CLINICAL STUDY PROTOCOL
GBT440-007

Study Number	**GBT440-007**
Study Title	A Phase 2a, Open-label, Single and Multiple Dose Study to Evaluate the Pharmacokinetics, Safety, Tolerability and Treatment Effect of GBT440 in Pediatric Participants with Sickle Cell Disease
Investigational Product	Voxelotor (previously GBT440)
IND Number	121,691
EudraCT Number	2016-004209-15
Sponsor	Global Blood Therapeutics, Inc. 181 Oyster Point Blvd. South San Francisco, CA 94080 United States of America
Study Director	PPD , PharmD PPD Global Blood Therapeutics, Inc. 181 Oyster Point Blvd. South San Francisco, CA 94080 United States of America Telephone: PPD (office) Email: PPD
Protocol Amendment 7	28 April 2021
Protocol Amendment 6	15 November 2019
Protocol Amendment 5	14 June 2018
Protocol Amendment 4	09 June 2017
Protocol Amendment 3	06 March 2017
Protocol Amendment 2	10 November 2016
Amendment 1	30 August 2016
Original Protocol	05 February 2016

CONFIDENTIALITY STATEMENT

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

STATEMENT OF APPROVAL AND COMPLIANCE

A Phase 2a, Open-label, Single and Multiple Dose Study to Evaluate the Pharmacokinetics, Safety, Tolerability and Treatment Effect of GBT440 in Pediatric Participants with Sickle Cell Disease

Protocol Amendment 7: 28 April 2021

SPONSOR APPROVAL

The signature of the Sponsor representative below represents that the above-referenced clinical trial is being conducted under FDA IND Number 121691 GBT440 for the treatment of sickle cell disease. This IND application is held by GBT. The protocol is being conducted in accordance with ICH GCP and all applicable federal, state and local regulations governing the conduct of this research, including DHHS 45 CFR Part 46, FDA 21 CFR Parts 50, 54, 56, 312 and 812. GBT will provide the Investigator with all information including safety information pertinent to the conduct of the study.

Sponsor Representative (Print):	
Signature:	
Date:	
Title:	

INVESTIGATOR APPROVAL

The signature of the Investigator below constitutes approval of this protocol as written and reflects the Investigator's commitment to conduct the study in accordance with the protocol, the applicable laws and regulations and in compliance with ICH GCP guidelines and the Declaration of Helsinki.

Principal Investigator (Print):	
Signature:	
Date:	

SYNOPSIS

Title	A Phase 2a, Open-label, Single and Multiple Dose Study to Evaluate the Pharmacokinetics, Safety, Tolerability and Treatment Effect of GBT440 in Pediatric Participants with Sickle Cell Disease
Protocol Number	GBT440-007
Sponsor	Global Blood Therapeutics, Inc. 181 Oyster Point Blvd. South San Francisco, CA 94080 United States of America
Study Drug	**Part A and Part B:** Voxelotor (previously GBT440) capsules or tablets: 300 mg, administered orally **Part C:** Voxelotor dispersible tablets: 100 and/or 300 mg, administered orally Voxelotor powder for oral suspension: 300, 400, 600, and/or 900 mg, administered orally **Part D:** Voxelotor powder for oral suspension 300, 400, 600, and/or 900 mg, administered orally Voxelotor dispersible tablets: 100 and/or 300 mg, administered orally
Part A Objectives	**Primary** • To characterize the pharmacokinetics (PK) of voxelotor in plasma and whole blood following a single dose in pediatric participants with sickle cell disease (SCD) **Secondary** • To evaluate the safety and tolerability of voxelotor following a single dose in pediatric participants with SCD
Part B Objectives	**Primary** • The primary objective is to assess the efficacy of voxelotor in pediatric participants with SCD as measured by improvement in anemia **Secondary** • To provide data on the electronic Patient-Reported Outcome (ePRO) measurement in establishing the longitudinal measurement properties of the PRO • To evaluate the effect of voxelotor on clinical measures of hemolysis • To characterize the PK of voxelotor in plasma, whole blood and red blood cells (RBCs) following multiple doses in pediatric participants with SCD

	• To evaluate the safety and tolerability of voxelotor following multiple doses in pediatric participants with SCD • To evaluate the effect of voxelotor on cerebral hemodynamics as assessed by transcranial Doppler (TCD) ultrasonography • To evaluate the effects of voxelotor on SCD symptom exacerbation and total symptom score (TSS) from the PRO measurement
Part C Objectives	**Primary** • To evaluate the effect of voxelotor on cerebral hemodynamics in pediatric participants with SCD with elevated or conditional TCD flow velocity as assessed by TCD ultrasonography **Secondary** • To evaluate the effect of voxelotor on clinical measures of anemia and hemolysis • To characterize the PK of voxelotor in plasma, whole blood and RBCs following multiple doses in pediatric participants with SCD • To evaluate the safety and tolerability of voxelotor following multiple doses in pediatric participants with SCD • To evaluate the proportion of participants with normal TCD flow velocity (< 170 cm/sec by nonimaging TCD or < 155 cm/sec by TCDi) at Week 48 • To evaluate the effect of voxelotor on the incidence of stroke and vaso-occlusive crisis (VOC)
Part D Objectives	**Primary** • To evaluate the safety and tolerability of voxelotor in pediatric participants with SCD aged 6 months to < 4 years **Secondary** • To characterize the PK of voxelotor in plasma, whole blood, and RBCs in pediatric participants with SCD aged 6 months to < 4 years • To evaluate the effect of voxelotor on clinical measures of anemia and hemolysis in pediatric participants with SCD aged 6 months to < 4 years • To evaluate the effect of voxelotor on the incidence of stroke and VOC in pediatric participants with SCD aged 6 months to < 4 years
Study Design	This study is a multicenter, open-label study to evaluate the safety, PK and efficacy of voxelotor in pediatric participants with SCD. This study consists of 4 parts, Part A, Part B, Part C, and Part D: **Part A** is a single dose PK study of voxelotor in pediatric participants with SCD aged 6 to 17 years. This study will involve 2 cohorts in this age range, Cohort 1 (12 to 17 years) and Cohort 2 (6 to 11years).

	Part B is a multiple dose, safety, PK and efficacy study of voxelotor in pediatric participants with SCD aged 12 to 17 years, inclusive. Participants' age for cohort assignment will be based on their most recent birthday. Upon completion of participation in Part A of the study, participants from Part A that are aged 12 to 17 years may be eligible for participation in Part B. Prior to proceeding from the 900 mg dose to the 1500 mg dose in Part B, the following data reviews will be conducted: A review of the PK data from at least 8 pediatric participants enrolled in Part B of Study GBT440-007, following at least 15 days of dosing with voxelotor 900 mg. Data and Safety Monitoring Board (DSMB) review of safety data from at least 8 pediatric participants enrolled in Part B of Study GBT440-007, following the completion of 28 days of dosing with voxelotor 900 mg to confirm acceptable safety and tolerability. DSMB review safety data from the first 6 adult participants 1500 mg dose level from Group 1 of Study GBT440-031 (HOPE study), following at least 28 days of dosing with study drug to confirm acceptable safety and tolerability. Sites will be notified when the above conditions have been met and enrollment in the 1500 mg cohort may begin. **Part C** will assess the safety, tolerability and PK, as well as the hematological effects and the effect on TCD flow velocity of voxelotor in pediatric participants with SCD who are 4 to 17 years of age. Up to 50 pediatric participants will be enrolled. • At least 30 participants must have a TCD velocity ≥ 140 and < 200 cm/sec by nonimaging TCD (≥ 125 and < 185 cm/sec by imaging transcranial Doppler [TCDi]) upon Screening AND • At least 20 participants must be between 4 to 11 years of age **Potential Modification**: To further characterize a potential effect on TCD data for those participants who have a TCD velocity ≥ 140 and < 170 cm/sec by nonimaging TCD (≥ 125 and < 155 cm/sec by TCDi) upon screening, approximately 20 participants may be added with a TCD velocity that falls within this range, depending on the emerging data. In this event, Part C will contain up to 70 pediatric participants. Participants' age will be the age at the time of assent/consent. During the 35-day screening period, participants will undergo TCD assessment and those who meet the criteria for TCD and the rest of the study eligibility criteria will be eligible for voxelotor treatment for up to 48 weeks. **Part D** will assess the safety, tolerability, and PK, as well as the hematological effects, of voxelotor in pediatric participants with SCD 6 months to < 4 years of age.

	Approximately 30 pediatric participants will be enrolled. • At least 10 participants must be 6 months to < 2 years of age.
Dose	**Part A:** Voxelotor 600 mg (two 300 mg capsules or tablets) single dose. **Part B:** Voxelotor 900 mg (administered as three 300 mg capsules or tablets) or 1500 mg (administered as five 300 mg capsules or tablets) once daily (QD) for 24 weeks. **Part C:** Participants who are between 12 and 17 years of age will receive voxelotor 1500 mg/day as dispersible tablets or powder for oral suspension for 48 weeks. Participants who are between 4 to 11 years of age will receive voxelotor 1500 mg/day EQUIVALENT based on body weight as dispersible tablets or powder for oral suspension for 48 weeks (see Table 3). **Part D:** Participants will receive voxelotor 1500 mg/day EQUIVALENT based on body weight as powder for oral suspension for 48 weeks (see Table 3). If powder for oral suspension is not available, dispersible tablets will be used.
Number of Participants	**Part A (Single-Dose PK Study)** • Approximately 6 pediatric participants (male or female) will be enrolled into the Part A 12 to 17 year age group (Cohort 1) • Approximately 6 pediatric participants (male or female) will be enrolled into the Part A 6 to 11 year age group (Cohort 2). Approximately 3 participants enrolled into the study will be between the ages of 6 and 8 years of age. Approximately 3 participants enrolled will be between the ages of 9 to 11 years of age. **Part B (Multiple-Dose PK, Safety, and Efficacy Study)** Approximately 36 pediatric participants (male or female) aged 12 to 17 years will be enrolled into Part B. • A minimum of 12 participants will be dosed with 900 mg. Enrollment at the 900 mg dose level may continue to further characterize the effect of multiple doses of voxelotor (not to exceed a total study size of approximately 36). A minimum of 6 of the participants at 900 mg will be 12 to 14 years old. • Upon a favorable review by the DSMB, dosing of a minimum of 6 participants at 1500 mg may commence (dependent on how many participants were enrolled at 900 mg, ie, not to exceed a total study size of approximately 36). Approximately half of the participants at 1500 mg will be 12 to 14 years old. **Part C (Multiple-Dose PK, Safety, and Efficacy Study)** Approximately 50 pediatric participants and up to 70 pediatric participants (male or female) aged 4 to 17 years will be enrolled into Part C. **Part D (Multiple-Dose PK, Safety, and Efficacy Study)**

	Approximately 30 pediatric participants aged 6 months to < 4 years will be enrolled into Part D.
Number of Centers	The study will be conducted at approximately 25 clinical sites
Duration of Study Participation	**Part A:** Up to 44 days from Screening to the final Follow-up visit **Part B:** Up to 233 days from Screening to the final Follow-up visit **Part C:** Up to 399 days from Screening to the final Follow-up visit **Part D:** Up to 399 days from Screening to the final Follow-up visit
Study Population	**Inclusion Criteria:** Participants who meet all of the following criteria will be eligible for study enrollment: 1. Male or female participants with homozygous hemoglobin SS (HbSS) or hemoglobin S beta^0 thalassemia (HbS β^0thal). 2. Age: • Part A – 6 to 17 years of age (Cohort 1 [12 to 17] and Cohort 2 [6 to 11] as defined in the Study Design) • Part B – 12 to 17 years of age • Part C – 4 to 17 years of age • Part D – 6 months to < 4 years of age 3. Hydroxyurea (HU) therapy: • Parts A, B, and C – A participant taking HU may be enrolled if the dose has been stable for at least 3 months with no anticipated need for dose adjustments during the study and no sign of hematological toxicity. • Part D – A participant taking HU may be enrolled if the dose has been stable for at least 1 month. Titration to the maximum tolerated dose (MTD) is allowed during the study. 4. Hemoglobin (Hb): • Part A – No restriction • Part B – Hb ≤ 10.5 g/dL • Part C – Hb ≤ 10.5 g/dL • Part D – Hb ≤ 10.5 g/dL 5. Written informed parental/guardian consent and participant assent has been obtained per institutional review board (IRB)/Ethics Committee (EC) policy and requirements, consistent with ICH guidelines. 6. Participants in Part B (only) of the study must complete a minimum of 14 days with ePRO to be enrolled. Investigator discretion will be used to determine if a participant who has previously been screen failed due to a lack of baseline ePRO data collection can be invited back for re-screening.

