terms are binding for all parties.

STATEMENT OF APPROVAL AND COMPLIANCE

Study Title: A Phase 3b, Randomized, Double-blind, Placebo-controlled, Multicenter Study to Evaluate the Treatment Effect of Voxelotor on Neurocognitive Function in Pediatric Participants 8 to < 18 Years of Age with Sickle Cell Disease

Short Title: Voxelotor Neurocognitive Function Study

SPONSOR APPROVAL

The signature of the Sponsor (Global Blood Therapeutics, Inc., "GBT") representative, below, signifies that the above-referenced clinical study is being conducted in accordance with applicable local regulatory requirements in all relevant jurisdictions where the study is being conducted. In addition, the study is being conducted in compliance with the procedures of International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use and Good Clinical Practice [ICH-GCP] and associated regulatory guidance. Furthermore, GBT, and the Independent Ethics Committee (IEC) will approve any changes to the protocol in writing before implementation. Global Blood Therapeutics will provide the Investigator with all information, including safety information, pertinent to the conduct of the study.

Sponsor Representative	PPD
Signature:	
Date:	
Title:	PPD

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 Declaration of Helsinki. All data obtained during the study will be provided to GBT. Global Blood Therapeutics requires that any presentation or publication of study data by an Investigator be reviewed by GBT, before release.

Principal Investigator (Print):	
Signature:	
Date:	
Title:	

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Description
ADHD	attention deficit hyperactivity disorder
ADL	activities of daily living
AE(s)	adverse event(s)
AF	assent form
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ARC	absolute reticulocyte count
AST	aspartate aminotransferase
AUC	area under curve
BUN	blood urea nitrogen
CFR	Code of Federal Regulations
CGI-C	Clinician Global Impression of Change
COVID-19	coronavirus disease of 2019
CRA	clinical research associate
CRF	case report form
CRO	contract research organization
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
CRF	case report form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
EOS	end of study
ESA	erythropoietin-stimulating agents
ET	early termination
FDA	Food and Drug Administration
FDA IID	Food and Drug Administration Inactive Ingredient Database
GBT	Global Blood Therapeutics, Inc.
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
Hb	hemoglobin
HbF	fetal hemoglobin
HbS	sickle hemoglobin
HbS/β^0	sickle hemoglobin and one beta thalassemia gene
HbSS	sickle hemoglobin with 2 sickle cell genes
HC	hydroxycarbamide
HIPAA	health insurance portability and accountability act

Abbreviation	Description
HIV	human immunodeficiency virus
HRQOL	health-related quality of life
HU	hydroxyurea
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
ID	identifier
IEC	Independent Ethics Committee
IID	Inactive Ingredient Database
IME	important medical events
IRB	Institutional Review Board
ITT	intent-to-treat
IQ	intelligence quotient
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IxRS	Interactive Response System
LDH	lactate dehydrogenase
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	medical Dictionary for Regulatory Activities
MMRM	mixed effect for repeated measures
MRA	magnetic resonance angiography
MRI	magnetic resonance imaging
NCI	National Cancer Institute
Neuro-QOL	Quality of Life in Neurological Disorders
NIH	National Institute of Health
O_2	oxygen
oxyHb	oxyhemoglobin
PBPK	physiologically-based pharmacokinetics
PD	pharmacodynamics
PE	physical examination
PfOS	powder for oral suspension
PGI-C	Patient Global Impression of Change
Ph Eur	European Pharmacopoeia
PI	Prescribing Information
PP	per protocol population
PPK	population pharmacokinetics
PRO	patient-reported outcome

Abbreviation	Description
QD	once daily
QOL	quality of life
RBC	red blood cell
RSI	Reference Safety Information
SAE	serious adverse event
SAP	statistical analysis plan
SCA	sickle cell anemia
SCD	sickle cell disease
SOA	schedule of assessments
SOC	standard of care (for SCD)
SUSAR	suspected unexpected serious adverse reaction
TCD	transcranial Doppler
TEAE	treatment-emergent adverse event
TIA	transient ischemic attack
USPI	United States Prescribing Information
ULN	upper limit of normal
US (A)	United States (of America)
WBC(s)	White blood cell(s)
WHO	World Health Organization

PROTOCOL SYNOPSIS

<table>
<tr><td>Study Number</td><td>GBT440-044</td></tr>
<tr><td>Study Title</td><td>A Phase 3b, Randomized, Double-blind, Placebo-controlled, Multicenter Study to Evaluate the Treatment Effect of Voxelotor on Neurocognitive Function in Pediatric Participants 8 to < 18 Years of Age with Sickle Cell Disease (SCD)</td></tr>
<tr><td>Short Title</td><td>Voxelotor Neurocognitive Function Study</td></tr>
<tr><td>Sponsor</td><td>Global Blood Therapeutics, Inc.
181 Oyster Point Blvd
South San Francisco, CA 94080
United States of America (USA)</td></tr>
<tr><td>Study Description</td><td>This is a Phase 3b, randomized, double-blind, placebo-controlled, multicenter study to assess the treatment effect of voxelotor on neurocognitive function as assessed by the National Institute of Health (NIH) Toolbox Cognition Module of executive abilities in pediatric participants (8 to < 18 years) with SCD.</td></tr>
<tr><td>Number of Clinical Sites</td><td>The study will be conducted at approximately 15 clinical trial sites globally including United States of America (USA) and Europe.</td></tr>
<tr><td>Number of Study Participants</td><td>Approximately 80 participants will participate in this study.</td></tr>
<tr><td>Investigational Products</td><td>Voxelotor tablets, administered orally as 3 × 500-mg tablets, weight-adjusted equivalent dose of powder for oral suspension (PfOS) (300 mg, 400 mg, 600 mg, and 900 mg).
Matching placebo, administered orally as 3 matching tablets or PfOS packet.</td></tr>
<tr><td>Treatment</td><td>During the Randomized Treatment Period, participants will be randomized in a 1:1 ratio to receive 1500 mg of voxelotor, (or the weight-adjusted equivalent dose for participants < 12 years old), once daily (administered orally as tablets/PfOS) or matching placebo for 12 weeks in addition to ongoing standard of care (SOC) treatment.
Voxelotor, in all dosage forms, may be taken with or without food. Voxelotor tablets should be swallowed whole. The PfOS dosage form should be mixed with liquid. Details regarding preparation of voxelotor for administration are provided in the Pharmacy Manual (provided separately).</td></tr>
<tr><td>Objectives</td><td>
<table>
<tr><th>OBJECTIVES</th><th>ENDPOINTS</th></tr>
<tr><td colspan="2">Primary</td></tr>
<tr><td>To assess the effect of voxelotor compared with placebo on neurocognitive functions in pediatric participants (8 to < 18 years of age) with SCD.</td><td>Change from baseline at Week 12 in the executive abilities composite score (using Dimensional Change Card Sort Test, Flanker Inhibitory Control and Attention Test, and List Sorting Test) as assessed by the NIH Toolbox Cognition Module.</td></tr>
</table>
</td></tr>
</table>

Study Number	GBT440-044	
	Secondary	
	To assess the effect of voxelotor compared with placebo on processing speed.	Change from baseline at Week 12 in processing speed as measured by Pattern Comparison Test score as assessed by the NIH Toolbox Cognition Module.
	To assess the effect of voxelotor compared with placebo in nonexecutive cognitive abilities composite score.	Change from baseline to Week 12 in nonexecutive cognitive abilities (Picture Vocabulary Test, Oral Reading Recognition Test, and Picture Sequence Memory Test) composite score as assessed by the NIH Toolbox Cognition Module.
	To evaluate the effect of voxelotor compared with placebo on changes in hemoglobin (Hb), and clinical measures of hemolysis.	• Change from baseline in Hb level over time up to Week 12 • Change and percent change from Baseline over time up to Week 12 in clinical measures of hemolysis, including unconjugated bilirubin, absolute reticulocyte, % reticulocytes, and lactate dehydrogenase (LDH)
	Exploratory	
	To assess the relationship between Hb levels and the executive abilities composite score.	Correlation between change from baseline in Hb level and change from baseline in executive abilities composite score
	To assess health-related quality of life (HRQOL) measures (patient- and clinician-reported).	HRQOL scores using: • Patient Global Impression of Change (PGI-C) at Week 12 • Change from baseline to Week 12 in Pediatric quality of life in neurological disorders (Neuro-QOL) score • Clinician Global Impression of Change (CGI-C) at Week 12
	Safety	
	To assess the safety and tolerability of voxelotor.	Incidence and severity of treatment emergent adverse events (AEs)
Study Design	The study is divided into a Screening Period, a Randomized Treatment Period, and follow-up: **Screening Period (within 2 weeks prior to randomization):** During this period (Day -14 to Day -1), participants will sign the informed consent form (ICF)/assent form (AF), after which they will complete the screening and Baseline assessments. All Screening and Baseline assessments must be completed within 2 weeks before the Randomized Treatment Period.	

Study Number	GBT440-044
	Randomized Treatment Period (12 weeks [±3 day window for each visit after Day 1 Visit]): Eligible participants will be randomized 1:1 to receive voxelotor or placebo once daily for 12 weeks. This period will be comprised of three clinical visits at Day 1 (Randomization day), Week 6, and Week 12. The first dose of study treatment is intended to be on Day 1, and as soon as possible after randomization. At the time of randomization, participants will be stratified by concurrent hydroxyurea (HU) therapy (yes, no). The Randomized Treatment Period is the continuous 12 weeks of voxelotor or placebo treatment from the date of randomization (Day 1).
	Follow-up/End of Study (EOS) Period (4 weeks after last dose [± 7-day window for EOS visit]): Following completion of the Randomized Treatment Period in this study, participants will be evaluated for an additional for 4 weeks after the last dose of treatment and instructed to return to the site to complete the EOS Visit. Safety and tolerability will be monitored during the entire study using standard measures, including the assessment of AEs, clinical laboratory tests, physical examinations (PEs), and vital signs.
Duration of Study Participation	The approximate study duration for an individual participant includes the Screening Period (within 2 weeks), Randomized Treatment Period of 12 weeks, and a Follow-up Period/EOS visit at 4 weeks [± 7 days] after the last dose of study drug). From screening through follow-up/EOS, total participation in this study for an individual participant is up to 18 weeks. Participants will continue to be followed for efficacy and safety, when possible, through at least the endpoint visit (treatment Week 12) regardless of treatment discontinuation. The study will end when the last participant's last visit occurs.
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 confirmed diagnosis of SCD (all genotypes).Documentation of SCD genotype is required and may be based on documented history of laboratory testing or confirmed by laboratory testing during Screening. 2. Aged 8 to < 18 years. 3. Screening Hb level 5.5 to 10.5 g/dL. 4. Able to answer NIH Toolbox Module questions validated and normed based on age and maternal education on tablet. 5. If participant is receiving HU they must have been on a stable dose for at least 90 days prior to signing the ICF/AF, with no dose modifications or initiation of HU planned or anticipated by the Investigator. 6. If participant is receiving erythropoiesis-stimulating agents (ESAs) they must have been on a stable dose for at least 12 weeks before enrollment with no dose modifications planned or anticipated by the Investigator.

