CLINICAL STUDY PROTOCOL

Study Number	**GBT440-038 (C5341023)**
Study Title	**An Open-Label Extension Study of Voxelotor Administered Orally to Participants with Sickle Cell Disease Who Have Participated in Voxelotor Clinical Trials**
Investigational Product	Voxelotor (GBT440)
IND Number	121691
EudraCT Number	2019-003144-76
Sponsor Legal Address	Global Blood Therapeutics, Inc., a wholly owned subsidiary of Pfizer Inc. 181 Oyster Point Blvd South San Francisco, CA 94080 United States of America
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Original Protocol	31 July 2019

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

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LIST OF ABBREVIATIONS

Abbreviation	Description
ACS	acute chest syndrome
ADR	adverse drug reaction
ALT	alanine transaminase
AE	adverse event
AST	aspartate transferase
CNS	central nervous system
COVID-19	coronavirus disease of 2019
CRO	contract research organization
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
deoxyHbS	deoxygenated sickle hemoglobin
DILI	drug-induced liver injury
DSMB	Data and Safety Monitoring Board
EDB	exposure during breastfeeding
EDP	exposure during pregnancy
EC	ethics committee
eCRF	electronic case report form
EDC	electronic data capture
EOS	End of Study
FDA	Food and Drug Administration
GBT	Global Blood Therapeutics
GCP	Good Clinical Practice
Hb	Hemoglobin
Hb-O_2	hemoglobin-oxygen
HbF	fetal hemoglobin
HbS	sickle hemoglobin
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HPFH	heredity persistence of fetal hemoglobin
HU	hydroxyurea
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
INR	international normalized ratio
IRB	Institutional Review Board

Abbreviation	Description
IRT	interactive response technology
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
LDH	lactate dehydrogenase
LFT	liver function test
MedDRA	Medical Dictionary for Regulatory Activities
MQI	Medically Qualified Individual
NCI	National Cancer Institute
OLE	open-label extension
oxyHb	oxyhemoglobin
PE	physical examination
PT	prothrombin time
QD	once daily
RBC	red blood cell
RSI	Reference Safety Information
SAE	serious adverse event
SCD	sickle cell disease
SOC	System Organ Class
SRSD	Single Reference Safety Document
SUSAR	suspected unexpected serious adverse reaction
TCD	transcranial Doppler
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
US	United States
USPI	United States Prescribing Information
VOC	vaso-occlusive crisis
WHO	World Health Organization

STUDY ADMINISTRATIVE STRUCTURE

Sponsor:	Global Blood Therapeutics, Inc. 181 Oyster Point Blvd. South San Francisco, CA 94080 USA Telephone: (650) 741-7700 Fax: (650) 741-7701
Sponsor's Responsible Medical Officer/Medical Monitor and Study Director:	The contact information is documented in the study contact list located in the Study Binder

PROTOCOL SYNOPSIS

Study Number	GBT440-038 (C5341023)
Study Title	An Open-Label Extension Study of Voxelotor Administered Orally to Participants with Sickle Cell Disease Who Have Participated in Voxelotor Clinical Trials
Investigational Product	Voxelotor 1500 mg or 1500-mg equivalent, administered orally, as tablets, dispersible tablets, or a powder for oral suspension dosage form (packaged as stick packs)
Sponsor	Global Blood Therapeutics, Inc.; a wholly owned subsidiary of Pfizer Inc. 181 Oyster Point Blvd South San Francisco, CA 94080 United States of America
Number of Clinical Sites	The study will be conducted at up to approximately 70 global clinical sites.
Number of Study Participants	Up to approximately 600 participants with sickle cell disease (SCD)
Treatment	All participants will receive voxelotor once daily (QD), administered orally as tablets, dispersible tablets, or a powder for oral suspension formulation (packaged as stick packs). Participants aged ≥ 12 years will receive a voxelotor dose of 1500 mg QD, regardless of their body weight. Participants aged < 12 years will receive a voxelotor dose based on their body weight, to provide exposure corresponding to the adult dose of 1500 mg QD. The participant's weight at study entry will be used to determine the starting voxelotor dose in this study. The dose should be adjusted if the participant's weight increases or decreases at a scheduled clinic visit. All dosage forms of voxelotor may be taken with or without food. Voxelotor tablets should be swallowed whole. Voxelotor dispersible tablets should be dispersed in liquid. Likewise, the powder for oral suspension dosage form should be mixed with liquid. Participants receiving a voxelotor dose of 1500 mg QD, regardless of age or weight, will receive tablets.
Objective	The objective of this open-label extension (OLE) study is to assess the safety of, and SCD-related complications with, long-term treatment with voxelotor, in participants who have completed treatment in a Global Blood Therapeutics (GBT)--sponsored voxelotor clinical study, based on the following parameters: • Adverse events (AEs), clinical laboratory tests, physical examinations, and other clinical measures • Frequency of SCD-related complications

	In addition, this study will assess predose whole blood and plasma concentrations of voxelotor in a subset of participants receiving a modified dose of voxelotor as dispersible tablets at select sites.
Study Design	This multicenter, nonrandomized, global OLE study will be available to eligible participants from GBT-sponsored voxelotor clinical studies. Participants must have completed participation in their originating clinical study and must meet the entry criteria for this study to be eligible for enrollment. Safety will be assessed during the study using standard measures, including AE monitoring, clinical laboratory tests, vital sign measurements, physical examinations, and concomitant medication use. Sickle cell disease-related complications also will be monitored.
Inclusion/ Exclusion Criteria	Eligibility will be based on assessments performed prior to receiving study drug on Day 1 in this study. A participant will be considered enrolled after signing of the informed consent form and/or the assent form for this study. Informed consent/assent must be properly executed prior to the performance of any protocol-required assessment or procedure. <u>Inclusion Criteria</u> Participants who meet all of the following criteria will be eligible for study enrollment: 1A. Male or female participant with SCD who participated and received study drug in a GBT-sponsored voxelotor clinical study. Note: Participants who discontinued study drug due to an AE, but who remained on study, may be eligible for treatment in this study provided the AE does not pose a risk for treatment with voxelotor. Note: Participants who discontinued Study GBT440-032 as the result of an abnormal transcranial Doppler (TCD) flow velocity assessment (≥ 200 cm/sec) are eligible for treatment in this study. 2. Female participants of childbearing potential are required to have a negative urine pregnancy test prior to dosing on Day 1. Note: Female participants who become childbearing during the study must be willing to have a negative urine pregnancy test to remain in the study. 3. If sexually active, female participants of childbearing potential must use highly effective methods of contraception until 30 days after the last dose of study drug. If sexually active, male participants must use barrier methods of contraception until 30 days after the last dose of study drug. 4A. Participant has provided written consent/assent (for pediatric participants, both the consent of the participant's legal representative or legal guardian and the participant's assent [where applicable] must be obtained). <u>Exclusion Criteria</u> Participants meeting any of the following exclusion criteria will not be eligible for study enrollment: 1. Female participant who is breastfeeding or pregnant

	2A. Participant withdrew consent from a GBT-sponsored voxelotor clinical study 3A. Participant was lost to follow-up from a GBT-sponsored voxelotor clinical study 4. Participant has any medical, psychological, safety, or behavioral conditions that, in the opinion of the Investigator, may confound safety interpretation, interfere with compliance, or preclude informed consent 5. Active symptomatic coronavirus disease of 2019 (COVID-19) infection 6. Known hypersensitivity to voxelotor or any other components of the study drug 7. Use of St. John's wort, sensitive cytochrome P450 (CYP) 3A4 substrates with a narrow therapeutic index, or moderate or strong CYP3A4 inducers within 30 days of Day 1
Duration of Study Participation	Participants may receive study drug as long as they continue to receive clinical benefit that outweighs risk as determined by the Investigator and/or until the participant has access to voxelotor from an alternative source (eg, through commercialization or a managed-access program). The study will end when the last participant's last visit occurs.
Statistical Methods	Endpoints *Safety* • Treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) *SCD-Related Complications* • Frequency of SCD-related complications Safety Analyses All participants who receive at least 1 dose of study drug in this study will be included in the safety population. Adverse Events Adverse events will be classified using the Medical Dictionary for Regulatory Activities (MedDRA). A TEAE is defined as an AE that emerges on or after initiation of study drug (having been absent pretreatment), or an AE that existed pretreatment and worsened on treatment (relative to the pretreatment state). The incidence of TEAEs will be tabulated by System Organ Class, Preferred Term, severity, and relationship to study drug (as assessed by the Investigator). Clinical Laboratory Evaluations and Vital Signs Clinical laboratory test and vital sign results over time will be summarized using descriptive statistics. SCD-Related Complications Sickle cell disease-related complications over the course of the treatment period will be recorded for each participant. SCD-related complications may include,

	but are not limited to, the following: sickle cell anemia with crisis, acute chest syndrome, pneumonia, priapism, splenic sequestration, hepatic sequestration, stroke, leg ulcers, and osteonecrosis. SCD-related complications will be summarized in a similar manner to TEAEs.

1. INTRODUCTION

1.1. Disease Background

Sickle cell disease (SCD) is a rare, devastating, and debilitating disease 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. In addition to unpredictable and recurrent episodes of severe pain, commonly referred to as painful crises, a systemic vasculopathy leads to chronic and progressive tissue injury across multiple organ systems. Multiple pathophysiologic mechanisms likely contribute to the systemic vasculopathy, including, importantly, chronic hemolytic anemia (Rother, 2005).

The most devastating complication of pediatric SCD is the development of central nervous system (CNS) events. This may present as overt stroke or silent strokes, which are subclinical cerebral infarctions detected on brain magnetic resonance imaging. Almost 50% of the SCD population is pediatric (Farber, 1985), and approximately 11% of patients with SCD have clinically apparent strokes before the age of 20 years. The risk of stroke is highest during the first decade, and it is most significant between the ages of 2 and 5, when it reaches 1.02% per year. In addition to overt strokes, another 17% to 22% of children suffer silent strokes, which can produce significant neuropsychological deficits (Ohene-Frempong, 1998; Verduzco, 2009). The pathogenesis of stroke in children with SCD is complex and not fully resolved, but in most cases involves occlusion or stenosis of the large intracranial arteries. Histopathology varies, but in general the pattern is one of smooth muscle proliferation with overlying endothelial damage and fibrosis (Rothman, 1986; Koshy, 1990). Smaller arterioles and capillaries show distention, thrombosis, and vessel wall necrosis (Tuohy, 1997). Damaged, aberrant red blood cells (RBCs) adhere abnormally to the vascular endothelium and thereby trigger endothelial cell activation. Endothelial cell activation cascades into further disturbances, including a hypercoagulable state and abnormal vasomotor tone. The greater risk of stroke in young children with SCD may be explained by the higher cerebral blood flow velocity observed in this population (Powars, 2000).

