CLINICAL STUDY PROTOCOL

Study Number	**GBT440-032**
Study Title	**A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of Voxelotor (GBT440) in Pediatric Participants with Sickle Cell Disease (HOPE Kids 2)**
Investigational Product	Voxelotor (GBT440)
IND Number	121691
EudraCT Number	2017-000903-26
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
Original Protocol	07 November 2017
Amendment 1.0	06 August 2019
Amendment 2.0	05 December 2019
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Amendment 4.0	24 April 2023

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	Definition
ACS	acute chest syndrome
ADL	activities of daily living
AE	adverse event
ALK	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate transferase
BP	blood pressure
CCI	[redacted]
CL	clearance
COVID-19	coronavirus disease of 2019
CRO	contract research organization
CYP	cytochrome P450
DILI	drug-induced liver injury
DSMB	Data and Safety Monitoring Board
EC	Ethics Committee
ECG	electrocardiogram
eCRF	electronic case report form
EDB	exposure during breastfeeding
EDP	exposure during pregnancy
EDC	electronic data capture
EOS	end of study
EOT	end of treatment
CCI	[redacted]
EOS	end of study
ETD	early treatment discontinuation
FDA	Food and Drug Administration
FEMA	Flavor and Extract Manufacturers Association of the United States
GBT	Global Blood Therapeutics, Inc.
GCP	Good Clinical Practice
GRAS	Generally Recognized as Safe
Hb	hemoglobin
HbF	fetal hemoglobin
Hb-O_2	hemoglobin-oxygen
HbS	sickle hemoglobin

Abbreviation	Definition
$HbS-O_2$	sickle hemoglobin-oxygen
Hct	hematocrit
HIV	human immunodeficiency virus
HU	hydroxyurea
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IID	Inactive Ingredient Database
INR	international normalized ratio
IPF	idiopathic pulmonary fibrosis
IRB	Institutional Review Board
ITT	Intent to Treat
IXRS	Interactive Response System
LC/MS/MS	liquid chromatography mass spectrometry
LDH	lactate dehydrogenase
LFT	liver function test
MMRM	mixed model for repeated measures
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NIH	National Institutes of Health
PD	pharmacodynamic(s)
PE	physical examination
Ph Eur	European Pharmacopoeia
PK	pharmacokinetic(s)
PPK	population pharmacokinetic(s)
PT	prothrombin time
O_2	oxygen
RBC	red blood cell
RSI	Reference Safety Information
SAE	serious adverse event
SAP	statistical analysis plan
SCA	sickle cell anemia
SCD	sickle cell disease
SRSD	Single Reference Safety Document
SUSAR	Suspected Unexpected Serious Adverse Reactions
TAMMV	time-averaged mean of the maximum
TCD	transcranial Doppler

Abbreviation	Definition
TEAE	treatment-emergent adverse event
TIA	transient ischemic attack
ULN	upper limit of normal
US	United States
USA	United States of America
USPI	United States Prescription Information
VOC	vaso-occlusive crisis
WBC	white blood cell

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	GBT440-032, Amendment 4
Study Title	A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of Voxelotor (GBT440) in Pediatric Participants with Sickle Cell Disease (HOPE Kids 2)
Investigational Product	Voxelotor as 500 mg tablets or as 300, 400, 600, and 900 mg powder for oral suspension (packaged in stick pack pouches) or as 100 and 300 mg dispersible tablets Matching placebo
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 approximately 50 international clinical sites.
Number of Study Participants	Approximately 224 participants with sickle cell disease (SCD), aged ≥ 2 to < 15 years.
Treatment	Participants will be randomized in a 1:1 ratio to receive voxelotor or placebo. All participants younger than 12 years of age and randomized to voxelotor will receive a dose based on their body weight to provide exposure corresponding to the adult dose of 1500 mg/day. Participants 12 years or older will take 1500 mg/day. Participants will receive study drug as a tablet dosage form or powder for oral suspension dosage form (packaged in stick pack pouches). If powder for oral suspension is not available, dispersible tablets will be used. Voxelotor, in all dosage forms, may be taken with or without food. Voxelotor tablets should be swallowed whole. The powder for oral suspension should be mixed with liquid. Likewise, voxelotor dispersible tablets should be dispersed in liquid. Details regarding preparation of voxelotor for administration are provided in the Pharmacy Manual (provided separately). The participant's weight at screening will be used to determine their initial treatment dose. Dosing should be adjusted if the participant's weight increases or decreases at any clinic visit. The participant's weight will be measured and dose adjustments will be made as needed, as outlined in the Pharmacy Manual.
Objectives	<u>Primary Objective:</u> The primary objective is to evaluate the effect of voxelotor compared to placebo on the transcranial Doppler (TCD) time-averaged mean of the maximum velocity (TAMMV) arterial cerebral blood flow at 24 weeks in SCD participants ≥ 2 to < 15 years of age with conditional (170 to < 200 cm/sec) TCD flow velocity. <u>Secondary Objectives:</u> The secondary objectives are to evaluate the effects of voxelotor compared to placebo on: • Change in TCD flow velocity at Week 48 and Week 96 • Conversion of TCD category from conditional to abnormal

Objectives (cont'd)	• Reversion of TCD category from conditional to normal • Proportion of participants with TCD response • Change in hemoglobin (Hb) over time • Change in clinical measures of hemolysis • Annualized incidence rate of vaso-occlusive crises (VOCs) CCI [redacted] <u>Safety Objectives:</u> The safety objective is to assess the safety and tolerability of voxelotor compared to placebo. <u>Pharmacokinetic Objectives:</u> The pharmacokinetic (PK) objective is to assess the PK of voxelotor as evaluated by population pharmacokinetics (PPK) analysis.
Study Design	The study will be conducted globally at approximately 50 clinical sites. The study consists of 3 periods: • Screening: up to 35 days prior to randomization • Treatment: 96 weeks • Follow-Up: 28 days (4 weeks) after the last dose Approximately 224 participants aged 2 to < 15 years will be randomized 1:1 to voxelotor or placebo. Participants ≥ 12 years old will be administered a fixed dose of voxelotor 1500 mg/day. Participants younger than 12 years of age will receive voxelotor at a weight-based (1500 mg-equivalent) dose. Following completion of study treatment, eligible participants will be given the option to enroll in an open-label extension study (under a separate protocol) to receive voxelotor for a minimum of 3 years (3 years or until commercial product becomes available or a managed access program, whichever is longer). At the time of randomization, participants will be stratified by hydroxyurea (HU) use (yes/no), age (2 to ≤ 8 years; > 8 to < 15 years), Screening TCD flow velocity value (170 to < 185 cm/sec; 185 to < 200 cm/sec) and geographic region (Africa including Middle East and North Africa [MENA]; rest of world). Stratification of participants by age was chosen to evenly balance by age distribution using the expected median age of 8 years.

	Dosing of participants between 2 and < 4 years of age: At least 15 participants from 2 to < 4 years of age will be enrolled. Enrollment of participants < 4 years of age will be initiated after the Data and Safety Monitoring Board (DSMB) has reviewed safety and PK data from at least 12 participants < 30 kg treated with voxelotor for at least 28 days. These data for at least 12 participants may be generated from any voxelotor clinical studies.
Duration of Study Participation	The duration of study involvement for an individual participant is expected to be approximately 105 weeks. The study will end when the last participant's last visit occurs.
Statistical Methods	<u>Primary Endpoint</u> The primary efficacy endpoint is the change from Baseline at 24 weeks in TAMMV arterial cerebral blood flow, as measured by TCD. <u>Secondary Endpoints</u> The secondary efficacy endpoints are as follows: • Change from Baseline in TCD flow velocity at Week 48 and Week 96 • Time to conversion to abnormal TCD flow velocity (≥ 200 cm/sec) • Time to reversion to normal TCD flow velocity (< 170 cm/sec) • Proportion of participants with TCD flow velocity reduction ≥ 15 cm/sec at Week 24, Week 48, and Week 96 • Change in Hb from Baseline at Week 24, Week 48, and Week 96 • Change in clinical measures of hemolysis (unconjugated bilirubin, % reticulocyte, absolute reticulocyte, and lactate dehydrogenase [LDH]) from Baseline at Week 24, Week 48, and Week 96 • Annualized incidence rate of reported VOCs CCI [redacted] <u>Safety Endpoints</u> The safety endpoints include adverse events (AEs), clinical laboratory assessments, and vital signs.

Statistical Methods (cont'd)	Pharmacokinetic Endpoint The endpoint is whole blood and plasma voxelotor PK as evaluated by PPK analysis using nonlinear mixed effects modeling. Sample Size The sample size is planned to provide sufficient statistical power for the primary efficacy analysis and for a robust safety database. In addition, the number of events required to assess secondary efficacy endpoints, eg, percentage conversion to abnormal TCD category, is also considered. For the primary endpoint (change from Baseline in TCD flow velocity [cm/sec]), assuming equal allocation across treatment groups and a common variance, an estimate of the number of participants in each of 2 treatment groups used the following assumptions in the power calculation: • Targeted treatment effect: difference in mean change from Baseline in TCD flow velocity is 15 cm/sec • Common standard deviation is 24 cm/sec • A significance level of 5% (2-sided) Assuming a 20% drop out rate, a sample size of 112 participants per group provides > 95% power to detect the targeted treatment effect for the following hypothesis test using a Student's t-test: $H_0: \mu_1=\mu_2$ versus $H_A: \mu_1\neq\mu_2$ where μ_1 and μ_2 stand for mean change from Baseline in TCD flow velocity at Week 24 in voxelotor and placebo groups, respectively. For the secondary efficacy endpoint of time to conversion to abnormal TCD category, assuming 35% of participant in the placebo group have experienced a TCD flow velocity > 200 cm/sec by Week 96, a hazard ratio of 0.5 between voxelotor group and placebo, a fixed follow up time of up to 96 weeks for each participant, and an overall 20% drop out rate, a total of 49 events is expected. This provides approximately 65% power for a log-rank test at a two-sided significance level of 5% and approximately 75% power at a two-sided significance level of 10% (PASS version 11). Efficacy Analyses The primary analysis of change in TCD flow velocity from Baseline to Week 24 will be performed using a mixed model for repeated measures (MMRM). Independent variables will include treatment, study visit, treatment by study visit interaction, and randomization stratification factors (ie, HU use, age, Screening TCD flow velocity, and geographic region). Within-subject variability will be modeled using an unstructured covariance matrix. The secondary endpoints will be analyzed as described below. • Change from Baseline endpoints: – Change in TCD flow velocity from Baseline to Week 48 and Week 96 will be analyzed with the same MMRM as described for the primary efficacy endpoint (ie, change from Baseline in TCD flow velocity at Week 24). A single model will be fit incorporating data from all timepoints. – Change in Hb and clinical measures of hemolysis (unconjugated bilirubin, % reticulocytes, absolute reticulocyte, and LDH) from Baseline at Week 24, Week 48, and Week 96 will be analyzed with a similar approach.