Study Number	GBT440-044
	7. Participants, who if female and of child-bearing potential, agree to use highly effective methods of contraception from study start to 30 days after the last dose of study drug and who if male, agree to use barrier methods of contraception and refrain from donating sperm from study start to 30 days after the last dose of study drug. 8. Females of child-bearing potential must have a negative pregnancy test before the administration of study drug. 9. Parental/guardian consent and participant assent per Institutional Review Board (IRB)/Independent ethics committee (IEC) policy and requirements, consistent with International Council for Harmonisation (ICH) guidelines. 10. Capable of complying with the requirements and restrictions in the protocol, and willing to participate in the study. **Exclusion Criteria:** Participants meeting any of the following exclusion criteria will not be eligible for study enrollment: 1. Receiving chronic transfusion therapy. 2. Red blood cell (RBC) transfusion within 3 months before initiation of study drug or receives scheduled RBC transfusion therapy (also termed chronic, prophylactic, or preventive transfusion). 3. History of overt stroke including hemorrhagic stroke or transient ischemic attack (TIA) or spinal cord injury, magnetic resonance angiography (MRA)-defined vasculopathy, or magnetic resonance imaging (MRI)/transcranial doppler (TCD)-documented silent cerebral infarcts. 4. Congenital brain malformation, previously diagnosed severe developmental disability (eg, autism and/or intelligence quotient [IQ] < 60, and/or severe attention deficit hyperactivity disorder [ADHD]), or impairment that would prevent the use of a computer tablet. 5. Participant is taking or has received voxelotor (Oxbryta®) within 90 days prior to the Screening Visit. 6. Surgery within 8 weeks before Day 1 or planned elective surgery during the study. 7. Anemia due to bone marrow failure (eg, myelodysplasia). 8. Absolute reticulocyte count (ARC) < 100 × 109/L. 9. Screening alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 4× upper limit of normal (ULN). 10. Severe renal dysfunction (estimated glomerular filtration rate [eGFR] < 30 mL/min/1.73 m2) or is on chronic dialysis.

Study Number	GBT440-044
	11. Clinically significant bacterial, fungal, parasitic, or viral infection which requires therapy. a. Participants with acute bacterial infection requiring antibiotic use should delay screening/enrollment until the course of antibiotic therapy has been completed. b. Participants with known active hepatitis A, B, or C or who are known to be human immunodeficiency virus (HIV) positive. 12. Symptomatic coronavirus disease of 2019 (COVID-19) infection. 13. Females who are breast-feeding or pregnant. 14. History of hematopoietic stem cell transplant or gene therapy. 15. Participants taking concomitant medications such as sensitive cytochrome P450 (CYP)3A4 substrates with a narrow therapeutic range, or strong CYP3A4 inducers 16. Participated in another clinical trial of an investigational product (or medical device) within 30 days or 5 half-lives of date of informed consent/assent, whichever is longer, or is currently participating in another trial of an investigational product (or medical device). 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/assent; or, render the participant unable/unlikely to comply with the study procedures.
Concomitant Medications and Restrictions	The following concomitant medications are **allowed**: • Hydroxyurea/hydroxycarbamide (HC) (stable dose for at least 90 days prior to signing the ICF/AF and with no dose modifications planned or anticipated by the Investigator and no sign of hematological toxicity) • L-glutamine, over-the-counter analgesics, and opioids • Erythropoietin-stimulating agents (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 inducers • Crizanlizumab (Adakveo®) • Cisapride • Other experimental SCD therapy

Study Number	GBT440-044
	• Cannabis, alcohol and opioids that can interfere with neurocognitive testing must not be consumed within 24 hours prior to NIH Toolbox Cognition Module assessment at Baseline and Week 12 Visit
Statistical Methods	**This is a 2-arm, 3-period study**: Screening, 12-week placebo-controlled Randomized Treatment Period with 1:1 randomization (voxelotor: placebo), and a Follow-up/EOS period. Randomization will be stratified by concurrent HU therapy (yes, no). **Analysis Population** Three main analyses populations defined for this study are: the intent-to-treat (ITT), the per protocol (PP) population, and the safety-evaluable population. Efficacy analyses will be conducted on the ITT population, defined as all randomized participants. This will be the primary population for all efficacy analysis. Participants will be grouped by the treatment group to which they are randomized. The PP population will include all participants who complete study treatment with no important protocol deviations which would impact the evaluation of efficacy. This analysis population may be used for sensitivity analyses of the primary and key secondary efficacy endpoints. Safety analysis will be based on the safety-evaluable population, defined as randomized participants who received at least 1 dose of study treatment. Participants will be grouped by the actual study treatment they received. **Sample Size** Sample size determination is based on statistical power considerations for the primary efficacy endpoint, change from baseline in executive abilities composite score at Week 12. A sample size of approximately 80 participants (40 participants per treatment arm voxelotor and placebo) provides approximately 80% power to detect a difference in mean change in executive abilities composite score from baseline to Week 12 between the voxelotor arm and the placebo arm of 5 points with a common standard deviation of 7.5 points, using a 2-sided test at an overall $\alpha = 0.05$ level. For the purposes of sample size calculation, a drop-out rate of 5% by Week 12 was assumed. **Primary Analysis** The executive abilities composite score will be measured using the NIH Toolbox Cognition Module. The primary endpoint will be the change from baseline in executive abilities composite score at Week 12 which will be summarized by treatment group using mean, SD, median, minimum and maximum. The analysis of the primary endpoint will compare voxelotor with placebo using analysis of covariance (ANCOVA) controlling for the baseline composite score, and HU use. **Secondary Analysis** Changes from baseline to Week 12 in processing speed and nonexecutive cognitive abilities composite score will be summarized using mean, SD, median, minimum and maximum. The analyses of these endpoints will compare voxelotor with placebo using ANCOVA and controlling for the corresponding baseline scores and HU use.

Study Number	GBT440-044
	Changes from baseline in Hb and clinical measures of hemolysis (unconjugated bilirubin, % reticulocytes, absolute reticulocyte, and LDH) over time up to Week 12 will be analyzed using a mixed effect for repeated measures (MMRM) model. The fixed effect terms include treatment, study visit, treatment by visit interaction. Within-subject variability will be modeled using an unstructured covariance matrix. **Exploratory Analysis** Exploratory endpoints will be summarized by descriptive statistics. Details will be provided in the statistical analysis plan (SAP). **Safety Analysis** Safety analysis will be performed on all participants receiving at least 1 dose of study drug. Adverse Events will be classified according to the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of participants with treatment emergent adverse events (TEAEs) will be tabulated by system organ class and preferred term. Treatment-emergent adverse events will also be presented by severity and relationship to study treatment. Changes in laboratory parameters and vital signs will be summarized descriptively.

1. INTRODUCTION

1.1. Disease Background

1.1.1. Sickle Cell Disease

Sickle cell disease is an inherited blood disorder caused by a point mutation in the β globin gene resulting in the formation of "sickle hemoglobin (HbS)", which polymerizes in the deoxygenated state and leads to red blood cell (RBC) sickling. The disease is marked by the pathophysiologic features of hemolytic anemia, vaso-occlusion, and progressive end-organ damage, with a clinical course characterized by life-long disability and early death (Gladwin, 2014; Nouraie, 2013). In addition to unpredictable and recurrent vaso-occlusive pain episodes, hemolytic anemia directly damages blood vessels, resulting in a systemic vasculopathy that leads to chronic and progressive tissue and organ injury (Kato, 2007). With improved survival in children, the natural history of SCD has shifted from a disease of childhood to a chronic, debilitating disease of young and middle-aged adults. Cumulative injury to multiple organ systems from repeated episodes of RBC sickling, vaso-occlusion, and chronic hemolytic anemia exact a high clinical burden in the aging adult, significantly impacting quality of life (QOL) and overall functioning (Swanson, 2011).

1.1.2. Rationale for This Study

There is well-established evidence that children with SCD have cognitive impairment with varying degrees of deficit. While the neurocognitive deficits are caused by neurologic damage from cerebral vascular accidents is consistently documented, the causes of cognitive deficits in children with no history of overt neurologic are not yet clear (Schatz, 2002; Wang, 1998). One of the direct potential causes suggested includes chronic brain hypoxia related to severe anemia (Schatz, 2002). There are several studies that support the hypothesis that neurocognitive deficits are associated with the severity of anemia (Bernaudin, 2000; Kral, 2003; Steen, 2003). Patients with SCD appear to have a decreased cerebral vascular reserve and may have a state of chronic cerebral ischemia resulting in neurocognitive dysfunction (Vichinsky, 2010). This is supported by the studies that find that blood transfusion and hydroxyurea (HU) may improve disease symptoms and reduce anemia severity, and may improve neurocognition in patients with SCD than in control group (Hood, 2019; Puffer, 2007). Similarly, in studies of healthy controls and other chronic diseases, anemia is associated with poorer neurocognitive performance, and increasing hemoglobin (Hb) levels improves test results (Weiskopf, 2000; Stivelman, 2000).

Voxelotor was approved in 2019 for use in the 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. Since voxelotor increases Hb concentration, it is speculated that improvement in anemia improves cerebral oxygen delivery and consequently, may enhance cognitive functions. Hence, study GBT440-044 hypothesizes that a disease modifying treatment, such as voxelotor may improve the executive abilities (a cognitive domain in which patients with SCD experience particular difficulty), by improving Hb, and cerebral oxygen delivery to the brain in pediatric participants 8 to < 18 years of age with SCD (see (Oxbryta USPI, 2019).

1.2. Voxelotor

Voxelotor (previously GBT440) is an 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 affinity (Eaton, 1999), stabilizing the oxyhemoglobin (oxyHb) state and inhibiting polymerization (Oksenberg, 2016). The voxelotor binding site (Kato, 2007) is distant from heme pockets and it can therefore increase oxygen (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 has the potential to subsequently achieve long-term disease modification. This principle is supported by the finding that in patients with sickle hereditary persistence of fetal hemoglobin (HbF), the dilution of HbS by 20% to 30% fetal 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 (Study GBT440-031) where 1500 mg of voxelotor, achieving Hb modification of 20% to 30%, administered daily orally for 24 weeks showed a significant and clinically meaningful increase in Hb and decrease in hemolysis.