As current treatment options are limited, there remains a significant unmet medical need for novel therapies and for the early treatment of pediatric patients with SCD to mitigate the consequences of the disease. Red blood cell transfusions are administered to alleviate symptomatic anemia, as well as for stroke treatment and prevention. Transfusions are costly, cumbersome, and not uniformly accessible and accompanied by risks, including iron overload (Wahl, 2009). The only curative treatment for SCD is bone marrow transplantation from a histocompatible donor (Platt, 2014). However, bone marrow transplantation carries significant risks and is associated with a ~5% mortality rate (Nathan, 2013). Despite the current standard of care, patients with SCD continue to suffer serious morbidity and premature mortality (Steinberg, 2003).

A primary and obligatory event in the molecular pathogenesis of SCD is the polymerization of deoxygenated sickle hemoglobin (deoxyHbS), which results in RBC membrane damage

and RBC destruction, and the resulting clinical consequences of hemolytic anemia and vaso-occlusion, leading to chronic organ injury, debilitating symptoms, and early mortality. To date, no drugs have been approved that specifically target sickle hemoglobin (HbS) polymerization. The mechanism of action of hydroxyurea (HU) involves a highly variable increase in the level of fetal hemoglobin (HbF) in a limited subset of RBCs (F-cells), resulting in limited protection from sickling. Fetal hemoglobin inhibits the polymerization of deoxyHbS due to its high oxygen affinity, as well as intrinsic structural characteristics that block polymer formation. Individuals who are homozygous for the βS gene show no disease manifestations until late in the first year of life when the declining level of HbF no longer protects against deoxyHbS polymerization. Data from patients with HbS and hereditary persistence of fetal hemoglobin (HPFH) suggest that a pancellular HbF level of 20% to 30% prevents SCD and that levels as low as 10% may be sufficient for protection (Akinsheye, 2011).

Because oxyhemoglobin (oxyHb) is a potent inhibitor of HbS polymerization, pharmacologically increasing the proportion of oxyHb is a promising strategy to achieve inhibition of HbS polymerization in all RBCs (Noguchi, 1988). This has been confirmed with voxelotor, which resulted in a clinically meaningful reduction in hemolytic anemia in patients with SCD (Vichinsky, 2019).

1.2. Voxelotor

Voxelotor (formerly known as GBT440) is an orally administered small molecule that inhibits HbS polymerization by allosterically modifying hemoglobin-oxygen (Hb-O_2) affinity. It is approved in the United States for the treatment of SCD in adults and pediatric patients 4 years of age and older (Oxbryta® United States Prescribing Information [USPI]). Marketing approval in other regions has been received or is being sought. For details on other country approvals for marketing, please refer to the latest Investigator's Brochure (IB), which is the Single Reference Safety Document (SRSD) for this study.

Voxelotor was designed to bind to HbS with preferential partitioning into RBCs. Voxelotor binds covalently and reversibly via Schiff base to the N-terminal valine of the hemoglobin (Hb) α-chain (ie, a single voxelotor molecule binding per HbS tetramer in a 1:1 stoichiometry) and allosterically increases HbS-O_2 affinity, stabilizing the oxyHb state and inhibiting polymerization (; Oksenberg, 2016). The voxelotor binding site is distant from heme pockets, and, therefore, it can increase O2 affinity without sterically blocking the release of O2. By stabilizing HbS in the oxyHb state, voxelotor delays in vitro HbS polymerization and prevents RBC sickling in blood from patients with SCD (Oksenberg, 2016). By inhibiting HbS polymerization, voxelotor has been shown to improve RBC deformability and reduce blood viscosity. Treatment with voxelotor has also led to significant reductions in sickle cell counts in the peripheral blood (Dufu, 2018), which supports the potential for voxelotor to serve as a disease-modifying therapy for SCD.

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 reduce hemolytic anemia, and it has the potential to subsequently achieve long-term disease modification with resultant improvement in end-organ damage, including stroke (Ataga, 2018).

1.3. Summary of Relevant Nonclinical Data and Clinical Data

1.3.1. Nonclinical Data

Primary pharmacodynamic studies of voxelotor consisted of in vitro and in vivo studies to characterize (1) voxelotor binding and affinity for Hb; (2) the effect of voxelotor on HbS modification using purified Hb, washed RBCs, and whole blood; and (3) the efficacy of voxelotor in vivo in a mouse model of SCD. The 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 showed 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-O_2 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 and metabolism) and toxicology is provided in the most current version of the voxelotor IB.

1.3.2. Clinical Data

The Phase 3 double-blind, randomized, placebo-controlled study, Study GBT440-031, in which adults and pediatric participants (aged 12 to 17 years) received placebo, voxelotor 900 mg, or voxelotor 1500 mg is completed. In this study, voxelotor was shown to significantly increase Hb, improve anemia, and reduce clinical measures of hemolysis in adult and pediatric participants 12 years of age and older with SCD.

Information regarding the safety and tolerability, and efficacy of voxelotor is provided in Section 1.4 and detailed in the current version of the voxelotor IB.

1.4. Summary of Known and Potential Risks and Benefits of Voxelotor

Clinical data to date have shown that treatment with voxelotor results in a dose-dependent increase in Hb within 2 weeks that is maintained through 24 weeks, with an associated decrease in clinical measures of hemolysis (including indirect bilirubin, reticulocytes, and lactate dehydrogenase [LDH]) that correlates with drug exposure (Brown, 2018; Vichinsky, 2019). Durability of response is sustained through 72 weeks of treatment (Howard, 2021). At the 1500 mg dose, 59% of participants showed an Hb response of > 1 g/dL ($p < 0.001$), with a mean increase of 1.1 g/dL.

Based on available clinical study data, voxelotor has been well tolerated over a range of tested doses up to and including 1500 mg once daily (QD) in adult and pediatric participants with SCD (Studies GBT440-031, GBT440-001, and GBT440-007). There have been no concerning safety findings arising from review of data from the completed and ongoing studies.

Based on the safety data from the Phase 3 study in adult and pediatric participants with SCD (Study GBT440-031), non-SCD–related treatment-emergent adverse events (TEAEs) were predominantly of low-grade severity and transient. Adverse drug reactions (ADRs) included diarrhea, abdominal pain, nausea, rash, and drug hypersensitivity. As expected, SCD-related TEAEs were common, and the overall incidence, including sickle cell anemia with crisis, was similar for the voxelotor and placebo groups. The profiles of non-SCD-related and SCD-related TEAEs in pediatric participants were similar to those in the adult population. Across all SCD studies, the overall incidence of TEAEs leading to study drug discontinuation was low (≤ 10%) and < 5% of serious adverse events (SAEs) were assessed as treatment related but rather due to underlying SCD, being predominantly sickle cell anemia with crisis.

Overall, no clinical safety concerns consistent with inadequate tissue oxygenation were identified in the voxelotor clinical development program, including in participants with SCD. Of note, the evidence generated by clinical studies and post-marketing experience suggests there is no increased risk of VOC after abrupt discontinuation of voxelotor. Furthermore, maximal exercise testing in participants with SCD (Howard, 2019) and healthy participants exposed to hypoxic (12.5%) conditions have shown no detrimental effects of voxelotor on clinically relevant physiologic parameters that would indicate hypoxic tissue stress (eg, vital signs, cardiac output, lactate, exercise capacity, dyspnea and perceived exertion, mental status) (Stewart, 2018a; Stewart, 2018b; Hutchaleelaha, 2019).

Taken together, the safety outcomes and efficacy from clinical studies to date demonstrate a favorable risk-benefit profile for voxelotor and support its continued development in adult and pediatric participants with SCD.

Additional information regarding the voxelotor clinical studies and efficacy and safety of voxelotor is provided in the current version of the voxelotor IB.

1.5. Rationale for the Study

This open-label extension (OLE) study is being conducted to assess the safety and the incidence of SCD-related complications associated with long-term voxelotor treatment by providing participants from Global Blood Therapeutics (GBT)-sponsored voxelotor clinical studies with continued access to voxelotor treatment after participating in their originating study and before the product is potentially available commercially. All participants enrolled in this study will receive voxelotor.

1.6. Justification for Dose Selection

Voxelotor is available in an oral dosage form and is intended for QD administration.

Participants will be administered a daily dose of 1500 mg or 1500-mg dose equivalent (in pediatric participants aged < 12 years), which has been shown to be well tolerated, to significantly increase Hb, and to reduce clinical measures of hemolysis. For participants who are receiving a reduced dose of voxelotor as a result of a drug-related adverse event (AE) during an antecedent study, an increase to the full dose of 1500 mg QD or equivalent is not required, but may be considered by the Investigator. See Section 5.1 for additional information regarding the dose selected for this study.

2. STUDY OBJECTIVES

The objective of this OLE study is to assess the safety of, and SCD-related complications with, long-term treatment with voxelotor in participants who have completed treatment in a GBT-sponsored voxelotor clinical study, based on the following parameters:

- Adverse events, clinical laboratory tests, physical examinations (PEs), and other clinical measures
- Frequency of SCD-related complications

In addition, this study will assess predose whole blood and plasma concentrations of voxelotor, in a subset of participants receiving a modified dose of voxelotor as dispersible tablets at select sites.

3. INVESTIGATIONAL PLAN

3.1. Study Design

This multicenter, nonrandomized OLE study is designed to assess the safety of, and SCD-related complications with, long-term treatment with voxelotor in participants with SCD. The study will be conducted globally and will be available to eligible participants from GBT-sponsored voxelotor clinical studies. Participants must have completed participation in their originating clinical study and must meet the entry criteria for this study to be eligible for enrollment (see Section 4). The study will be conducted at up to approximately 70 global clinical sites, and up to approximately 600 participants will be enrolled. The collection of voxelotor predose whole blood and plasma concentrations in participants receiving a modified dose of voxelotor dispersible tablets will be conducted in approximately 20 participants at selected sites.

3.1.1. Study Treatment

Dosage and treatment administration are described in Section 5.