	7. 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. 8. Females of child-bearing potential are required to have a negative pregnancy test before the administration of study drug. 9. Sufficient venous access to permit collection of PK samples and monitoring of laboratory safety variables, in the opinion of the Investigator. 10. For Part C only, participants 12 to 17 years of age must have a TCD velocity ≥ 140 cm/sec by nonimaging TCD or ≥ 125 cm/sec by TCDi measured anytime during screening. **Exclusion Criteria:** Participants meeting any of the following exclusion criteria will not be eligible for study enrollment: 1. Any one of the following requiring medical attention within 14 days prior to signing the informed consent form (ICF): • Vaso-occlusive crisis (VOC) • Acute chest syndrome (ACS) • Splenic sequestration crisis • Dactylitis 2. Requires chronic transfusion therapy. 3. History of stroke or meeting criteria for primary stroke prophylaxis (history of two TCD measurements ≥ 200 cm/sec by nonimaging TCD or ≥ 185 cm/sec by TCDi). • For the potential modification, addition of approximately 20 participants enrolled in Part C, TCD ≥ 170 cm/sec by nonimaging TCD or ≥ 155 cm/sec by TCDi. 4. Transfusion within 30 days prior to signing the ICF. 5. Renal dysfunction requiring chronic dialysis or creatinine ≥ 1.5 mg/dL. 6. Hepatic dysfunction characterized by alanine aminotransferase (ALT) > 4× upper limit of normal (ULN) for age. 7. Clinically relevant cardiac abnormality, in the opinion of the Investigator, such as: • Hemodynamically significant heart disease, eg, congenital heart defect, uncompensated heart failure, or any unstable cardiac condition • An arrhythmic heart condition requiring medical therapy

	8. QTcF > 450 msec, congenital long QT syndrome, second or third degree heart block at rest (with the exception of asymptomatic Mobitz type I second degree heart block). 9. Received an investigational drug within 30 days or 5 half-lives, whichever is longer, of signing the ICF. 10. Heavy smoker (defined as smoking more than 10 cigarettes/day or its nicotine equivalent including e-cigarettes). 11. Unlikely to comply with the study procedures. 12. Other medical, psychological, or addictive condition that, in the opinion of the Investigator, would confound or interfere with evaluation of safety and/or PK of the investigational drug, prevent compliance with the study protocol, or preclude informed consent. 13. Participants who do not have a TCD window (Part B and C only) (ie, participants who are unable to have a TCD due to skull ossification). 14. For Part C only, prior participation in Part B. 15. Active symptomatic COVID-19 infection. In addition, for Part D only: 16. Body weight < 5 kg for 1 month prior to the screening visit and at the screening visit. 17. Any condition affecting drug absorption, such as major surgery involving the stomach or small intestine (prior cholecystectomy is acceptable). 18. 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). 19. Clinically significant bacterial, fungal, parasitic, or viral infection currently receiving or that will require therapy. • 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. • Known active hepatitis A, B, or C infection or human immunodeficiency virus (HIV)-positive. • Known active malaria.
Pharmacokinetic Assessments	**Part A (Single-Dose PK Study)** Plasma and whole blood samples for PK assessment will be collected as follows: Predose (within 60 minutes prior to dosing) and postdose starting on Day 1 at 2, 8, 24 hours (Day 2), 48 hours (Day 3), 96 hours (Day 5) and 168 hours (Day 8) and Day 15. **Part B (Multiple-Dose PK, Safety, and Efficacy Study)** Plasma and whole blood samples for PK assessment will be collected as follows:

	• Day 1 (following the first voxelotor dose): Predose (within 60 minutes before dosing) and postdose at 2, 8 and 24 hours (Day 2) following the first voxelotor dose • Week 2 (Day 14): Pre- or postdose • Week 4 (Day 28): Predose (within 30 minutes before dosing) and between 1 to 4 hours and between 6 to 8 hours postdose • Weeks 8, 12, 16, 20 and 24: Pre- or postdose **Part C (Multiple-Dose PK, Safety, and Efficacy Study)** Plasma and whole blood samples for PK assessment will be collected as follows: • Day 1: Postdose (within 15 minutes to 2 hours postdose) • Week 4 (Day 28), Week 8 (Day 56), Week 12 (Day 84), Week 16 (Day 112), Week 20 (Day 140), Week 24 (Day 168), Week 36 (Day 252) and Week 48 (Day 336): Predose **Part D (Multiple-Dose PK, Safety, and Efficacy Study)** Plasma and whole-blood samples for PK assessment will be collected as follows: • Day 1: within 15 minutes to 2 hours postdose • Week 2 (Day 14), Week 8 (Day 56), Week 12 (Day 84), Week 16 (Day 112), Week 24 (Day 168), Week 36 (Day 252), and Week 48 (Day 336): Predose **Parts A, B, C, and D** In Part A, noncompartmental methods will be used for determination of PK parameters. All PK parameters will be presented by individual listings and summary statistics (eg, mean, geometric mean, median, standard deviation, 95% confidence interval, coefficient of variation, minimum and maximum, and number of participants). Preliminary metabolite profiling of plasma and/or whole blood may be conducted. In Part B, RBC concentrations will be calculated from whole blood and plasma concentrations. The following plasma, whole blood and RBC PK parameters will be calculated for GBT440, as appropriate: Maximum observed concentration (C_{max}), Time of maximum concentration (T_{max}), Area under the concentration-time curve from zero (predose) to time of last quantifiable concentration ($AUC_{0\text{-}last}$), Area under the concentration-time curve from time zero (predose) extrapolated to infinity ($AUC_{0\text{-}inf}$), Area under the concentration-time curve from time zero (predose) to 24 hours ($AUC_{0\text{-}24}$) following the first and last day of dosing (Part B only), accumulation ratio (Part B), blood/plasma ratio, RBC/plasma ratio, terminal elimination half-life ($t_{1/2}$) and percent Hb occupancy. In Parts C and D, population PK modeling will be used to determine the whole-blood and plasma PK parameters of voxelotor in the study population.

	The PK parameters to be determined will include C_{max}, AUC, $t_{1/2}$, and percent Hb occupancy. Plasma and whole blood concentrations will be determined using validated liquid chromatography/ mass spectrometry (LC/MS) methods.
Safety Assessments	Participant safety and tolerability will be monitored during the study using standard measures, including physical examinations, vital signs (including blood pressure, pulse rate, body temperature, respiratory rate), 12-lead electrocardiograms (ECGs, collected in triplicate) (Parts A, B, and C only), clinical laboratory tests, concomitant medication usage, and adverse event (AE) monitoring. For Parts B and C, TCD measurements are being obtained to determine a preliminary treatment effect. However, abnormal values can indicate a safety concern and will be followed up as appropriate for standard clinical care.
Data and Safety Monitoring Board (DSMB)	An independent DSMB will monitor the safety and conduct of the trial. The DSMB membership will be composed of medical and statistical representatives. The DSMB may provide recommendations to the Sponsor regarding stopping the study or discontinuing a treatment arm or otherwise modifying the study design or conduct. The DSMB for this study will review: • Safety data from at least 8 pediatric participants enrolled in Part B of Study GBT440-007, following the completion of 28 days of dosing with voxelotor 900 mg to confirm acceptable safety and tolerability. • Safety data on a periodic basis as defined in the DSMB Charter. Sites will be informed of the DSMB recommendations only if the recommendations lead to changes in the study conduct. The composition, responsibilities, and other details of the DSMB will be described in a DSMB Charter as appropriate for each part of the study. Prior to proceeding from the 900 mg dose to the 1500 mg dose in Part B, the following DSMB review will also take place: • A review of safety data from the first 6 adult participants at the 1500 mg dose level from Group 1 from the HOPE Study, following at least 28 days of dosing with study drug, to confirm acceptable safety and tolerability. For Part D, enrollment of participants aged 2 to < 4 years will commence after DSMB review of safety, tolerability, and PK data from ≥ 12 participants from Part C of this study who weigh < 30 kg and were treated with voxelotor for ≥ 28 days. In addition, enrollment of participants aged 6 months to < 2 years will commence after Sponsor review of safety, tolerability, and PK data from ≥ 6 participants aged 2 to < 4 years who were treated with voxelotor for ≥ 28 days from Part D of this study or other GBT studies. The DSMB may be consulted if warranted.
Efficacy Assessments	Clinical measures of hemolysis are included under the hematology and chemistry assessments described above (Hb, reticulocyte count, erythropoietin, lactate dehydrogenase [LDH], indirect bilirubin). Clinical

	measures of hemolysis and TCD time-averaged mean of the maximum (TAMM) blood velocity will be assessed as measures of potential treatment effect. TCD measurements will be performed in Parts B and C of the study only.
Concomitant Medications and Restrictions	• Parts A, B, and C: HU therapy is allowed, provided that the dose and regimen have been stable for at least 3 months prior to signing the ICF and with no anticipated need for dose adjustments during the study. • Part D: HU therapy is allowed provided that the dose and regimen have been stable for at least 1 month prior to signing the ICF. Titration to the MTD is allowed during the study. • Voxelotor should be not be coadministered with sensitive cytochrome P450 (CYP) 3A4 substrates with a narrow therapeutic index. • Concomitant use of strong inducers of CYP3A4 with voxelotor is not allowed.
Statistical Methods	Sample Size The sample size was not selected based on statistical considerations but to determine preliminary safety, tolerability, PK, laboratory effects and treatment response of voxelotor in pediatric participants with SCD. **Part A:** A cohort size of approximately 6 participants for each age group, 6 to 11 years and 12 to 17 years, is based on a typical size for a single-dose PK study. **Part B:** Approximately 12 participants at 900 mg were selected to determine preliminary safety, tolerability, PK, laboratory effects and treatment response of voxelotor in pediatric participants with SCD. The number of participants may be increased to approximately 36 to further characterize the effect of multiple doses of voxelotor. Upon a favorable review by the DSMB, dosing of a minimum of 6 participants at 1500 mg may commence (dependent on how many participants were enrolled at 900 mg, ie, not to exceed a total study size of approximately 36). For the endpoint of change from baseline to Week 24 in Hb, power calculations assume normally distributed data, a mean treatment effect of 0.8 g/dL, with a standard deviation (SD) of 0.6 g/dL. For a 2-sided alpha = 0.05 and N = 12 participants, power exceeds 90% with a paired t-test to reject the null hypothesis of equality of post-treatment and baseline Hb means. The estimates of 0.8 and 0.6 g/dL for the mean and SD, respectively, are based on available Day 90 data from Cohorts 16 and (partial) 17 from the GBT440-001 study. **Part C:** Up to 50 pediatric participants who are 4 to 17 years of age with SCD will be enrolled. For the primary efficacy endpoint, change from baseline in TAMM TCD velocity at Week 48, a sample size of 30 participants achieves greater than 95% power to detect a mean difference of 15 cm/sec with an estimated sample standard deviation of 22 cm/sec using a paired t-test (2-sided) with a significance level (alpha) of 0.10.

	Part D: Approximately 30 pediatric participants with SCD who are 6 months to < 4 years of age will be enrolled. The sample size was selected to provide descriptive assessment of safety, tolerability, and PK effects of voxelotor in this younger age group with no formal statistical assumptions.
Study Endpoints: Part A	**Primary** • C_{max}, area under the concentration-time curve (AUC) from time 0 to the time of the last quantifiable concentration ($AUC_{0\text{-last}}$) and $AUC_{0\text{-inf}}$ of voxelotor in whole blood **Secondary** • C_{max}, $AUC_{0\text{-last}}$ and $AUC_{0\text{-inf}}$ of voxelotor in plasma and RBC • The time that C_{max} was observed (t_{max}), terminal elimination half-life ($t_{½}$) in RBC, whole blood and plasma, and percent Hb occupancy **Safety** • Treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) • Clinical laboratory tests, physical examination findings, vital signs, and ECGs
Study Endpoints: Part B	**Primary** • Change from baseline to Week 24 in Hb **Secondary** • Proportion of days with SCD symptom exacerbation during the first 24 weeks of treatment • Change from baseline to Weeks 21–24 in the sickle cell disease severity measure (SCDSM) TSS • Change from baseline to 12 and 24 weeks in LDH, indirect bilirubin, and reticulocyte count • Voxelotor PK to 24 weeks (C_{max}, $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, $AUC_{0\text{-24}}$, $t_{1/2}$, accumulation ratio, blood/plasma ratio, RBC/plasma ratio, if appropriate) and percent Hb occupancy • Change from baseline to 12 and 24 weeks in cerebral blood flow as measured by the TAMM TCD velocity **Safety** • TEAEs and SAEs • Clinical laboratory tests, vital signs, and ECGs

Study Endpoints **Part C**	**Primary Endpoint:** • Change from baseline to 48 weeks in cerebral blood flow as measured by the TAMM TCD velocity **Secondary Endpoints:** • Change from baseline to Weeks 24 and 48 in Hb, LDH, indirect bilirubin, and reticulocyte count • Change from baseline to 24 weeks in cerebral blood flow as measured by the TAMM TCD velocity • Time to initial Hb response, defined as change from baseline in Hb > 1g/dL • Whole blood and plasma voxelotor PK (C_{max}, AUC, and $t_{1/2,}$) and percent Hb occupancy • Proportion of participants with normal TCD flow velocity (< 170 cm/sec by nonimagining TCD or < 155 cm/sec by TCDi) at 48 weeks • Incidence of stroke and VOC during the study **Safety Endpoints:** • TEAEs and SAEs • Clinical laboratory tests, vital signs, and ECGs
Study Endpoints **Part D**	**Primary Endpoints:** • TEAEs and SAEs **Secondary Endpoints:** • Whole blood and plasma voxelotor PK (C_{max}, AUC, $t_{1/2}$, if appropriate) and occupancy • Change from baseline to Week 24 and Week 48 in Hb, LDH, indirect bilirubin, and reticulocyte count • Time to initial Hb response, defined as change from baseline in Hb > 1g/dL • Incidence of stroke and VOC during the study **Safety Endpoints:** • Clinical laboratory tests and vital signs