Voxelotor was approved in 2019 for use in the US under the tradename Oxbryta® by the FDA and is indicated for the treatment of SCD in adults and pediatric patients 12 years of age and older. Voxelotor is considered an investigational drug for this study.

1.3. Summary of Relevant Nonclinical Data and Clinical Data

1.3.1. Nonclinical Data

Primary pharmacodynamics (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 Hb-O_2 via hemoximetry, quantifying stabilization of the oxyHb state conformation, delaying HbS polymerization at low O_2 tension, preventing in vitro sickling induced by a low O_2 environment, decreasing viscosity, and improving deformability of RBCs in blood from patients with SCD (Dufu, 2018). In addition, these studies show that voxelotor-modified Hb retains the Bohr Effect, which is the ability to offload O_2 from Hb in metabolically active (low pH) tissues.

Collectively, these studies demonstrate that voxelotor increases Hb-O_2 affinity with high specificity of binding to Hb, stabilizes the oxy or R-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 half-life, while decreasing ex vivo sickling and reticulocyte count in a SCD mouse model.

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

1.3.2. Clinical Data

Data from the Phase 3 randomized controlled trial (GBT440-031, HOPE ClinicalTrials.gov number, NCT03036813) demonstrated that administration of voxelotor in participants with SCD resulted in a statistically significant and clinically meaningful improvement in Hb (> 1 g/dL increase) at 24 weeks compared to placebo (Vichinsky, 2019). Concomitant with the improved anemia there was a reduction in laboratory measures of hemolysis, including reticulocytes, lactate dehydrogenase (LDH), and indirect bilirubin. Additionally, in the Phase 1/2 study (GBT440-001) and extension study (GBT440-024), treatment with voxelotor led to reductions in the percentage of sickled red cells in the peripheral blood (Howard, 2019).

Additional information regarding the safety and tolerability, and efficacy of voxelotor is provided in Section 1.4 of this protocol, in the most current version of the voxelotor IB, provided separately, and voxelotor PI (Oxbryta® USPI, 2021).

1.4. 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 improve anemia and reduce clinical measures of hemolysis in adult and pediatric participants 12 years of age and older with SCD.

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.

Further information regarding the potential benefits and risks of voxelotor and guidance for the investigator are provided in the current version of the IB.

1.5. Description of and Justification for the Route of Administration, Dosage, Dosage Regimen, and Treatment Period(s)

During the Randomized Treatment Period, participants will be randomized in a 1:1 ratio to receive voxelotor once daily or matching placebo for 12 weeks, in addition to ongoing current standard of care (SOC) for SCD. The SOC selected for any given participant is determined by the Investigator and may vary among participants. Participants ≥ 12 years old will receive a voxelotor dose of 1500 mg once daily, administered orally as tablets, while participants < 12 years old will receive a weight-adjusted equivalent dose.

1.5.1. Dose Rationale for Voxelotor

Voxelotor is available in an oral form and is intended for once daily administration. See Section 5.1 for additional information regarding the dose to be used in this study.

The voxelotor dose of 1500 mg orally once daily is the currently approved dose for the treatment of SCD in the US in adults and pediatric patients 12 years of age and older (see Oxbryta® USPI, 2021).

The recommended dosage of voxelotor for pediatric participants 12 to 17 years is 1500 mg taken orally once daily (QD) with or without food. Population pharmacokinetic (PPK) modeling, physiologically-based PK (PBPK) modeling and allometric scaling (Washington, 2018) were used to estimate weight-based equivalent of 1500 mg for the pediatric population. These weight-based doses are outlined in (Table 1) and are anticipated to provide PK exposures similar to those observed in pediatric participants 12 to 17 years of age and adults receiving voxelotor 1500 mg. Weight-based dosing for voxelotor is being evaluated in an ongoing pediatric study (Study GBT440-007) and clinical efficacy, safety and PK results from this study support the continued evaluation of these doses.

Table 1: Voxelotor Weight-based Doses for Participants Less than 12 Years of Age

Population	Voxelotor Doses (1500 mg Equivalent)
5 to < 10 kg	400 mg (PfOS packet only)
10 to < 20 kg	600 mg (PfOS packet only)
20 to < 40 kg	900 mg (PfOS packet only)
≥ 40 kg	1500 mg (3× 500 mg Tablets only)

Abbreviations: PfOS, powder for oral suspension.

1.5.2. Use of a Placebo Control

This study will use placebo as a comparator on the background of SOC treatment. Placebo was chosen as the control because it is necessary to determine the effect of voxelotor on neurocognition while controlling for background changes with SOC. The use of a placebo control will also allow safety signals to be distinguished from AEs occurring due to SCD.

Randomization to placebo treatment in this study does not place study participants at increased risk, as the SOC treatment for SCD will be provided during the study.

2. STUDY OBJECTIVES, ENDPOINTS, AND PURPOSE

Table 2: Objectives and Endpoints

OBJECTIVES	ENDPOINTS
Primary	
To assess the effect of voxelotor compared with placebo on neurocognitive functions in pediatric participants (8 to < 18 years of age) with SCD.	Change from baseline at Week 12 in the executive abilities composite score (using Dimensional Change Card Sort Test, Flanker Inhibitory Control and Attention Test, and List Sorting Test) as assessed by the NIH Toolbox Cognition Module.
Secondary	
To assess the effect of voxelotor compared with placebo on processing speed.	Change from baseline at Week 12 in processing speed as measured by Pattern Comparison Test score as assessed by the NIH Toolbox Cognition Module.
To assess the effect of voxelotor compared with placebo in nonexecutive cognitive abilities composite score.	Change from baseline to Week 12 in nonexecutive cognitive abilities (Picture Vocabulary Test, Oral Reading Recognition Test, and Picture Sequence Memory Test) composite score as assessed by the NIH Toolbox Cognition Module.
To evaluate the effect of voxelotor compared with placebo on changes in Hb, and clinical measures of hemolysis.	Change from baseline in Hb level over time up to Week 12 Change and percent change from Baseline over time up to Week 12 in clinical measures of hemolysis, including unconjugated bilirubin, absolute reticulocyte, % reticulocytes, and LDH
Exploratory	
To assess the relationship between Hb levels and the executive abilities composite score.	Correlation between the change in Hb level and change in executive abilities composite score.
To assess health-related quality of life (HRQOL) measures (patient- and clinician-reported).	HRQOL scores using: Patient Global Impression of Change (PGI-C) at Week 12 Change from baseline to Week 12 in Pediatric Neuro-QOL score Clinician Global Impression of Change (CGI-C) at Week 12
Safety	
To assess the safety and tolerability of voxelotor.	Incidence and severity of treatment emergent AEs

3. INVESTIGATIONAL PLAN

3.1. Study Design

This study is a Phase 3b, randomized, double-blind, placebo-controlled, multicenter study evaluating the impact of voxelotor treatment on neurocognitive functions in pediatric participants with SCD aged between 8 to < 18 years. The study is divided into 3 study periods: Screening, Randomized Treatment, and Follow-up/End of Study (EOS).

The study will include approximately 80 eligible participants at approximately 15 clinical trial sites globally including United States of America (USA)and Europe. The overall study design is illustrated in the Study Schema provided in Figure 1.

Safety and tolerability will be monitored during the entire study using standard measures, including the assessment of AEs, clinical laboratory tests, physical examinations (PEs), and vital signs.

Screening Period (within 2 weeks prior to the Randomization)

During this period (Day -14 to Day -1), participants will sign the informed consent form (ICF)/assent form (AF), after which they will complete the Screening assessments, as detailed in the Schedule of Assessments (SOA) in Appendix 1. All Screening assessments must be completed within 2 weeks before the start of the Randomized Treatment Period.

Randomized Treatment Period (12 weeks [± 3-day window for each visit after Day 1 Visit])

Eligible participants will be randomized 1:1 to receive voxelotor or placebo once daily for 12 weeks. At the time of randomization, participants will be stratified by concurrent HU therapy (yes, no).

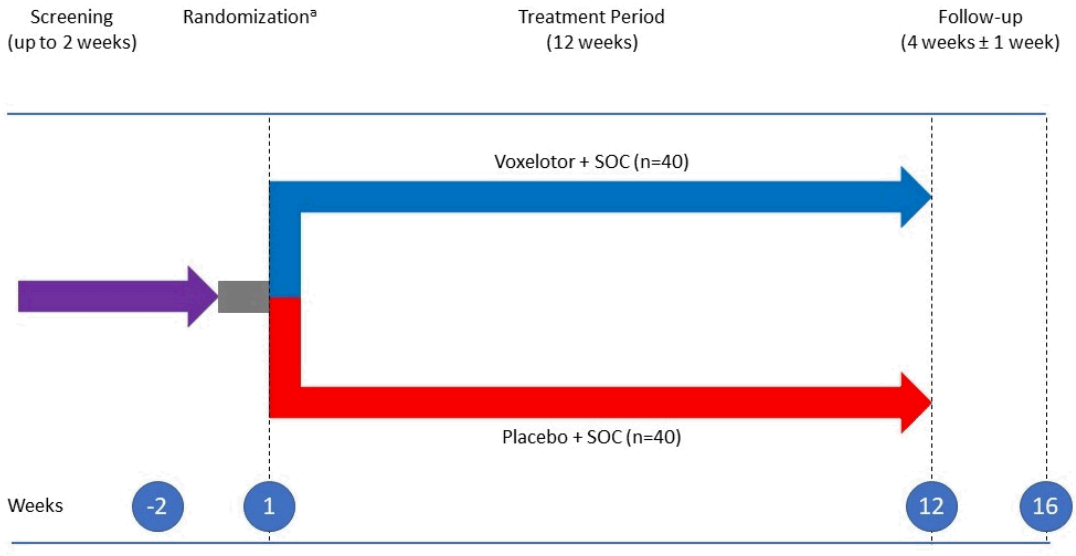
This period will be comprised of 3 clinical visits at Day 1 (Randomization day), Week 6, and Week 12.

The first dose of study treatment is intended to be on Day 1, and as soon as possible after randomization. The randomized treatment period is the continuous 12 weeks of voxelotor or placebo treatment from the date of randomization (Day 1).

Follow-up Period/EOS (4 weeks after last dose [± 7-day window for EOS Visit])

Following completion of the Randomized Treatment Period in this study, participants will be evaluated for an additional 4 weeks after the last dose for safety and tolerability including PE, vital signs, hematology and AEs as detailed in the SOA (Appendix 1).

Figure 1: Study Schema



Abbreviations: SOC, standard of care (as determined by the investigator for an individual participant); SOC treatment will be ongoing throughout all phases of study.
[a] Randomization will be stratified by concurrent HU use (yes, no).