Statistical Methods (cont'd)	• TCD responder endpoint: – The TCD responder endpoint, defined as a TCD flow velocity reduction from Baseline ≥ 15 cm/sec at a given timepoint, eg, Week 24, Week 48, or Week 96, will be analyzed using an exact Cochran-Mantel-Haenszel (CMH) general association test stratified by the randomization stratification factors for the treatment difference between voxelotor and placebo. • Time to events endpoints: – For time to conversion from conditional to abnormal TCD, the Kaplan-Meier method will be used to estimate the landmark rates and the associated 95% confidence intervals in the voxelotor and placebo groups at Week 24, Week 48, and Week 96. A log-rank test stratified for the randomization stratification factors will be used to test the difference between voxelotor and placebo groups. A Cox proportional hazard model may be used to estimate the hazard ratio, as appropriate. – Time to reversion from conditional to normal TCD will be analyzed using a similar approach. <u>Safety and Tolerability Analyses</u> Safety analysis will be performed on all participants receiving at least one dose of study drug. Adverse events (AEs) will be classified according to the Medical Dictionary for Regulatory Activities (MedDRA). The incidence of treatment-emergent adverse events (TEAEs), defined as an event that occurs on or after Day 1 of study treatment or the worsening of a preexisting condition on or after Day 1 of study treatment, will be tabulated by System Organ Class (SOC), preferred term, severity, and relationship to study drug. Changes in laboratory parameters (hematology, serum chemistry, and liver function tests) and vital signs (eg, blood pressure [BP], pulse, and body temperature) over time will be summarized descriptively. SCD-related AEs will be collected and summarized separately (including VOC, acute chest syndrome, osteonecrosis, priapism, etc.) <u>Pharmacokinetic Analyses</u> PPK analysis will consist of all participants who receive active study drug and have at least one measured concentration at a scheduled PK time point after the start of dosing. If any participants are found to be noncompliant with respect to dosing or have incomplete data, protocol deviations, or clinical events that affect PK, a decision will be made on a case-by-case basis as to their inclusion in the analysis. Participants in this population will be used for all PK summaries. PPK analyses using nonlinear mixed effects modeling will be performed to characterize voxelotor PK in plasma and whole blood. The influence of demographic covariates (such as body weight, height, age, gender) on voxelotor PK parameters (ie, clearance [CL] and volume of distribution) will be investigated. If appropriate, the voxelotor PK data may be pooled with PK data from other studies. Continuous variables will be descriptively summarized using mean, standard deviation (SD), coefficient of variation (CV%, as appropriate), median, minimum, maximum, and as appropriate, geometric mean. Categorical variables will be descriptively summarized by presenting the number (frequency) and percentage in each category.

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 events such as overt stroke or silent cerebral infarcts which can produce significant physical and neurocognitive deficits (Ohene-Frempong, 1998; DeBaun, 2016). Transcranial Doppler (TCD) ultrasonography to assess cerebral artery blood flow velocity in children with SCD has been shown to be a reliable predictor of stroke (Adams, 1992). Patients with "abnormal" TCD flow velocities ($\geq$ 200 cm/sec) are at high risk of stroke, which can be mitigated by chronic red blood cell (RBC) transfusion or hydroxyurea (HU) (Adams, 1998; Adams, 2005; Ware, 2016). Because of these findings, practice guidelines recommend that all children with Sickle Cell Anemia (HbSS or HbSβ^0thal) should be screened annually with TCD according to methods employed in the STOP (Optimizing Primary Stroke Prevention in SCD) studies, beginning at age 2 and continuing until at least age 16 (NIH, 2014; Yawn, 2014).

Patients with "conditional" TCD flow velocities ($\geq$ 170 to < 200 cm/sec) are at lower risk of stroke than patients with abnormal TCD flow velocities (risk for conditional is approximately 2% per year, for abnormal is approximately 9% per year, and for healthy children without SCD is < 0.1% per year), but still have significantly elevated stroke risk. Practice guidelines recommend that patients with conditional TCD flow velocities undergo more frequent screening and referral to specialist care for stroke prevention. Currently there is no standard-of-care therapy indicated to reduce stroke risk or prevent future need for transfusions in patients with conditional TCD flow velocities.

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 (Steinberg, 2003). None of the currently-approved SCD therapies target the underlying mechanism of the disease to prevent the polymerization of sickle hemoglobin (HbS) and the sickling of RBCs which in turn underlies the serious and life-threatening clinical complications of SCD (Bunn, 1997).

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, and is approved in the United States (US) for use in patients with sickle cell disease (SCD) who are 12 years and older (Oxbryta® United States Prescription Information [USPI]). Marketing approval in other regions has been received or is being sought. For details on the global

registration status, please refer to the current 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. It binds covalently and reversibly via Schiff base to the N-terminal valine of the Hb α chain (ie, a single voxelotor molecule binding per HbS tetramer in a 1:1 stoichiometry) and allosterically (Eaton, 1999) increases sickle hemoglobin-oxygen (HbS-O_2) affinity (Oksenberg, 2016), stabilizing the oxyHb state and inhibiting polymerization (Oksenberg, 2016). The voxelotor binding site is distant from heme pockets and therefore it can increase oxygen (O_2) affinity without sterically blocking the release of O_2.

A primary and obligatory event in the molecular pathogenesis of SCD is the polymerization of deoxygenated HbS which results in RBC membrane damage, destruction, and resulting clinical consequences of hemolytic anemia and vaso-occlusion leading to chronic organ injury, debilitating symptoms, and early mortality. Because oxyhemoglobin (oxyHb) is a potent inhibitor of HbS polymerization, increasing the proportion of oxyHb in all RBCs with voxelotor can reduce HbS polymerization, decrease RBC membrane damage and destruction and has the potential to subsequently achieve long term disease modification. This principle is supported by the finding that in patients with sickle hereditary persistence of fetal hemoglobin, the dilution of HbS by 20% to 30% fetal hemoglobin (HbF) in all RBCs is sufficient to inhibit HbS polymerization, preventing RBC damage and SCD clinical sequelae. This suggests that pharmacologically maintaining approximately 20% to 30% of hemoglobin (Hb) in the nonpolymerizing oxygenated state in all RBCs may be an effective approach for the treatment of SCD. By addressing the multiple underlying mechanistic culprits of stroke in patients with SCD including low Hb, hemolysis and mechanistic culprits of stroke in patients with SCD including low Hb, hemolysis and polymerization (Adams, 2005; Kwiatkowski, 2010; Platt, 2008), voxelotor has the potential to constitute a disease modifying therapy and alleviate clinical manifestations of SCD (Perrine, 1972; Natta, 1974; Bethlenfalvay, 1975; Stamatoyannopoulos, 1975; Talbot, 1983; Akinsheye, 2011; Akinsheye, 2012).

In this study, the neurologic and the overall benefits and risks of long-term treatment (up to 96 weeks) with voxelotor in pediatric participants 2 to < 15 years of age will be investigated.

1.3. Summary of Relevant Nonclinical Data and Clinical Data

1.3.1. Nonclinical Data

Primary pharmacodynamics (PD) studies of voxelotor consisted of in vitro and in vivo studies to characterize (a) voxelotor binding and affinity for Hb, (b) the effect of voxelotor on HbS modification using purified Hb, washed RBCs, and whole blood, and (c) the efficacy of voxelotor in vivo in a mouse model of SCD. These in vitro assays of increasing complexity included measuring Hb-O_2 via hemoximetry, quantifying stabilization of the oxyhemoglobin state conformation, delaying HbS polymerization at low O_2 tension, preventing in vitro sickling induced by a low O_2 environment, decreasing viscosity and improving deformability of RBCs in blood from patients with SCD (Dufu, 2018). In addition, these studies show that voxelotor-modified Hb retains the Bohr Effect, which is the ability to offload O_2 from Hb in metabolically active (low pH) tissues.

Collectively, these studies demonstrate that voxelotor increases Hb-O_2 affinity with high specificity of binding to Hb, stabilizes the oxy or R-state conformation of Hb, prevents HbS polymerization and RBC sickling in vitro, and improves sickle blood viscosity and deformability in vitro. In addition, voxelotor increases HbS-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, provided separately.

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 the 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, and with an associated decrease in clinical measures of hemolysis (including indirect bilirubin, reticulocytes, and LDH), which correlates with drug exposure (Brown, 2018; Vichinsky, 2018). Durability of response is sustained through 72 weeks of treatment (Howard, 2021). By stabilizing HbS in the oxy-Hb 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 RBCs 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 support the potential for voxelotor to serve as a disease-modifying therapy for SCD.

Based on available data, voxelotor has been well tolerated over a range of tested doses up to and including 1500 mg daily in adult and pediatric clinical study 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 Phase 3 Study GBT440-031 and the ongoing Phase 2 pediatric study, GBT440-007.

Based on the safety data from the Phase 3 study in adult and adolescent participants with SCD, non-SCD-related treatment-emergent adverse events (TEAEs) were predominantly of low-grade severity and were transient. Identified risks include the adverse drug reactions (ADRs) of diarrhea, abdominal pain, nausea, rash, and drug hypersensitivity. As expected, SCD-related TEAEs were common, and the incidence of SCD-related TEAEs, including sickle cell anemia (SCA) with crisis, was similar for the voxelotor and placebo treatment groups. The profile of non-SCD-related and SCD-related TEAEs in adolescent participants was similar to the voxelotor treatment groups in the adult population.

Across all SCD studies, the overall incidence of TEAEs leading to study treatment discontinuation was low and the most commonly reported serious adverse events (SAEs) were predominantly assessed as not related to study treatment but to underlying SCD; predominantly SCA with crisis.

Overall, no clinical safety concerns consistent with inadequate tissue oxygenation were identified in the voxelotor clinical development program, including participants with SCD. Of particular note, maximal exercise testing in patients with SCD (Howard, 2019) and healthy volunteers 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).

The evidence generated by clinical studies and post-marketing experience suggests there is no increased risk of VOC after abrupt discontinuation of voxelotor.

Taken together, the safety outcomes and efficacy from clinical studies to date demonstrate an acceptable risk-benefit profile of voxelotor and support its continued development in pediatric participants with SCD. In Study GBT440-032, participants with conditional TCD flow velocities ($\geq$ 170 to < 200 cm/sec) will be enrolled. Currently there are no standard-of-care therapies indicated to reduce stroke risk or prevent future need for transfusions in patients with conditional TCD flow velocities. Treatment with voxelotor may reduce the stroke risk in participants with conditional TCD flow velocity at baseline.

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

1.5. Study Rationale

The purpose of Study GBT440-032 is to evaluate the effect of voxelotor on stroke reduction, as measured by TCD flow velocity in participants 2 to < 15 years of age with SCD who have conditional TCD flow velocity at baseline.