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LIST OF ABBREVIATIONS

Abbreviation	Description
ACS	acute chest syndrome
ADL	activities of daily living
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC_{0-24}	area under the concentration-time curve from time zero (predose) to 24 hours
AUC_{0-inf}	area under the concentration-time curve from time zero to extrapolated to infinity
AUC_{0-last}	area under the concentration-time curve from time 0 to the time of the last quantifiable concentration
AUC_t	area under the curve at designated time
BID	twice daily
BP	blood pressure
BUN	blood urea nitrogen
%CV	percent coefficient of variation
CFR	(United States) Code of Federal Regulations
C_{max}	maximum observed concentration
C_{min}	minimum drug concentration
CNS	central nervous system
CRA	clinical research associate
CRF	case report form
CRO	contract research organization
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DDI	drug-drug interaction
DSMB	data safety monitoring board
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EOS	end of study

Abbreviation	Description
FDA	(United States) Food and Drug Administration
GBT	Global Blood Therapeutics, Inc.
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GRAS	(United States) generally recognized as safe
Hb	hemoglobin
HbA	hemoglobin – adult
HbF	hemoglobin – fetal
HbS	sickle hemoglobin
HbS β^0 thal	sickle hemoglobin (S) and one beta thalassemia gene (β^0 thal)
HbSS	sickle hemoglobin with two sickle cell genes (SS)
Hct	hematocrit
HDPE	high density polyethylene
hERG	human ether-á-go-go-related gene
HPFH	hereditary persistence of fetal hemoglobin
hr	hour
HU	hydroxyurea
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IIG	(United States) inactive ingredient
INR	international normalized ratio
IRB	institutional review board
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
LDH	lactate dehydrogenase
LC/MS	liquid chromatography/ mass spectrometry
MedDRA	Medical Dictionary for Regulatory Activities (MedDRA®)
min	minimum
mL	milliliter
MRI	magnetic resonance imaging
MTD	maximum tolerated dose

Abbreviation	Description
NAUC	$AUC_{0-\infty}$ normalized by dose
NCI	National Cancer Institute
NC_{max}	C_{max} normalized by dose
NSAID	non-steroidal inti-inflammatory drug
PD	pharmacodynamics
PI	Principal Investigator
PK	pharmacokinetics
POP	population
PP	polypropylene
PR	pulse rate
PT	prothrombin time
PTT	partial thromboplastin time
QD	once daily
QT	QT interval
QTc	corrected QT interval
QTcF	QT corrected by Federica's formula
RBC	red blood cell
R State	relaxed, or high oxygenated, state of hemoglobin
SAE	serious adverse event
SCD	sickle cell disease
SCDS	sickle cell disease severity
SCDSM	sickle cell disease severity measure
SOP	standard operating procedure
$t_{1/2}$	terminal elimination half-life
TAMM	time-averaged mean of the maximum
T_{max}	time of maximum concentration
TCD	transcranial Doppler
TCDi	imaging transcranial Doppler
TEAE	treatment-emergent adverse event
TIBC	total iron-binding capacity
TSS	total symptom score
T State	tense, or low oxygenated, state of hemoglobin

Abbreviation	Description
ULN	upper limit of normal
VOC	vaso-occlusive crisis
Vss	volume of distribution at steady-state
WBC	white blood cell
WHO	World Health Organization

1. INTRODUCTION

1.1. Disease Background

Sickle cell disease (SCD), the first human disorder whose molecular basis was uncovered, is an autosomal recessive condition in which the glutamic acid residue normally found at the 6th position of the hemoglobin β-subunit (β^A) is replaced by a valine residue (β^S) (Itano, 1949) (Ingram, 1956). Functional hemoglobin tetramers that contain β^S subunits (HbS) bind and release oxygen analogously to normal hemoglobin tetramers (HbA). However, deoxygenated HbS tends to polymerize into long chains that damage and distort red cells. Polymerization of deoxyHb is the single trigger to all the pathological manifestations of SCD which is characterized by hemolytic anemia and vaso-occlusion leading to progressive end-organ damage with a clinical course of life-long pain, disability and early death.

Among the earliest manifestations of sickle-related organ damage is loss of splenic function in the first two years of life which places children at high risk of sepsis, particularly from encapsulated organisms such as *Streptococcus pneumoniae* and *Haemophilus influenzae*. Furthermore, renal concentrating ability is also impaired and signals the beginning of the decline in renal function that may lead to chronic renal failure and end-stage renal disease. Pain is also an important component of the disease and in young children, presents as dactylitis or hand-foot syndrome and can be the first sign of SCD. The most devastating complication of pediatric SCD is the development of central nervous system (CNS) events. This may present as overt stroke or silent strokes which are subclinical cerebral infarctions detected on brain magnetic resonance imaging (MRI). Almost 50% of the SCD population is pediatric (Farber, 1985) and approximately 11% of SCD patients have clinically apparent strokes before the age of 20 years. The risk of stroke is highest during the first decade, and it is most significant between ages 2 and 5, when it reaches 1.02% per year. In addition to overt strokes, another 17% to 22% of children suffer silent strokes which can produce significant neuropsychological deficits (Ohene-Frempong, 1998; Verduzco, 2009). The pathogenesis of stroke in children with SCD is complex and not fully resolved but in most cases involves occlusion or stenosis of the large intracranial arteries. Histopathology varies, but in general the pattern is one of smooth muscle proliferation with overlying endothelial damage and fibrosis (Rothman, 1986; Koshy, 1990). Smaller arterioles and capillaries show distention, thrombosis and vessel wall necrosis (Tuohy, 1997). Damaged, aberrant red cells adhere abnormally to the vascular endothelium and thereby trigger endothelial cell activation. Endothelial cell activation cascades into further disturbances, including a hypercoagulable state and abnormal vasomotor tone. The greater risk of stroke in young children with SCD may be explained by the higher cerebral blood velocity observed in this population (Powars, 2000).

Transcranial Doppler (TCD) ultrasonography can be used to assess cerebral blood flow and predict CNS events in SCD. TCD shows a higher mean intracranial arterial flow velocity in children with SCD (about 130 to 140 cm/sec) relative to those without SCD (about 90 cm/sec). The National Heart, Lung, and Blood Institute recommends chronic transfusion therapy for children with a TCD velocity exceeding 200 cm/sec based on the results of the STOP trial (Adams, 1998). TCD velocities of 170 to 200 cm/sec are designated as "conditional" and can progress into the abnormal range. Children in this category require close observation. Based on the results of the TWiTCH study, children on a chronic transfusion protocol for elevated TCD

velocity > 200 cm/sec for at least 12 months, can be safely transitioned to hydroxyurea (HU) (Ware, 2015).

Overall, the management strategies for SCD have evolved very slowly, and treatment of SCD remains a serious unmet medical need. In children, routine vaccination beginning in the 1970s contributed to the reduction in death rate as a result of infectious complication. Red blood cell (RBC) transfusions are administered to alleviate symptomatic anemia as well as for stroke treatment and prevention. Transfusions are costly, cumbersome, and not uniformly accessible and accompanied by risks, including iron overload (Wahl, 2009). HU therapy for SCD is limited by its side effect profile, poor patient adherence, variable patient responses, and concerns of long-term toxicity (Brandow, 2010). The only curative treatment is bone marrow transplantation from a histocompatible donor, an option that has been available since the 1990s (Platt, 2014), but bone marrow transplantation carries significant risks and is associated with a ~5% mortality rate (Nathan, 2013). Despite the current standard of care, including HU, blood transfusion, and palliative therapy for acute attacks, patients with SCD continue to suffer serious morbidity and premature mortality (Steinberg, 2003).

To date, no drugs have been approved that specifically target the underlying mechanism of SCD. The mechanism of action of HU involves a highly variable increase in the level of fetal hemoglobin (HbF) in a limited subset of RBCs (F-cells), resulting in limited protection from sickling. HbF is the predominant hemoglobin during fetal development and begins to decline in production shortly after birth. Synthesis of adult hemoglobin (HbA) begins shortly before birth and nears its adult proportion approximately 6 to 9 months postpartum. HbF powerfully inhibits the polymerization of deoxyHbS due to its high oxygen affinity as well as intrinsic structural characteristics that block polymer formation. Individuals who are homozygous for the β^S gene show no disease manifestations until late in the first year of life when the declining level of HbF no longer protects against deoxyHbS polymerization. The protective effect of HbF has been further validated by the observation that rare individuals who are compound heterozygotes for the β^S gene and a gene deletion resulting in persistent HbF expression (HbS-HPFH) do not have manifestations of SCD. HbS-HPFH is typically associated with 20-30% HbF levels distributed equally among erythrocytes (pancellular). In addition, a form of deletional HbS-HPFH has been described with pancellular HbF levels of 10% and few, if any, sickle cell-related events (Akinsheye, 2011). Taken together, the data from subjects with HbS-HPFH suggests that pancellular HbF of 20% to 30% prevents SCD and that levels as lows as 10% may be sufficient for protection.

Because oxyhemoglobin is a potent inhibitor of HbS polymerization, allosteric modification of hemoglobin to increase the proportion of oxyhemoglobin is a promising strategy to achieve inhibition of HbS polymerization in all RBCs (Noguchi, 1988). Prior experimental hemoglobin-modifying agents (BW12C and tucaresol) have provided proof of concept for the hemoglobin modification approach by demonstrating an increase in oxyhemoglobin and a decrease in clinical biomarkers of haemolysis (Keidan, 1986; Arya, 1996). Despite the increase in hemoglobin oxygen affinity, these drugs were well tolerated by healthy volunteers, and they remained well-compensated both at near maximal exercise and at rest with little change in basal oxygen consumption or resting heart rate (Nicholls, 1989; Ngo, 2012).

1.2. Voxelotor

Global Blood Therapeutics, Inc. (GBT) has developed voxelotor (previously GBT440), a small molecule allosteric modulator of hemoglobin oxygen affinity, for the treatment of SCD. On 25 November 2019, voxelotor was approved for use in the United States (US) under the tradename Oxbryta® by the Food and Drug Administration (FDA), and is indicated for the treatment of SCD in adults and pediatric patients 12 years of age and older.

The mechanism of action of voxelotor involves inhibition of HbS polymerization by increasing the affinity of hemoglobin for oxygen. Hemoglobin exists in both a relaxed (R) and a tense (T) state with high and low affinity for oxygen, respectively (Eaton, 1999). Upon binding to HbS, voxelotor effectively maintains a targeted fraction of HbS in the R state. Hemoglobin S molecules that are in the R (oxygenated) state are potent inhibitors of HbS polymerization and, conversely, only deoxygenated HbS is capable of polymerizing to create sickling of RBCs. Thus, HbS that is modified by voxelotor mimics HbF and prevents SCD manifestations by maintaining an R-state conformation and inhibiting deoxyHbS polymerization. Because voxelotor binds to the hemoglobin α chain, its effects on the oxygen equilibrium curves are expected to be similar in normal and sickle blood. Nonclinical data and data from prior experimental hemoglobin-modifying agents demonstrate that only a fraction of hemoglobin must be maintained in the R state in order to inhibit sickling. Based on data from prior experimental compounds and genetic data from high-affinity hemoglobin mutations in humans, 10% to 30% hemoglobin modification by voxelotor should be safely achievable in humans (Akinsheye, 2011; Arya, 1996; Gonzalez, 2009).

Voxelotor was rationally designed, based on knowledge of the chemical structure and mode of hemoglobin binding of prior hemoglobin-modifying agents in order to improve potency and specificity for hemoglobin (Safo, 2004; Abdulmalik, 2011). A medicinal chemistry program was used to optimize activity in *in vitro* hemoximetry and polymerization assays and to achieve a 1:1 stoichiometry of binding per hemoglobin tetramer compared to the 2:1 stoichiometry of prior compounds. Subsequently, voxelotor was found to be considerably more potent than all reported predecessor compounds in *in vitro* assays and to have sustained exposure following oral dosing in multiple animal species.

Voxelotor is currently in clinical studies exploring the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD) and treatment response in adolescent and adult SCD participants as well as in clinical pharmacology studies in healthy adult participants (refer to Section 1.4.2).