3.1.1. Study Treatment

See Section 5 for dosage and treatment administration of voxelotor and placebo.

3.1.2. Study Assessments

Study procedures and assessments are described in Section 6. The timing for the study procedures and assessments is provided in the SOA (Appendix 1).

Participant safety and tolerability will be monitored during the entire study using standard measures, including PEs, vital signs (including blood pressure, heart rate, oxygen saturation, and temperature), clinical laboratory tests, and AE monitoring.

3.1.3. Study Endpoints

See Table 2 for details.

3.1.4. Minimization of Bias

This study uses a double-blind, randomized, multicenter design to minimize bias in treatment assignment, participant monitoring, and assessment of efficacy. Participants will be randomized 1:1 using an Interactive Response System (IxRS). Laboratory results that may suggest the treatment assignment will be redacted to the Investigator (see Section 5.4.1.1). Participants and Study site personnel will be blinded to treatment assignment throughout the study.

3.2. Duration of Study Participation and of the Study

The approximate study duration for an individual participant includes the Screening Period (within 2 weeks), a Randomized Treatment Period of 12 weeks, and a Follow-up Period/EOS visit (4 weeks [± 7 days] after the last dose of study drug). From Screening through Follow-up/EOS, total participation in this study for an individual participant is up to 18 weeks. Participants will continue to be followed for efficacy and safety, when possible, through the endpoint visit (Week 12), and subsequent Follow-up Visit regardless of treatment discontinuation.

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

3.3. Stopping Rules

3.3.1. Early Termination of the Study

The Sponsor has the right to terminate this 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 with voxelotor indicating a potential health risk to participants.

In any instance of early termination (ET) of the study, the Sponsor will notify, in writing, the Investigators, regulatory authorities, and Independent Review Boards (IRBs)/Independent Ethics Committees (IECs) and will specify the reason(s) for termination.

3.3.2. Discontinuation of Individual Participants

Participants who withdraw or are discontinued from the study should return to the study site for an ET Visit as soon as possible after the last dose of study treatment, as indicated in the SOA and if possible complete and EOS visit 28 days after the ET visit.

3.3.2.1. Withdrawal of Consent/Assent

Participants and/or their caregiver/legal representative will be informed that participation is voluntary and that they may discontinue treatment or withdraw from the 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. Early Discontinuation from Study

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

- Any serious adverse event (SAE), clinically significant AE, severe laboratory abnormality, intercurrent illness, or other medical condition that indicates that continuation in the study is not in the best interest of participants
- Participant is lost to follow-up
- Participant failure to comply with protocol requirements including the requirement of prohibited concomitant medications or study related procedure
- Withdrawal of participant consent/assent
- Pregnancy: study treatment will be discontinued immediately (see also Section 7.4)
- Discretion of the Investigator

3.3.2.3. Early Discontinuation of Study Treatment

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

- Any SAE, clinically significant AE, severe laboratory abnormality, intercurrent illness, or other medical condition that indicates that continuation of study treatment is not in the best interest of participants
- Participant failure to comply with protocol requirements including the requirement of prohibited concomitant medications or study related procedure
- Withdrawal of participant consent/assent
- Pregnancy: study treatment will be discontinued immediately (see also Section 7.4)
- Discretion of the Investigator

For participants discontinuing the study treatment, every attempt should be made to keep the participant in the study and continue to perform the required study-related follow-up and procedures even after pre-mature discontinuation of treatment. Participants discontinuing the study early should return to the study site for an EOS/ET visit approximately 28 days (± 7 days) after the last dose of study treatment, as indicated in the SOA.

4. SELECTION OF STUDY PARTICPANTS

Eligibility will be based on assessments performed during the Screening Period. A participant will be enrolled after signing the ICF/AF 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 criteria will be eligible for study enrollment:

1. Male or female participants with confirmed diagnosis of SCD (all genotypes).

   Documentation of SCD genotype is required and may be based on documented history of laboratory testing or confirmed by laboratory testing during Screening.
2. Aged 8 to < 18 years.
3. Screening Hb level 5.5 to 10.5 g/dL.
4. Able to answer NIH Toolbox Module questions validated and normed based on age and maternal education on tablet.
5. If participant is receiving HU, they must have been on a stable dose for at least 90 days prior to signing the ICF/AF, with no dose modifications or initiation of HU planned or anticipated by the Investigator.
6. If participant is receiving erythropoiesis-stimulating agents (ESAs) they must have been on a stable dose for at least 12 weeks before enrollment with no dose modifications planned or anticipated by the Investigator.
7. Participants, who if female and of child-bearing potential, agree to use highly effective methods of contraception from study start to 30 days after the last dose of study drug and who if male, agree to use barrier methods of contraception and refrain from donating sperm from study start to 30 days after the last dose of study drug.
8. Females of child-bearing potential must have a negative pregnancy test before the administration of study drug.
9. Parental/guardian consent and participant assent per IRB/IEC's policy and requirements, consistent with International Council for Harmonisation (ICH) guidelines.
10. Capable of complying with the requirements and restrictions in the protocol, and willing to participate in the study.

4.2. Exclusion Criteria

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

1. Receiving chronic transfusion therapy.
2. RBC transfusion within 3 months before initiation of study drug or receives scheduled RBC transfusion therapy (also termed chronic, prophylactic, or preventive transfusion).
3. History of overt stroke including hemorrhagic stroke or transient ischemic attack (TIA) or spinal cord injury, magnetic resonance angiogram (MRA)-defined vasculopathy, or

magnetic resonance imaging (MRI)/transcranial doppler (TCD)-documented silent cerebral infarcts.

4. Congenital brain malformation, previously diagnosed severe developmental disability (eg, autism and/or IQ < 60, and/or severe attention deficit hyperactivity disorder [ADHD]), or impairment that would prevent the use of a computer tablet.
5. Participant is taking or has received voxelotor (Oxbryta®) within 90 days prior to the Screening Visit.
6. Surgery within 8 weeks before Day 1 or planned elective surgery during the study.
7. Anemia due to bone marrow failure (eg, myelodysplasia).
8. Absolute reticulocyte count (ARC) < 100×10^9/L.
9. Screening alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 4× upper limit of normal (ULN).
10. Severe renal dysfunction (estimated glomerular filtration rate [eGFR] < 30 mL/min/1.73 m^2) or is on chronic dialysis.
11. Clinically significant bacterial, fungal, parasitic, or viral infection which requires therapy:
    a. Participants with acute bacterial infection requiring antibiotic use should delay screening/enrollment until the course of antibiotic therapy has been completed.
    b. Participants with known active hepatitis A, B, or C or who are known to be human immunodeficiency virus (HIV) positive.
12. Symptomatic COVID-19 infection.
13. Females who are breast-feeding or pregnant.
14. History of hematopoietic stem cell transplant or gene therapy.
15. Participants taking concomitant medications such as sensitive CYP3A4 substrates with a narrow therapeutic range, strong CYP3A4 inducers
16. Participated in another clinical trial of an investigational product (or medical device) within 30 days or 5 half-lives of date of informed consent/assent, whichever is longer, or is currently participating in another trial of an investigational product (or medical device).
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/assent; or render the participant unable/unlikely to comply with the study procedures.

5. TREATMENTS OF SUBJECTS

5.1. Treatment Regimen

During the Randomized Treatment Period, participants will be randomized in a 1:1 ratio to receive voxelotor once daily or matching placebo for 12 weeks. Participant ≥ 12 years old will receive a voxelotor dose of 1500 mg once daily, administered orally as tablets, while participants < 12 years old will receive a weight-adjusted equivalent dose. In this study, all participants will receive the SOC for SCD during the Randomized Treatment Period and throughout all phases of the study.

Voxelotor, in all dosage forms, may be taken with or without food. Voxelotor tablets should be swallowed whole. The PfOS dosage form should be mixed with liquid. Details regarding preparation of voxelotor for administration are provided in the Pharmacy Manual (provided separately).

5.1.1. Dose Frequency

Participants will receive a voxelotor or matching placebo 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 the day of a missed dose, should not be increased or decreased).

5.1.2. Dose Modification

Participants should adhere to their assigned dose level. However, reducing or holding the dose for a short period of time during the study may be used for AEs that impact the participant's safety and tolerability. All instances of study drug dose modification (dose reduction, interruption, or discontinuation) should be documented in the participants' medical record and recorded in the CRF. If the conditions/event leading to the dose modification have resolved, the original dose level should be resumed unless, in the judgment of the Investigator, this cannot be done safely. Dose modifications may be determined by the Investigator in consultation with the Sponsor's Medical Monitor (Table 3 and Table 4).

Table 3: Dose Modification Guidelines for Study Drug-related Adverse Events (12-17 years)

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	
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; NCI, National Cancer Institute.

Table 4: Voxelotor Weight-based Dose Reduction for Participants Less than 12 Years of Age

Population	Voxelotor Doses (1500 mg Equivalent)	Dose Reduction 1 - New Dose
5 to < 10 kg	400 mg (PfOS packet only)	300 mg (PfOS packet only)
10 to < 20 kg	600 mg (PfOS packet only)	400 mg (PfOS packet only)
20 to < 40 kg	900 mg (PfOS packet only)	600 mg (PfOS packet only)
≥ 40 kg	1500 mg (3X 500 mg Tablets only)	1000 mg (2X 500 mg Tablets only)

Abbreviations: PfOS, powder for oral suspension.

5.2. Physical Description of Voxelotor

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.

5.3. Dosage Forms

5.3.1. Voxelotor

Voxelotor 500 mg tablets contain voxelotor drug substance along with several dosage form excipients. In this study, voxelotor will be administered as tablets for participants ≥ 12 years old. Participants < 12 years old receiving voxelotor will be administeredas a powder for oral suspension (PfOS) (packaged as stick packets) at a dose based on their body weight. The participant's weight will be measured according to the SOA (Appendix 1), and dose adjustments made as needed and as indicated in Table 1. While the dose should be adjusted if the participant's weight changes, the PfOS dosage form of voxelotor administered to participants < 12 years old need not be changed if the participant crosses the cut-off age of 12 years during the consecutive 12-week Randomized Treatment visit.

All of the excipients used in the dosage forms are listed in the FDA Inactive Ingredient Database (IID) or are pharmaceutical excipient mixtures entirely composed of FDA IID components). All of the excipients used in the dosage forms are either compendial per European Pharmacopoeia (Ph Eur) or are composed of mixtures which are compendial per Ph Eur or accepted by E number or European Commission regulation.

Additional details are provided in the Pharmacy Manual.