The primary endpoint of this study is change from baseline at 24 weeks in time averaged maximum of mean velocity (TAMMV) arterial cerebral blood flow as measured by TCD.

A reduction in stroke risk, using TCD flow velocity as an endpoint is based on the following:

- Anemia was the single most powerful predictor of stroke in a multivariate analysis in patients with SCD without prior history of stroke/transient ischemic attack (TIA) (RR: 1.85 per 1 g/dL decrease in Hb for stroke; $p < 0.001$) (Ohene-Frempong, 1998).
- TCD flow velocity is strongly associated with long-term stroke risk reduction after adjustment for other patient factors (Adams, 1992).
- An abnormal TCD flow velocity is an indication for primary stroke prophylaxis with chronic blood transfusion; conditional TCD flow velocity also confers elevated stroke risk (2% to 5% [Hankins, 2008]) and requires frequent monitoring (Adams, 1997; NHLBI, 2014; Zétola, 2012), and a 15 cm/s reduction in TCD flow velocity is clinically meaningful (Hankins, 2015).

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

Voxelotor is available in an oral form and is intended for once daily administration. See below, and Section 3.1.1 and Section 5.1 for additional information regarding the dose to be used in this study.

1.6.1. Dose Rationale

The doses of voxelotor to be evaluated in this study are 1500 mg orally daily for participants ≥ 12 years of age or a 1500-mg weight-based adult equivalent (see Table 1) for participants < 12 years of age. This dose of voxelotor is supported by: (1) absence of concerning exposure-related safety findings from the pivotal Phase 3 study GBT440-031 in adults and adolescents with SCD; (2) a statistically significant and clinically meaningful increase in Hb, and reductions in clinical measures of hemolysis observed with voxelotor 1500 mg, which were more robust than those observed with voxelotor 900 mg (Vichinsky, 2018); 3) the efficacy of the 1500-mg dose in adolescents is supported by similar improvements in Hb and hemolysis measures observed in the Phase 2a Study GBT440-007 (Brown, 2018); 4) exposure-response analyses using data from both Study GBT440-031 and Study GBT440-007 demonstrating dose-dependent treatment effects of voxelotor on Hb and hemolysis measures; 5) the majority of adult and adolescent participants receiving voxelotor 1500 mg in the GBT440-031 study achieved the intended therapeutic target of 20% to 30% mean % Hb occupancy.

Dosing for participants < 12 years of age will be weight based, as presented in Table 1 and Table 2, and is anticipated to provide exposures similar to adolescent participants receiving voxelotor 1500 mg. These doses are based on population pharmacokinetics (PPK) utilizing allometric scaling and are expected to provide exposures of voxelotor equivalent to exposures observed in adults (Study GBT440-031) and adolescents (Studies GBT440-007 and GBT440-031) (Washington, 2018).

Two dosage forms of voxelotor may be evaluated in this study for participants < 12 years of age; powder for oral suspension or dispersible tablet. To estimate appropriate doses of voxelotor powder for oral suspension to be evaluated in pediatric participants (2 years to < 12 years) with SCD, multiple doses of voxelotor were simulated by weight group (5 kg to < 10 kg, 10 kg to < 20 kg, and 20 kg to < 40 kg). The simulations were based on a voxelotor whole blood PPK model, including data from adults, adolescents, and children aged 6 to 11 years. The model used the same model structure (ie, 2-compartment model with first-order absorption) as the adult PPK model. The clearance (CL) and central volume (V_c) were scaled allometrically based on participant weights sampled from age-stratified normal distributions for children with homozygous SCD (Thomas, 2000).

A bioequivalence study in healthy volunteers (Study GBT-0119) showed that a single dose of the powder for oral suspension dosage form had an approximately 35% greater exposure than the same milligram dose of dispersible tablet. Therefore, for participants in this study receiving the dispersible tablet dosage form, the dose of the dispersible tablet will be increased by 35% relative to the powder for oral suspension dose to adjust for the difference in the dosage form (see Table 1 and Table 2).

It is intended that the powder for oral suspension dosage form will be used throughout the entire study. The dispersible tablet dosage form will only be used in this study if the supply of powder for oral suspension is insufficient to complete the study.

Table 1: Voxelotor Powder for Oral Suspension Weight-Based Doses for Participants Less than 12 Years of Age

Population	1500 mg-Equivalent Adult Dose
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: Voxelotor Dispersible Tablet Weight-Based Doses for Participants Less than 12 Years of Age

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

1.6.2. Use of a Placebo Control

This study uses placebo as a comparator on the background of standard of care treatment. Placebo was chosen as the control because it is necessary to determine the efficacy, safety, and tolerability of voxelotor by allowing safety signals to be distinguished from AEs occurring due to SCD.

With the exception of the initiation of HU during screening or after randomization and chronic transfusion, all approved therapies for SCD are allowed under this protocol. This includes analgesics, HU, and L-glutamine, according to the local standard of care.

Randomization to placebo treatment in this study does not place study participants at increased risk, as the standard of care for patients with conditional TCD flow velocities is continued observation, including repeat TCD assessments.

2. STUDY OBJECTIVES

See Section 3 for details regarding the investigational plans.

2.1. Primary Objective

The primary objective is to evaluate the effect of voxelotor compared to placebo on the TCD time-averaged mean of the maximum velocity (TAMMV) arterial cerebral blood flow at 24 weeks in SCD participants ≥ 2 to < 15 years of age with conditional (170 to < 200 cm/sec) TCD flow velocity.

2.2. Secondary Objectives

The secondary objectives are to evaluate the effects of voxelotor compared to placebo on:

- Change in TCD flow velocity at Week 48 and Week 96
- Conversion of TCD category from conditional to abnormal
- Reversion of TCD category from conditional to normal
- Proportion of participants with TCD response
- Change in Hb over time
- Change in clinical measures of hemolysis
- Annualized incidence rate of vaso-occlusive crises (VOCs)

CCI

[redacted]

2.4. Safety Objective

The safety objective is to assess the safety and tolerability of voxelotor compared to placebo.

2.5. Pharmacokinetic Objective

The pharmacokinetic (PK) objective is to assess the PK of voxelotor as evaluated by PPK analysis.

3. INVESTIGATIONAL PLAN

This multicenter SCD study is a randomized, placebo-controlled, double-blind, prospective study of the efficacy and safety of voxelotor in pediatric participants ≥ 2 to < 15 years of age.

3.1. Study Endpoints

Study endpoints are described in Section 8.

3.1.1. Study Design

The study will be conducted globally at approximately 50 clinical sites. Study procedures and assessments are outlined in Section 6. The timing of these procedures and assessments are provided in Appendix A, Appendix B, and Appendix C. Dosage and treatment administration are outlined in Section 5.

The study consists of 3 periods (Figure 1):

- Screening: up to 35 days prior to randomization
- Treatment: 96 weeks
- Follow-Up: 28 days (4 weeks) after the last dose

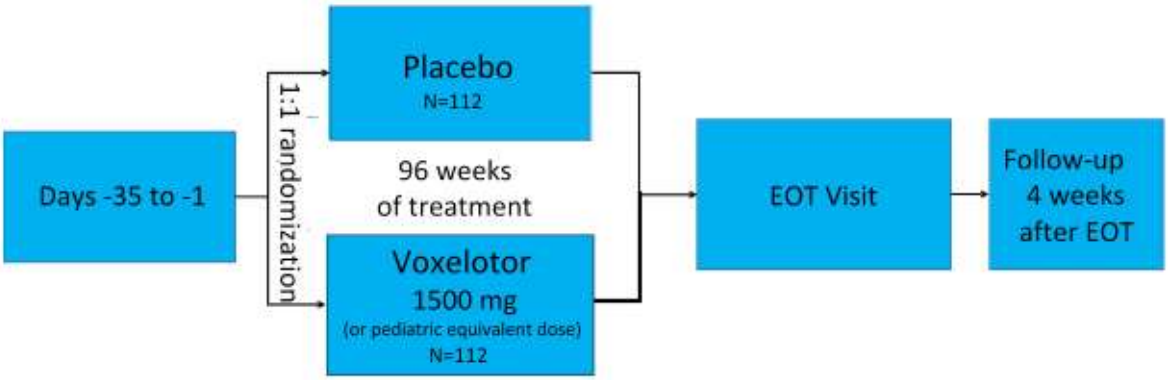
Approximately 224 participants aged 2 to < 15 years will be randomized 1:1 to voxelotor or placebo.

Participants ≥ 12 years old will be administered a fixed dose of voxelotor 1500 mg/day. Participants younger than 12 years of age will receive voxelotor at a weight-based (1500 mg-equivalent) dose, as described in Section 1.6 (Table 1).

Following completion of study treatment, eligible participants will be given the option to enroll in an open label extension study (under a separate protocol) to receive voxelotor for a minimum of 3 years (3 years or until commercial product becomes available or a managed access program, whichever is longer).

At the time of randomization, participants will be stratified by HU use (yes; no), age (2 to ≤ 8 years; > 8 to < 15 years), Screening TCD flow velocity value (170 to < 185 cm/sec; 185 to < 200 cm/sec), and geographic region (Africa including Middle East and North Africa [MENA]; rest of world). Stratification of participants by age was chosen to evenly balance by age distribution using the expected median age of 8 years.

Figure 1: Study Schema



Abbreviations: EOT, end of treatment.
Note: Primary endpoint will be assessed at Week 24.

In this study, TCD flow velocities are categorized as follows:

1. Normal: < 170 cm/sec
2. Conditional: 170 to < 200 cm/sec – the eligible participant population for this study
3. Abnormal: ≥ 200 cm/sec

Enrolled participants with TCD flow velocity values ≥ 200 but < 220 cm/sec may continue in the study and must have a repeat TCD within 2 to 4 weeks (timing based on Principal Investigator clinical judgement). If the repeat TCD flow velocity is abnormal, study drug will be discontinued (see Section 3.4.2 for information on discontinuation requirements) and the participant is required to return for the End of Study (EOS) visit (28 days after the last dose of study drug). Participants will be treated according to local standard of care for abnormal TCD flow velocity.

Enrolled participants with TCD flow velocity value of ≥ 220 cm/sec will have study drug discontinued and return for the EOS visit (28 days after the last dose of study drug). Patients will be treated according to local standard of care for abnormal TCD flow velocity.

3.1.2. Dosing of Participants Between 2 Years and < 4 Years of Age

At least 15 participants from 2 years to < 4 years of age will be enrolled. Enrollment of participants < 4 years of age will be initiated after the DSMB has reviewed safety and PK data from at least 12 participants < 30 kg treated with voxelotor for at least 28 days. These data for at least 12 participants may be generated from any of the voxelotor studies.

3.1.3. Assessments

Assessments and procedures are described in Section 6 and in Appendix A, Appendix B, and Appendix C.

3.1.4. Data and Safety Monitoring Board

An independent DSMB will monitor the safety and conduct of the study. The responsibilities, and other details of the DSMB will be 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.