1.3. Rationale for Study

Mechanism-based therapies which may modify the course of SCD are urgently needed. Based on the observation that voxelotor has been well tolerated in adult and adolescent participants (14 May 2018 DSMB review), and has shown rapid, significant and sustained improvement in hemoglobin and hemolysis measures over that achieved on standard of care therapy including HU (Lehrer-Graiwer, 2015; Hoppe, 2017) (refer to Section 1.4.2), exploration of the effect of voxelotor in pediatric participants who are deemed to potentially have the greatest benefit from a disease-modifying therapy is warranted. TCD as a predictor of stroke risk is an endpoint of particular interest because stroke has high incidence and devastating consequences in pediatric patients with SCD. TCD velocity and stroke risk are inversely correlated with hemoglobin levels;

predictor of stroke risk in patients with SCD who have not had prior stroke or transient ischemic attack is hemoglobin level (Ohene-Frempong, 1998). For this reason, an important rationale for this study is to explore the potential benefit of voxelotor on reducing TCD velocity in pediatric participants with SCD.

This study proposes to evaluate the safety of voxelotor at exposures comparable to those studied in adults as well as to assess the effect on TCD flow velocity in the oldest pediatric age group of 12 to 17 years of age in participants who have a TCD window (Part B only). Part C will include participants with TCD flow velocity in the normal range (< 140 cm/sec by nonimaging TCD; < 125 cm/sec by imaging transcranial Doppler [TCDi]), elevated TCD flow velocity (140-169 cm/sec by nonimaging TCD; 125–154 cm/sec by TCDi), and conditional TCD flow velocity (170–199 cm/sec by nonimaging TCD; 155–184 cm/sec by TCDi) (DeBaun, 2014). The age range for Part C will include participants from 4-17 years old as this is the primary age range at risk for elevated TCD velocity and for which annual TCD screening is already performed based on standard of care guidelines. Guidelines recommend TCD screening beginning at 2 years of age (Expert Panel Report, 2014); however, this study will not require children younger than 4 years of age to undergo TCD due to the potential need for sedation. Based on the recent DSMB safety review of data from adults and adolescents with SCD treated with voxelotor in the ongoing Phase 3 study (GBT440-031) and adolescents with SCD treated in this study (GBT440-007), the DSMB supports treating children down to 2 years of age with voxelotor. Participants with unevaluable TCD at baseline (eg, due to a TCD window which is inadequate to obtain an accurate measurement) will not be eligible for enrollment.

The rationale for including the TCD endpoint includes the following: 1) based on the mechanism of action of voxelotor, a decrease in HbS polymerization should decrease RBC damage and resulting organ injury including cerebral vasculopathy (refer to Section 1.1), 2) elevated TCD correlates independently with low hemoglobin and elevated lactate dehydrogenase (LDH) (Bernaudin, 2008), and both of these abnormal biomarkers have shown improvement with voxelotor therapy. Interventional clinical studies with similar sample sizes have demonstrated reductions in TCD velocity with HU (Kratovil, 2006). The data from this age group will inform future development in pediatric participants as well as the development of voxelotor in the younger age groups. In particular, the PK data and effect on hematologic biomarkers will inform dose selection for pediatric participants in future clinical studies. In addition, it will be informative to compare the effect on hematologic markers after 24 weeks of voxelotor treatment (Part B) or after 48 weeks of voxelotor treatment (Part C) in pediatric participants in this study to effects observed in adults (GBT440-001 study), given that pediatric participants do not have as much cumulative bone marrow or renal damage, which can secondarily affect erythropoiesis. Lastly, the safety and efficacy of voxelotor treatment in the younger patient population aged 6 months to < 4 years will be evaluated in Part D.

The study will be conducted in 4 parts:

Part A will evaluate safety, tolerability, and PK of a single dose of voxelotor in pediatric participants aged 6 to 17 years.

Part B will assess the safety, tolerability, and PK, as well the hematological effects and the effect on TCD flow velocity of multiple doses of voxelotor for 24 weeks in pediatric participants aged 12 to 17 years.

Part C will assess the safety, tolerability, and PK, as well as the hematological effects and the effect on TCD flow velocity of multiple doses of voxelotor for 48 weeks in pediatric participants aged 4 to 17 years.

Part D will assess the safety, tolerability, and PK, as well as the hematological effects, of multiple doses of voxelotor for up to 48 weeks in pediatric participants aged 6 months to < 4 years.

1.3.1. Study Endpoints

1.3.1.1. Sickle Cell Disease Severity Measure and Patient-Reported Outcomes

A key objective of the sickle cell disease severity measure (SCDSM) was to develop an instrument (electronic Patient-Reported Outcome, ePRO) that measures pain exacerbations/pain crisis as experienced by participants, due to the lack of sensitivity that affects the traditionally defined vaso-occlusive crisis (VOC) endpoint. Specifically, VOC is a measure of healthcare utilization, not participant symptoms. Prior research has shown that VOC is the "tip of the iceberg" in that severe pain is very frequent, while VOC is rare, and that the vast majority of pain crisis days occur without utilization of medical care and thus, are not classified as VOC (Smith, 2008). This severity score is being included as a key secondary endpoint in Phase 3 Study GBT440-031, because it is anticipated to be a sensitive, specific and valid measure of SCD crisis pain and overall SCD severity, and therefore has greater power to detect an improvement in symptoms than VOC. The measure is being developed as a clinical outcomes assessment in accordance with FDA Guidance for Industry on Patient-Reported Outcome Measures (FDA Voice, 2014) and final qualification will be established using the analysis of in Phase 3 Study GBT440-031 (including longitudinal measurement properties, ability to detect change and use for endpoint analysis to establish clinical benefit). An ePRO device will be used in Part B (only) of this study to provide information relative to the secondary endpoints.

1.4. Summary of Relevant Nonclinical Data and Clinical Data

1.4.1. 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 oxygen tension, preventing in vitro sickling induced by a low oxygen environment, decreasing viscosity and improving deformability of RBCs in blood from patients with SCD. In addition, these studies show that voxelotor-modified Hb retains the Bohr Effect, which is the ability to augment oxygen delivery in metabolically active (low pH) tissues.

Collectively, these studies demonstrate that voxelotor potently increases 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; improves sickle blood viscosity, and deformability in vitro. In addition, voxelotor increases HbS-oxygen affinity and RBC half-life, while decreasing ex vivo sickling and reticulocyte count in a SCD mouse model.

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

1.4.2. Clinical Data

Details regarding GBT's clinical development program for SCD are available in the current version of the IB.

The Phase 3 double-blind, randomized, placebo-controlled study, GBT440-031, in which adults and adolescents (aged 12–17 years) received placebo, voxelotor 900 mg, or voxelotor 1500 mg is completed, and the results are summarized in the most current version of the voxelotor IB.

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

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

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

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

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

1.5. Dose Rationale

1.5.1. Dose Rationale for Single Voxelotor Doses to be Evaluated in Pediatric Participants (6 to 11 Years) in Part A

Single doses (300, 600, and 900 mg) of voxelotor for pediatric participants 6 to 11 years were simulated based on the adolescent POP PK model described in Table 2 to compare to pediatric participants' (6 to 11 years) exposures to adults administered a single dose of voxelotor 900 mg. The clearance in pediatric participants was assumed to be allometrically scaled to the adults using the following equation:

$$CL_{child} = CL_{adult} \times \left(\frac{WT_{child}}{70\ kg}\right)^{0.75} \times e^{\eta}$$

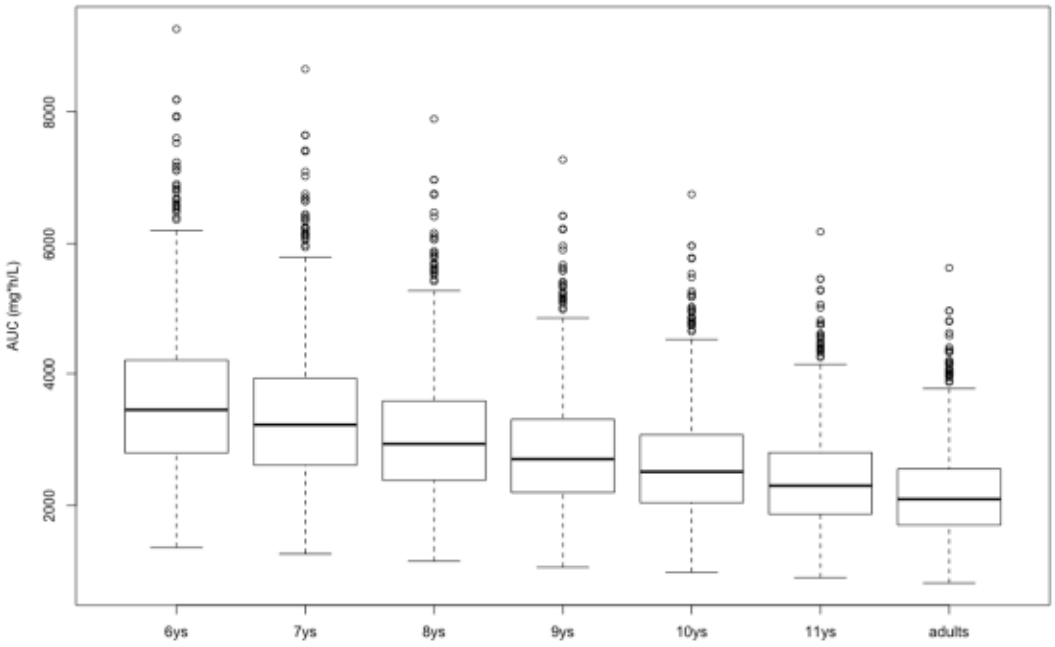
Where η is randomly sample value from normal distribution with 0 mean and variance equal to estimated CL variance in adult analysis. Centers for Disease Control and Prevention (CDC)

growth charts (http://www.cdc.gov/growthcharts) were used to assign pediatric participant's weights to age categories. Exposure was calculated according to the following equation:

$$AUC\left(\frac{mg \times h}{L}\right) = \frac{Dose\ (mg)}{CL\left(\frac{L}{h}\right)}$$

Simulated exposures following administration of 600-mg dose to children aged 6 to 11 years is compared to the simulated exposures in adults receiving 900-mg dose as shown in Figure 1.

Figure 1: Simulations of Voxelotor 900 mg in Adults and 600 mg in Children (6 to 11 years)



Abbreviations: AUC, area under the concentration-time curve; ys, years.

Based on these simulations, a single 600-mg dose in children 6 to 11 years is most comparable to a single 900-mg dose of voxelotor in adults. Thus, a single 600-mg dose in children aged 6 to 11 years was selected to be evaluated in Cohort 2 of Part A of this study.

1.5.2. Rationale for the Voxelotor Dose to be Evaluated in Part B

Based on the single dose safety and preliminary PK of voxelotor in adolescents, 900- and 1500-mg doses have been selected to be evaluated in Part B of GBT440-007. The doses of voxelotor 900 and 1500 mg to be evaluated in pediatric participants in Part B of GBT440-007 are the same as the doses selected to be evaluated in GBT440-031 (Group 1, Phase 3 study). The doses of voxelotor 900 and 1500 mg to be evaluated in Study GBT440-031 are based on the 20% to 30% optimal treatment target for efficacy based on genetic data (HbS/ hereditary persistence of fetal hemoglobin [HPFH]), genetic data for safety (high affinity Hb mutations that are well

tolerated with Hb oxygen affinity corresponding to Hb modification of 30% or higher), and on response and safety data from the Phase 1/2 study GBT440-001. To achieve optimal efficacy, HbS polymerization and sickling should be inhibited at all times, therefore the efficacy target of 20% to 30% is based on the minimum occupancy target based on minimum drug concentration (C_{min}) voxelotor blood levels.

- Individuals with the deletional form of HbS/HPFH have HbF levels in the range of approximately 20% to 30% with no clinical manifestations of SCD (Ngo, 2012). Because in vitro experiments have shown that voxelotor modified Hb delays HbS polymerization with similar potency to hemoglobin fetal (HbF), 20% to 30% is a reasonable target for voxelotor Hb occupancy.
- The target range of 20% to 30% Hb modification is supported by treatment response data from study GBT440-001. Participants with SCD treated in study GBT440-001 at 700 mg, 900 mg and 1000 mg per day achieved Hb occupancy in the range of approximately 20% to 30%. Hematologic responses (on hemolysis markers and sickle cell counts) were seen at all dose levels tested, and a dose response was evident for some hemolysis measures (bilirubin and reticulocytes). The greatest Hb increase was seen in cohorts dosed for 90 days. Participants who achieved > 20% Hb occupancy showed an improved hematologic response compared to those who did not. In addition, individual participants with dose reductions gave evidence of improved response while maintaining Hb occupancy > 20%.
- Exposure response analysis and PK/PD modeling of GBT440-001 data demonstrate a highly significant and liner relationship between exposure and improvement in hemolysis measures (ie, at the doses tested, a plateau on improvement in hemolysis measures has not been reached)
- Modeling and simulation predictions based on data derived from GBT400-001 for the hemolysis measures, indirect bilirubin, reticulocyte counts, LDH and Hb for voxelotor doses of 900 and 1500 mg are summarized in Table 1. To date, doses up to 1000 mg have been evaluated clinically. Since 1500 mg has not been previously evaluated, the exposure response analysis and simulations were based on an E_{max} model.

Modeling and simulation based on adult data predict that voxelotor 900- and 1500-mg doses will achieve voxelotor blood concentrations at C_{min} in the median participant equivalent to Hb modification of 16% (2.5th to 97.5th percentile 7% to 31%) and 26% (2.5th to 97.5th percentile 12% to 52%), respectively. Based on this prediction, 25% of participants at 900 mg, and 76% of participants at 1500 mg, will maintain > 20% Hb occupancy, respectively.