5.3.2. Placebo

The matching placebo tablets, and PfOS, dosage form contain several formulation excipients. All of the excipients used in the dosage forms are listed in the FDA IID or are pharmaceutical excipient mixtures entirely composed of FDA IID components.

All of the excipients used in the dosage form s are either compendial per Ph Eur or are composed of mixtures which are compendial per Ph Eur or accepted by E number or European Commission regulation. The matching placebos do not contain any voxelotor drug substance.

5.4. Randomization and Unblinding

5.4.1. Randomization

Randomization will be carried out through an IxRS. Permuted blocks within randomization strata will be used. Eligibility of the participant will be confirmed by the Investigator prior to randomization.

5.4.1.1. Preventing Unblinding due to Laboratory Assessments

Because knowledge of certain laboratory assessments (Hb, hematocrit, RBC count, total and unconjugated bilirubin, or absolute and % reticulocyte count) may suggest the treatment

assignment in the Randomized Treatment Period, these measurements will be redacted to the Investigator.

Results of redacted laboratory tests will be communicated to the Investigator if a participant's ARC declines to < 80 × 10^9/L, or Hb declines to < 5.0 g/dL, or if the Hb declines ≥ 2 g/dL from Screening. This does not require breaking of the treatment assignment blind. This is to ensure participant safety by allowing the Investigator to monitor for potential bone marrow suppression, as described in HU monitoring guidelines (McGann, 2015; Yawn, 2014. De-identified laboratory results will be available to the Sponsor.

5.4.1.2. Unblinding for Medical Need

The Investigator and site personnel will remain blinded to the treatment assignment during the study. Treatment assignment for a study participant may be unblinded by the Investigator only in an emergency, and only if knowledge of the treatment assignment is urgently needed for the clinical management or welfare of the participant. The Investigator should contact the medical monitor or project manager before unblinding, when possible, but priority should be given to treatment of the participant. The Investigator should promptly document and explain to the Sponsor any premature unblinding (eg, accidental unblinding, unblinding due to an SAE) of the study participant. Pregnancy is considered a medical condition that requires unblinding. Unblinding procedures will be followed as outlined in the IxRS Manual and documented in the Investigator site file and the CRF.

5.5. Packaging and Labeling

Voxelotor tablets, and placebo tablets will be supplied to clinical sites in high-density polyethylene bottles with induction sealed polypropylene child resistant caps. Voxelotor PfOS (packaged as stick packets) and matching placebo dosage forms will be supplied to clinical sites in a tamper-sealed carton. Bottles and/or cartons will be labeled according to applicable regulations. All study drug packaging must be returned at each visit, regardless of whether they are empty or contain unused study drug (voxelotor).

Additional details are provided in the Pharmacy Manual.

5.6. Investigational Product Supply

Global Blood Therapeutics, Inc. (GBT) or their representative will supply the packaged and labeled drug product to the investigational sites. Participants will receive either 60-days or 70 days supply of voxelotor 1500 mg tablet or voxelotor PfOS, respectively, at the Randomized Day 1 (Visit 2) and Week 6 (Visit 3). Additional details are provided in the Pharmacy Manual.

5.7. 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 a secure, temperature-controlled and locked environment with restricted access in the storage area of the investigational site pharmacy, which is a secure, temperature controlled, locked environment with restricted access.

The Sponsor or its representatives will be permitted upon request to audit the supplies, storage, dispensing procedures, and records, provided that the blind of the study is not compromised.

5.8. Concomitant and Prohibited Medications

5.8.1. Concomitant Medications

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 study participants who initiate study treatment, all medications administered from signing the consent/assent until 14 days (2 weeks) after the participant's last dose of study drug are considered concomitant medications and, must be recorded on the participant's case record form (CRF).

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

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

5.8.2. Restrictions Regarding Usage of Concomitant Medications

Concomitant treatment with HU/hydroxycarbamide (HC) is allowed, provided that the dose has been stable for at least 90 days prior to signing the ICF/AF. Participants who are on HU/HC may have their dose adjusted (based on change in their weight) if the mg/kg dose is stable, in the opinion of the Investigator. If HU/HC treatment is initiated after a participant has been screened or after being randomized, the eligibility of the participant to continue in the study must be discussed with the Sponsor's Medical Monitor.

5.8.3. Transfusion

Participants who require a transfusion (either for acute treatment or the start of a chronic transfusion program) during the study will continue with study drug treatment after their transfusion. However, the final assessments (Day 85) must be conducted a minimum of 30 days after a transfusion. If a transfusion occurs within 30 days of the scheduled Day 85 Visit, the Investigator will contact the Sponsor to determine when the Day 85 assessments will be conducted. These participants will be monitored for safety through the Day 113 EOS Visit.

5.8.4. Other Therapies

Vaccinations, including those for COVID-19, are allowed in accordance with SOC.

Other concomitant medications are allowed, unless the restrictions in Section 5.8.5 apply. Permitted concomitant medications include L-glutamine, over-the-counter analgesics, and opioids, which are among the chronic medications commonly taken by participants with SCD. Erythropoietin-stimulating agents (stable dose for at least 4 weeks with no dose modifications planned or anticipated by the Investigator) are allowed.

5.8.5. Prohibited Concomitant Medications

Use of an investigational product other than voxelotor in this study, regardless of its intended use, is prohibited throughout the trial and for 28 days after the last dose. Additionally, concomitant medications (eg, crizanlizumab [Adakveo®]) that confound the ability to interpret data from the study are prohibited.

Voxelotor is a moderate cytochrome P450 (CYP)3A4 inhibitor and should be not be coadministered with sensitive CYP3A4 substrates with a narrow therapeutic index (refer to Table 5 for examples).

Table 5: Sensitive CYP3A4 Substrates with Narrow Therapeutic Range

Alfentanil, sirolimus, and tacrolimus

Abbreviation: CYP, cytochrome P450.
Note: **This is not an exhaustive list.** Country-specific lists may be used if available.
For an updated list, refer to the following link:
https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#table 3-2.

Since concomitant use of voxelotor with rifampin (a strong CYP3A4 inducer) is predicted to decrease voxelotor area under curve (AUC) in participants by up to 40%, concomitant use of voxelotor with rifampin or other strong CYP3A4 inducers is not allowed (refer to Table 6 for examples).

Table 6: Examples of Strong CYP Inducers

CYP3A4	Examples
Strong CYP3A4 inducers	Rifampin, apalutamide, phenytoin, carbamazepine, enzalutamide, St John's wort, and mitotane

Abbreviation: CYP, cytochrome P450.
Note: **This is not an exhaustive list.** Country-specific lists may be used if available.
For an updated list, refer to the following link:
https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#table3-3.

Additional prohibited medications are shown in Table 7.

Table 7: Additional Prohibited Medications

• Cisapride
• Crizanlizumab (Adakveo®)
• Cannabis, alcohol and opioids that can interfere with neurocognitive testing must not be consumed within 24 hours prior to NIH Toolbox Cognition Module assessment at Baseline and Week 12 Visit.

5.9. Fertility/Contraceptive Requirements

All female participants of child-bearing potential (post menarche) should avoid pregnancy, and all sexually active male participants should avoid fathering a child. Pregnancy is considered a medical condition that requires unblinding (for details refer to Section 7.4).

5.9.1. Instructions for Female Participants of Child-Bearing Potential

For female participants of child-bearing potential (post menarche) and 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 5.10. Pregnancy reporting requirements are outlined in Section 7.4.

Female participants who become pregnant during the study will be withdrawn from the study.

5.9.2. Female Participants of Non-Child-Bearing Potential

Female study participants who have not experienced menarche will not be assessed for pregnancy. However, if a female participant experiences menarche during the study, the participant will be considered as a female of child-bearing potential and will undergo urine pregnancy testing as per the SOA, (Appendix 1).

5.9.3. 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 (Section 5.9).

5.10. Acceptable Forms of Contraception for Sexually Active Participants

For female participants:

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. Highly effective methods of birth control are as follows:

1. Hormonal contraceptives (must be supplemented with a barrier method, preferably male condom).
    a. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:
        - Oral
        - Intravaginal
        - Transdermal

b. Progestogen-only hormonal contraception associated with inhibition of ovulation:
   - Oral
   - Injectable
   - Implantable

2. Intrauterine device (IUD)
3. Intrauterine hormone-releasing system (IUS)
4. Bilateral tubal occlusion
5. Sexual abstinence:
   a. 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 study and the preferred and usual lifestyle of the participant.

For male participants with female partners capable of reproduction:

Barrier methods of contraception:

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

5.11. Assessment of Treatment Compliance

Drug disposition records will be maintained, specifying the amount 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 tablets/ packets and participant dosing diaries. Details regarding dosing, including the dose administered (number of tablets/packets) and the date of dosing, will be recorded by the participant/caregiver daily between study visits. The date and reasons(s) for missed doses will also be recorded by the participant.

6. STUDY PROCEDURES AND ASSESSMENTS

The timing for the required study procedures and assessments are outlined in the SOA (Appendix 1).

The Screening Period for a participant commences at the point at which the participant undergoes the first study-specific screening assessment. All screening assessments must be completed within 2 weeks before the start of the Randomized Treatment Period. Randomization takes place on Day 1 of the study and the first dose of study treatment is intended to be on Day 1, and as soon as possible after randomization.

6.1. Informed Consent/Assent

A signed and dated ICF and/or AF 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 Investigational Site policy) or the participant's legal representative. Guidelines for the informed consent/assent process are outlined in Section 11.3.

6.2. Participant ID Number

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

Interactive Response System user manual contains the information needed for registering participant status (eg, assigning participant numbers, indicating screen failure, temporary suspension of treatment, and end of treatment).

6.3. Eligibility Assessment, Inclusion/Exclusion Review

Eligibility assessment will be conducted during Screening and, prior to receiving study drug on treatment Day 1. Both at Screening and prior to randomization, the Investigator should determine that the participant is in stable clinical condition at their steady state.

The first dose of study treatment is intended to be on Day 1, and as soon as possible after randomization which occurs on study Day 1. If a participant is randomized and withdrawn from the study prior to the first dose of study drug, a reason must be provided

Re-screening may be considered at the discretion of the Investigator and in consultation with the Sponsor, if it is likely the previously screened participant will be eligible. Participants who re-screen will have all assessments redone and a new participant ID assigned.

6.4. Medical History/Demographics

Clinically significant medical history (as determined by the Investigator), will be recorded at the time of the Screening.

Demographics and baseline characteristics (including age, sex, race, ethnicity, and participant's and maternal/primary caregiver's level of education) will also be recorded at the time of the Screening.