Sites and their respective Institutional Review Boards (IRBs)/Ethics Committees (ECs) will be informed of the DSMB recommendations if the recommendations affect study participant safety and/or lead to changes to the study conduct.

3.1.5. Minimization of Bias

This study uses a double-blind, randomized, multi-center design to minimize bias.

3.2. Treatment

See Section 5 for voxelotor and placebo information.

3.3. Duration of Study Participation and of the Study

The duration of study involvement for an individual participant is expected to be approximately 105 weeks (See Section 3.1.1 for additional information regarding the study periods for this study).

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

3.4. Stopping Rules

3.4.1. 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 termination of the study, the Sponsor will notify, in writing, the Investigators, regulatory authorities, and IRBs/ECs and will specify the reason(s) for termination.

3.4.2. Early Discontinuation of Individual Participants

3.4.2.1. Withdrawal of Consent

Participants and/or their caregiver/legal representative 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.

3.4.2.2. Early Discontinuation of Study Treatment

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

- Participant is lost to follow-up
- Adverse event(s)
- Abnormal TCD flow velocity
- Discretion of the Investigator

- Discretion of the Sponsor
- Pregnancy

If a participant is discontinued from study drug at a scheduled visit, that scheduled visit will become the Early Treatment Discontinuation (ETD) visit and all required assessments for the ETD visit (see Appendix B) should be completed. The participant should then return to the study site for an EOS visit approximately 28 days after the last dose of study treatment as indicated in Appendix B.

If a participant is discontinued between scheduled visits, there is no requirement for an ETD visit. End of Study visit for such participants should be scheduled for 28 days after the last dose of study drug.

3.5. Randomization and Unblinding

3.5.1. Randomization

Randomization will be carried out through an Interactive Response System (IXRS). Permuted blocks within randomization strata will be used. Eligibility of the participant should be confirmed by the Investigator prior to randomization.

3.5.1.1. Preventing Unblinding Due to Laboratory Assessments

Because knowledge of certain laboratory assessments over time (Hb, hematocrit [Hct], RBC count, total and unconjugated bilirubin) may suggest the treatment assignment, these measurements will be redacted to the Investigator.

Results of redacted laboratory tests will be communicated to the Investigator if a participant's Hb declines to < 5.0 g/dL, or if the Hb declines ≥ 2 g/dL from screening. This does not require breaking of the treatment assignment blind. This is to ensure participant safety by allowing the Investigator to monitor for worsening anemia which could require intervention (eg, due to a viral infection). Anonymized laboratory results will be available to the Sponsor.

3.5.1.2. Unblinding for Medical Need

If a medical condition should arise for which appropriate treatment cannot be decided without knowledge of the study treatment assignment, the Investigator may unblind a study participant. The Investigator should promptly document and notify the Sponsor of any premature study treatment unblinding (eg, accidental unblinding, unblinding due to a treatment-related SAE). Pregnancy is considered an event that requires unblinding. Unblinding procedures specified in the IXRS Manual will be followed and documented in the Investigator site file.

3.5.1.3. Unblinding for Pharmacokinetic Analysis

To facilitate the PK analysis, the bioanalytical laboratory and the contract research organization (CRO) analyzing the PK/PD data will be unblinded to treatment assignments during the study. Interim analysis may be performed and data summarized per treatment arm; however, the blinded Sponsor study team will not be unblinded to individual treatment assignment.

4. SELECTION OF STUDY POPULATION

If a participant is found to meet inclusion/exclusion criteria at screening but then has a clinically significant change in status prior to randomization (eg, hospitalized for sickle cell VOC, acute infection with drop in Hb from participant's baseline), the participant should be withdrawn from screening and not randomized or administered study treatment. The participant may be rescreened at the Investigator's discretion and in consultation with the Sponsor. Participants who are re-screened will have all assessments repeated except for iron testing and Hb genotyping.

4.1. Inclusion Criteria

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

1. Age $\geq$ 2 to < 15 years at the time of informed caregiver/legal guardian consent
2. Male or female study participants with SCA (HbSS, HbSβ^0 thalassemia genotype)
    a. Documentation of SCA genotype is required and may be based on documented history of laboratory testing or must be confirmed by laboratory testing during screening
3. TCD TAMMV arterial cerebral blood flow $\geq$ 170 to < 200 cm/sec during the Screening Period
4. Hb $\geq$ 5.5 and $\leq$ 10.5 g/dL during screening
5. Participant is in stable clinical condition with stable Hb level near their usual baseline as determined by the Investigator
6. For participants taking HU, the dose of HU (mg/kg) must be stable for at least 90 days prior to signing the informed consent form (ICF) and/or assent form, and with no anticipated need for dose adjustments (other than weight based). For participants not taking HU, no anticipated need for initiation of HU in the opinion of the Investigator
7. Adequate venous access, in the opinion of the Investigator, to permit monitoring of blood variables including laboratory safety variables and collection of PK samples
8. Ability to undergo TCD assessment without sedation
9. If sexually active and female, must agree to abstain from sexual intercourse or to use a highly effective method of contraception throughout the study period and for 30 days after discontinuation of study drug. If sexually active and male, must agree to abstain from sexual intercourse or willing to use barrier methods of contraception throughout the study period and for 30 days after discontinuation of study drug.
10. Females of child-bearing potential are required to have a negative pregnancy test before the administration of study drug.
11. Written informed parental/guardian consent and participant assent (where applicable) has been obtained per IRB/EC policy and requirements, consistent with ICH guidelines.

4.2. Exclusion Criteria

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

1. Body weight < 10 kg at the screening visit.
2. Hospitalization for VOC or acute chest syndrome (ACS) within the 14 days prior to execution of informed consent/assent (see Section 7.2.5.1 for the definition of VOC).
3. More than 10 VOCs within the past 12 months that required hospitalization, emergency room, or clinic visit.
4. Stroke resulting in focal neurological deficit; previous silent infarcts are permitted.
5. Known history or findings suggestive of significant cerebral vasculopathy (eg, moyamoya or significant vasculopathy).
6. History of seizure disorder.
7. Has been treated with erythropoietin or other hematopoietic growth factors within 28 days of signing informed consent/assent or if, in the opinion of the Investigator, there is an anticipated need for such agents during the study.
8. RBC transfusion therapy (also termed chronic, prophylactic, or preventative transfusion) or has received an RBC transfusion or exchange transfusion for any reason within 90 days of signing the informed consent/assent.
9. Planned initiation of HU prior to the completion of study participation.
10. Severe renal dysfunction (estimated glomerular filtration rate [eGFR]< 30 mL/min/1.73 m^2 by Schwartz formula).
11. Alanine aminotransferase (ALT) > 4× upper limit of normal (ULN) for age.
12. History of unstable or deteriorating cardiac or pulmonary disease within 6 months prior to consent including severe or unstable pulmonary hypertension.
13. Clinically significant bacterial, fungal, parasitic, or viral infection currently requiring or will require therapy.
    a. Participants with acute bacterial infection requiring antibiotic use should delay screening until the course of antibiotic therapy has been completed and the infection has resolved, in the opinion of the investigator.
14. Known active hepatitis A, B, or C or human immunodeficiency virus (HIV)-positive.
15. Positive test indicative of active malaria infection at screening.
    (Malaria test to be performed only if there is suspicion of active malaria infection).
16. Any condition affecting drug absorption, such as major surgery involving the stomach or small intestine (prior cholecystectomy is acceptable).
17. History of malignancy within the past 2 years prior to treatment Day 1 requiring chemotherapy and/or radiation (with the exception of local therapy for non-melanoma skin malignancy).
18. Received an investigational drug within 30 days or 5 half-lives, whichever is longer, of the parent/legal guardian signing the ICF.
19. Parent or legal guardian/participants are unlikely to comply with the study procedures.

20. Other medical, psychological, or addictive condition that, in the opinion of the Investigator, would: confound or interfere with evaluation of safety, efficacy, and/or PK of the investigational drug; prevent compliance with the study protocol; preclude informed consent; or, render the participant, parent, or caretaker unable/unlikely to comply with the study procedures.
21. Use of herbal medications (eg, St. John's wort) or sensitive CYP3A4 substrates with a narrow therapeutic index.
22. Active symptomatic coronavirus disease of 2019 (COVID-19) infection.
23. Known hypersensitivity to voxelotor or any other components of the study drug.

5. TREATMENTS ADMINISTERED

5.1. Treatments Administered

Participants will be randomized in a 1:1 ratio to receive voxelotor or placebo.

All participants younger than 12 years of age randomized to voxelotor will receive a dose based on their body weight to provide exposure corresponding to the adult dose of 1500 mg/day. Participants 12 years or older will take 1500 mg/day. Section 1.6.1 provides details regarding dose selection for this study.

Participants will receive study drug as a tablet dosage form or powder for oral suspension dosage form (packaged in stick pack pouches). If powder for oral suspension is not available, dispersible tablets will be used.

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

Details regarding preparation for administration are provided in the Pharmacy Manual (provided separately). Detailed instructions will be provided to participants and their caregiver/legal guardian prior to the first dose of study drug.

The participant's weight at screening will be used to determine their initial treatment dose (Table 1). Dosing should be adjusted if the participant's weight increases or decreases at the clinic visit. Participant's weight will be measured according to the schedule indicated (Appendix A and Appendix B) and dose adjustments made as outlined in the Pharmacy Manual.

5.1.1. Dose Frequency

Participants will receive a voxelotor dosage form or matching placebo administered orally, once daily. If a participant misses a dose, the participant should resume normal dosing the next day (ie, the dose, on the day after the day of a missed dose, should not be increased or decreased).

5.1.2. Dose Modification

Participants should adhere to their dose level assigned at Day 1.

For AEs that impact 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 electronic case report form (eCRF). If the conditions/event leading to the dose modification have resolved, the original dose level should be resumed unless in the judgment of the Investigator this cannot be done safely. Dose reductions due to AEs are provided in Table 3 and Table 4 for participants < 12 years of age and Table 5 for participants ≥ 12 years of age.

Table 3: Weight-based Dose Reductions for Participants < 12 Years of Age Receiving Powder for Oral Suspension

Weight	Voxelotor 1500 mg Dose Equivalent	Dose Reduction 1 New Dose	Dose Reduction 2 New Dose
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

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

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

Weight	Voxelotor 1500 mg Dose Equivalent	Dose Reduction 1 New Dose	Dose Reduction 2 New Dose
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

[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, dose interruption, or permanent discontinuation of study drug for study drug-related AEs are provided in Table 6. If in the opinion of the Investigator, the AE resolves after a dose reduction, participants may resume study drug at the original dose The Medical Monitor should be notified of all dose modifications due to AEs within 5 days. The Medical Monitor may be consulted as needed.