Table 1: Simulated Hemolysis Measures Outcomes Based on Data in Adult Participants (% Change from Baseline) for Voxelotor 900 and 1500 mg

Hemolysis Measure	Dose of Voxelotor	
	900 mg	1500 mg
Bilirubin (%)	-47 (27–84)	-66 (51–78)[a]
Reticulocytes (%)	-53 (30–93)	-84 (61–94)[a]
LDH (%)	-30 (17–54)	-64 (37–84)[a]
Hemoglobin (%)	11.9 (6.7–21.1)	—[b]
Hemoglobin (change from baseline)[c]	1.06 (0.60–1.9)	—[b]

Abbreviation: LDH, lactate dehydrogenase.
Note: Values represent median (2.5th to 97.5th percentiles).
[a] Based on E_{max} model.
[b] The E_{max} model underestimated the change in Hb and cannot be used and the linear model may overestimate.
[c] Based on a Baseline Hb of 9 g/dL.

A population (POP) PK model was developed for adolescents using the same model structure (2-compartment model with first order absorption) as the adult POP PK model. Voxelotor PK parameters were estimated and compared to the adult values. Overall, all major (eg, clearance, volume) PK parameters for the whole blood voxelotor are projected to be similar (Table 2) between adult and adolescent participants indicating that there is no significant difference between these two participant populations. Based on these data, the same doses are recommended for adolescents and adults.

Table 2: Parameter Estimates From the Whole Blood Voxelotor Population PK Model (Adults Versus Adolescents)

PK Parameters	Voxelotor Whole Blood Adults (RSE %)	Voxelotor Whole Blood Adolescents (RSE %)
CL (L/h)	0.43 (5)	0.37 (13)
V (L)	21.4 (6)	15 (17)
KA (1/h)	0.34 (13)	0.19 (30)
Proportional error (%)	28 (8)	70 (8)
Additive error (ng/mL)	4.6 (41)	-

Abbreviations: CL, clearance; KA, absorption rate constant; RSE, relative standard error; V, volume of distribution.

1.5.3. Rationale for the Voxelotor Dose to be Evaluated in Children 4 to 11 Years Old in Part C and Children 6 Months to < 4 Years Old in Part D

Participants (aged 12 to < 18 years) in Part B received 1500 mg. Currently, participants in Part C are receiving voxelotor 1500 mg once daily or, if younger than 12 years of age or with weight < 40 mg, a 1500-mg equivalent once daily using a weight-based design (see Table 3). Participants in Part D will receive a 1500-mg equivalent once daily using a weight-based design (see Table 3).

Table 3: Voxelotor Weight-Based Doses Determined for Pediatric Participants

Population	Voxelotor Doses
	1500 mg-Equivalent Adult Dose
5 to < 10 kg	400 mg
10 to < 20 kg	600 mg
20 to < 40 kg	900 mg
≥ 40 kg	1500 mg

The doses of voxelotor to be evaluated in Parts C and D of this study are based on targeting clinical efficacy in adult and adolescent participants, combined with population PK (PPK) modeling, physiologically based PK (PBPK) modeling, and allometric scaling and are expected to provide exposures of voxelotor equivalent to exposures observed in adults and adolescents (Study GBT440-031) and adolescents (Study GBT440-007) following multiple doses of 1500 mg.

To estimate appropriate doses to be evaluated in pediatric participants (6 months to < 12 years) with SCD, multiple doses of voxelotor were simulated by weight group (10 to < 20 kg and 20 to < 40 kg). The dose simulations were based on a voxelotor whole blood PPK model, including data from adults, adolescents, and children age 6 to 11 years old. The model used the same model structure (2-compartment model with first-order absorption) as the adult PPK model. The clearance (CL) and central volume (Vc) were scaled allometrically (exponents of 0.75 for CL and 1 for Vc) based on participant weights sampled from age-stratified normal distributions for children with homozygous SCD (Thomas, 2000). Summary exposure metrics (AUC, $C_{max,ss}$, and minimum drug concentration $[C_{min}]_{,ss}$) in children (9 months to < 12 years) were compared to the interquartile range of exposures simulated for the equivalent dose in adolescent participants.

Weight-based groups were identified to target median exposures within the adolescent interquartile range. Based on simulations in the pediatric population, doses of 400, 600, and 900 mg, respectively, are supported to provide exposures similar to adolescent participants at 1500 mg. Participants with weights > 40 kg will receive the same dose as adolescent or adult participants.

1.6. Risk Assessment

Based on the mechanism of action of voxelotor and findings in the nonclinical safety toxicology studies, voxelotor could cause tissue hypoxia. In GLP toxicology studies, rats dosed for 28 days with ≥ 250 mg/kg/day demonstrated increased erythropoietin and red cell mass (hematocrit [Hct], RBC, or Hb) with extramedullary hematopoiesis and bone marrow hypercellularity. These findings are consistent with expected physiologic compensation to hypoxia, were well tolerated in the rat, were not considered adverse, and were reversible.

In prior clinical experience with other agents, no adverse reactions related to tissue hypoxia were reported at the highest tested doses of tucaresol administered in either healthy participants (maximum 40% Hb-modification) or participants with SCD (maximum 24% Hb -modification), or BW12C infusions in either healthy participants (maximum 40% Hb -modification) or participants with SCD (23% Hb modification) (Arya, 1996 ; Keidan, 1986; Nicholls, 1989; Rolan, 1995). Appropriate acute and chronic compensatory physiologic responses to tissue hypoxia were observed, including an increase in heart rate during moderate exercise and a slight increase in reticulocyte counts at high doses (Nicholls, 1989; (Rolan, 1995; Rolan, 1993). Importantly, healthy participants were well-compensated both at rest and at near maximal exercise with little change in resting heart rate (Nicholls, 1989). Potential tissue hypoxia can be monitored by hematology laboratory studies, erythropoietin levels, and cardiovascular parameters.

Gastrointestinal effects (primarily emesis, and soft or liquid feces) were observed in all species and were dose-limiting in dogs and monkeys. Gastrointestinal erosions, ulcers, or epithelial hyperplasia were observed at high doses in rats.

The most common AEs with an incidence of at least 20% were headache and diarrhea (Vichinsky, 2019). The majority of these TEAEs were Grade 1 or 2 in severity. The percentages of participants who had a Grade 3 event, a serious adverse event (SAE), and/or treatment discontinuation due to an AE did not differ substantially among the 3 treatment arms (1500 mg voxelotor, 900 mg voxelotor, or placebo).

In addition, the decline in erythropoietin levels suggest an improvement in oxygen delivery either by increase in hemoglobin or improvement in microvascular blood flow, or both (Vichinsky, 2019; Howard, 2019).

2. STUDY OBJECTIVES

2.1. Part A (Single Dose)

Part A of the study will include participants 6 to 17 years of age (inclusive). Part A will be divided into 2 cohorts in this age range, Cohort 1 (12 to 17 years) and Cohort 2 (6 to 11years).

2.1.1. Primary Objective:

- To characterize the PK of voxelotor in plasma and whole blood following a single dose in pediatric participants with SCD

2.1.2. Secondary Objective:

- To evaluate the safety and tolerability of voxelotor following a single dose in pediatric participants with SCD

2.2. Part B (Multiple Dose)

2.2.1. Primary Objective:

- The primary objective is to assess the efficacy of voxelotor in pediatric participants with SCD as measured by improvement in anemia

2.2.2. Secondary Objectives:

- To provide data on the ePRO measurement in establishing the longitudinal measurement properties of the PRO
- To evaluate the effect of voxelotor on clinical measures of hemolysis
- To characterize the PK of voxelotor in plasma, whole blood and red blood cells (RBCs) following multiple doses in pediatric participants with SCD
- To evaluate the safety and tolerability of voxelotor following multiple doses in pediatric participants with SCD
- To evaluate the effect of voxelotor on cerebral hemodynamics as assessed by TCD ultrasonography
- To evaluate the effects of voxelotor on SCD symptom exacerbation and total symptom score (TSS) from PRO measurement

2.3. Part C (Multiple Dose)

2.3.1. Primary Objective

- To evaluate the effect of voxelotor on cerebral hemodynamics in pediatric participants with SCD with elevated or conditional TCD flow velocity as assessed by TCD ultrasonography

2.3.2. Secondary Objective

- To evaluate the effect of voxelotor on clinical measures of anemia and hemolysis
- To characterize the PK of voxelotor in plasma, whole blood and RBCs following multiple doses in pediatric participants with SCD
- To evaluate the safety and tolerability of voxelotor following multiple doses in pediatric participants with SCD
- To evaluate the proportion of participants with normal TCD flow velocity (< 170 cm/sec by nonimaging TCD or < 155 cm/sec by TCDi) at 48 weeks
- To evaluate the effect of voxelotor on the incidence of stroke and vaso-occlusive crisis (VOC)

2.4. Part D (Multiple Dose)

2.4.1. Primary Objective

- To evaluate the safety and tolerability of voxelotor in pediatric participants with SCD aged 6 months to < 4 years

2.4.2. Secondary Objectives

- To characterize the PK of voxelotor in plasma, whole blood, and RBCs in pediatric participants with SCD aged 6 months to < 4 years
- To evaluate the effect of voxelotor on clinical measures of anemia and hemolysis in pediatric participants with SCD aged 6 months to < 4 years
- To evaluate the effect of voxelotor on the incidence of stroke and VOC in pediatric participants with SCD aged 6 months to < 4 years

2.4.3. Exploratory Objective

- To evaluate the effect of voxelotor on growth and development in pediatric participants with SCD aged 6 months to < 4 years

3. INVESTIGATIONAL PLAN

3.1. Study Design

This study is an integrated Phase 2a protocol consisting of 4 parts, Parts A, B, C, and D, which will explore single and multiple doses of voxelotor in pediatric participants with SCD. Pediatric participants who are 6 to 17 years of age will be included in Part A, 12 to 17 years of age in Part B, 4 to 17 years of age in Part C, and 6months to < 4 years of age in Part D.

3.1.1. Part A (Single-Dose Administration)

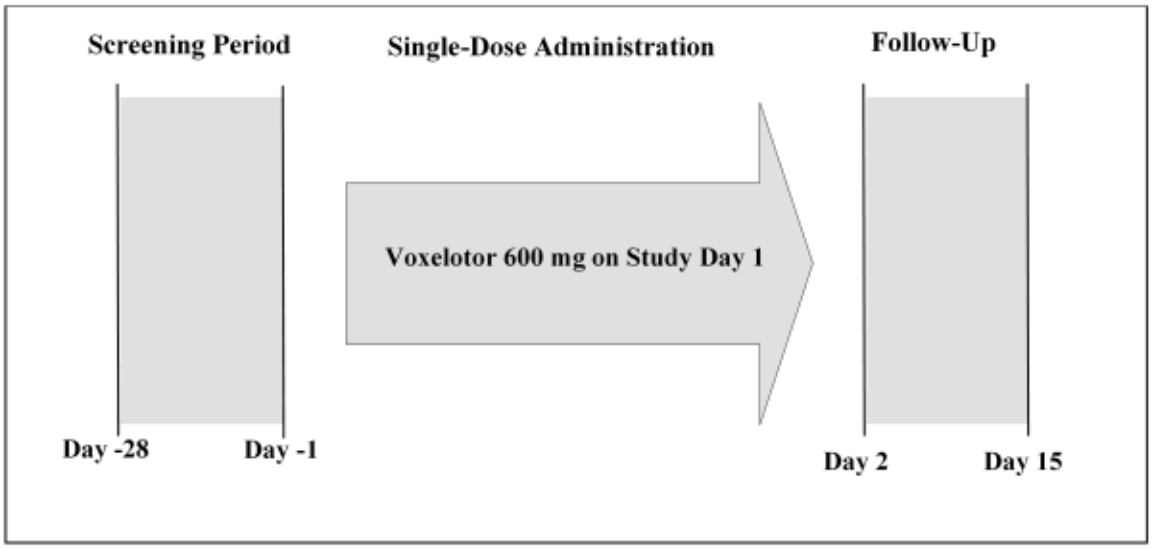
The Study Schematic for Part A is provided in Figure 2. Approximately 12 pediatric participants with SCD will participate in Part A.

- Approximately 6 pediatric participants will be enrolled into Cohort 1: age 12 to 17 years, inclusive.
- Approximately 6 pediatric participants will be enrolled into Cohort 2: age 6 to 11 years, inclusive. Approximately 3 participants enrolled into the study will be between the ages of 6 to 8 years of age. Approximately 3 participants enrolled will be between the ages of 9 to 11 years of age.

Participants' age will be the age at the time of the assent/consent.

Following a 28-day Screening Period, voxelotor will be administered orally on Day 1 and participants will undergo PK sampling as indicated in the Schedule of Assessments (Appendix 1).