6.5. Physical Examination

The PE will be a complete PE according to the standard at the site performed at the Screening Visit. Physical examinations after the Screening Visit may be abbreviated PEs driven by signs and symptoms. An abbreviated PE will be conducted at the scheduled study visits: Day 1 (Week 1), Week 6, Week 12, and EOS/ET, as detailed in the SOA (Appendix 1).

- The complete PE will include at a minimum: height, weight, general appearance, examination of head, eyes, ears, nose, and throat, skin, cardiovascular and respiratory systems, abdominal examination, neurologic, and musculoskeletal.
- An abbreviated PE will be driven by signs and symptoms.

6.6. Vital Signs

Vital signs (blood pressure, heart rate, oxygen saturation, and temperature) will be measured at every visit during the study, as outlined in SOA (Appendix 1), after a participant has rested comfortably for at least 5 minutes in the supine or sitting position, as feasible. A repeated measurement of any of the vital signs parameters will be taken within 5 minutes if the first reading is outside the normal range and deemed clinically significant.

6.7. NIH Toolbox Assessments

The NIH Toolbox Cognition Module is a standardized cognitive battery comprising of executive function, episodic memory, language, processing speed, working memory, and attention as subdomains. Seven tests are designed within these subdomains that are validated and normed based on age and maternal education (Hood, 2019). Using standardized procedures, instructions will be presented visually on a tablet computer using a tablet app.

Cannabis, alcohol and opioids that can interfere with neurocognitive testing must not be consumed within 24 hours prior to NIH Toolbox Cognition Module assessment at Baseline and Week 12 Visit.

Further details on the NIH Toolbox Module will be provided in NIH Toolbox assessment and Measurement Manual. Assessment timepoints are specified in the SOA (Appendix 1).

For analysis purpose, tests of the NIH Toolbox have been categorized as executive abilities (Dimensional Change Card Sort Test, Flanker Inhibitory Control and Attention Test, and List Sorting Test) and nonexecutive abilities (Picture Vocabulary Test, Oral Reading Recognition Test, and Picture Sequence Memory Test). The Pattern Comparison Test, which measures processing speed will be assessed separately. (Hood, 2019).

6.8. Adverse Events and Concomitant Medications

Adverse events and concomitant medications will be recorded at every visit during the study, as detailed in the SOA (Appendix 1). See Section 7.2 for details regarding AE reporting period for this study.

6.9. Laboratory Assessments

All laboratory assessments will be performed through a central laboratory. Hematology will be collected at the Screening Visit, Week 6, Week 12, and Follow-up/EOS Visit (See Section 6.9.1 and Section 6.9.2) and Serum chemistry will be collected only at Screening and Week 12 Visit. A serum pregnancy test will be performed at the Screening Visit, and urine pregnancy tests will be performed at Baseline (Day 1), Week 6, Week 12, and EOS for female participants of childbearing potential (see Section 6.9.3 for more information on pregnancy testing). The serum pregnancy test will be done only if the urine pregnancy outcome is positive. Refer to the SOA (Appendix 1) for the additional details of laboratory tests.

It is the responsibility of the Investigator or designee to assess the clinical significance of all abnormal clinical laboratory values, as defined by the applicable list of normal values on file (ie, local or central laboratory).

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. All clinically significant laboratory value abnormalities are to be recorded as AEs.

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; it is preferred for the analyses to be conducted by the central laboratory unless medical need necessitates urgent results reporting. Repeat laboratory testing of abnormal potentially clinically significant or clinically significant results for the screening evaluation of the participant may be repeated at the discretion of the Investigator.

If blood specimens collected at the Day 1 visit and Week 12 visit are found to be inadequate for laboratory testing, the blood sample must be redrawn and submitted for laboratory testing within 7 days of the study visit.

6.9.1. Hematology

Hematology assessments include the following:

- RBCs
- Hematocrit
- Hb
- Platelets
- White blood cells (WBCs) with differential (basophils, eosinophils, neutrophils, monocytes, and lymphocytes)
- % and absolute reticulocytes count (ARC)
- Mean corpuscular volume (MCV)
- Mean corpuscular hemoglobin concentration (MCHC)

- Sickle cell genotype (sickle hemoglobin with 2 sickle cell genes [HbSS], and sickle hemoglobin and one beta thalassemia gene [HbS/β^0 thalassemia]) test at Screening only if the SCD genotype is not known

6.9.2. Serum Chemistry

Chemistry assessments include the following:

- AST and ALT
- Albumin
- Alkaline phosphatase (ALP)
- Bicarbonate
- Blood urea nitrogen (BUN)
- Chloride
- Calcium
- Creatinine
- Glucose
- LDH
- Sodium
- Potassium
- Bilirubin (total, direct, and indirect)

6.9.3. Pregnancy Testing

Female study participants who have not experienced menarche will not undergo pregnancy testing. Should a female participant experience menarche during the study, the participant will be considered a female of child-bearing potential and will undergo urine pregnancy testing as per the SOA (Appendix 1).

If a urine pregnancy test is positive, the result must be confirmed per local standards at each site (eg, ultrasound, serum pregnancy test). See Section 7.4 for reporting a pregnancy.

6.10. Patient/Caregiver-Reported Outcomes

Patient reported outcomes (PROs) will be evaluated by the following measures:

- The PGI-C assessment will be performed using a 7-point scale to measure the participant's overall improvement at Week 12.
- Change from baseline to Week 12 in Pediatric quality of life in neurological disorders (Neuro-QOL) score.

These assessments will be self-administered by study participants at visits specified in the SOA (Appendix 1).

6.11. Clinical Global Impression of Change

The CGI-C is the Investigator's assessment of change in the overall health condition of the participant. The CGI-C assessment will be administered by the Investigator using a 7-point scale to measure the participant's overall improvement at Week 12 as specified in the SOA (Appendix 1).

6.12. Missed Assessments

Missed assessments should be rescheduled and performed as close to the originally scheduled date as possible. An exception is made when rescheduling becomes, in the Investigator's opinion, medically unnecessary or unsafe because it is too close in time to the next scheduled evaluation. In that case, the missed evaluation should be abandoned.

7. ADVERSE AND SERIOUS ADVERSE EVENTS

Safety assessments will consist of recording all AEs and SAEs, protocol-specified hematology and clinical chemistry variables, clinical examination findings, measurement of protocol-specified vital signs, 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 Section 7.1. 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 PE findings, weight, vital signs, and clinical laboratory parameters 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 associated with the use of a drug in humans, whether or not considered drug related. 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. An AE may also constitute complications occurring as a result of protocol-mandated interventions (eg, invasive procedures such as biopsies) or SOC procedures, including the period prior to receiving the first dose of the study drug (eg, medication wash out). In addition to new events, any increase in the severity or frequency of a preexisting condition that occurs after the participant signs the ICF/AF 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 GBT, 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 “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 GBT, 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 (IME) 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) are not considered SAEs. Hospitalizations that occur for preexisting conditions that are scheduled after study enrollment are considered SAEs.

The Investigator will assess each AE for seriousness, severity, and relationship to investigational product.

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 5.0.

For AEs not adequately addressed in the NCI CTCAE Version 5.0, the following criteria should be used (Table 8).

Table 8: 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 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 post 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 Investigational Product

The relationship of an AE to the investigational product 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 the investigational product administration makes the relationship unlikely. If an SAE is not considered related to 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 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 until the EOS or Early Termination (ET) visit. All SAEs must be reported within 24 hours of SAE awareness on the AE CRF via the electronic data capture (EDC) system. The Investigator is responsible for evaluating all AEs, obtaining supporting documents, and ensuring documentation of the event is complete. Details of each reported AE must include, at minimum, severity, relationship to study treatment, duration, and outcome. All (both serious and nonserious) AEs 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 treatment at any time, at the discretion of the Investigator. The Sponsor and the contract research organization's (CRO) Medical Monitor 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 CRF 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 CRF. 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 on the AE CRF (eg, abnormalities that have clinical sequelae, require study drug dose modification, discontinuation of study treatment, more frequent follow-up assessments, further diagnostic investigation). If the clinically significant laboratory abnormality is a sign of a disease or syndrome (eg, ALP and bilirubin 5 × the ULN associated with cholecystitis), only the diagnosis (eg, cholecystitis) needs to be recorded in the CRF.

If the clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded in the CRF. 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 on the AE CRF, unless their severity, seriousness, or etiology changes.

7.2.4. Pre-existing Medical Conditions

A pre-existing medical condition is one that is present at the start of the study. Such conditions should be recorded on the Medical History and Baseline Conditions CRF.

If a pre-existing medical condition increases in frequency or severity, or if the character of the condition worsens during the study, the condition should be recorded as an AE or SAE. When recording such events on the AE CRF, it is important to convey the concept that the pre-existing condition has changed by including applicable descriptors (eg, "more frequent headaches").

7.2.5. Worsening of Sickle Cell Disease

Sickle cell disease-related AEs that are common complications associated with the study participant's SCD may not be considered related to voxelotor unless judged by the Investigator to have worsened in severity and/or frequency or changed in nature during the study. Sickle cell disease- related AEs include: SCD with vaso-occlusive pain crisis, acute chest syndrome, pneumonia, priapism, and osteonecrosis (Kato, 2018).

7.3. Serious Adverse Events, Serious Adverse Drug Reactions, and Requirements for Immediate Reporting

All SAEs, regardless of causal attribution, must be reported by the Investigator/designee or site personnel within 24 hours of SAE awareness on the AE CRF via the EDC system. In the event that the EDC system is not available, paper SAE report forms will be used to report the SAE and faxed or emailed to GBT Pharmacovigilance or CRO designee. The information reported on the paper SAE report form should be entered into the EDC once available.

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 ensure that participant identifier information (eg, name, medical record number) are 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, 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 its designee is responsible for reporting suspected unexpected serious adverse reactions (SUSARs) to regulatory agencies, competent authorities, IRBs/IECs, 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 CRO 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 CRO designee's first knowledge of the event. The Investigator is responsible for notifying the local IRB/IECs of all SAEs that occur at his/her site as required by local regulations or IRB/IEC policies, if this responsibility resides with the site.

Investigators are required to report any urgent safety matters to the Sponsor or its designee within 24 hours of awareness. The Sponsor or its designee will inform regulatory authorities, IRB/IECs, 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 treatment will be immediately discontinued, and the pregnancy must be reported to the Sponsor or designated Drug Safety CRO 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 counseling 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). Pregnancies in partners of male study participants will similarly 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: an elective abortion is not considered an SAE. Pregnancy and pregnancy outcomes must be reported on a Pregnancy Notification or Pregnancy Outcome Form, respectively, and sent to the Sponsor or designated Pharmacovigilance CRO within 24 hours of the Investigator, designee, or site personnel learning of the pregnancy or pregnancy outcome.