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	Study drug: Confirm by repeat testing within 48 to 72 hours, if possible, then repeat liver panel at least weekly until ALT level improves.

compromised liver function such as elevated PT, PTT, INR, elevated conjugated bilirubin, jaundice, or hepatic pain	**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 remains eligible for continuing the Study, 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 Form

5.3.1. Voxelotor

Voxelotor will be supplied as 500 mg tablets or as 300, 400, 600, and 900 mg powder for oral suspension (packaged in stick pack pouches). If powder for oral suspension is not available, dispersible tablets will be used and will be supplied as 100 or 300 mg tablets. All study drug dosage forms will be supplied with matching placebo drug products.

All the excipients used in the dosage forms are listed in the Food and Drug Administration (FDA) Inactive Ingredient Database (IID) or are pharmaceutical excipient mixtures entirely composed of FDA IID components except for grape flavor which is listed under Flavor and Extract Manufacturers Association of the United States (FEMA) Generally Recognized as Safe (GRAS).

All the excipients used in the dosage forms are either compendial per European Pharmacopoeia (Ph Eur) or are composed of mixtures which are compendial per Ph Eur or accepted by E number or European Commission regulation.

Details regarding drug administration will be provided in the Pharmacy Manual.

5.3.2. Placebo

The placebo matching tablet, powder for oral suspension, and dispersible tablet dosage forms contain several excipients. All the excipients used in the dosage forms are listed in the FDA IID or are pharmaceutical excipient mixtures entirely composed of FDA IID components except for grape flavor which is listed under FEMA GRAS.

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

5.4. Packaging and Labeling

Voxelotor STs, DTs, and matching placebos will be supplied to clinical sites in high-density polyethylene (HDPE) bottles with induction sealed polypropylene child resistant caps. Voxelotor PfOS and matching placebo dosage form will be supplied to clinical sites in sealed child resistant white foil laminate stick pack pouches. At each visit (except for Week 2, EOT, and EOS), participants will be supplied a sufficient quantity of study drug to ensure continuous dosing through to the next clinic visit. All study drug packaging must be returned at each visit, regardless if they are empty or contain unused study drug.

5.5. Investigational Product Supply

The Sponsor or their representative will supply the packaged and labeled drug product to the investigational sites. Additional details are provided in the Pharmacy Manual.

5.6. Storage and Handling Procedure

All study medications will be stored at controlled room temperature between 15°C to 25°C (59°F to 77°F), in the storage area of the investigational site pharmacy, which is a secure, temperature controlled, locked environment with restricted access. The Sponsor or its representatives will be permitted upon request to audit the supplies, storage, dispensing procedures, and records, provided that the blind of the study is not compromised.

5.7. Concomitant and Prohibited Medications

5.7.1. Prior and Concomitant Medications

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

In the interests of participant safety and acceptable standards of medical care, the Investigator will be permitted to prescribe treatment(s) at his/her discretion. For all study participants, all administered concomitant medications from signing the ICF/assent until 28 days (4 weeks) after the participant's last dose of study drug, must be recorded on the participant's eCRF.

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

5.7.2. HU Treatment

HU treatment is allowed, provided that the dose has been stable for at least 90 days prior to signing the ICF. Participants who start HU therapy for chronic use any time after randomization will be discontinued from the study.

Participants who are on HU may have their dose adjusted (based on change in their weight) if the mg/kg dose is stable.

5.7.3. Transfusion

Participants who require chronic transfusion will be discontinued from study treatment and 28 days later undergo the EOS visit. Transfusion for surgery or trauma is permitted.

5.7.4. Other Therapies

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

Other concomitant medications are allowed, unless the restrictions in Section 5.7.5 apply. Permitted concomitant medications include folic acid, L-glutamine, over-the-counter analgesics, and opioids, which are among the chronic medications commonly taken by participants with SCD.

The use of erythropoietin is prohibited during the study.

Participants who are already on malaria prophylaxis therapy may be allowed to participate in the study at the discretion of the Investigator. Participants may also be initiated on malaria prophylaxis therapy during study at the discretion of the Investigator and as per standard of care.

Participants who test positive for acute malaria during the study should be provided standard-of-care treatment and may continue in the study at the discretion of the Investigator and the Sponsor.

Participants who test positive for acute hepatitis or HIV during the study will be discontinued from study drug. An ETD visit should occur for cases when the study visit is feasible. In all cases, the participant should return for the EOS visit (28 days after the last dose of study drug).

5.7.5. Contraindicated Medications

- The use of herbal medications (eg, St. John's wort) is not allowed.
- No experimental drugs of any kind are permitted.
- Voxelotor is a moderate CYP3A4 inhibitor and should not be co-administered with sensitive CYP3A4 substrates with a narrow therapeutic index (refer to Table 7 for examples).
- Concomitant use of moderate or strong inducers of CYP3A4 with voxelotor is not allowed (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 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.
Note: Substrates with a 'narrow therapeutic range' refers to drugs whose exposure-response relationship indicates that small increases in their exposure levels by the concomitant use of CYP inhibitors may lead to serious safety concerns. Adapted from: FDA DRAFT Guidance for Industry: Drug Interactions Studies-Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations. February 2012.

Table 8: Examples of Moderate and Strong CYP3A4 Inducers

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

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 5 March 2023).

5.8. Fertility/Contraceptive Requirements

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

5.8.1. Instructions for Female Participants of Child-Bearing Potential

For female participants of child-bearing potential (post-menarche) and sexually active, pregnancy should be avoided by either abstinence from sex/sexual intercourse or the use of highly effective means of contraception for the duration of the study, and for a total period of 30 days after the participant has taken her last dose of voxelotor. Highly effective means of contraception are listed below in Section 5.9. 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 Non-Child-Bearing Potential

Female participants of non-child-bearing 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 effects that voxelotor could have on the development of the fetus in humans. Therefore, it is important that the partners of male participants do not become pregnant during the study and for a total period of 30 days after the male participant has taken the last dose of voxelotor.

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

5.9. Acceptable Forms of Contraception for Sexually Active Participants

<u>For female participants:</u>

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

1. Hormonal contraceptives
    a. Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
        - Oral
        - Intravaginal
        - Transdermal
    b. Progestogen-only hormonal contraception associated with inhibition of ovulation:
        - Oral
        - Injectable
        - Implantable

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

2. Intrauterine device (IUD)
3. Intrauterine hormone-releasing system (IUS)
4. Bilateral tubal occlusion
5. Sexual abstinence:
   a. Sexual abstinence is considered a highly effective method only if the participant is refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the participant.

For male participants with female partners capable of reproduction:

Barrier methods of contraception:

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

5.10. Assessment of Treatment Compliance

Drug disposition records will be maintained, specifying the amount dispensed to each participant and the date of dispensation. This record will be available for Sponsor review at any time.

Compliance will be determined by returned tablet, dispersible tablet, or stick pack pouch counts.

6. STUDY PROCEDURES AND EVALUATIONS

Procedures that are to occur during screening and study visits are summarized in Section 6.1 through Section 6.19.3. The screening period for a participant commences at the point at which the participant undergoes the first study-specific screening assessment. All screening assessments must be completed within 35 days before the first dose of study drug.

The required study procedures, and timing that they need to occur, are outlined in the Schedule of Assessments (Appendix A, Appendix B, and Appendix C).

6.1. Informed Consent/Assent

A signed and dated consent and/or assent form will be obtained before any protocol-specified screening procedures are performed. Care will be taken to avoid coercion of this vulnerable population of parents of children with SCD.

Consent should be obtained from at least one parent (or both if it is required per Investigational Site policy) or the participant's legal representative. Guidelines for the informed consent/assent process are outlined in Section 11.10.

6.2. Participant Study Number

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

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

6.3. Medical History

Clinically significant medical history (as determined by the Investigator) will be recorded at the time of the screening. Results from all available TCD examinations within 1 year of screening will be collected.

6.4. Physical Examination

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

- Complete PE should include at a minimum: Examination of head, eyes, ears, nose, and throat (HEENT), skin, cardiovascular and respiratory systems, abdominal examination, neurologic, musculoskeletal and symptom directed examination.
- Abbreviated PE should include at a minimum: Examination of eyes, skin, cardiovascular and respiratory systems, abdominal examination, neurologic, and symptom-directed examination.

6.5. Vital Signs

Vital signs (blood pressure [BP], heart rate and temperature will be measured, as outlined in Schedule of Assessments, after a participant has rested comfortably for at least 5 minutes in the supine or sitting position, as age appropriate and feasible. A repeated measurement of any of the vital sign parameters will be taken within 5 minutes if the first reading is outside the normal range and deemed clinically significant.

6.6. Transcranial Doppler Ultrasonography

TCD assessments will be performed per the Schedule of Assessments (Appendix A and Appendix B) and prior to all other assessments on that study visit day, if feasible. TCD assessments will be performed using a Multi-Dop T digital machine manufactured by Compumedics DWL (Germany). The assessments will be sent for central quality review and interpretation. For additional information, please refer to the study TCD Manual.

TCD examiners will be trained and certified on study-specific TCD assessment requirements using the Multi-Dop T machine prior to screening patients.

CCI

[redacted]

6.9. Electrocardiograms.

Electrocardiogram (ECGs) (12-lead) will be recorded in the supine position after at least 5 minutes of rest (refer to the Schedule of Assessments (Appendix A).

6.10. Eligibility Assessment, Inclusion/Exclusion Review

Eligibility assessment will be conducted during screening and prior to receiving study drug on treatment Day 1. Both at screening and prior to randomization, Investigator should determine that the participant is in stable clinical condition with Hb level near their baseline.

Randomization must occur on the same day as treatment Day 1 (the first dose of study drug). If a participant is randomized and withdrawn from the study prior to the first dose of study drug, they may not be re-screened.

6.11. Adverse Events and Concomitant Medications

AEs and concomitant medications will be recorded throughout the study. See Section 7.2 for details regarding AE reporting period for this study.

6.12. Laboratory Assessments

All laboratory assessments will be performed through a central laboratory.

Refer to the Schedule of Assessments (Appendix A and Appendix B) for the specific timing that laboratory tests are to occur.

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

Additional and repeat laboratory safety testing for the evaluation of abnormal results and/or AEs during the study may be performed at the discretion of the Investigator or upon request of the Sponsor; it is preferred for the analyses to be conducted by the central laboratory unless medical need necessitates urgent results reporting. Repeat laboratory testing of abnormal potentially clinically significant or clinically significant results for the screening evaluation of the participant may be repeated at the discretion of the Investigator.

6.12.1. Hematology

Hematology assessments include the following:

- RBCs
- Hct
- Hb
- Platelets
- White blood cells (WBCs) with differential (basophils, eosinophils, neutrophils, monocytes, and lymphocytes)
- % and absolute reticulocytes
- RBC distribution width (RDW)
- Mean corpuscular volume (MCV)
- Mean corpuscular hemoglobin concentration (MCHC)
- Hemoglobin A (HbA) (Screening only)
- Alpha Thalassemia and Haplotype (Week 8 Only)
- Additional exploratory non-genomic testing may be conducted for SCD and treatment response biomarkers (dense cells, albumin:creatinine ratio)

Note: Haplotype and dense cells will be assessed only if feasible.