Figure 2: Part A Study Schematic



Upon completion of participation of Cohort 1 (12–17 year age group) and Cohort 2 (6–11 year age group) in Part A (Single Dose) of the study, participants may be eligible for participation in

Part B or Part C. If a participant from Part A wishes to participate in Part B or Part C, they will be required to complete screening procedures for Part B or Part C as appropriate. This will include re-consenting of eligible participants for participation in Part B or Part C of the study. Part B participants will not be eligible for participation in Part C. Please consult the Interactive Response System manual for further information.

3.1.2. Part B (Multiple-Dose Administration)

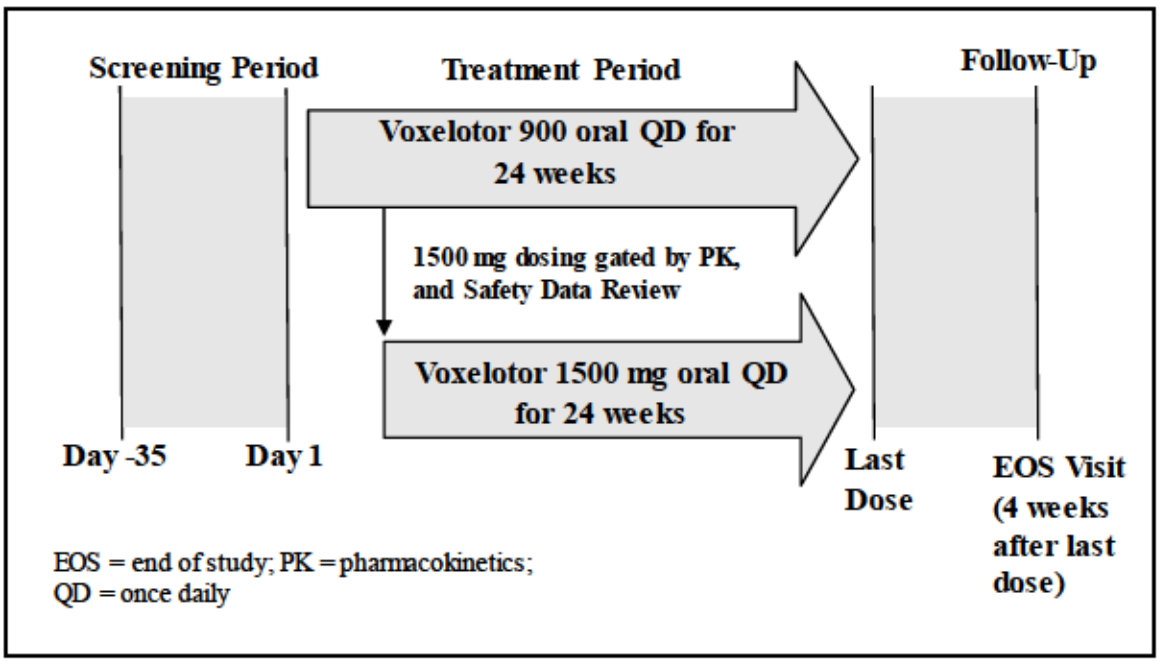
Upon satisfactory review of the safety and PK data in Part A as outlined in Section 3.5.1, Part B may commence. Approximately 36 pediatric participants with SCD who are 12 to 17 years of age will be evaluated.

- A minimum of 12 participants will be dosed with 900 mg. Enrollment at the 900 mg dose level may continue to further characterize the effect of multiple doses of voxelotor (not to exceed a total study size of approximately 36). A minimum of 6 of the participants at 900 mg will be 12 to 14 years old.
- Upon a favorable review by the DSMB, dosing a minimum of 6 participants at 1500 mg may commence (dependent on how many participants were enrolled at 900 mg, ie, not to exceed a total study size of approximately 36). Approximately half of the participants at 1500 mg will be 12 to 14 years old.

Participants' age will be the age at the time of the assent/consent.

Participants will receive multiple doses of voxelotor (up to 24 weeks). Following a 35-day Screening Period, pediatric participants will return to the clinic on Days 1, 2 and 8 and Weeks 2, 4, 8, 12, 16, 20, and 24 (refer to Appendix 3). On Study Day 1, participants will receive their first oral dose of voxelotor (Figure 3).

Figure 3: Part B Multiple-Dose Safety Study Schematic



3.1.3. Part C (Multiple-Dose Administration)

The Study Schematic for Part C is provided in Figure 4. Up to 50 pediatric participants who are 4 to 17 years of age with SCD will be enrolled.

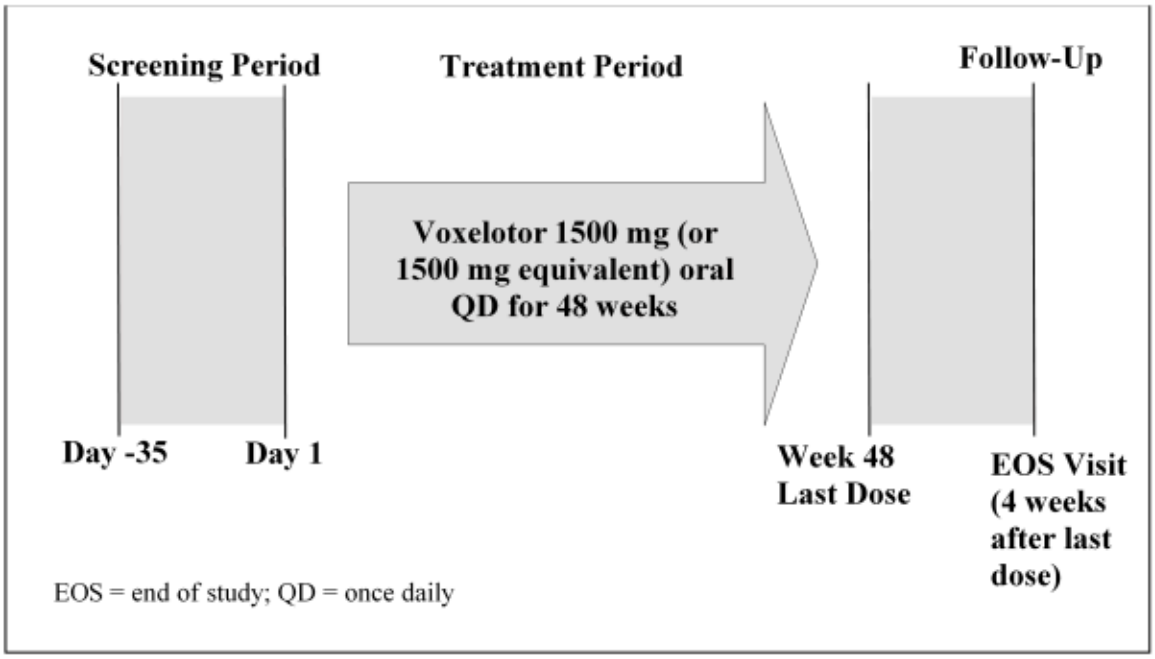
- At least 30 participants must have a TCD velocity ≥ 140 and < 200 cm/sec by nonimaging TCD (≥ 125 and < 185 cm/sec by TCDi) upon Screening AND
- At least 20 participants must be between 4 to 11 years of age

Participants' age will be the age at the time of the assent/consent.

During the 35-day screening period, participants will undergo TCD assessment and those who meet the criteria for TCD and the rest of the study eligibility criteria will be eligible for treatment and will receive multiple doses of voxelotor (up to 48 weeks).

Following completion of study treatment in Part C, eligible participants may be given the option to enroll in an open-label extension study (under a separate protocol) to receive voxelotor.

Figure 4: Part C Multiple-Dose Schema



Part C: Potential Modification

To further characterize a potential effect on TCD data for those participants who have a TCD velocity ≥ 140 and < 170 cm/sec by nonimaging TCD (≥ 125 and < 155 cm/sec by TCDi) upon screening, approximately 20 participants may be added with a TCD velocity that falls within this range, depending on the emerging data. In this event, Part C will contain up to 70 pediatric participants.

3.1.4. Part D (Multiple-Dose Administration)

The Study Schematic for Part D is provided in Figure 5. Approximately 30 pediatric participants who are 6 months to < 4 years of age with SCD will be enrolled.

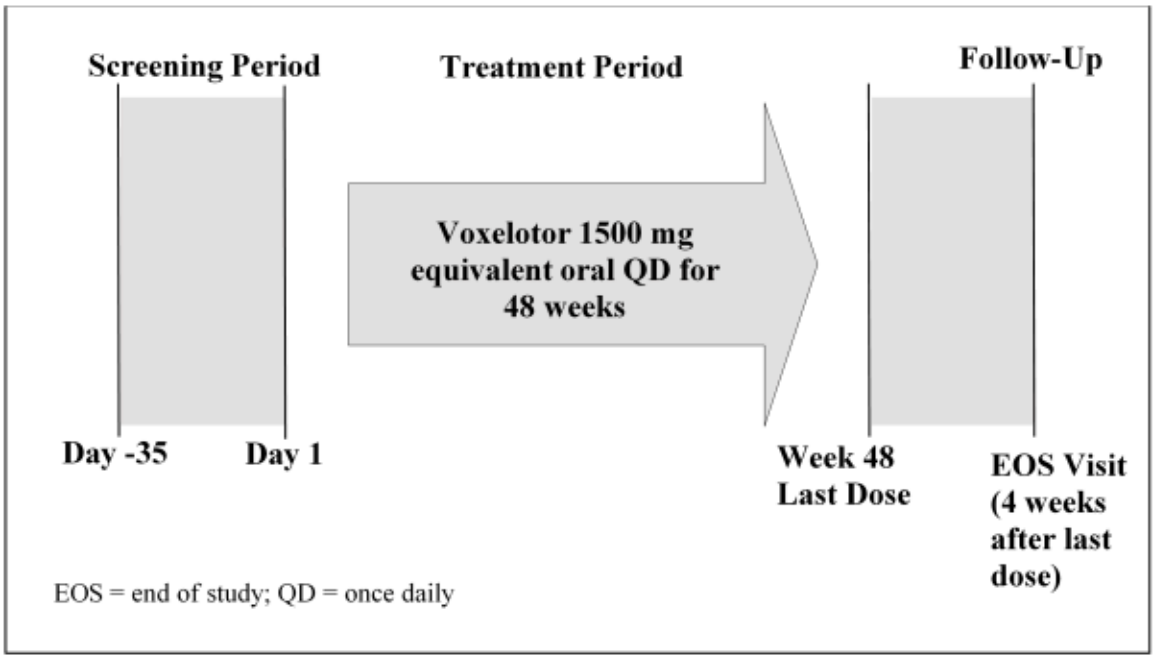
- At least 10 participants must be 6 months to < 2 years of age.

Participants' ages will be determined at the time of the assent/consent.

During the 35-day screening period, participants who meet the study eligibility criteria will be eligible for treatment and will receive multiple doses of voxelotor (for up to 48 weeks).

Following completion of study treatment in Part D, eligible participants may be given the option to enroll in an open-label extension study (under a separate protocol) to receive voxelotor.

Figure 5: Part D Multiple-Dose Study Schematic



3.2. Duration of Study

For Part A (single dose), participant participation is expected to last up to 44 days, including a 28-day Screening Period, one dosing day, and the 15-day follow-up visit.

For Part B (multiple dose), participant participation is expected to last approximately 33 weeks (including a 35-day Screening Period, a 24-week dosing period and an End-of-Study (EOS) visit approximately 4 weeks after the last dose of study drug).

For Part C (multiple dose), participation is expected to last approximately 57 weeks (including a 35-day Screening Period, a 48-week dosing period and an EOS visit approximately 4 weeks after the last dose of study drug for participants who do not enroll in the open-label extension study).

For Part D (multiple dose), participation is expected to last approximately 57 weeks (including a 35-day Screening Period, a 48-week dosing period, and an EOS visit approximately 4 weeks after the last dose of study drug for participants who do not enroll in the open-label extension study).

3.3. End-of-Study Visit

EOS procedures will be performed at the follow-up visit on Day 15 ± 1 day for Part A (single-dose portion), at 4 weeks ± 2 days after the last dose of study drug (the EOS visit) for Part B and Part C (multiple-dose portion), and at 4 weeks ± 7 days after the last dose of study drug (the EOS visit) for Part D (multiple-dose portion). For Parts C and D, the EOS visit will be performed for participants who do not enroll into the open-label extension study.

3.4. Early Termination Visit

Participants who terminate from the study early (early termination) will have EOS procedures performed at the time of discontinuation. Participants with ongoing clinically significant clinical or laboratory findings will be followed until the finding is resolved or medically stable; reasonable attempts will be made to follow-up with participants. The participant's participation will end once all study assessments and follow-up has been completed.

3.5. Ongoing Safety and Data Review

PK and safety data from study GBT440-007 will be reviewed on an ongoing basis.

The Sponsor will review PK and safety data from 6 participants enrolled in Part A (in the age group of 12 to 17 years) after the participants have undergone a minimum of 8 days of PK and safety data collection prior to proceeding to Part B of the study. In the event the PK exposure is not consistent with target exposure described in Section 1.5, the dose for Part B may be modified. Part B will not proceed until a formal review of the completed 8 days of PK and safety data of participants from Part A (in the age group of 12 to 17 years) occurs.