All participants will receive voxelotor QD, administered orally as tablets, dispersible tablets, or a powder for oral suspension dosage form (packaged as stick packs). Participants aged ≥ 12 years will receive a voxelotor dose of 1500 mg QD. Participants aged < 12 years will receive a voxelotor dose based on their body weight, to provide exposure corresponding to the adult dose of 1500 mg QD. Participants receiving a voxelotor dose of 1500 mg QD, regardless of age or weight, will receive tablets.

3.1.2. Study Assessments

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

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

3.1.3. Study Endpoints

Study endpoints are described in Section 8.1.

3.2. Duration of Study Participation and of the Study

Participants may receive study drug as long they continue to receive clinical benefit that outweighs risk as determined by the Investigator and/or until the participant has access to voxelotor from an alternative source (eg, through commercialization or a managed access program).

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

3.3. Stopping Rules

3.3.1. Early Discontinuation of the Study

The sponsor has the right to terminate 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 indicating a potential health risk to participants.

In any instance of early discontinuation of the study, the sponsor will notify, in writing, the investigators, regulatory authorities, and institutional review boards (IRBs)/ethics committees (ECs) and will specify the reason(s) for termination.

3.3.2. Discontinuation of Individual Participants

3.3.2.1. Withdrawal of Consent

Participants and/or their caregivers/legal representatives will be informed that they are free to discontinue treatment or withdraw from the study at any time and for any reason.
The Investigator must withdraw from the study any participant who requests to be withdrawn or whose caregiver/legal guardian requests withdrawal.

3.3.2.2. Discontinuation of Study Treatment

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

- Participant is lost to follow-up
- AE(s)
- Discretion of the Investigator, including decision to discontinue voxelotor for participants who start chronic transfusion
- Discretion of the sponsor
- Pregnancy

The participant should return to the study site for an End of Study (EOS) visit within 4 weeks (28 days) of the last dose of study drug, as indicated in Appendix A.

3.4. Randomization and Unblinding

This is a nonrandomized, open-label study.

4. SELECTION OF STUDY POPULATION

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

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

4.1. Inclusion Criteria

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

1. Male or female participant with SCD who participated and received study drug in a GBT-sponsored voxelotor clinical study

   Note: Participants who discontinued study drug due to an AE, but who remained on study, may be eligible for treatment in this study provided the AE does not pose a risk for treatment with voxelotor.

   Note: Participants who discontinued Study GBT440-032 as a result of an abnormal transcranial Doppler (TCD) flow velocity assessment (≥ 200 cm/sec) are eligible for treatment in this study.

2. Female participant of childbearing potential is required to have a negative urine pregnancy test prior to dosing on Day 1.

   Note: Female participants who become childbearing during the study must be willing to have a negative urine pregnancy test to remain in the study.

3. If sexually active, female participant of childbearing potential must use highly effective methods of contraception until 30 days after the last dose of study drug. If sexually active, male participant must use barrier methods of contraception until 30 days after the last dose of study drug.

4. Participant has provided written consent/assent (for pediatric participants, both the consent of the participant's legal representative or legal guardian and the participant's assent [where applicable] must be obtained).

4.2. Exclusion Criteria

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

1. Female participant who is breastfeeding or pregnant
2. Participant withdrew consent from a GBT-sponsored voxelotor clinical study
3. Participant was lost to follow-up from a GBT-sponsored voxelotor clinical study
4. Participant has any medical, psychological, safety, or behavioral conditions that, in the opinion of the investigator, may confound safety interpretation, interfere with compliance, or preclude informed consent
5. Active symptomatic coronavirus disease of 2019 (COVID-19) infection
6. Known hypersensitivity to voxelotor or any other components of the study drug
7. Use of St. John's wort, sensitive cytochrome P450 (CYP) 3A4 substrates with a narrow therapeutic index, or moderate or strong CYP3A4 inducers within 30 days of Day 1

5. TREATMENTS ADMINISTERED

5.1. Treatments Administered

All participants will receive voxelotor QD, administered orally as tablets, dispersible tablets, or a powder for oral suspension dosage form (packaged as stick packs).

Participants aged ≥ 12 years will receive a voxelotor dose of 1500 mg QD administered as 3 × 500 mg tablets regardless of their body weight.

Participants aged < 12 years will receive a voxelotor dose based on their body weight to provide exposure corresponding to the adult dose of 1500 mg QD. The participant's weight at study entry will be used to determine their starting voxelotor dose in this study, as indicated in Table 1 and Table 2. The dose should be adjusted if the participant's weight increases or decreases at a scheduled clinic visit. The participant's weight will be measured according to the Schedule of Assessments (Appendix A), and dose adjustments made as needed and as indicated in Table 1 and Table 2.

The 1500 mg-equivalent dose in participants aged < 12 years will be administered as powder for oral suspension or as dispersible tablets based on the availability of each formulation.

A bioequivalence study in healthy volunteers (Study GBT-0119) comparing the voxelotor powder for oral suspension and dispersible tablet dosage forms showed that a single dose of the powder for oral suspension had an approximately 35% greater exposure than the same mg dose of dispersible tablets. Therefore, for all participants taking dispersible tablets in this study, the dose of the dispersible tablets will be increased by approximately 35%. This increase allows for a dose adjustment for the dispersible tablets ensuring that all participants taking the dispersible tablet dosage form receive the same exposure as participants receiving the powder for oral suspension dosage form (Table 1 and Table 2).

All participants < 12 years of age will receive the doses shown in Table 1 until sites are instructed by the Sponsor to switch these participants to the modified dispersible tablet doses shown in Table 2 at their next regularly scheduled visit (Appendix A). The date of the switch will be recorded on the dosing electronic case report form (eCRF).

Table 1: Voxelotor (Powder for Oral Suspension or Dispersible Tablet) Weight-Based Doses for Participants Less than 12 Years of Age

Weight	1500 mg-Equivalent Adult Dose
5 to < 10 kg	400 mg
10 to < 20 kg	600 mg
20 to < 40 kg	900 mg
≥ 40 kg [a]	1500 mg

Note: All participants ≥ 12 years of age will take voxelotor 1500 mg administered as tablets, regardless of their weight.

[a] Voxelotor will be administered as 500 mg tablets.

Table 2: Modified Dispersible Tablet Voxelotor Weight-Based Doses for Participants Less than 12 Years of Age

Population	1500 mg-Equivalent Adult Dose
5 to < 10 kg	500 mg
10 to < 20 kg	800 mg
20 to < 40 kg	1200 mg

Note: All participants ≥ 12 years of age will take voxelotor 1500 mg administered as tablets, regardless of their weight. All participants < 12 years of age and ≥ 40 kg will take voxelotor 1500 mg administered as tablets.

Participants receiving a voxelotor dose of 1500 mg QD, regardless of age or weight, will receive tablets.

All dosage forms of voxelotor may be taken with or without food. Voxelotor tablets should be swallowed whole. Voxelotor dispersible tablets should be dispersed in liquid. Likewise, the powder for oral suspension dosage form should be mixed with liquid. Details regarding preparation of voxelotor for administration are provided in the Pharmacy Manual (provided separately).

Detailed instructions for study drug administration will be provided to participants and their caregivers/legal guardians, as needed.

5.1.1. Dose Frequency

Participants will receive the voxelotor dosage form orally QD. 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 the dose level assigned to them.

For AEs that affect safety and tolerability, a trial of reducing or holding the dose may be used. All instances of study drug dose modification (dose reduction, interruption, or discontinuation) should be documented in the participants' medical record and recorded on the eCRF. If the condition/event leading to the dose modification has resolved, the original dose level should be resumed, unless in the judgment of the Investigator this cannot be done safely. Dose reductions due to AEs are provided in Table 3 for participants < 12 years of age and Table 5 for participants ≥ 12 years of age.

When participants switch to the modified dose of dispersible tablet, they will be asked to report any AEs to the clinical site, regardless of when the event occurs relative to the first day of switching to the modified dose. The investigator will determine, based on the participant's reporting of the event, whether a dose decrease is warranted.

Participants with a dose decrease due to an AE should be contacted by the site every 7 days (± 2 days) for follow-up of the AE until the new dose is deemed tolerable; at which time the Investigator may attempt to return to the prior dose or maintain the participant at the lowered dose.

Table 3: Weight-Based Dose Reductions for Participants < 12 years of Age Receiving Voxelotor Powder for Oral Suspension

Weight	Voxelotor 1500 mg Dose Equivalent	Dose Reduction 1 New Dose	Dose Reduction 2 New Dose
5 to < 10 kg	400 mg	300 mg	NA
10 to < 20 kg	600 mg	400 mg	300 mg
20 to < 40 kg	900 mg	600 mg	400 mg
≥ 40 kg [a]	1500 mg	1000 mg	500 mg

Abbreviations: NA, not applicable.
Note: All participants ≥ 12 years of age will take voxelotor 1500 mg administered as tablets, regardless of their weight.
[a] Voxelotor will be administered as 500 mg tablets.

Table 4: Weight-Based Dose Reductions for Participants < 12 Years of Age Receiving Voxelotor Dispersible Tablet

Weight	Voxelotor 1500 mg Dose Equivalent	Dose Reduction 1 New Dose	Dose Reduction 2 New Dose
5 to < 10 kg	500 mg	300 mg	200 mg
10 to < 20 kg	800 mg	500 mg	300 mg
20 to < 40 kg	1200 mg	900 mg	300 mg
≥ 40 kg [a]	1500 mg	1000 mg	500 mg

Note: All participants ≥ 12 years of age will take voxelotor 1500 mg administered as tablets, regardless of their weight.
[a] Voxelotor will be administered as 500 mg tablets.

Table 5: Dose Reductions for Participants ≥ 12 years of Age Receiving Voxelotor Tablets

Initial Dose	Dose Reduction 1 New Dose	Dose Reduction 2 New Dose
1500 mg [a]	1000 mg	500 mg

[a] Voxelotor will be administered as 500 mg tablets.

Guidelines for dose reduction, hold, or permanent discontinuation of study drug for study drug-related AEs are provided in Table 6. If the AE resolves after a dose reduction, participants may resume study drug at the original dose, subject to the Investigator's discretion. The Medical Monitor may be consulted as needed regarding dose modifications.