6.12.2. Serum Chemistry

Chemistry assessments include the following:

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

6.12.3. Hemoglobin Genotype

Unless documented in their medical record, participants will be tested for Hb genotype at screening.

All participants will be tested for alpha thalassemia as indicated in the Schedule of Assessments (Appendix B) when viable and feasible.

6.12.4. Haplotype

All participants will undergo testing for haplotype as indicated in the Schedule of Assessments (Appendix B) when viable and feasible.

6.12.5. Serum Erythropoietin

Serum erythropoietin will be measured as indicated in the Schedule of Assessments (Appendix B).

6.12.6. Fetal Hemoglobin

HbF levels will be measured at Screening (Appendix A).

6.12.7. Urinalysis

Urine will be assessed for color and appearance. Dipstick analysis will be conducted for: Specific gravity, pH, protein, glucose, ketones, leucocytes, bilirubin, urobilinogen, nitrite,

creatinine, and occult blood. Microscopic analysis (RBCs, WBCs, bacteria, and casts) collected as clinically indicated.

Urinalysis will be performed (when urine sample is available) at screening and on study as indicated in the Schedule of Assessments (Appendix A and Appendix B).

6.12.8. Malaria Screening

Malaria tests will be conducted at local laboratories in malaria-prevalent regions at screening per the Investigator's discretion, and/or at any point during the study, if there is a clinical suspicion of active infection with malaria. Participants may also be tested for malaria at screening in non-malaria prevalent regions if deemed necessary by the Investigator. All testing will be done by a local laboratory.

Participants whose test is consistent with acute malaria at screening may be re-screened upon completion of treatment and complete resolution of malaria infection.

Participants whose test is consistent with acute malaria (active infection) while on study will be managed as per standard of care and may continue in the study at the discretion of the Investigator and the Sponsor. Cases of new onset of malaria will be reported as an AE or SAE (see Section 7 for guidance).

6.12.9. Serum Virology

Serum virology will include HIV, hepatitis B surface antigen (HBsAg), hepatitis A immunoglobulin M (IgM), and hepatitis C virus (HCV) and will be conducted at screening only if clinically indicated.

6.12.10. Iron Studies

Iron studies will include Serum ferritin, iron, and transferrin calculated (% transferrin saturation).

6.12.11. Pharmacokinetic Sample Collection

Blood samples for whole blood and plasma PK assessments will be collected according to the Schedule of Assessments (Appendix C). Whole blood and plasma concentrations of voxelotor will be measured using a validated liquid chromatography mass spectrometry (LC/MS/MS) assay.

6.12.12. 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, bleeding events, or if otherwise deemed appropriate.

Due to total volume restrictions in pediatric research, assessments will be prioritized in the following order:

Priority	Test
1	Hematology
2	Chemistry

Priority	Test
3	Hb genotype [a]
4	PK
5	EPO
6	HbF
7	Alpha thalassemia/haplotype
8	Iron studies
9	CCI [redacted]

Abbreviations: EPO, erythropoietin; Hb, hemoglobin; HbF, fetal hemoglobin; PK, pharmacokinetics.
[a] If needed per Inclusion Criterion #2 and Section 6.12.3 of the protocol.

CCI [redacted]

CCI

[redacted]

6.18. 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 abandoned.

6.19. Assessment of Safety

Safety assessments will consist of recording all AEs and SAEs; protocol-specified hematology and clinical chemistry variables; clinical examination findings; measurement of protocol-specified vital signs; and the results from other protocol-specified tests that are deemed critical to the safety evaluation of voxelotor.

6.19.1. Safety Parameters

Participant safety and tolerability will be monitored during the study using standard measures, including PEs, vital signs (including BP), safety laboratory tests, concomitant medication usage and AE monitoring).

Assessments will be performed as outlined in Section 6 and at defined times during the study as indicated in the Schedule of Assessments (Appendix A and Appendix B).

More frequent assessments, as per Investigator or health care provider judgement, will be conducted if needed for management of AEs or per standard of care at each site.

6.19.2. Demographic/Medical History

Medical history will be recorded at screening.

6.19.3. 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 a female of childbearing potential and will undergo urine pregnancy testing as per the Schedule of Assessments.

Female study participants of childbearing potential will have a serum pregnancy test performed at screening. Urine pregnancy tests will be performed at defined times during the study as indicated in the Schedule of Assessments (Appendix A and Appendix B). Female study participants with a positive serum pregnancy test at 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).

7. ADVERSE AND SERIOUS ADVERSE EVENTS

Safety assessments will consist of recording all AEs and SAEs, protocol-specified hematology and clinical chemistry variables, clinical examination findings, measurement of protocol-specified vital signs, and the results from other protocol-specified tests that are deemed critical to the safety evaluation of voxelotor.

In order 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).

The determination, evaluation, reporting, and follow-up of AEs will be performed as outlined in Section 7.1. At each visit, the study participant or participant caregiver will be asked about any new or ongoing AE since the previous visit. Assessments of AEs will occur at each study visit. See Section 7.2 for details regarding the required time periods for AE reporting.

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

7.1. Adverse Events

7.1.1. Definition of Adverse Events

An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational product, whether or not thought to be related to the investigational product. An AE may also constitute complications occurring as a result of protocol-mandated interventions (eg, invasive procedures such as biopsies), including the period prior to receiving the first dose of the study drug (eg, medication wash out). In addition to new events, any increase in the severity or frequency of a pre-existing condition that occurs after the participant signs the ICF is considered an AE. This includes any side effect, injury, toxicity, or sensitivity reaction.

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

Life-threatening AE or life-threatening suspected adverse reaction is an AE or suspected adverse reaction that, in the view of either the Investigator or the 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 "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 The 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 (IME) that may not result in death, be immediately life-threatening, or require hospitalization may be considered serious when based upon medical judgement, they may jeopardize the study participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

NOTE: Hospitalization planned prior to study enrollment (eg, for elective surgeries) are not considered SAEs. Hospitalizations that occur for 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 following criteria should be used (Table 9).

Table 9: 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 non-invasive intervention indicated; limited age-appropriate instrumental ADL
Grade 3 – Severe	Medically significant but not immediately life threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
Grade 4 – Life threatening	Life threatening consequences; urgent intervention indicated
Grade 5 – Fatal	Death

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

To make sure there is no confusion or misunderstanding between the terms "serious" and "severe", which are not synonymous, the following note of clarification is provided. The term "severe" is often used to describe the intensity (severity) of a specific event (ie, mild, moderate,

or severe); the event itself, however, may be of relatively minor medical significance (eg, severe headache). This is not the same as "serious" which is based on the study participant/event outcome or action criteria associated with events that post a threat to a participant's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

7.1.3. Relationship to Investigational Product

The relationship of an AE to the investigational product should be determined by the Investigator according to the following definitions:

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

7.1.4. Unexpected Adverse Reactions

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

7.2. Adverse Event Reporting

7.2.1. General

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

Any participant who experiences an AE may be discontinued from study treatment at any time at the discretion of the Investigator. The Sponsor and the CRO's Medical Monitors must be notified of the study participant discontinuation.

Note: For urgent safety issues and questions, the study Medical Monitor can be contacted 24 hours a day, 7 days a week. Contact information is located in the study binder.

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, further diagnostic investigation). If the clinically significant laboratory abnormality is a sign of a disease or syndrome (eg, ALK and bilirubin 5 × the ULN associated with cholecystitis), only the diagnosis (eg, cholecystitis) needs to be recorded on the eCRF.

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

Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded 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 D. (*This note is included to support Study transition to Pfizer Pharmacovigilance processes and systems.*)

7.2.4. Preexisting Medical Conditions

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

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

7.2.5. Worsening of Sickle Cell Disease

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

7.2.5.1. Vaso-Occlusive Crisis

VOC is defined as a composite of acute painful crisis and/or ACS. In order 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/designee or site personnel within 24 hours of SAE awareness on the AE eCRF via the EDC system. In the event that the EDC system is not available, paper SAE report forms will be used to report the SAE and faxed or emailed to the Sponsor or designee. The information reported on paper SAE report form should be entered into the EDC once available.

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

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

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 its 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 CRO designee first knowledge of the event and follow-up information submitted within an additional 8 calendar days, or as otherwise required per local laws and regulations. All other SUSARs will be submitted within 15-calendar days of the Sponsor's or CRO designee first knowledge of the event. The Investigator is responsible for

notifying the local IRB or local 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 its designee within 24 hours of awareness. The Sponsor or its 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 designated Drug Safety CRO within 24 hours of awareness. The Investigator will discuss the risks and concerns of investigational agent exposure to a developing fetus and counsel the participant and/or pregnant partner (or ensure such counseling is provided).

Reported pregnancy of a participant or a participant's partner while participating in this study will be monitored for the full duration of the pregnancy, and/or followed through a definitive outcome (ie, birth, 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 an AE or SAE. Pregnancy complications such as spontaneous abortion/miscarriage and congenital anomalies are considered SAEs and must be reported as described in Section 7.3. Note: an elective abortion is not considered an SAE. Pregnancy and pregnancy outcomes must be reported on a Pregnancy Notification or Pregnancy Outcome Form, respectively, and sent to the Sponsor or designated Drug Safety CRO within 24 hours of the Investigator, designee, or site personnel learning of the pregnancy or pregnancy outcome.

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

Information regarding pregnancy testing (including definition of females of child-bearing potential) is provided in Section 5.8. 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 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 investigational agent 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:

1. Contact the study Medical Monitor within 24 hours.
2. Closely monitor the participant for any AEs/SAEs and laboratory abnormalities medically appropriate and follow up until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up.
3. Document the quantity of the excess dose as well as the duration of the overdose in the eCRF.
4. 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 for 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 criteria 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 10: 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 for 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 eCRF.

7.8. Data and Safety Monitoring Board

See Section 3.1.4 for information regarding the DSMB.

8. DATA ANALYSIS AND STATISTICAL PLANS

8.1. Endpoints

8.1.1. Primary Endpoint

The primary efficacy endpoint is the change from Baseline at 24 weeks in TAMMV arterial cerebral blood flow, as measured by TCD.

8.1.2. Secondary Endpoints

The secondary endpoints are:

- Change from Baseline in TCD flow velocity at Week 48 and Week 96
- Time to conversion to abnormal TCD flow velocity (≥ 200 cm/sec)
- Time to reversion to normal TCD flow velocity (< 170 cm/sec)
- Proportion of participants with TCD flow velocity reduction ≥ 15 cm/sec at Week 24, Week 48, and Week 96
- Change in Hb from Baseline at Week 24, Week 48, and Week 96
- Change in clinical measures of hemolysis (unconjugated bilirubin, % reticulocyte, absolute reticulocyte, and lactate dehydrogenase [LDH]) from Baseline at Week 24, Week 48, and Week 96
- Annualized incidence rate of reported VOCs

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8.1.4. Safety Endpoints

The safety endpoints include AEs, clinical laboratory assessments, and vital signs.