The child born to a female participant or participant's partner 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 designated Drug Safety CRO. 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 (including definition of females of child-bearing potential) is provided in Section 5.9.1. Highly effective means of contraception are listed in Section 5.10.

7.5. Reporting Overdose

If a participant takes more than the protocol-defined dose in a day and experiences a drug-related AE, this will be reported as an overdose 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. Parents, guardians, or participants are to be instructed to contact their study site immediately if an overdose of study drug is suspected. A suspected overdose with AEs should be reported to the Sponsor's designated CRO's Drug Safety Department within 24 hours of the Investigator, designee, or site personnel's knowledge of the event. An overdose with AEs must be followed until the adverse effects are resolved or stabilized, or until reasonable attempts to determine resolution of the event are exhausted.

8. DATA ANALYSIS AND STATISTICAL PLANS

The primary study analysis will be based on data from the complete study (including the 4-week Follow-up Period), and will be performed after all participants have completed the study or discontinued early and all data from the study are in the database and the database is locked.

A statistical analysis plan (SAP) will be developed and finalized before database lock and will describe in more detail procedures for accounting for missing data, additional sensitivity analyses of the primary and secondary variables as well as the analyses of the exploratory endpoints.

8.1. Analysis Populations

Three main analyses populations are defined for this study: the intent-to-treat (ITT) population, the per protocol (PP) population, and the safety-evaluable population.

The ITT population includes all randomized participants. For analyses based on this population, participants will be grouped according to the treatment assigned at randomization. This is the primary analysis population for efficacy, demographics, and baseline characteristics data.

The PP population will include all participants who complete study treatment with no important protocol deviations which would impact the evaluation of efficacy. This analysis population may be used for sensitivity analyses of the primary and key secondary efficacy endpoints.

The safety-evaluable population includes all participants who receive at least 1 dose of study drug. For analyses based on this population, participants will be grouped according to the actual study treatment received. This is the primary analysis population for safety and exposure data.

8.2. Summary of Study Conduct

The number of participants randomized will be tabulated by country, study site, and treatment group. Participant disposition (the number of participants randomized, receiving at least 1 dose of study treatment, completing the study through the 12-week blinded Randomized Treatment Period and Follow-up Visit) will be summarized by treatment group. Reasons for early discontinuation from study treatment and early discontinuation from the study will be summarized. Major protocol deviations will be listed and evaluated for potential impact on the interpretation of study results.

8.3. Summary of Demographics, Baseline Characteristics, and Concomitant Medications

Demographic and baseline characteristics such as age, sex, race, ethnicity, and participant's and maternal/ primary caregiver's level of education along with baseline disease characteristics (including sickle cell genotype, Hb levels, clinical measures of hemolysis, and HU use). Baseline will be defined as the last assessment performed prior to receiving the first dose of study treatment. Concomitant medications will be coded using the WHO Drug Dictionary and summarized.

8.4. Efficacy Analysis

8.4.1. Primary Endpoint

The executive abilities composite score will be measured using the NIH Toolbox Cognition Module. The primary endpoint will be the change from baseline in executive abilities composite score at Week 12 which will be summarized by treatment group using mean, SD, median, minimum and maximum. The analysis of the primary endpoint will compare voxelotor with placebo using analysis of covariance (ANCOVA) controlling for the baseline composite score, and HU use.

8.4.2. Secondary Endpoints

The secondary endpoints are:

- Change from baseline at Week 12 in processing speed as measured by Pattern Comparison Test score
- Change from baseline at Week 12 in nonexecutive cognitive abilities (Picture Vocabulary Test, Oral Reading Recognition Test, and Picture Sequence Memory Test) composite score
- Change from baseline in Hb over time up to Week 12
- Change and percent change from baseline over time up to Week 12 in clinical measures of hemolysis, including unconjugated bilirubin, absolute reticulocyte, reticulocytes %, and LDH

Changes from baseline at Week 12 in processing speed and nonexecutive cognitive abilities composite score will be summarized using mean, SD, median, minimum and maximum. The analyses of these endpoints will compare voxelotor with placebo using ANCOVA controlling for the corresponding baseline scores and HU use.

Changes from baseline in Hb and clinical measures of hemolysis (unconjugated bilirubin, % reticulocytes, absolute reticulocyte, and LDH) over time up to Week 12 will be analyzed using a mixed effect for repeated measures (MMRM) model. The fixed effect terms include treatment, study visit, treatment by visit interaction. Within-subject variability will be modeled using an unstructured covariance matrix.

8.4.3. Exploratory Endpoints

Exploratory endpoints will be summarized by descriptive statistics. Details will be provided in the SAP.

8.5. Safety Analysis

Safety analysis will be performed on all participants receiving at least 1 dose of study drug.

Adverse events will be classified according to Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of participants with treatment emergent AEs will be tabulated by system organ class and preferred term. Treatment-emergent adverse events will also be presented by severity and relationship to study treatment.

Changes in laboratory parameters and vital signs will be summarized descriptively.

8.6. Determination of Sample Size

Sample size determination is based on statistical power considerations for the primary efficacy endpoint, change from baseline in executive abilities composite score at Week 12.

A sample size of approximately 80 participants (40 participants per treatment arm [voxelotor and placebo]) provides approximately 80% power to detect a difference in mean change in executive abilities composite score from baseline at Week 12 between the voxelotor arm and the placebo arm of 5 points with a common standard deviation of 7.5 points, using a 2-sided test at an overall $\alpha = 0.05$ level. For the purposes of sample size calculation, a drop-out rate of 5% by Week 12 was assumed.

8.7. Missing Data Handling

Detailed considerations of missing data handling will be described in the SAP.

8.8. Adjustment for Multiple Comparisons

A fixed sequence hierarchical test procedure will be used to control Type I error when evaluating the treatment effect of voxelotor compared with placebo for the primary and secondary efficacy endpoints. The endpoints will be tested sequentially based on the following prespecified order:

- Change from baseline in executive abilities composite score at Week 12 (primary endpoint)
- Change from baseline in processing speed at Week 12
- Change from baseline in nonexecutive cognitive composite score at Week 12
- Change from baseline in Hb over time up to Week 12

Each endpoint will be tested at a 2-sided alpha level of 0.05. Formal testing of endpoints will continue until the first nonsignificant result. Testing of endpoints subsequent to a nonsignificant result will be considered exploratory in nature.

9. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

9.1. 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, microfiches, photographic negatives, microfilm or magnetic media, X-rays, participant files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical study), and all relevant sections of the participant's medical records and all other data collection made specific to this study constitute source documents.

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

9.2. Data Collection

The Investigator will be responsible for maintaining accurate and adequate case records (source documents) from which data will be transcribed to CRFs 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, investigational treatment administration, a record of sample collection, clinical assessments, AEs, and final evaluation(s). The monitor (clinical research associate [CRA]) will review all CRFs and compare data to that contained in clinic notes and participants' source documents/medical records.

Data for each participant will be recorded in the CRF except when provided electronically, eg, central laboratories, NIH output. A CRF must be completed for every participant enrolled in the study. When data are complete, the Investigator or medically qualified sub-Investigator listed on Form FDA 1572 (or Investigator's Agreement if applicable) will apply his/her signature in the CRF indicating he/she has reviewed and approves of the data collected in the CRF.

10. QUALITY CONTROL AND QUALITY ASSURANCE

10.1. Monitoring

Site personnel will be provided with training on how to collect quality data for the study, and a Sponsor monitor (CRA) will be contacting the site periodically to review study conduct and data recorded at the site. At the Sponsor's discretion, on-site monitoring visits may be conducted prestudy, during the study, and following study completion. These visits are to provide the Sponsor with the opportunity to evaluate study progress; verify the accuracy and completeness of source data and CRFs; and ensure that all protocol and Good Clinical Practice (GCP) requirements, applicable to US FDA or country-specific regulations, and Investigator obligations are being fulfilled. The Sponsor may terminate study participation by a clinical study site if study-site personnel do not follow the protocol or GCPs. Additionally, individual participants may be excluded if a medical records review indicates protocol deviations or if other factors appear to jeopardize the validity of the study.

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

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 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.

10.2. Quality Control and Quality Assurance

Global Blood Therapeutics may conduct a quality assurance audit(s) of this study. If such an audit occurs, the Investigator agrees to allow the auditor direct access to all relevant documents (eg, all participant records, medical records and CRFs) and access to all corresponding portions of the office, clinic, laboratory, or pharmacy which may have been involved with the study. The Investigator will allocate his/her time and that of the study-site personnel to the auditor to discuss findings and any relevant issues. In addition, regulatory agencies may conduct a regulatory inspection of this study. If such an inspection occurs, the Investigator agrees to notify GBT upon notification by the regulatory agency. The Investigator agrees to allow the inspector direct access to all relevant documents and to allocate his/her time and that of the study-site personnel to the inspector to discuss findings and any relevant issues. The Investigator will allow GBT personnel to be present as an observer during a regulatory inspection, if requested.

10.3. Laboratory Accreditation

The laboratory facility used for analysis of clinical laboratory samples must provide evidence of adequate licensure or accreditation. Copies of laboratory certification, licensure, and reference ranges (as appropriate) will be supplied to the Sponsor prior to study initiation. The Sponsor or designee should be notified of any changes in reference range values or certification/license renewal during the course of the study.

11. REGULATORY, ETHICAL, AND LEGAL OBLIGATIONS

The study will comply with the 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 study number only on 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/informed consent and/or assent form for the study will inform the participant of their rights and provide appropriate contact details of the Data Protection Officer.

11.1. 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/IEC 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 CRFs. 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/IEC prior to implementation (refer to Section 11.4).

11.2. Good Clinical Practice

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

11.3. 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/AF 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 AF, according to local institution/IEC 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 (HIPAA), if applicable, that authorizes the use and disclosure of the participants' protected health information.

Participants who initially sign the AF 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.

The participant should be given a copy of the ICF (and the AF, if applicable) in their native language. The informed consent and assent processes should be recorded in the source documentation. The original copies of the signed and dated ICF (and AF, if applicable), must be retained in the institution's records and are participant to inspection by representatives of the Sponsor, or representatives from regulatory agencies.

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

11.4. Independent Ethics Committee and Regulatory Approval

The Investigator must inform, and obtain approval from, the IRB/IEC for the conduct of the study at named sites, for the protocol, the Participant ICF/AF, 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/IEC for approval as well as submitted to regulatory authorities for approval prior to implementation. Amendments may be implemented only after a copy of the IEC approval letter has been transmitted to the Sponsor. Amendments that are intended to eliminate an apparent immediate hazard to participants may be implemented prior to receiving Sponsor or IRB/IEC 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/IEC to facilitate their continuing review of the study (if needed) and that the IRB/IEC 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/IEC of any reportable AEs.