Table 6: Dose Modification Guidelines for Study Drug–Related Adverse Events

Dose Reduction	
Event	**Recommended Action**
Grade ≥ 2 (NCI grading scale) AE deemed considered related to study drug by the Investigator AND Precludes continued dosing at the current dose level due to safety concern or lack of tolerability (in the Investigator's judgment)	**Study drug**: May be reduced by one dose reduction. 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.
ALT ≥ 3 × ULN if ALT within normal limits at baseline OR > 3 × ULN AND a ≥ 2-fold increase above baseline value if elevated ALT value at baseline in the absence of additional signs of compromised liver function such as elevated PT, PTT, INR, elevated conjugated bilirubin, jaundice, or hepatic pain	**Study drug**: Confirm by repeat testing within 48 to 72 hours if possible, then repeat liver panel at least weekly until ALT level improves. **Additional Actions**: If ALT level continues to increase, reduce dose by one dose reduction and notify the Medical Monitor.
ALT ≥ 5 × and < 8 × ULN (confirmed by repeat testing within 48 to 72 hours) in the absence of additional signs of compromised liver function such as elevated PT, PTT, elevated conjugated bilirubin, jaundice, or hepatic pain	**Study drug**: Reduce dose by one dose reduction. **Additional actions**: Repeat liver panel test within 48 to 72 hours if possible and then at least weekly until resolution to < 5 × ULN; if ALT does not improve within 2 weeks of dose reduction, the Medical Monitor should be notified. If ALT continues to increase within 1 week after a dose reduction, dose should be interrupted, and the Medical Monitor should be notified.
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 dose reduction. 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.
NOTE: Study drug-related rash Grade 2 study drug-related rash that persists after a dose reduction	Management: Consider antihistamines, topical steroids, as clinically indicated. **Study Drug**: If rash does not resolve or improve to Grade 1 after a dose reduction, consider a dose hold. Once the rash has resolved or improved, dosing may be resumed at the reduced level or if, in the opinion of the Investigator, participant may resume study drug at the original dose. The Medical Monitor may be contacted for further discussion. Maximum dose hold is 5 continuous days. If, in the opinion of the Investigator, a longer dose hold is clinically needed, the Medical Monitor should be contacted for discussion.

Drug Discontinuation	
Event	**Recommended Action**
Grade ≥ 3 study drug-related AE that, at the discretion of the Investigator, warrants discontinuation of study drug (eg, has not improved or resolved after dose hold or reduction).	**Study drug:** Discontinue study drug. If the Investigator considers that the participant would benefit from continuing treatment, the Medical Monitor should be contacted.
Consider drug discontinuation if: • **ALT > 8 × ULN** • **ALT > 3 × ULN or ≥ 2-fold increase above baseline value** if elevated ALT value at baseline with additional signs of compromised liver function such as elevated PT, PTT, INR, elevated conjugated bilirubin, jaundice, or hepatic pain, appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia.	**Study drug**: Hold dose, confirm by repeat testing within 48 to 72 hours if possible, and assess potential reversible causes of liver function test abnormalities. Contact the Medical Monitor for discussion of study drug discontinuation.

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; INR, international normalized ratio; NCI, National Cancer Institute; PT, prothrombin time; PTT, partial thromboplastin time; ULN, upper limit of normal.

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

Voxelotor will be supplied as 500 mg tablets, 100 and/or 300 mg dispersible tablets, or 300, 400, 600, and 900 mg powder for oral suspension (packaged as stick packs).

5.4. Packaging and Labeling

Voxelotor tablets and dispersible tablets will be supplied to clinical sites in high-density polyethylene bottles with induction-sealed polypropylene child-resistant caps. The voxelotor powder for oral suspension (packaged as stick packs) will be supplied to clinical sites in a tamper-sealed carton. All study drug packaging must be returned at each visit, regardless of whether they are empty or contain unused study drug.

5.5. Investigational Product Supply

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

5.6. Storage and Handling Procedure

Study drug will be stored at controlled room temperature between 15°C and 25°C (59°F to 77°F), in a secure, temperature-controlled, and locked environment with restricted access. The sponsor or its representatives will be permitted, upon request, to audit the study drug supplies, storage, dispensing procedures, and records at any participating site.

5.7. Concomitant and Prohibited Medications

See Section 6.8 for details regarding the definition and recording of concomitant medications.

5.7.1. Prohibited Medications

Use of an investigational product other than that under study in this trial, regardless of its intended use, is prohibited throughout the trial and for 28 days after the last dose.

Voxelotor is a moderate cytochrome P450 (CYP) 3A4 inhibitor and should not be coadministered with sensitive CYP3A4 substrates with a narrow therapeutic index (refer to Table 7 for examples).

Table 7: Sensitive CYP3A4 Substrates with Narrow Therapeutic Index

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

Abbreviations: 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.

Concomitant use of voxelotor and moderate or strong inducers of CYP3A4 is not allowed within 30 days of Day 1 or during the study (refer to Table 8 for examples). In the event that concomitant use of voxelotor with a moderate or strong CYP3A4 inducer is unavoidable, the Investigator should contact the Medical Monitor.

Table 8: Examples of Moderate and Strong CYP3A4 Inducers

CYP3A4	Examples
Moderate CYP3A4 inducers	Bosentan, cenobamate, dabrafenib, efavirenz, etravirine, lorlatinib, pexidartinib, phenobarbital, primidone, and sotorasib
Strong CYP3A4 Inducers	Apalutamide, carbamazepine, enzalutamide, ivosidenib, lumacaftor, mitotane, phenytoin, rifampin, and St. John's wort

Abbreviations: 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 (last accessed 30 March 2023).

5.7.2. Other Therapies

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

Concomitant medications are allowed, unless the restrictions in Section 5.7.1 apply. Permitted concomitant medications include, but are not limited to, folic acid, commercial medications for the treatment of SCD (eg, HU, L-glutamine, crizanlizumab), over-the-counter- analgesics, and opioids, which are among the chronic medications commonly taken by patients with SCD.

Participants who test positive for acute hepatitis or human immunodeficiency virus (HIV) per standard of care during the study will be discontinued from study drug and will return for the EOS visit.

5.8. Fertility/Contraceptive Requirements

All female participants of childbearing potential (post menarche) should avoid pregnancy, and all sexually active male participants should avoid fathering a child.

5.8.1. Instructions for Female Participants of Childbearing Potential

For female participants of childbearing potential (post menarche) who are sexually active, pregnancy should be avoided by either abstinence from sex/sexual intercourse or the use of highly effective means of contraception for the duration of the study and for a total period of 30 days after the participant has taken her last dose of voxelotor. Highly effective means of contraception are listed in Section 5.9. Pregnancy reporting requirements are outlined in Section 7.4.

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

5.8.2. Female Participants of Nonchildbearing Potential

Female participants of nonchildbearing potential are defined as those who have not started their menarche.

5.8.3. Instructions for Male Participants Capable of Fathering a Child

There is no information about the 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 his 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 (see Section 5.9).

5.9. Acceptable Forms of Contraception for Sexually Active Participants

For Female Participants:

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

1. Hormonal contraceptives:

Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation

- Oral
- Intravaginal
- Transdermal

Progestogen-only hormonal contraception associated with inhibition of ovulation

- Oral
- Injectable
- Implantable

Hormonal contraception must be supplemented with a barrier method (preferably male condom).

Intrauterine device (IUD)

Intrauterine hormone-releasing system (IUS)

Bilateral tubal occlusion

Sexual abstinence:

- Sexual abstinence is considered to be a highly effective method only if the participant is refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. 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.
- In addition to a barrier method, the female partner should also use a highly effective contraceptive method as outlined above

5.10. Assessment of Treatment Compliance

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

6. STUDY PROCEDURES AND EVALUATIONS

Procedures to be performed during the study are summarized in Section 6.1 through Section 6.13, and scheduled procedures are indicated by visit in the Schedule of Assessments (Appendix A). More frequent assessments, as per Investigator or health-care-provider judgment, will be conducted if needed for management of AEs or per standard of care at each site.

Note: Week 12 and Week 36 planned visits for participants who roll over to this study from Study GBT440-042 will be for drug dispensing, collection of adverse events, and concomitant medications only.

Enrollment in this study, optimally, will occur on the same day as the last visit of the antecedent GBT voxelotor in which participants are eligible to participate in this open-label extension.

Note: The end-of treatment assessments performed upon completion of the antecedent study may serve as the Day 1 assessments for Study GBT440-038 and may be used as the baseline evaluations for Study GBT440-038. The investigational site is not required to repeat the assessments on Day 1 of participation in Study GBT440-038. As these end-of-treatment assessments were performed under the provisions of the antecedent study; it is not considered a protocol deviation if they are used for baseline assessments in Study GBT440-038 prior to obtaining informed consent in Study GBT440-038 since the assessments are covered under the antecedent study.

6.1. Informed Consent/Assent

A signed and dated ICF and/or assent form must be obtained before any protocol-specified eligibility assessments are performed. Care will be taken to avoid coercion of the vulnerable population of parents of children with SCD.

For pediatric participants, consent should be obtained from at least one parent (or both if it is required per clinical site policy) or the participant's legal representative. Guidelines for the informed consent/assent process are outlined in Section 11.2.

6.2. Participant Study Number

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

The interactive response technology (IRT) user manual contains the information needed for registering participant status.

6.3. Inclusion/Exclusion Criteria Review

Eligibility assessment will be conducted prior to receiving study drug on Day 1 of this study. Prior to dosing with study drug, the investigator should determine that the participant is in stable clinical condition.

6.4. Medical History

Ongoing AEs and ongoing concomitant medications from the antecedent studies will be recorded as medical history and concomitant medications, respectively, in this study.

6.5. Height and Weight

Height and weight will be collected for participants < 18 years of age at the time points indicated in the Schedule of Assessments (Appendix A).

6.6. Physical Examination

An abbreviated PE will be completed at the time points indicated in the Schedule of Assessments (Appendix A).

The abbreviated PE will include the following: general appearance; examination of eyes, skin, cardiovascular system, and respiratory system; abdominal examination; and a symptom-directed examination.

6.7. Vital Signs

Vital signs (blood pressure and heart rate) will be measured at the time points indicated in the Schedule of Assessments (Appendix A), after the participant has rested comfortably for at least 5 minutes in the supine or sitting position, as age-appropriate and feasible. If the first vital sign measurement is outside the normal range and deemed clinically significant, the measurement will be repeated within 5 minutes.

6.8. Concomitant Medications

Concomitant medications will be recorded throughout the study at the time points indicated in the Schedule of Assessments (Appendix A).