The Sponsor will also review PK and safety data from 6 participants enrolled in Part A (in the age group of 6 to 11 years) after the participants have undergone a minimum of 8 days of PK and safety data collection.

3.5.1. Part B Safety Requirements for Dose Escalation to the 1500 mg Treatment Arm

Prior to proceeding from the voxelotor 900 mg dose to the 1500 mg dose in Part B, the following will take place with data reviews confirming the selected dose to be generally well tolerated:

- A review of the PK data from at least 8 pediatric participants enrolled in Part B of Study GBT440-007 will take place, following at least 15 days of dosing with voxelotor 900 mg.
- DSMB review of safety data from at least 8 pediatric participants enrolled in Part B of Study GBT440-007 will take place, following the completion of 28 days of dosing with voxelotor 900 mg to confirm acceptable safety and tolerability.
- DSMB review of safety data from the first 6 adult participants at the 1500 mg dose level from Group 1 of Study GBT440-031 (HOPE study) will take place, following at least 28 days of dosing with study drug to confirm acceptable safety and tolerability.

The decision to proceed from the voxelotor 900 mg dose to the 1500 mg dose will be recorded in a dose decision document that will be signed by the GBT440-007 Study Director/Medical Monitor and relevant GBT personnel.

3.5.2. Part C

A DSMB monitors the safety and conduct of an ongoing Phase 3, GBT440-031 in adults and adolescents (aged 12–17 years) on a periodic basis. At a recent DSMB meeting safety data from 154 participants treated in GBT440-031 (randomized to placebo, 900 mg or 1500 mg) and 32 adolescents enrolled in this ongoing study, GBT440-007 (25 at 900 mg and 7 at 1500 mg) were reviewed. This safety review included 34 adolescents from GBT440-031. The DSMB agreed that the safety data supports continued treatment with both voxelotor 900 mg and voxelotor 1500 mg in GBT440-031 and in this study. The DSMB also agreed that the cumulative safety data from adults and adolescents supports the initiation of treatment of participants 4 to < 12 years old with voxelotor.

Safety data from children aged 4 to 11 years of age will be monitored on an ongoing basis by GBT. Additionally, the DSMB has reviewed safety data from Part C..

3.5.3. Part D

Safety data from children aged 6 months to < 4 years will be monitored on an ongoing basis by the Sponsor.

In addition, a DSMB may review safety data from Part D in consultation with the Sponsor if warranted (see Section 3.7).

3.6. Stopping Rules

Individual Participant Discontinuation

Dosing for any individual participant will be stopped if the participant experiences a SAE or a clinically significant nonserious AE, which in the opinion of the Principal Investigator or Sponsor's Medical Monitor, warrants discontinuation of the study for that participant's well-being.

Study Discontinuation

The occurrence of significant safety events will require that further dosing of participants be evaluated by the Medical Monitor to determine study discontinuation. Significant safety events may include those which are deemed to be related to study drug, have not been described in the voxelotor IB or otherwise represent a concern to the Investigator or the Sponsor.

3.7. Data and Safety Monitoring Board

An independent DSMB will monitor the safety and conduct of the trial. The DSMB membership will be composed of medical and statistical representatives. The DSMB may provide recommendations to the Sponsor regarding stopping the study or discontinuing a treatment arm or otherwise modifying the study design or conduct.

The DSMB for this study will review:

- Safety data from at least 8 pediatric participants enrolled in Part B of Study GBT440-007, following the completion of 28 days of dosing with voxelotor 900 mg to confirm acceptable safety and tolerability.
- Safety data on a periodic basis as defined in the DSMB Charter.

Sites will be informed of the DSMB recommendations only if the recommendations lead to changes in the study conduct.

The composition, responsibilities, and other details of the DSMB will be described in a DSMB Charter as appropriate for each part of the study.

Prior to proceeding from the 900 mg dose to the 1500 mg dose in Part B, the following DSMB review will also take place:

- A review of safety data from the first 6 adult participants at the 1500 mg dose level from Group 1 from the HOPE Study, following at least 28 days of dosing with study drug, to confirm acceptable safety and tolerability.

Part C: The DSMB reviewed safety data and agreed that the cumulative safety data from adults and adolescents enrolled in GBT440-031 and GBT440-007 supports the initiation of treatment of participants 4 to < 12 years old with voxelotor.

Part D: The DSMB has reviewed safety data from Part C and agreed that the cumulative data support the initiation of treatment in participants aged 2 to < 4 years. In addition, enrollment of participants aged 6 months to < 2 years will commence after Sponsor review of safety, tolerability, and PK data from ≥ 6 participants aged 2 to < 4 years who were treated with voxelotor for ≥ 28 days from Part D of this study or other GBT studies. The DSMB may be consulted if warranted.

3.8. End of Study

The end of study (EOS) is defined as the date when the last participant has completed all study procedures up to and including the final study/early termination visit as outlined in the Schedule of Assessments (Appendix 1 for Part A, Appendix 3 for Part B, Appendix 5 for Part C, and Appendix 7 for Part D).

3.9. Endpoints

3.9.1. Endpoints for Part A

3.9.1.1. Primary Endpoints

- Maximum observed concentration (C_{max}), area under the concentration-time curve from time zero to the time of the last quantifiable concentration ($AUC_{0\text{-last}}$), and area under the concentration-time curve from time zero extrapolated to infinity ($AUC_{0\text{-inf}}$) of voxelotor in whole blood

3.9.1.2. Secondary Endpoints

- C_{max}, $AUC_{0\text{-last}}$, and $AUC_{0\text{-inf}}$ of voxelotor in plasma and RBC

- The time of maximum concentration (T_{max}), terminal elimination half-life ($t_{1/2}$), percent Hb occupancy

3.9.1.3. Safety Endpoints

- TEAEs and SAEs
- Clinical laboratory tests, physical examination findings, vital signs, and ECGs

3.9.2. Endpoints for Part B

3.9.2.1. Primary Endpoints

- Change from baseline to Week 24 in Hb

3.9.2.2. Secondary Endpoints

- Proportion of days with SCD symptom exacerbation during the first 24 weeks of treatment.
- Change from Baseline to Weeks 21–24 in the SCDSM TSS; for each participant, the TSS will be computed as follows: The Baseline TSS is the average of the score during the 35-day Screening period; during the treatment period, the TSS is the average score each 4-week period on treatment. The 4-week periods are Weeks 1–4, 5–8, 9–12, 13–16, 17–20 and 21–24 (and follows similarly for participants whose participation exceeds 24 weeks).
- Change from baseline to Week 24 in LDH, indirect bilirubin and reticulocyte count
- Voxelotor PK (C_{max}, $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, $AUC_{0\text{-24}}$, $t_{1/2}$, accumulation ratio, blood/plasma ratio, RBC/plasma ratio, if appropriate), and percent Hb occupancy
- Change from baseline to 12 and 24 weeks in cerebral blood flow as measured by the time-averaged mean of the maximum (TAMM) TCD velocity

3.9.2.3. Safety Endpoints

- TEAEs and SAEs
- Clinical laboratory tests, vital signs, and ECGs

3.9.3. Endpoints for Part C

3.9.3.1. Primary Endpoint

- Change from baseline to 48 weeks in cerebral blood flow as measured by the TAMM TCD velocity

3.9.3.2. Secondary Endpoints

- Change from baseline to Weeks 24 and 48 in Hb, LDH, indirect bilirubin, and reticulocyte count

- Change from baseline to 24 weeks in cerebral blood flow as measured by the TAMM TCD velocity
- Time to initial Hb response, defined as change from baseline in Hb > 1g/dL
- Whole blood and plasma voxelotor PK (C_{max}, AUC, $t_{1/2,}$), and percent Hb occupancy
- Proportion of participants with normal TCD flow velocity (< 170 cm/sec by nonimagining TCD or < 155 cm/sec by TCDi) at 48 weekIncidence of stroke and VOC during the study

3.9.3.3. Safety Endpoints

- TEAEs and SAEs
- Clinical laboratory tests, vital signs, and ECGs

3.9.4. Endpoints for Part D

3.9.4.1. Primary Endpoints

- TEAEs and SAEs

3.9.4.2. Secondary Endpoints

- Whole blood and plasma voxelotor PK (C_{max}, AUC, $t_{1/2,}$ if appropriate) and percent Hb occupancy
- Change from baseline to Week 24 and Week 48 in Hb, LDH, indirect bilirubin, and reticulocyte count
- Time to initial Hb response, defined as change from baseline in Hb > 1g/dL
- Incidence of stroke and VOC during the study

3.9.4.3. Exploratory Endpoints

- Growth and development as assessed by change from baseline to Weeks 24 and 48 in height, weight, and head circumference

3.9.4.4. Safety Endpoints

- Clinical laboratory tests and vital signs

4. STUDY POPULATION

4.1. Inclusion Criteria

All participants must meet the following inclusion criteria:

1. Male or female with homozygous hemoglobin SS (HbSS) or hemoglobin S beta^0 thalassemia (HbS β^0 thal).
2. Age:
   - Part A – 6 to 17 years of age (Cohort 1 [12-17] and Cohort 2 [6-11] as defined in the Study Design)
   - Part B – 12 to 17 years of age
   - Part C – 4 to 17 years of age
   - Part D – 6 months to < 4 years of age
3. HU therapy:
   - Parts A, B, and C – A participant taking HU may be enrolled if the dose has been stable for at least 3 months with no anticipated need for dose adjustments during the study and no sign of hematological toxicity.
   - Part D – A participant taking HU may be enrolled if the dose has been stable for at least 1 month. Titration to the maximum tolerated dose (MTD) is allowed during the study.
4. Hemoglobin (Hb):
   - Part A – No restriction
   - Part B – Hb $\leq$ 10.5 g/dL
   - Part C – Hb $\leq$ 10.5 g/dL
   - Part D – Hb $\leq$ 10.5 g/dL
5. Written informed parental/guardian consent and participant assent has been obtained per institutional review board (IRB)/Ethics Committee (EC) policy and requirements, consistent with ICH guidelines.
6. Participants in Part B (only) of the study must complete a minimum of 14 days with ePRO to be enrolled. Investigator discretion will be used to determine if a participant who has previously been screen failed due to a lack of baseline ePRO data collection can be invited back for re-screening.
7. 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. Refer to Section 8.5.

8. Females of child-bearing potential are required to have a negative pregnancy test before the administration of study drug.
9. Sufficient venous access to permit collection of PK samples and monitoring of laboratory safety variables, in the opinion of the Investigator.
10. For Part C only: participants 12 to 17 years of age must have a TCD velocity ≥ 140 cm/sec by nonimaging TCD or ≥ 125 cm/sec by TCDi measured anytime during screening.

4.2. Exclusion Criteria

Any participant who meets one or more of the following criteria will be excluded from participation:

1. Any one of the following requiring medical attention within 14 days of signing the informed consent form (ICF):
   - Vaso-occlusive crisis (VOC)
   - Acute chest syndrome (ACS)
   - Splenic sequestration crisis
   - Dactylitis
2. Requires chronic transfusion therapy.
3. History of stroke or meeting criteria for primary stroke prophylaxis (history of two TCD measurements ≥ 200 cm/sec by nonimaging TCD or ≥ 185 cm/sec by TCDi).
   - For the potential modification, addition of approximately 20 participants enrolled in Part C, TCD ≥ 170 cm/sec by nonimaging TCD or ≥ 155 cm/sec by TCDi
4. Transfusion within 30 days prior to signing the ICF.
5. Renal dysfunction requiring chronic dialysis or creatinine ≥ 1.5 mg/dL.
6. Hepatic dysfunction characterized by alanine aminotransferase (ALT) > 4× upper limit of normal (ULN) for age.
7. Clinically relevant cardiac abnormality, in the opinion of the Investigator, such as:
   - Hemodynamically significant heart disease, eg, congenital heart defect, uncompensated heart failure, or any unstable cardiac condition.
   - An arrhythmic heart condition requiring medical therapy.
8. QTcF > 450 msec, congenital long QT syndrome, second or third degree heart block at rest (with the exception of asymptomatic Mobitz type I second degree heart block).
9. Received an investigational drug within 30 days or 5 half-lives, whichever is longer, of signing the ICF.
10. Heavy smoker (defined as smoking more than 10 cigarettes/day or its nicotine equivalent including e-cigarettes).

11. Unlikely to comply with the study procedures.
12. Other medical, psychological or addictive condition that, in the opinion of an Investigator, would confound or interfere with evaluation of safety and/or PK of the investigational drug, prevent compliance with the study protocol, or preclude informed consent.
13. Participants who do not have a TCD window (Part B and Part C only) (ie, participants who are unable to have a TCD due to skull ossification).
14. For Part C only, prior participation in Part B.
15. Active symptomatic COVID-19 infection.

In addition, for Part D only:

16. Body weight < 5 kg for 1 month prior to the screening visit and at the screening visit.
17. Any condition affecting drug absorption, such as major surgery involving the stomach or small intestine (prior cholecystectomy is acceptable).
18. 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).
19. Clinically significant bacterial, fungal, parasitic, or viral infection currently receiving or that will require therapy.
    - 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.
    - Known active hepatitis A, B, or C infection or human immunodeficiency virus (HIV)-positive.
    - Known active malaria.