11.5. 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.

11.6. Confidentiality

The Investigator must ensure that the participant's privacy is maintained. In the CRF and 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/AF) should be kept in a strictly confidential file by the Investigator.

The Investigator shall permit authorized representatives of the Sponsor, regulatory agencies, and IRB/IECs 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/assent, the participant must be informed that his/her records will be reviewed in this manner.

11.7. 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 12.2. Participant files and other source data (including copies of protocols, original reports of test results, study drug dispensing logs, correspondence, records of informed consent/assent, 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.

12. DATA HANDLING AND RECORDKEEPING

12.1. Inspection of Records

Global Blood Therapeutics 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 Sponsor's monitor (CRA) 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 11.5 (Essential Documents). The Investigator agrees to make this binder accessible to the monitor (CRA), auditor, and representatives of regulatory agencies and the IRB/IEC.

12.2. Retention of Records

The Investigator will maintain adequate records, including participants' medical records, laboratory reports, signed consent/assent 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 investigational product under study. 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. Global Blood Therapeutics must be notified with retention if the Investigator/institution is 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/IEC approvals, copies of the Form FDA 1572 (or Investigator's Agreement if applicable), signed and dated consent/assent forms, medical records, CRFs, 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.

12.3. 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. Participant 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/IEC, 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 to not 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.

13. 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.

14. 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 prepublication 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.

15. REFERENCES

Bernaudin F, Verlhac S, Freard F, Foudot-Thoraval F, Benkerrou M, Thuret I, et al. Multicenter prospective study of children with sickle cell disease: Radiographic and psychometric correlation. Journal of Child Neurology. 2000;15:333–43.

Dufu K, Patel M, Oksenberg D, Cabrales P. GBT440 improves red blood cell deformability and reduces viscosity of sickle cell blood under deoxygenated conditions. Clin Hemorheol Microcirc. 2018;70(1):95-105.

Eaton WA, Henry ER, Hofrichter J, Mozzarelli A. Is cooperative oxygen binding by hemoglobin really understood? Nat Struct Biol. 1999;6(4):351-58.

Gladwin MT, Barst RJ, Gibbs JSR, Hildesheim M, Sachdev V, Nouraie M, 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.

Hood AM, King AA, Fields ME, Ford AL, Guilliams KP, Hulbert ML, Lee JM, White DA. Higher executive abilities following a blood transfusion in children and young adults with sickle cell disease. Pediatr Blood Cancer. 2019.

Howard J, Hemmaway CJ, Telfer P, Layton DM, Porter J, Awogbade M, et al. A phase 1/2 ascending dose study and open-label extension study of voxelotor in patients with sickle cell disease. Blood. 2019;133(17):1865-75.

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(1):37-47.

Kato GJ, Piel FB, Reid CD, Gaston MH, Ohene-Frempong K, Krishnamurti L, et al. Sickle cell disease. Nat Rev Dis Primers. 2018;4:18010. doi: 10.1038/nrdp.2018.10.

Kral, MC, Brown, RT, Nietert PJ, Abboud MR, Jackson SM, Hynd GW. Transcranial Doppler ultrasonography and neurocognitive functioning in children with sickle cell disease. Pediatrics. 2003;112:324–31.

McGann PT, Ware RE. Hydroxyurea therapy for sickle cell anemia. Expert Opin Drug Saf. 2015;14(11):1749-58.

Nouraie M, Lee JS, Zhang Y, Kanias T, Zhao X, Xiong Z. 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.

Oksenberg D, Dufu K, Patel MP, Chuang C, Li Z, Xu Q, et al. GBT440 increases hemoglobin oxygen affinity, reduces sickling and prolongs RBC half-life in a murine model of sickle cell disease. Br J Haematol. 2016;175(1):141-53.

Oxbryta® [prescribing information]. South San Francisco, CA: Global Blood Therapeutics, Inc.; 2021. prescribing-information.pdf (oxbryta.com).

Puffer ES, Schatz J, Roberts CW. The association of oral hydroxyurea therapy with improved cognitive functioning in sickle cell disease. Child Neuropsychol. 2007;13(2):142-54.

Schatz J, Finke RL, Kellett JM, Kramer JH. Cognitive functioning in children with sickle cell disease: a meta-analysis. J Pediatr Psychol. 2002;27(8):739-48.

Steen RG, Miles MA, Helton KJ, Strawn S, Wang W, Xiong X, et al. Cognitive impairment in children with hemoglobin SS sickle cell disease: Relationship to MR imaging findings and hematocrit. American Journal of Neuroradiology. 2003;24:382–89.

Stivelman JC. Benefits of anemia treatment on cognitive function. Nephrology, dialysis, transplantation: Official publication of the European Dialysis and Transplant Association -European Renal Association. 2000;15:29–35.

Swanson ME, Grosse SD, Kulkarni R. Disability among individuals with sickle cell disease: literature review from a public health perspective. Am J Prev Med. 2011;41(6 Suppl 4):S390-97.

Vichinsky EP, Neumayr LD, Gold JI, Weiner MW, Rule RR, Truran D, et al. Neuropsychological Dysfunction and Neuroimaging Adult Sickle Cell Anemia Study Group. Neuropsychological dysfunction and neuroimaging abnormalities in neurologically intact adults with sickle cell anemia. JAMA. 2010;303(18):1823–31.

Vichinsky E, Hoppe C, Howard J, Ataga K, Nduba V, El-Beshlawy A, et al. HOPE Trial Investigators. A Phase 3 Randomized Trial of Voxelotor in Sickle Cell Disease. N Engl J Med. 2019 Aug 8; 381(6):509-19.

Wang WC, Langston JW, Steen RG, Wynn LW, Mulhern RK, Wilimas JA, et al. Abnormalities of the central nervous system in very young children with sickle cell anemia. J Pediatr. 1998;132(6):994-98.

Washington C, Green M, Inati A, Estepp J, Brown, C, Abboud M, et al. Pharmacokinetics of voxelotor (GBT440) using population pharmacokinetic and physiologically-based pharmacokinetic modeling in pediatric subjects with sickle cell disease. European Hematology Association 2018. Poster Presentation.

Weiskopf RB, Kramer JH, Viele M, Neumann Mireille, Feiner John R, Watson Jessica J, et al. Acute Severe Isovolemic Anemia Impairs Cognitive Function and Memory in Humans. Anesthesiology. 2000;92:1646–52.

Yawn BP, Buchanan GR, Afenyi-Annan AN, Ballas SK, Hassell KL, James AH, et al. Management of sickle cell disease. Summary of the 2014 evidence-based report by expert panel memers. JAMA. 2014;312(10):1033-48.

APPENDIX 1. SCHEDULE OF ASSESSMENTS

Period	**Screening**	**12-week Randomized Treatment**			**Follow-up/EOS Visit**
Visit Number (Week)	**Visit 1 (Week -2 to -1) Screening**	**Visit 2 (Week 1)**	**Visit 3 (Week 6)**	**Visit 4 (Week 12) (EOT/ET)[h]**	**Visit 5 (Week 16)[a]**
Visit Day	**-14 to -1**	**1**	**43 ± 3**	**85 ± 3**	**113 ± 7**
Visit Window			**± 3 days**	**± 3 days**	**± 7 days**
Informed consent/assent	X				
Inclusion/exclusion[b]	X	X	-	-	-
Medical history[c]	X				
Physical examination[d]	X	X	X	X	X
Vital signs[e]	X	X	X	X	X
Serum pregnancy test[f]	X				
Urine pregnancy test[g]		X	X	X	X
Hematology[h]	X		X	X	X
Serum chemistry[i]	X			X	
NIH Toolbox[j]		X		X	
PGI-C/CGI-C				X	
Neuro-QOL		X		X	
Randomization		X			
Dispense study drug[k] and participant dosing diary[l]		X	X		
Collect study drug[k] and participant dosing diary[l]			X	X	
Concomitant medications	X	X	X	X	X
Adverse events	X	X	X	X	X

Abbreviations: CGI-C, Clinician Global Impression of Change; EOS, End of study; EOT, End of treatment; ET, Early termination; NIH toolbox, National institutes of Health Toolbox; QOL, Quality of Life; PGI-C, Patient Global Impression of Change.

Footnotes for Appendix I: Schedule of Assessments

[a] Participants who discontinue study early will undergo the EOT evaluations at an ET Visit and when possible, a subsequent Follow-up Visit.
[b] All Screening evaluations must be completed and reviewed before Visit 2 (Randomization) to confirm all eligibility criteria are met. Inclusion and exclusion criteria should be reviewed at Screening and just prior to randomizing each participant to ensure study eligibility is met.
[c] If the SCD genotype is unknown, genotype testing should be performed at Screening.
[d] Physical examinations after the Screening Period may be abbreviated, focused on abnormalities identified on the Screening examination and as related to adverse events.
[e] Vital signs (blood pressure, heart rate, oxygen saturation, and temperature) will be measured after a participant has rested for at least 5 minutes in the supine or sitting position. A repeated measurement of any of the vital signs parameters will be taken within 5 minutes if the first reading is outside the normal range and deemed clinically significant.
[f] Females of child-bearing potential females will have a serum pregnancy test at Screening.
[g] Urine pregnancy tests will be performed at scheduled visits for females of child-bearing potential. If a urine pregnancy test is positive, the result must be confirmed with a serum pregnancy test. See Section 6.9.3.
[h] Hematology assessments will include WBC (with differential), RBC count, Hb, hematocrit, MCHC, MCV, platelet count, reticulocyte percentage, and ARC. Blood specimens collected at the Day 1 visit and Week 12 visit and found to be inadequate for laboratory testing will be redrawn and submitted for laboratory testing within 7 days of the study visit. See Section 6.9.1.
[i] Serum chemistry will include sodium, potassium, bicarbonate, chloride, calcium, BUN, creatinine, glucose, bilirubin (total, direct, and indirect), albumin, ALT/AST, ALP, and LDH. See Section 6.9.2.
[j] Cannabis, alcohol and opioids that can interfere with neurocognitive testing must not be consumed within 24 hours prior to NIH Toolbox Cognition Module assessment at Baseline and Week 12 Visit.
[k] Study drug is dispensed at Day 1 (Week 1) and Week 6 of Randomized Treatment Period. Study drug administration occurs daily over the 12 weeks of randomized treatment, concurrently with the Investigator-designated standard of care for SCD.
[l] Participant dosing diary is dispensed starting at Day 1(Week 1) and Week 6. Participants/caregiver should be instructed to complete the diary each day and return it at the next visit for collection and site review. Reason(s) and dates for missed doses should be recorded by the participant.