8.1.5. Pharmacokinetic Endpoints

The endpoint is whole blood and plasma voxelotor PK as evaluated by PPK analysis using nonlinear mixed effects modeling.

8.2. Sample Size

The sample size is planned to provide sufficient statistical power for the primary efficacy analysis and for a robust safety database. In addition, the number of events required to assess secondary efficacy endpoint, eg, percentage conversion to abnormal TCD category, is also considered.

For the primary endpoint (change from Baseline in TCD flow velocity [cm/sec]), assuming equal allocation across treatment groups and a common variance, an estimate of the number of participants in each of 2 treatment groups used the following assumptions in the power calculation:

- Targeted treatment effect: difference in mean change from Baseline in TCD flow velocity is 15 cm/sec
- Common standard deviation is 24 cm/sec
- A significance level of 5% (2 -sided)

Assuming a 20% drop out rate, a sample size of 112 participants per group provides > 95% power to detect the targeted treatment effect for the following hypothesis test using a Student's t-test:

$$H_0: \mu_1=\mu_2 \qquad \text{versus} \qquad H_A: \mu_1\neq\mu_2,$$

where μ_1 and μ_2 stand for mean change from Baseline in TCD flow velocity at Week 24 in voxelotor and placebo groups, respectively.

For the secondary efficacy endpoint of time to conversion to abnormal TCD category, assuming 35% of participants in the placebo group have experienced a TCD flow velocity > 200 cm/sec by Week 96, a hazard ratio of 0.5 between voxelotor group and placebo, a fixed follow up time of up to 96 weeks for each participant, and an overall 20% drop out rate, a total of 49 events is expected. This provides approximately 65% power for a log-rank test at a two-sided significance level of 5% and approximately 75% power at a two-sided significance level of 10% (PASS version 11).

8.3. Populations for Analysis

The following populations will be considered in the analysis of data. Assignment or exclusion of participants from the analysis populations will be performed prior to study unblinding.

Intent to Treat (ITT) Population: The ITT population includes all randomized participants. This is the primary analysis population for efficacy, demographics, and baseline characteristics data. Participants will be grouped according to the treatment group to which they are randomized.

Safety Population: All participants who receive at least 1 dose of study treatment will be included in the safety population. This is the primary analysis population for safety and exposure data. Participants will be grouped according to the study treatment they receive.

PK Population: The PK population will consist of all participants who receive active study drug and have at least 1 measured concentration at a scheduled PK time point after the start of dosing. If any participants are found to be noncompliant with respect to dosing or have incomplete data, protocol violations, or clinical events that affect PK, a decision will be made on a case-by-case basis as to their inclusion in the analysis. Participants in this population will be used for all PK summaries.

8.4. Efficacy Analysis

8.4.1. Efficacy Analysis

8.4.1.1. Primary Endpoint

The primary analysis of change in TCD flow velocity from Baseline to Week 24 will be performed using a mixed model for repeated measures (MMRM). Independent variables will include treatment, study visit, treatment by study visit interaction, and randomization stratification factors (ie, HU use, age, Screening TCD flow velocity, and geographic region). Within-subject variability will be modeled using an unstructured covariance matrix.

8.4.1.2. Secondary Endpoints

The secondary endpoints will be analyzed as described below.

Change from Baseline endpoints

Change in TCD flow velocity from Baseline to Week 48 and Week 96 will be analyzed with the same MMRM as described for the primary endpoint (change from Baseline in TCD flow velocity at Week 24). A single model will be fit incorporating data from all timepoints.

Change in Hb and clinical measures of hemolysis (unconjugated bilirubin, % reticulocytes, absolute reticulocyte, and LDH) from Baseline at Week 24, Week 48, and Week 96 will be analyzed with a similar approach.

TCD responder endpoint

The TCD responder endpoint, defined as a TCD flow velocity reduction from Baseline $\geq$ 15 cm/sec at a given timepoint, eg, Week 24, Week 48, or Week 96, will be analyzed using an exact Cochran-Mantel-Haenszel (CMH) general association test stratified by the randomization stratification factors for the treatment difference between voxelotor and placebo.

A sensitivity analysis will be performed to assess TCD response definition with various TCD cutoff values in addition to the proposed 15 cm/sec.

Time to event endpoints

For time to conversion from conditional to abnormal TCD, the Kaplan-Meier method will be used to estimate the landmark rates and the associated 95% confidence intervals in the voxelotor and placebo groups at Week 24, Week 48, and Week 96. A log-rank test stratified for the randomization stratification factors will be used to test the difference between voxelotor and

placebo groups. A Cox proportional hazard model may be used to estimate the hazard ratio, as appropriate.

Time to conversion to abnormal will be calculated as the number of weeks from the date of randomization to the date of TCD assessment when a TCD flow velocity ≥ 200 cm/sec is first observed. For participants who withdraw from the study without conversion to abnormal or who reached analysis data cutoff date without TCD flow velocity reaching abnormal range, their time to conversion to abnormal will be censored at the date of last TCD assessment prior to study withdraw or analysis data cutoff date, as applicable.

Time to reversion from conditional to normal TCD will be analyzed using a similar approach.

Annualized incidence rate of VOCs will be calculated for each treatment group (total number of events)/(total subject-years). The associated 95% exact Poisson confidence limits will be reported. Mean cumulative functions for VOC incidences will be presented for each treatment group.

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8.4.2. Missing Data Handling

The analysis of change from Baseline in TCD flow velocity using MMRM will primarily be based on all available data. For participants discontinued from study treatment due to conversion to abnormal TCD flow velocity (Section 3.1.1), TCD values post study drug discontinuation will be imputed with last observation carried forward. Sensitivity analysis may be performed with various methods of missing data imputation, eg, multiple imputation, to assess the robustness of the MMRM analysis outcomes.

Participants who discontinue treatment prior to the endpoint visit due to conversion to abnormal TCD or stroke or TIA will be considered non-responders. Participants with a missing TCD flow

velocity value will be assessed for TCD response based on the most recent non-missing TCD flow velocity prior to the endpoint visit.

Detailed considerations of missing data handling are described in the statistical analysis plan (SAP).

8.4.3. Adjustment for Multiple Comparisons

To control the overall significance level (alpha) for the study at a 2-sided 5% level, a fixed sequence hierarchical test procedure will be used to formally evaluate voxelotor treatment effect in comparison to placebo at Weeks 24, 48, and 96. The primary and key secondary endpoints will be tested in the following order:

1. TCD flow velocity change from Baseline at Week 24
2. TCD flow velocity change from Baseline at Week 48
3. TCD flow velocity change from Baseline at Week 96
4. TCD flow velocity response rate at Week 24
5. Time to conversion to abnormal TCD flow velocity
6. Time to reversion to normal TCD flow velocity

Each endpoint will be tested at a 2-sided alpha level of 5%. Testing of endpoints subsequent to a non-significant result will be considered exploratory in nature. Final analysis of change from Baseline in TCD flow velocity at Week 24 will be performed when all randomized participants have reached the Week 24 visit or discontinued from the study early. No interim analysis is planned for the primary endpoint.

Final analysis of change from Baseline in TCD flow velocity at Week 48 will be performed when all randomized participants have reached the Week 48 visit or discontinued from the study early.

Final analysis of change from Baseline in TCD flow velocity at Week 96 will be performed when all randomized participants have reached the Week 96 visit or discontinued from the study early. Analysis of Week 48 or Week 96 endpoints based on earlier analysis timepoints will be considered exploratory.

Final analysis of time to conversion to abnormal TCD flow velocity and time to reversion to normal TCD flow velocity will be performed when all participants have completed the Week 96 visit or discontinued from the study early.

8.5. Safety and Tolerability Analyses

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

Adverse events will be classified according to the Medical Dictionary for Regulatory Activities (MedDRA). The incidence of TEAEs, defined as an event that occurs on or after Day 1 of study treatment or the worsening of a preexisting condition on or after Day 1 of study treatment, will be tabulated by System Organ Class (SOC), preferred term, severity, and relationship to study drug. Changes in laboratory parameters (hematology, serum chemistry, and liver function tests)

and vital signs (eg, BP, pulse, and body temperature) over time will be summarized descriptively.

SCD-related AEs will be collected and summarized separately (including VOC, ACS, osteonecrosis, priapism, etc.)

8.6. Pharmacokinetic Analyses

PPK analysis will consist of all participants who receive active study drug and have at least one measured concentration at a scheduled PK time point after the start of dosing. If any participants are found to be noncompliant with respect to dosing or have incomplete data, protocol deviations, or clinical events that affect PK, a decision will be made on a case-by-case basis as to their inclusion in the analysis. Participants in this population will be used for all PK summaries. PPK analyses using nonlinear mixed effects modeling will be performed to characterize voxelotor PK in plasma and whole blood. The influence of demographic covariates (such as body weight, height, age, gender) on voxelotor PK parameters (ie, CL and volume of distribution) will be investigated. If appropriate, the voxelotor PK data may be pooled with PK data from other studies.

Continuous variables will be descriptively summarized using mean, standard deviation (SD), coefficient of variation (CV%, as appropriate), median, minimum, maximum, and, as appropriate, geometric mean. Categorical variables will be descriptively summarized by presenting the number (frequency) and percentage in each category.

9. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

9.1. Source Data

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

The completed 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 case records (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 that 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 sub-Investigator listed on Form 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.

9.3. 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.

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 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 pre-study, 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 US FDA or country-specific regulations, and Investigator obligations are being fulfilled. The Sponsor may terminate study participation by a clinical study site if study-site personnel do not follow the protocol or GCPs. Additionally, individual participants may be excluded if a medical records review indicates protocol 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 a quality assurance audit(s) of this study. If such an audit occurs, the Investigator agrees to allow the auditor direct access to all relevant documents (eg, all participant records, medical records and eCRFs) and access to all corresponding portions of the office, clinic, laboratory, or pharmacy which may have been involved with the study. The Investigator will allocate his 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 the Sponsor's personnel to be present as an observer during a regulatory inspection, if requested.

10.3. Laboratory Accreditation

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

11. REGULATORY, ETHICAL, LEGAL, AND STUDY 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. Written Informed Consent

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 for the conduct of the study at named sites, for the protocol, the Participant ICF, and any other written information that will be provided to the participants and any advertisements that will be used. Written approval must be obtained prior to recruitment of participants into the study and shipment of investigational agent.