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

In the interest 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, all administered concomitant medications, from signing the ICF/assent form until 28 days (4 weeks) after the participant's last dose of study drug, must be recorded on the participant's eCRF.

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

6.9. Adverse Events

AEs and SAEs will be recorded from signing of the ICF/assent form until 28 days after the last dose of study drug. See Section 7 for details regarding the definitions of and reporting requirements for AEs and SAEs.

6.10. Clinical Laboratory Assessments

Blood and urine samples for clinical laboratory tests will be collected at the time points indicated in the Schedule of Assessments (Appendix A).

The clinical laboratory tests that will be performed are listed in Table 9. All tests will be performed at the local clinical laboratory.

Table 9: Clinical Laboratory Tests

Hematology	Serum Chemistry	Other
– Hematocrit – Hemoglobin – Mean corpuscular hemoglobin concentration – Mean corpuscular volume – Platelet count – RBC count – RBC distribution width – Reticulocyte count (absolute and percent) – WBC count with differential (basophils, eosinophils, neutrophils, monocytes, lymphocytes)	– Alanine aminotransferase – Albumin [b] – Alkaline phosphatase – Aspartate aminotransferase – Bicarbonate [b, c] – Bilirubin (total, direct, and indirect) – Blood urea nitrogen – Calcium [b] – Chloride [b] – Creatinine – Glucose [b] – Lactate dehydrogenase – Potassium [b] – Sodium [b]	– Urine pregnancy test [a]

Abbreviations: RBC, red blood cell; WBC, white blood cell.

[a] For female participants of childbearing potential.

[b] Only record on the CRF if the laboratory value is abnormal and considered clinically significant by the Investigator.

[c] After implementation of Amendment 2 record bicarbonate values only; if the local laboratory only provides carbon dioxide values, do not record on the CRF.

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

Additional and repeat clinical laboratory tests 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.

6.10.1. Pregnancy Test

Female study participants of childbearing potential will have a urine pregnancy test predose on Day 1 and at defined times during the study as indicated in the Schedule of Assessments (Appendix A). Female study participants with a positive urine pregnancy test on Day 1 will not be eligible to participate in the study.

If a urine pregnancy test is positive, the result must be confirmed per local standard of care (eg, ultrasound, serum pregnancy test).

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 to be a female of childbearing potential and will undergo urine pregnancy testing as per the Schedule of Assessments (Appendix A).

6.10.2. Total Blood Volume

On-study blood volume collections will not exceed 2.4 mL/kg in any given 4-week period. Specific blood specimens (eg, exploratory measures) may be omitted at the discretion of the

Investigator, if warranted, such as in the context of blood loss associated with standard clinical care or bleeding events, or if otherwise deemed appropriate.

Due to total volume restrictions in pediatric research, assessments will be prioritized as indicated in Table 10.

Table 10: Priority of Study Assessments

Priority	Test
1	Hematology
2	Serum chemistry

6.11. Taste and Palatability Questionnaire

Upon introduction of a new dosage form (either powder for oral suspension or dispersible tablets) to participants, a taste and palatability questionnaire will be administered to parents and/or children (aged ≥ 5 years) during the first visit when the transition is made and at the subsequent 2 scheduled visits.

6.12. Sickle Cell Disease–Related Complications

Frequency of SCD-related complications over the course of the treatment period will be recorded for each participant and summarized. SCD-related complications may include, but are not limited to, the following: sickle cell anemia with crisis, acute chest syndrome (ACS), pneumonia, priapism, splenic or hepatic sequestrations, stroke, leg ulcers, and osteonecrosis.

6.13. Transcranial Doppler Ultrasonography

Transcranial Doppler assessments performed as part of standard of care will be recorded on the eCRF. Participants having an abnormal TCD (ie, ≥ 200 cm/sec) during the study will be treated according to the institution's standard of care (eg, initiation of HU or chronic transfusions). Continuation of voxelotor is at the discretion of the investigator.

For participants who discontinued Study GBT440-032 (HOPE Kids 2) as a result of an abnormal TCD ≥ 200 cm/sec, TCD assessments will be performed using a Multi-Dop T digital machine manufactured by Compumedics DWL (Germany).

6.14. Missed Assessments

Missed assessments should be rescheduled and performed as close to the original 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 omitted.

7. ADVERSE AND SERIOUS ADVERSE EVENTS

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

The determination, evaluation, reporting, and follow-up of AEs will be performed as outlined in Section 7.1 and Section 7.2. At each study visit, including phone follow-ups, 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 test results will be recorded as AEs or SAEs, as appropriate.

7.1. Adverse Events

7.1.1. Definition of Adverse Events

An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered to be 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), including the period prior to receiving the first dose of the study drug (eg, medication washout). In addition to new events, any increase in the severity or frequency of a preexisting condition that occurs after the participant signs the ICF is considered to be an AE. This includes any side effect, injury, toxicity, or sensitivity reaction.

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

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

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

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

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

medical or surgical intervention to prevent one of the outcomes listed in this definition.

NOTE: Hospitalization planned prior to study enrollment (eg, for elective surgeries) is not considered to be an SAE. Hospitalizations that occur for pre-existing conditions that are scheduled after study enrollment are considered SAEs.

The investigator will assess each AE for seriousness, severity, and relationship to 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 criteria presented in Table 11 should be used.

Table 11: 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 ADLs
Grade 3 – Severe	Medically significant but not immediately life threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADLs
Grade 4 – Life Threatening	Life-threatening consequences; urgent intervention indicated
Grade 5 – Fatal	Death

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

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

7.1.3. Relationship to 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 to be 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, and makes a causal relationship possible or probable. It cannot be readily explained by the participant's clinical state or concomitant therapies and may appear, with some degree of certainty, to be related based on the known therapeutic and pharmacologic actions of the drug. Good clinical judgment should be used for determining causal assessment.

7.1.4. Unexpected Adverse Reactions

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

7.2. Adverse Event Reporting

7.2.1. General

All AEs will be recorded from the time the study participant signs the ICF/assent form until 28 days after the last dose of study drug (EOS) via the electronic data capture (EDC) system. The investigator is responsible for evaluating all AEs, obtaining supporting documents, and ensuring that documentation of the event is complete. Details of each reported AE must include at a minimum severity, relationship to study treatment, duration, and outcome. All (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 (CRO) medical monitors must be notified of the study participant discontinuation.

7.2.2. Diagnosis Versus Signs and Symptoms

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

7.2.3. Abnormal Laboratory Values

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

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

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

Note: Potential drug-induced liver injury (DILI; Hy's law) cases are to be reported as SAEs (Section 7.3). For suggested actions and follow-up assessments in the event of potential DILI, refer to Appendix C. (*This note is included to support Study transition to Pfizer Pharmacovigilance processes and systems*.)

7.2.4. Worsening of Sickle Cell Disease

SCD-related AEs that are common complications associated with the study participant's SCD may not be considered to be related to voxelotor unless judged by the investigator to have worsened in severity and/or frequency or changed in nature during the study. Sickle cell disease-related AEs include, but are not limited to, the following: sickle cell anemia with crisis, ACS, pneumonia, priapism, splenic or hepatic sequestrations, stroke, leg ulcers, and osteonecrosis (Kato, 2018). These events will be recorded on the AE eCRF.

Vaso-Occlusive Crisis

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

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

All SAEs, regardless of causal attribution, must be reported by the investigator or designee or site personnel within 24 hours of SAE awareness on the AE eCRF via the EDC system. If the EDC system is not available, paper SAE report forms will be used to report the SAE and faxed or emailed to the sponsor or designee. The information reported on the paper SAE report form should be entered in the EDC when it is available again.

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

Follow-up SAE information must be submitted within 24 hours of awareness as additional information becomes available.

Note: The following guidelines are included to support Study transition to Pfizer Pharmacovigilance processes and systems.

Follow-up by the investigator continues throughout the active collection period and until the AE or SAE or its sequelae resolve or stabilize at a level acceptable to the investigator. For participants who are screen failures, the active collection period ends when screen failure status is determined.

If the participant withdraws from the study and also withdraws consent for the collection of future information, the active collection period ends when consent is withdrawn.

If a participant permanently discontinues or temporarily discontinues voxelotor because of an AE or SAE, the AE or SAE must be recorded on the CRF.Investigators are not obligated to actively seek information on AEs or SAEs after the participant has concluded study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has completed the study, and they consider the event to be reasonably related to voxelotor, the investigator must promptly report the SAE to the Sponsor.

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

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

Investigators are required to report any urgent safety matters to the sponsor or designee within 24 hours of awareness. The sponsor or designee will inform regulatory authorities, IRBs/ECs, 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 designee within 24 hours of awareness. The investigator will discuss the risks and concerns of study drug exposure to a developing fetus and counsel the participant and/or pregnant partner (or ensure such counseling is provided).

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

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

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

Information regarding pregnancy testing (including definition of females of childbearing potential) is provided in Section 5.8 and Section 6.10.1. Highly effective means of contraception are listed in Section 5.9.

7.5. Reporting Overdose

If a participant takes more than the protocol-defined dose of study drug 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. 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.

In the event of an overdose, the Investigator or treating physician should:

- Contact the study Medical Monitor within 24 hours.
- Closely monitor the participant for any AEs/SAEs and laboratory abnormalities as medically appropriate and follow up until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up.
- Document the quantity of the excess dose as well as the duration of the overdose in the eCRF.
- Report to Sponsor Safety only when associated with an SAE.

7.6. Environmental Exposure, Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

Note: This section is included to support Study transition to Pfizer Pharmacovigilance processes and systems.

Environmental exposure occurs when a person not enrolled in the study as a participant receives unplanned direct contact with or exposure to voxelotor. Such exposure may or may not lead to the occurrence of an AE or SAE. Persons at risk for environmental exposure include healthcare providers, family members, and others who may be exposed. An environmental exposure may include exposure during pregnancy (EDP), exposure during breastfeeding (EDB), and occupational exposure.

Any such exposures to voxelotor under study are reportable to the Sponsor or designee within 24 hours of Investigator awareness.

7.6.1. Exposure During Pregnancy

An EDP occurs if:

- A female participant is found to be pregnant while receiving or after discontinuing voxelotor.
- A male participant who is receiving or has discontinued voxelotor inseminates a female partner.
- A female nonparticipant is found to be pregnant while being exposed or having been exposed to voxelotor because of environmental exposure. Below is an example of environmental EDP:
    - A female family member of healthcare provider reports that she is pregnant after having been exposed to voxelotor by all possible routes of exposure, eg, ingestion, inhalation, or skin contact.
    - A male family member or healthcare provider who has been exposed to voxelotor by all possible routes of exposure, eg, ingestion, inhalation, or skin contact, then inseminates his female partner prior to or around the time of conception.
- The Investigator must report EDP to the Sponsor or designee within 24 hours of the Investigator's awareness, irrespective of whether an SAE has occurred. The initial information submitted should include the anticipated date of delivery (see below of information related to termination of pregnancy).
- If EDP occurs in a participant/participant's partner, the Investigator must report this information to the Sponsor or designee regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of voxelotor and until at least 140 days after the last dose.
- If EDP occurs in the setting of environmental exposure, the Investigator must report information to the Sponsor or designee. Since the exposure information does not pertain to the participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed report is maintained in the Investigator site file.

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The Investigator will follow the pregnancy until completion (or until pregnancy termination) and notify the Sponsor or designee of the outcome as a follow-up to the initial report. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

Abnormal pregnancy outcomes are considered SAEs. If the outcome of the pregnancy meets the criterial for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death), the Investigator should follow the procedures

for reporting SAEs. Additional information about pregnancy outcomes that are reported to the Sponsor or designee as SAEs follows:

- Spontaneous abortion including miscarriage and missed abortion should be reported as an SAE;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the Investigator assesses the infant death as related or possibly related to exposure to voxelotor.

Additional information regarding the EDP may be requested by the Sponsor. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the Investigator will provide the participant with the Parental Partner: Information Sheet and Informed Consent Form to deliver to his partner. The Investigator must document in the source documents that the participant was given the Pregnant Partner Release of Information Form to provide to his partner.

7.6.2. Exposure During Breastfeeding

An EDB occurs if:

- A female participant is found to be breastfeeding while receiving or after discontinuing voxelotor.
- A female nonparticipant is found to be breastfeeding while exposed or having been exposed to voxelotor (ie, environmental exposure). An example of environmental EDB is a female family member or healthcare provider who reports that she is breastfeeding after having been exposed to voxelotor by all possible routes of exposure, eg, ingestion, inhalation, or skin contact.

The Investigator must report EDB to the Sponsor or designee within 24 hours of the Investigator's awareness, irrespective of whether an SAE has occurred. When EDB occurs in the setting of environmental exposure, the exposure information does not pertain to the participant enrolled in the study, so the information is not recorded on a CRF. However, a copy of the completed report is maintained in the Investigator site file.

7.6.3. Occupational Exposure

The Investigator must report any instance of occupational exposure to the Sponsor or designee within 24 hours of the Investigator's awareness regardless of whether there is an associated SAE. Since the information about the occupational exposure does not pertain to a participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed report is maintained in the Investigator site file.

7.7. Medication Errors

Note: This section is included to support Study transition to Pfizer Pharmacovigilance processes and systems.

Medication errors may result from the administration or consumption of voxelotor by the wrong participant, or at the wrong time, or at the wrong dosage strength.

Medication errors are recorded and reported as follows:

Table 12: Reporting of Medication Errors

Recorded on the Medication Page of the CRF	Recorded on the Adverse Event Page of the CRF	Reported to the Sponsor Within 24 Hours of Awareness
All (regardless of whether associated with an AE)	Any AE or SAE associated with the medication error	Only if associated with an SAE

Abbreviations: AE, adverse event; CRF, case report form; SAE, serious adverse event.

Medication errors include:

- Medication errors involving participant exposure to the study drug
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the study participant;
- The administration of an incorrect dosage;
- The administration of expired study drug;
- The administration of an incorrect study drug;
- The administration of study drug that has undergone temperature excursion from the specified storage range unless it is determined by the Sponsor that the study drug under question is acceptable to use.

Whether or not the medication error is accompanied by an AE, as determined by the Investigator, such medication errors occurring to a study participant are recorded on the medication page of the CRF, and, if applicable, any associated serious and nonserious AE(s) are recorded on the AE page of the CRF.

In the event of a medication dosing error, the Sponsor or designee should be notified within 24 hours.

Medication errors resulting in an AE or SAE should be reported to the Sponsor or designee within 24 hours via the CRF.

7.8. Data and Safety Monitoring Board

An independent Data and Safety Monitoring Board (DSMB) will monitor safety data from Study GBT440-038 for participants whose originating study was Study GBT440-032. The responsibilities, and other details of the DSMB are described in the DSMB Charter.

The DSMB will be comprised of medical and statistical representatives and may provide recommendations to the Sponsor regarding stopping or modifying the study for participants from Study GBT440-032.

Sites and their respective IRBs/ECs will be informed of the DSMB recommendations if the recommendations affect study participant safety and/or lead to changes to the study conduct.

8. DATA ANALYSIS AND STATISTICAL PLANS

Statistical programming and analyses will be performed using established statistical methods.

Study data will be reported using summary tables, figures, and select data listings. Continuous variables will be summarized using mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized by presenting the number (frequency) and percentage in each category. All statistical analyses conducted will be descriptive and no formal statistical tests are planned. As appropriate, study data may be summarized separately based on the antecedent study.

8.1. Endpoints

8.1.1. Safety

- TEAEs and SAEs

8.1.2. Sickle Cell Disease–Related Complications

- Frequency of SCD-related complications

8.2. Sample Size

The sample size for this study will not exceed total enrollment in the GBT-sponsored voxelotor clinical studies.

8.3. Populations for Analysis

Safety Population: All participants who receive at least 1 dose of study drug in this study will be included in the safety population.

8.4. Analysis of Safety

8.4.1. Adverse Events

Adverse events will be classified using the Medical Dictionary for Regulatory Activities (MedDRA). A TEAE is defined as an AE that emerges on or after initiation of study drug (having been absent pretreatment), or an AE that existed pretreatment and worsened on treatment (relative to the pretreatment state). The incidence of TEAEs will be tabulated by system-organ-class (SOC), Preferred Term, severity, and relationship to study drug (as assessed by the investigator).

8.4.2. Clinical Laboratory Tests and Vital Signs

Clinical laboratory test and vital sign results over time will be summarized using descriptive statistics.

8.4.3. Frequency of Sickle Cell Disease–Related Complications

Sickle cell disease-related complications over the course of the treatment period will be recorded for each participant. SCD-related complications may include, but are not limited to, the following: sickle cell anemia with crisis, ACS, pneumonia, priapism, splenic or hepatic sequestrations, stroke, leg ulcers, and osteonecrosis. SCD-related complications will be summarized in a manner similar to that for TEAEs, as described in Section 8.4.1.

8.5. Handling of Missing Data

Data will be summarized as observed with no imputation for missing values, except for partially missing dates.

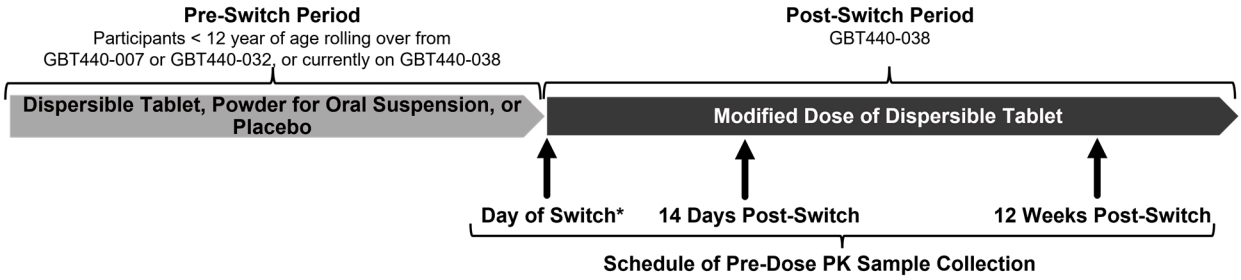
8.6. Pharmacokinetic Sample Collection and Analysis

Whole blood and plasma concentrations of participants taking the modified dose of voxelotor dispersible tablet will be collected predose on the day participants switch to modified dose dispersible tablet (Day of Switch), 14 days after the switch date (14 Days Post-Switch), and 12 weeks after the switch date (12 Weeks Post-Switch) at select sites (Figure 1, Appendix B). Participants should be encouraged to take their voxelotor dose at a regular time every day. However, on the days of PK sample collection, the PK sample should be obtained approximately 24 hours after the subject's administration of voxelotor. Therefore, the site should instruct the subject to take the dose approximately 24 hours prior to their scheduled visit The participant or their caregiver are to record the time of the voxelotor dose taken prior to each of these visits.

Whole blood and plasma voxelotor levels will be evaluated by comparison of predose voxelotor concentration on 14 Days Post-Switch and 12 Weeks Post-Switch with predose voxelotor concentration on the Day of Switch.

A population pharmacokinetic (PK) analysis may be conducted using nonlinear mixed effects modeling.

Figure 1: Pharmacokinetic Sample Collection



* Day of Switch is a regularly scheduled visit (Day 1 or other) at which participant starts modified dose dispersible tablet.

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, laboratories, and 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 eCRF is not a source document. The investigator/institution will permit study-related monitoring, audits, IRB/EC 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 source documents from which data will be transcribed to eCRFs designed to record data pertinent to this study. All relevant observations and data related to the study will be recorded. This will include medical and medication history, PEs, a checklist of inclusion and exclusion criteria, investigational treatment administration, a record of sample collection, clinical assessments, AEs, and final evaluation(s). The monitor will review all eCRFs and compare data to those contained in clinic notes and participants' source documents/medical records.

Data for each participant will be recorded on the eCRF. An eCRF must be completed for every participant enrolled in the study. When data are complete, the investigator or medically qualified subinvestigator listed on Form Food and Drug Administration (FDA) 1572 (or Investigator's Agreement if applicable) will apply his/her signature on the eCRF indicating he/she has reviewed and approves of the data collected on the eCRF.

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 or designee 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 eCRFs; and ensure that all protocol and Good Clinical Practice (GCP) requirements, applicable United States (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 GCP. Additionally, individual participants may be excluded if a medical record review indicates protocol violations or if other factors appear to jeopardize the validity of the study.