Proposed amendments to the protocol and documents must be discussed with the Sponsor and CRO, and then submitted to the IRB for approval as well as submitted to regulatory authorities for approval prior to implementation. Amendments may be implemented only after a copy of the local 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 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 EC to facilitate their continuing review of the study (if needed) and that the IRB is informed about the end of the study. Copies of the update, subsequent approvals and final letter must be sent to the Sponsor. The Investigator will inform the IRB/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. Informed Consent and Assent

It is the Investigator's responsibility to obtain written informed consent from the parent(s) of the participant and assent from the participant after adequate explanation of the objectives, methods, anticipated benefits, and potential risks of the study and before any study procedures are commenced. The parent or legal guardian should be given a copy of the ICF and the participant should be given a copy of the assent in their native language. The informed consent and assents processes should be recorded in the source documentation. The original copies of the signed and dated informed consent and assent must be retained in the institution's records and are subject to inspection by representatives of the Sponsor, or representatives from regulatory agencies.

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

11.11. 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.

11.12. 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/informed consent for the study will inform the patient of their rights and provide appropriate contact details of the Data Protection Officer.

11.13. 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 United States of America (USA) or an ICH region and until (1) there are no pending or contemplated marketing applications in the USA or an ICH region or (2) at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product under study. The Investigator/institution should retain participant identifiers for at least 15 years after the completion or discontinuation of study. Study participant files and other resource data must be kept for the maximum period of time permitted by the hospital, institution but not less than 15 years. These documents should be retained for a longer period, if required by the applicable regulatory requirements or by the Sponsor. The Sponsor must be notified with retention should the Investigator/institution are unable to continue with the maintenance of study participant files for the full 15 years. All study records must be stored in a secure and safe facility.

The Investigators must retain protocols, amendments, IRB/IEC approvals, copies of the Form FDA 1572 (or Investigator's Agreement if applicable), signed and dated consent 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 to the appropriate medical personnel responsible for the participant's participation in this clinical study. Data generated in this study will be available for inspection on request by the FDA or other government regulatory agency auditors, the sponsor, the sponsor's Medical Monitor (or designee), and their designated representatives, the IRB/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) are considered confidential and shall remain the sole property of the Sponsor. The Investigator agrees to use this information only in conducting this study and to not use it for other purposes without the Sponsor's prior written consent. The information developed in this clinical study will be used by the Sponsor in the clinical development of voxelotor and therefore, may be disclosed by the Sponsor as required, to authorized parties (including its corporate partners for the study drug, if any, and their designated representatives), other clinical Investigators, pharmaceutical companies, the FDA, and other government agencies. Any information, inventions, discoveries (whether patentable or not), innovations, suggestions, ideas, and reports made or developed by the Investigator(s) as a result of conducting this study shall be promptly disclosed to the Sponsor and shall be the sole property of the Sponsor. The Investigator agrees, upon the Sponsor's request and at the Sponsor's expense, to execute such documents and to take such other actions as the sponsor deems necessary or appropriate to obtain patents in the sponsor's name covering any of the foregoing.

13. INSURANCE AND FINANCIAL DISCLOSURE

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

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

14. PUBLICATION POLICY

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

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

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

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APPENDIX A. SCHEDULE OF ASSESSMENTS: SCREENING

Procedure	Screening Up to 35 Days Before Dosing
Informed Consent and Assent, as appropriate	X
Medical History	X
Full Physical Examination	X
Blood Pressure [a]	X
Pulse Rate [a]	X
Body Temperature [a]	X
Body Weight	X
Height	X
ECG (12-lead) [b]	X
Urinalysis	X
Serum Pregnancy Test (females, **post menarche**)	X
Hematology [c]	X
Serum Chemistry [d]	X
Fetal Hemoglobin	X
Hemoglobin A	X
Hemoglobin Genotype (if not already available) [e]	X
Malaria Test (performed at local laboratory) ONLY if there is clinical suspicion of active malaria infection [f]	X
Hepatitis and HIV Serology – only if clinically indicated	X
Iron Studies (ferritin, transferrin, and serum iron)	X
Transcranial Doppler (2 sonograms performed per TCD Manual)	X
Concomitant Medications	X
Adverse Events	X

Abbreviations: ECG, electrocardiogram; HIV, human immunodeficiency virus; TCD, transcranial Doppler.

[a] Vital signs (blood pressure, pulse rate, body temperature) will be measured after a participant has rested for at least 5 minutes in the supine or recumbent position, as age appropriate and feasible. A repeated measurement of any of the vital sign parameters will be taken within 5 minutes if the first reading is outside the normal range and deemed clinically significant.

[b] ECG (12-lead) will be recorded in the supine position after at least 5 minutes of rest.

[c] Hematology assessments include the following: red blood cells; hematocrit; hemoglobin; platelets; white blood cells with differential (basophils, eosinophils, neutrophils, monocytes, and lymphocytes); % and absolute reticulocytes; red blood cell distribution width; mean corpuscular volume; mean corpuscular hemoglobin concentration; hemoglobin A (Screening only); alpha thalassemia and haplotype (Week 8 Only).

[d] Chemistry assessments include the following: alanine aminotransferase; albumin; alkaline phosphatase; aspartate aminotransferase; bicarbonate; blood urea nitrogen; chloride; calcium; creatinine; glucose; lactate dehydrogenase; sodium; potassium; bilirubin (total, direct and indirect).

[e] Hemoglobin genotype can be based on previously documented medical records, ie, previous laboratory tests.

[f] Further tests will be conducted per the Investigator's discretion, at any point through the rest of the study, if there is a clinical suspicion of malarial infection.

APPENDIX B. SCHEDULE OF ASSESSMENTS: TREATMENT PERIOD TO END OF STUDY

	Treatment Period *Assessments are pre-dose unless otherwise specified*														EOS (28 days post last dose) [a]	ETD [b]
	D 1	Wk 2 (D 14)	Wk 4 (D 28)	Wk 8 (D 56)	Wk 12 (D 84)	Wk 16 (D 112)	Wk 24 (D 168)	Wk 28 (D 196)	Wk 36 (D 252)	Wk 48 (D 336)	Wk 60 (D 420)	Wk 72 (D 504)	Wk 84 (D 588)	Wk 96/ EOT		
Procedure	±7 days															
Check Inclusion/Exclusion Criteria	X															
Review Medical History	X															
Randomization	X															
Study Drug Administration	< < <							X			> > >					
Full Physical Examination	X	X					X			X				X	X	X
Abbreviated Physical Examination			X	X	X	X			X		X	X	X			
Blood Pressure [c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Heart Rate [c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Body Temperature [c]	X													X	X	X
CCI																
Urine Pregnancy Test, for females, **post-menarche** (if positive confirm with serum test) [d]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology [e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Alpha Thalassemia, Haplotype (when feasible)				X												
Serum Chemistry [f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum Erythropoietin	X				X		X			X		X		X	X	X
CCI																
PK Sample Collection	See Appendix C															
TCD (2 sonograms performed at each visit per TCD Manual) [h]				X		X	X	X	X	X	X	X	X	X	X	X
CCI																

Procedure	Treatment Period *Assessments are pre-dose unless otherwise specified*														EOS (28 days post last dose) [a]	ETD [b]
	D 1	Wk 2 (D 14)	Wk 4 (D 28)	Wk 8 (D 56)	Wk 12 (D 84)	Wk 16 (D 112)	Wk 24 (D 168)	Wk 28 (D 196)	Wk 36 (D 252)	Wk 48 (D 336)	Wk 60 (D 420)	Wk 72 (D 504)	Wk 84 (D 588)	Wk 96/ EOT		
		±7 days														
CCI																
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study Drug Dispensing (for Daily dosing until following study visit), Visit day dose to be taken at the study site.	X		X	X	X	X	X	X	X	X	X	X	X			

Abbreviations: CCI EOS, end of study; EOT, end of treatment; ETD, Early Treatment Discontinuation; NIH, National Institutes of Health; PK, pharmacokinetic; TCD, transcranial Doppler; Wk, week.

Note: During the treatment period, study assessments are to be performed pre-dose unless otherwise specified.

[a] An EOS visit will not be required if the participant rolls into an open-label extension study within 28 days (± 7 days) of the Wk96/EOT or ETD visit.

[b] If a participant is discontinued from study drug at a scheduled visit, that scheduled visit will become the ETD visit, and all required assessments for the ETD visit should be completed. If a participant is discontinued between scheduled visits, there is no requirement for an ETD visit. In addition, the EOS visit should be scheduled for 28 days (± 7 days) after the last dose of study drug.

[c] Vital signs (blood pressure, heart rate, body temperature) will be measured after a participant has rested for at least 5 minutes in the supine or recumbent position, as age appropriate and feasible. A repeated measurement of any of the vital sign parameters will be taken within 5 minutes if the first reading is outside the normal range and deemed clinically significant.

[d] Pregnancy tests will be performed on female participants who are post menarche. A positive urine pregnancy test at any time during the study requires confirmation via a serum pregnancy test.

[e] Hematology assessments include the following: red blood cells; hematocrit; hemoglobin; platelets; white blood cells with differential (basophils, eosinophils, neutrophils, monocytes, and lymphocytes); % and absolute reticulocytes; red blood cell distribution width; mean corpuscular volume; mean corpuscular hemoglobin concentration; alpha thalassemia and haplotype (Week 8 Only).

[f] Chemistry assessments include the following: alanine aminotransferase; albumin; alkaline phosphatase; aspartate aminotransferase; bicarbonate; blood urea nitrogen; chloride; calcium; creatinine; glucose; lactate dehydrogenase; sodium; potassium; bilirubin (total, direct and indirect).

CCI

TCD assessments should be performed prior to all other assessments on the scheduled study visit day, if feasible

[i] Will be implemented in each country when available (pending translation and cultural validation requirements). The taste and palatability questionnaire will be administered only to participants receiving the powder for oral suspension dosage form.

APPENDIX C. PHARMACOKINETIC SAMPLING SCHEDULE

Procedure	Day 1[a]		Wk 2 D14	Wk 4 D28	Wk 8 D56	Wk 12 D84	Wk 16 D112	Wk 24 D168	Wk 28 D196	Wk 36 D262	Wk 48 D336	Wk 60 D420	Wk 72 D504	Wk 84 D558	Wk 96/ EOT	EOS (28 days post last dose)	Early Treatment Discontinuation
	Sample 1	Sample 2	± 7 days														
PK Sample (Plasma and Whole Blood)	15 min to 2 h postdose	2 to 4 h postdose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose		
	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: D, day; EOS, end of study; EOT, end of treatment; PK, pharmacokinetic; Wk, week.

[a] Sample 2 should be collected at least 1 hour after Sample 1.

APPENDIX D. LIVER SAFETY: SUGGESTED ACTIONS AND FOLLOWUP 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 the 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 or 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 or ALT baseline values above the normal range: AST or 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 or ALT and total bilirubin for suspected Hy's law cases, additional laboratory tests should include albumin, creatine kinase, direct and indirect bilirubin, gammaglutamyl 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.

Document Approvals for GBT440-032 Protocol Amendment 4.0v4.0

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