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

10.2. Quality Control and Quality Assurance

The sponsor may conduct quality assurance audits 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 eCRFs) and access to all corresponding portions of the office, clinic, laboratory, or pharmacy that may have been involved with the study. The investigator will allocate his or 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 the sponsor upon notification by the regulatory agency. The investigator agrees to allow the inspector direct access to all relevant documents and to allocate his or her time and that of the study-site personnel to the inspector to discuss findings and any relevant issues. The investigator will allow sponsor 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.

10.4. Sponsor's Medically Qualified Individual

The contact information for the sponsor's Medically Qualified Individual (MQI; ie, Medical Monitor) for the study is documented in the study contact list located in the Study Binder.

To facilitate access to their Investigator and the Sponsor's MQI for study-related medical questions or problems from nonstudy healthcare professionals, participants are provided with an emergency contact card (ECC) at the time of informed consent. The ECC contains, at a minimum (a) protocol and study intervention identifiers, (b) participant's study identification number, and (c) site emergency phone number active 24 hours/day, 7 days per week.

The ECC is intended to augment, not replace, the established communication pathways between the participant and their Investigator and site staff, and between the Investigator and Sponsor study team. The ECC is only to be used by healthcare professionals not involved in the research study, as a means of reaching the Investigator or site staff related to the care of a participant.

11. REGULATORY, ETHICAL, LEGAL, AND OVERSIGHT OBLIGATIONS

11.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and CIOMS International Ethical Guidelines;
- Applicable ICH GCP guidelines;
- Applicable laws and regulations, including applicable privacy laws.

The protocol, protocol amendments, ICD, SRSD(s), and other relevant documents (eg, advertisements) must be reviewed and approved by the sponsor, submitted to an IRB/EC by the investigator, and reviewed and approved by the IRB/EC before the study is initiated.

Any amendments to the protocol will require IRB/EC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC;

- Notifying the IRB/EC of SAEs or other significant safety findings as required by IRB/EC procedures;
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH GCP guidelines, the IRB/EC, European regulation 536/2014 for clinical studies, European Medical Device Regulation 2017/745 for clinical device research, and all other applicable local regulations.

11.1.1. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the study intervention, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study participants against any immediate hazard, and of any serious breaches of this protocol or of the ICH GCP guidelines that the investigator becomes aware of.

11.2. Informed Consent and Assent

The Investigator or the Investigator's representative will explain the nature of the study, including the risks and benefits, to the participant (or their legally authorized representative) and answer all questions regarding the study. The participant (or their legally authorized representative) should be given sufficient time and opportunity to ask questions and to decide whether or not to participate in the trial.

Participants must be informed that their participation is voluntary. Participants (or their legally authorized representative [if allowed by local regulation]) will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/EC or study center.

The Investigator must ensure that each participant (or their legally authorized representative) is fully informed about the nature and objectives of the study, the sharing of data related to the study, and possible risks associated with participation, including the risks associated with the processing of the participant's personal data.

The participant (or their legally authorized representative) must be informed that their personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant (or their legally authorized representative).

The participant (or their legally authorized representative) must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/EC members, and by inspectors from regulatory authorities.

The Investigator further must ensure that each study participant (or their legally authorized representative) is fully informed about their right to access and correct their personal data and to withdraw consent for the processing of their personal data.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date on which the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Participant (or their legally authorized representative) must be reconsented to the most current version of the IRB/EC-approved ICF(s) during their participation in the study as required per local regulations.

A copy of the ICF(s) must be provided to the participant (or their legally authorized representative).

11.3. Data Protection

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of participant data.

Participant's personal data will be stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site will be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of participants with regard to the processing of personal data, participants will be assigned a single, participant-specific numerical code. Any participant records or data sets that are transferred to the Sponsor will contain the numerical code; participant names will not be transferred. All other identifiable data transferred to the Sponsor will be identified by this single, participant-specific code. The study site will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to their actual identity and medical record ID. In case of data transfer, the Sponsor will protect eh confidentiality of participant' personal data consistent with the clinical study agreement and applicable privacy laws.

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.

The Sponsor maintains standard operating procedures on how to respond in the event of unauthorized access, use, or disclosure of Sponsor information or systems.

11.4. Institutional Review Board and Regulatory Approval

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

Proposed amendments to the protocol and documents must be discussed with the sponsor and CRO, and then submitted to the IRB/EC for approval, as well as submitted to regulatory authorities for approval prior to implementation. Amendments may be implemented only

after a copy of the local IRB/EC 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/EC 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/EC to facilitate their continuing review of the study (if needed) and that the IRB/EC 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/EC 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. Dissemination of Clinical Study Data

The Sponsor fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the EudraCT/CTIS, and/or www.pfizer.com, and other public registries and websites in accordance with applicable local laws/regulation. In addition, the Sponsor reports study results outside of the requirement of local laws/regulations pursuant to its standard operating procedures.

In all cases, study results are reported by the Sponsor in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

The Sponsor posts clinical trial results on www.clinicaltrials.gov for GBT/Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a product, regardless of the geographical location in which the study is conducted. These results are submitted for posting in accordance with the format and timelines set forth by US law.

EudraCT/CTIS

The Sponsor posts clinical trial results on EudraCT/CTIS for GBT/Pfizer-sponsored interventional studies in accordance with the format and timelines set forth by EU requirements.

www.pfizer.com

The Sponsor posts clinical study report (CSR) synopses and plain-language study results summaries on www.pfizer.com for GBT/Pfizer-sponsored interventional studies at the same time the corresponding study results are posted to www.clinicaltrials.gov. CSR synopses will have personally identifiable information anonymized.

Documents within marketing applications

The Sponsor complies with applicable local laws/regulations to publish clinical documents included in marketing applications. Clinical documents include summary documents and

CSRs including the protocol and protocol amendments, sample CRFs, and SAPs. Clinical documents will have personally identifiable information anonymized.

Data sharing

The Sponsor provides researchers secure access to participant-level data or full CSRs for the purposes of "bona-fide scientific research" that contributes to the scientific understanding of the disease, target, or compound class. The Sponsor will make data from these trials available 18 months after study completion. Participant-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information anonymized.

Data requests are considered from qualified researchers with the appropriate competencies to perform the proposed analyses. Research teams must include a biostatistician. Data will not be provided to applicants with significant conflicts of interest, including individuals requesting access for commercial/competitive or legal purposes.

11.7. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

Guidance on completion of CRFs will be provided in the CRF Completion Requirement document.

The Investigator must ensure that the CRFs are securely stored at the study site in encrypted electronic and/or paper form and are password-protected or secured in a locked room to prevent access by unauthorized third parties.

The Investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source records and documents. This verification may also occur after study completion. It is important that the Investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time in devoted to the process.

Monitoring details describing strategy, including definition of study-critical data items and processes (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, virtual, or on-site monitoring), are provided in the data management plan maintained and utilized by the Sponsor or designee.

The Sponsor or designee is responsible for the data management of this study, including quality checking of the data.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the Sponsor. The

Investigator must ensure that the records continue to be stored securely for as long as they are maintained.

When participant data are to be deleted, the Investigator will ensure that all copies of such data are promptly and irrevocably deleted from all systems.

The Investigator(s) will notify the Sponsor or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the Investigator will cooperate with the Sponsor or its agents to prepare the Investigator site for the inspection and will allow the Sponsor or its agent, whenever feasible, to be present during the inspection. The Investigator site and Investigator will promptly resolve any discrepancies that are identified between the study data and the participant's medical records. The Investigator will promptly provide copies of the inspection findings to the Sponsor or its agent. Before response submission to the regulatory authorities, the Investigator will provide the Sponsor or its agents with an opportunity to review and comment on responses to any such findings.

11.8. Study and Site Start and Closure

The study start date is the date of the first participant's first visit.

The Sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor, including (but not limited to) regulatory authority decision, change in opinion of the IRB/EC, or change in benefit-risk assessment. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The Investigator may initiate study-site closure at any time upon notification to the Sponsor or designee/CRO if requested to do so by the responsible IRB/EC or if such termination is required to protect the health of study participants.

Reasons for the early closure of a study site by the Sponsor may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the Sponsor's procedures, or the ICH GCP guidelines;
- Inadequate recruitment of participants by the Investigator;
- Discontinuation of further study intervention development.

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the ECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

Study termination is also provided for in the clinical study agreement. If there is any conflict between the contract and this protocol, the contract will control as to termination rights.

11.9. Publication Policy

For multicenter trials, the primary publication will be a joint publication developed by the Investigator and the Sponsor reporting the primary endpoint(s) of the study covering all study sites. The Investigator agrees to refer to the primary publication in any subsequent publications. The Sponsor will not provide any financial compensation for the Investigator's participation in the preparation of the primary congress abstract, poster, presentation, or primary manuscript for the study.

Investigators are free to publish individual center results that they deem to be clinically meaningful after publication of the overall results of the study or 12 months after primary completion date or study completion at all sites, whichever occurs first, subject to the other requirements described in this section.

The Investigator will provide the Sponsor an opportunity to review any proposed publication or any other type of disclosure of the study results (collectively, "publication") before it is submitted or otherwise disclosed and will submit all publications to the Sponsor 30 days before submission. If any patent action is required to protect intellectual property rights, the Investigator agrees to delay the disclosure for a period not to exceed an additional 60 days upon request from the Sponsor. This allows the Sponsor to protect proprietary information and to provide comments, and the Investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study intervention or Sponsor-related information necessary for the appropriate scientific presentation or understanding of the study results. For joint publications, should there be disagreement regarding interpretation and/or presentation of specific analysis results, resolution of, and responsibility for, such disagreements will be the collective responsibility of all authors of the publication.

For all publications relating to the study, the investigator and the Sponsor will comply with recognized ethical standards concerning publications and authorship, including those established by the International Committee of Medical Journal Editors. The Investigator will disclose any relationship with the Sponsor and any relevant potential conflicts of interest, including any financial or personal relationship with the Sponsor, in any publications. All authors will have access to the relevant statistical tables, figures, and reports (in their original format) required to develop the publication.

11.10. Confidentiality

The investigator must ensure that the participant's privacy is maintained. On the eCRF 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) should be kept in a strictly confidential file by the investigator.

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

11.11. 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 patient information sheet/ICF for the study will inform the patient of their rights and provide appropriate contact details of the Data Protection Officer.

11.12. 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, investigational agent dispensing logs, correspondence, records of informed consent, and other documents pertaining to the conduct of the study) must be kept for the maximum period of time permitted by the institution. Documents should be stored in such a way that they can be accessed/data retrieved at a later date. Consideration should be given to security and environmental risks.

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

12. DATA HANDLING AND RECORDKEEPING

12.1. Inspection of Records

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

The investigator agrees to maintain a regulatory binder in a current, organized fashion; this binder will contain documentation supportive of the protocol- and GCP-compliance of the study. The contents of the binder will be organized according to the standards of ICH E6, Section 8 (Essential Documents). The investigator agrees to make this binder accessible to the monitor, auditor, and representatives of regulatory agencies and the IRB/EC.

12.2. Retention of Records

The investigator will maintain adequate records, including participants' medical records, laboratory reports, signed consent forms, drug accountability records, safety reports, information regarding participants who discontinued the protocol, and any other pertinent data. All study records must be retained for at least 2 years after the last approval of a marketing application in the US or an ICH region and until (1) there are no pending or

contemplated marketing applications in the US or an ICH region, or (2) at least 2 years have elapsed since the formal discontinuation of clinical development of the 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 or 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. The sponsor must be notified should the investigator/institution be 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 investigator must retain protocols, amendments, IRB/IEC approvals, copies of the Form FDA 1572 (or Investigator's Agreement if applicable), signed and dated consent forms, medical records, eCRFs, drug accountability records, all correspondence, and any other documents pertaining to the conduct of the study.

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

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. Subject to any applicable authorization(s), all reports and communications relating to participants in this study will identify participants only by initials and number. Medical information resulting from a participant's participation in this study may be given to the participant's personal physician, other authorized parties, or 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, and their designated representatives; the IRB/EC; and other authorized parties. All information concerning the study medication 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) is considered to be confidential and shall remain the sole property of the sponsor. The investigator agrees to use this information only in conducting this study and not to use it for other purposes without the sponsor's prior written consent. The information developed in this clinical study will be used by the sponsor in the clinical development of voxelotor and, therefore, may be disclosed by the sponsor as required to authorized parties (including its corporate partners for the study drug, if any, and their designated representatives), other clinical investigators, pharmaceutical companies, the US 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 data have 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.

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Appendix A. SCHEDULE OF ASSESSMENTS

Study Day/Week	**Treatment Period**								**EOS + 7 days** [c]
	First 48 Weeks					**After Week 48**			
	Day 1 [a]	**Week 12** [b] **± 5 days**	**Week 24 ± 10 days**	**Week 36** [b] **± 10 days**	**Week 48 ± 10 days**	**Q12Wk ± 10 days**	**Q24 Wk ± 10 days**	**Q48 Wk ± 10 days**	
Informed Consent/Assent	X								
Review Inclusion/Exclusion Criteria	X								
Medical History	X								
Weight and Height [d]	X		X		X			X	
Abbreviated Physical Examination [e]	X				X				
Vital Signs [f]	X	X	X	X	X		X	X	X
Adverse Events	X	X	X	X	X		X	X	X
Concomitant Medications	X	X	X	X	X		X	X	X
Hematology [g]	X	X	X	X	X		X	X	X
Serum Chemistry [h]	X		X		X			X	X
Urine Pregnancy Test [i]	X	X	X	X	X		X	X	X
Taste and Palatability Questionnaire with In--Clinic Dosing [j]	Performed on Day of Switch, and at the following two consecutive visits								
Transcranial Doppler [k]	Performed as standard of care								
Study Drug Dispensing and Accountability [l]	X	X	X	X	X	X	X	X	X

Abbreviations: CRF, case report form; EOS, End of Study; Q12Wk, every 12 weeks; Q24 Wk, every 24 weeks; Q48 Wk, every 48 weeks; TCD, transcranial Doppler.

Study Day/Week	Treatment Period								EOS + 7 days [c]
	First 48 Weeks					After Week 48			
	Day 1 [a]	Week 12 [b] ± 5 days	Week 24 ± 10 days	Week 36 [b] ± 10 days	Week 48 ± 10 days	Q12Wk ± 10 days	Q24 Wk ± 10 days	Q48 Wk ± 10 days	

a. Day 1 assessments will be performed prior to dosing. If any of the Day 1 assessments were performed at the last study visit in the originating (parent) clinical study, and the Day 1 visit occurs on the same date, the tests do not need to be repeated.
b. Week 12 and Week 36 planned visits for participants who roll over to this study from Study GBT440-042 will be for drug dispensing, collection of adverse events and concomitant medications only.
c. The EOS visit should be conducted 4 weeks (28 days) after the last dose of study drug (+ 7-day window).
d. Height and weight will be collected only for participants < 18 years of age.
e. Will include general appearance; examination of eyes, skin, cardiovascular system, and respiratory system; abdominal examination; and a symptom-directed examination.
f. Heart rate and blood pressure will be measured after participant has rested for ≥ 5 minutes in the seated or supine position. If the first vital sign measurement is outside the normal range and deemed clinically significant, the measurement will be repeated within 5 minutes.
g. Will include the following: hematocrit, hemoglobin, mean corpuscular hemoglobin concentration, mean corpuscular volume, platelet count, red blood cell count, red blood cell distribution width, reticulocytes (absolute and percent), and white blood cell count with differential.
h. Will include the following: alanine aminotransferase, albumin, alkaline phosphatase, aspartate aminotransferase, bilirubin (total, direct, and indirect), blood urea nitrogen, creatinine, lactate dehydrogenase. Laboratory values for bicarbonate, calcium, chloride, glucose potassium, and sodium should only be recorded on the CRF if the laboratory value is abnormal and considered clinically significant by the Investigator).
i. Will be performed for female participants of childbearing potential only. If the urine pregnancy test is positive, the result must be confirmed per local standard of care (eg, ultrasound or serum pregnancy test).
j. Upon introduction of a new dosage form (either powder for oral suspension or dispersible tablets) or switch to higher dose (ie, modified dispersible tablet) to participants, a brief questionnaire will be administered to parents and/or children (aged ≥ 5 years) during the first visit when the transition is made and at the subsequent 2 scheduled visits.
k. For all participants, results from TCD assessments performed as part of standard of care at each site will be recorded on the CRF.
l Voxelotor will be dispensed in 12-week (~90-day) intervals with instruction to participants to return any used/unused bottles/stick packs to the clinic. At the Day 1 Visit, only study drug dispensing will be performed. At the EOS visit, only study drug accountability will be performed.

APPENDIX B. SCHEDULE OF ASSESSMENTS FOR SELECT SITES PARTICIPATING IN VOXELOTOR PLASMA AND WHOLE BLOOD PK COLLECTIONS UPON SWITCHING TO THE MODIFIED DOSE DISPERSIBLE TABLETS [a]

Study Day/Week	Day of Switch	14 Days Post-Switch	12 Weeks Post-Switch
PK Sample Collection (plasma and whole blood)	X (Predose)	X (Predose)	X (Predose)
Other Assessments	Per Scheduled Visit on Day of Switch (Appendix A) and must include Safety Assessments [b] Concomitant Medications Update	Safety Assessments [b] Concomitant Medications Update	Safety Assessments [b] Concomitant Medications Update
Taste and Palatability Questionnaire	X	X	X

Abbreviations: PK, pharmacokinetic.
Note: The last dose of voxelotor should be taken 24 hours (± 1 hour) before PK sampling. The participant or their caregiver are to record the time of the voxelotor dose taken prior to each of these visits.
[a] Once the modified dose DT is available, switching to the modified dose DT will begin for subjects starting this study after completion of their parent study. For subjects that are already enrolled on this study, switching will begin at the subject's next scheduled visit (eg, Week 12, Week 24, etc.).
[b] Safety assessments include AE and SAE monitoring, protocol-specified hematology and serum chemistry tests, abbreviated PEs, and protocol-specified vital sign measurements.

Appendix C. LIVER SAFETY: SUGGESTED ACTIONS AND FOLLOW-UP ASSESSMENTS [AND STUDY DRUG RECHALLENGE GUIDELINES]

This appendix is included to support Study transition to Pfizer Pharmacovigilance processes and systems.

Potential Cases of Drug-Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed "tolerators," while those who show transient liver injury but adapt are termed "adaptors." In some participants, transaminase elevations are a harbinger of a more serious potential outcome. These participants fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as DILI. Participants who experience a transaminase elevation above 3 × the upper limit of normal (ULN) should be monitored more frequently to determine if they are "adaptors" or are "susceptible."

Liver function tests (LFTs) are not required as a routine safety monitoring procedure in this study. However, should an investigator deem it necessary to assess LFTs because a participant presents with clinical signs/symptoms, such LFT results should be managed and followed as described below.

In the majority of DILI cases, elevations in AST (aspartate transaminase) and/or ALT (alanine transaminase) precede total bilirubin elevations (> 2 × ULN) by several days or weeks. The increase in total bilirubin typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and total bilirubin values will be elevated within the same laboratory sample). In rare instances, by the time total bilirubin elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST or ALT in addition to total bilirubin that meet the criteria outlined below are considered potential DILI (assessed per Hy's law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the participant's individual baseline values and underlying conditions. Participants who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy's law) cases to definitively determine the etiology of the abnormal laboratory values:

- Participants with AST/ALT and total bilirubin values within the normal range who subsequently present with AST/ALT values ≥ 3 × ULN AND a total bilirubin value ≥ 2 × ULN with no evidence of hemolysis and an alkaline phosphatase value < 2 × ULN or not available.

- For participants with baseline AST **OR** ALT **OR** total bilirubin values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:
    - Preexisting AST/ALT baseline values above the normal range: AST/ALT values ≥ 2 times the baseline values AND ≥ 3 × ULN; or ≥ 8 × ULN (whichever is smaller).

- Preexisting values of total bilirubin above the normal range: total bilirubin level increased from baseline value by an amount of ≥ 1 × ULN **or** if the value reaches ≥ 3 × ULN (whichever is smaller).

Rises in AST/ALT and total bilirubin separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor.

The participant should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

In addition to repeating measurements of AST and ALT and total bilirubin for suspected Hy's law cases, additional laboratory tests should include albumin, creatine kinase, direct and indirect bilirubin, gamma-glutamyl transferase, prothrombin time/international normalized ratio, eosinophils (%), and alkaline phosphatase. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen/paracetamol (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, or supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection, total bile acids, liver imaging (eg, biliary tract), and collection of serum samples for acetaminophen/paracetamol drug and/or protein adduct levels may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and total bilirubin elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the LFT abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.