5. STUDY PROCEDURES AND EVALUATIONS

5.1. Participant Screening

A signed and dated informed parental/guardian consent and participant assent must be obtained before any screening procedures or study-specific tests may be performed. Evaluations obtained as part of routine medical care and performed during the Screening Period may be used in place of the study-specific evaluations, provided they meet the time windows described below. Participants will acknowledge and agree to the possible use of this information for the study by giving informed consent.

All participants who sign consent 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.

The Screening Period for a particular participant commences at the point at which the participant undergoes the first study-specific screening assessment and must be completed within 28 days after signing the ICF for Part A, within 35 days after signing the ICF for Parts B, C, and D.

All study visits are to be scheduled relative to the Day 1 visit date.

5.2. Electronic Patient Reported Outcomes (ePRO) Screening

Participants in Part B (only) of the study will be given an ePRO device during the Screening Period. To establish a baseline ePRO Sickle Cell Disease Severity (SCDS) Measure, participants must complete a minimum of 14 days with ePRO to be enrolled. Investigator discretion will be used to determine if a participant who has previously been screen failed due to a lack of baseline ePRO data collection can be invited back for re-screening.

5.3. Clinical Assessments

Screening assessment must be conducted within 28 days prior to initiation of dosing for Part A, and within 35 days prior to initiation of dosing for Parts B, C, and D. Laboratory assessments, vital signs and physical examinations conducted on Day 1 predose may be conducted on Day -1. Refer to Appendix 1, Appendix 3, Appendix 5, and Appendix 7 for additional details.

Clinical assessments, including weight, vital signs, ECGs, AEs, and concomitant medications will be conducted at specified time points during the study (refer to Appendix 1, Appendix 3, Appendix 5, and Appendix 7). Vital signs data to be collected include supine systolic and diastolic blood pressure, pulse rate, respiration rate and temperature (in ℃). 12-lead ECGs will be collected in triplicate. Any other medical condition present at baseline should be followed during the study, and a change from the baseline status (intensity or frequency) should be reported as an AE if deemed clinically significant by the Investigator (refer to Section 9).

Height and weight will be recorded as outlined in Appendix 1,Appendix 3, Appendix 5, and Appendix 7. There is no weight restriction for Parts A, B, or C of the study. Height (in centimeters) and weight (in kilograms) should be measured with the participant's shoes off. Head circumference will be recorded in Part D as outlined in Appendix 7.

5.4. Safety Assessments

5.4.1. Clinical Laboratory Studies

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

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

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

All laboratory safety testing will be performed by the local laboratory.

Refer to Appendix 1, Appendix 3, Appendix 5, and Appendix 7, Schedule(s) of Study Assessments, for all time points.

The clinical laboratory tests that will be performed are listed in Table 4 for Parts A, B, and C, and in Table 5 for Part D.

Table 4: Parts A, B, and C: Clinical Laboratory Tests

Hematology	Serum Chemistry	Urine	Other
• Hematocrit • Hemoglobin • MCV • Platelet count • RBC count • RBC distribution width • Reticulocyte count (percent) • WBC count with differential (basophils, eosinophils, neutrophils, monocytes, lymphocytes) • Hb electrophoresis [d]	• Albumin • Alkaline phosphatase • ALT • AST • Bicarbonate • Bilirubin (total, direct, and indirect) • BUN • Calcium [c] • Chloride • Cholesterol [c] • CPK [c] • Creatinine • Ferritin [c] • GGT [c] • Glucose • Iron [c] • LDH • Magnesium [c] • Phosphorus [c] • Potassium • Serum erythropoietin • Sodium • TIBC [c] • Total protein • Transferrin [c] • Triglycerides [c] • Uric acid [c]	• pH • Specific gravity • Blood • Glucose • Protein • Ketones • Bilirubin • Urobilinogen • Nitrite • Leukocytes • Microscopic examination of sediment, if clinically indicated	• Coagulation panel (PT, PTT, INR) [a] • Pregnancy test [b]

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CPK, creatine phosphokinase; GGT, gamma-glutamyl transferase; Hb, hemoglobin; INR, international normalized ratio; LDH, lactate dehydrogenase; MCV, mean corpuscular volume; PT, prothrombin time; PTT, partial thromboplastin time; RBC, red blood cell; TIBC, total iron-binding capacity; WBC, white blood cell.

[a] Coagulation panel will only be collected at Screening in Parts A and B and not in Part C.

[b] Pregnancy tests will be performed for female participants who are post menarche. A serum β-human chorionic gonadotropin pregnancy test will be performed at Screening and urine pregnancy tests will be performed prior to the first dose of study drug and at other times during the study.

[c] These tests will be performed at Screening and more frequently if clinically indicated.

[d] Hb electrophoresis will be performed at Screening only.

Table 5: Part D: Clinical Laboratory Tests

Hematology	Serum Chemistry
• Hematocrit • Hemoglobin • MCV • Platelet count • RBC count • RBC distribution width • Reticulocyte count (absolute and percent) • WBC count with differential (basophils, eosinophils, neutrophils, monocytes, lymphocytes) • Hb electrophoresis[a]	• Albumin • Alkaline phosphatase • ALT • AST • Bicarbonate • Bilirubin (total, direct, and indirect) • BUN • Calcium[b] • Chloride • Creatinine • GGT[b] • Glucose • LDH • Magnesium[b] • Phosphorus[b] • Potassium • Serum erythropoietin • Sodium • Total protein

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; GGT, gamma-glutamyl transferase; Hb, hemoglobin; LDH, lactate dehydrogenase; MCV, mean corpuscular volume; RBC, red blood cell; WBC, white blood cell.
[a] Hb electrophoresis will be performed at Screening only.
[b] These tests will be performed at Screening and more frequently if clinically indicated.

5.4.2. Hemoglobin Genotype

The Investigator or designee will record the participant's historical Hb genotype.

5.4.3. Exploratory Assessments (Part C only)

Prior to implementation of Protocol Amendment 7, blood samples for the assessment of relevant measures of SCD pathophysiology (eg, RBC deformability, RBC phosphatidylserine, and dense cells) were collected at select study centers. Under Protocol Amendment 7, these assessments will no longer be performed.

5.4.4. Vital Signs

Vital signs will be measured at the time points specified in Appendix 1, Appendix 3, Appendix 5, and Appendix 7.

Blood pressure and pulse rate will be measured after the participant has been resting for at least 5 minutes in the seated or supine position. Systolic and diastolic blood pressure will be measured

using a calibrated manual or automatic blood pressure device. Pulse rate will be recorded by palpation of the radial pulse over a 60-second period or by the automated blood pressure device.

Body temperature will be measured (oral, tympanic, or axillary) using a digital thermometer and recorded in degrees Celsius.

Any screening or predose vital sign outside the normal range may be repeated once (in duplicate) at the discretion of the Investigator.

5.4.5. Electrocardiograms (ECGs)

Twelve-lead ECGs will be collected in triplicate (at least 1 minute apart) at each scheduled time point as specified in Appendix 1, Appendix 3, Appendix 5, and Appendix 7 after the participant has been resting in the supine position for at least 10 minutes. If the Screening triplicate ECGs are collected less than 24 hours before study drug dosing, the triplicate ECGs prior to dosing may be omitted.

ECGs will be collected at screening and as clinically indicated for participants enrolled in Part D.

5.4.6. Physical Examinations

Physical examinations will include general appearance; eyes, skin, and cardiovascular and respiratory system examinations; abdominal examination, and symptom-directed examination.

5.4.7. Transcranial Doppler (Parts B and C)

TCD results from the 3 years prior to signing ICF, if available, will be recorded as part of the Medical history for participants in Part C.

TCD TAMM blood flow velocity is also being obtained (in accordance with the TCD reference manual) as an assessment to determine treatment effect (refer to Section 5.5 and Appendix 3 and Appendix 5); however, abnormal values can indicate a safety concern and will be followed up as appropriate. Specifically, standard clinical practice for primary stroke prevention will be followed (eg, any TCD values ≥ 200 cm/sec by nonimaging TCD or ≥ 185 cm/sec by TCDi will require repeat TCD within 4 weeks. In the case of a second TCD value ≥ 200 cm/sec by nonimaging TCD or ≥ 185 cm/sec by TCDi, the site Investigator may offer the participant treatment with a stroke prevention protocol utilizing prophylactic transfusion as per standard clinical care if in place at that site's hospital or clinic).

5.5. Eligibility Assessment

Eligibility assessment will be conducted during Screening and also prior to receiving study drug on treatment Day 1. If a participant is found to meet inclusion/exclusion criteria at the screening visit, but then has a clinically significant change in status prior to administration of the first dose of study drug (for example is hospitalized for sickle cell crisis), the participant should be withdrawn from the study. Re-screening may be considered at the discretion of the Investigator and in consultation with the Sponsor. Participants who re-screen will have all assessments redone except for iron testing (Parts A, B, and C only).

5.6. Treatment Response Assessments

Clinical measures of hemolysis and TCD TAMM blood flow velocity (Parts B and C, Appendix 3 and Appendix 5) will be assessed as measures of potential efficacy. Details of requirements for TCD measurements will be described in a separate study manual. Hemolysis markers are included under the hematology and chemistry assessments described above (Hb, reticulocyte count, erythropoietin, LDH, indirect bilirubin).

5.7. Pharmacokinetic Assessments

5.7.1. Part A

Blood samples for plasma (if applicable) and whole blood PK assessments will be collected at the following time points listed below (refer to Appendix 2):

- **Day 1**
  - Predose (within 60 minutes prior to dosing)
  - Postdose at 2 hours (± 15 minutes) and 8 hours (± 30 minutes)
- **Day 2**
  - At 24 hours (± 1 hour)
- **Day 3**
  - At 48 hours (± 2 hours)
- **Day 5**
  - At 96 hours (± 2 hours)
- **Day 8**
  - At 168 hours (± 2 hours)
- **Day 15** (± 1 day)
- **Early Termination/Withdrawal**

Whole blood and plasma concentrations of voxelotor will be measured using a validated assay.

5.7.2. Part B

Blood samples for plasma (if applicable) and whole blood PK assessments will be collected at the following time points listed below (refer to Appendix 4):

- **Day 1**
  - Predose (within 60 minutes prior to dosing)
  - Postdose at 2 hours (± 15 minutes) and 8 hours (± 30 minutes)
- **Day 2**
  - Postdose at 24 hours (± 1 hour)

- **Week 2** (Day 14) (± 2 days)
  - Pre or postdose (± 2 hours of the dose)
- **Week 4** (Day 28) (± 3 days)
  - Predose (within 30 minutes prior to dosing)
  - Between 1 to 4 hours postdose
  - Between 6 to 8 hours postdose
- **Week 8** (Day 56) (± 3 days)
- **Week 12** (Day 84) (± 3 days)
- **Week 16** (Day 112) (± 3 days)
- **Week 20** (Day 140) (± 3 days)
- **Week 24** (Day 168) (± 3 days)
- **Follow-up**
- **Early Termination/Withdrawal**

5.7.3. Part C

Blood samples for plasma and whole blood PK assessments will be collected at the following time points listed below (refer to Appendix 6).

- **Day 1**
  - Postdose (within 15 minutes to 2 hours postdose)
- **Week 4** (Day 28) (± 3 days): Predose
- **Week 8** (Day 56) (± 3 days): Predose
- **Week 12** (Day 84) (± 3 days): Predose
- **Week 16** (Day 112) (± 5 days): Predose
- **Week 20** (Day 140) (± 5 days): Predose
- **Week 24** (Day 168) (± 5 days): Predose
- **Week 36** (Day 252) (± 5 days): Predose
- **Week 48** (Day 336) (± 5 days): Predose
- **Early Termination/Withdrawal**

5.7.4. Part D

Blood samples for plasma and whole-blood PK assessments will be collected at the following time points (refer to Appendix 8):

- **Day 1**
  - Postdose (within 15 minutes to 2 hours postdose)
- **Week 2** (Day 14) (± 3 days): predose
- **Week 8** (Day 56) (± 3 days): predose
- **Week 12** (Day 84) (± 5 days): predose
- **Week 16** (Day 112) (± 5 days): predose
- **Week 24** (Day 168) (± 5 days): predose
- **Week 36** (Day 252) (± 5 days): predose
- **Week 48** (Day 336) (± 5 days): predose
- **Early Termination/Withdrawal**

5.7.5. Concentration Measurements

Whole blood and plasma concentrations of voxelotor will be measured using validated assays.

The following PK parameters will be calculated, if appropriate:

RBC Concentration	RBC concentration of voxelotor (µg/mL) at each time point will be calculated from whole blood and plasma concentration data using the following equation: $C_{RBC} = \frac{C_b - [(1 - Hct) * C_p]}{Hct}$ Where C_b = whole blood concentration in µg/mL C_p = Plasma concentration in µg/mL Hct = Hematocrit value measured on or prior to PK sampling day
C_{max}	Maximum observed concentration for whole blood and plasma
t_{max}	The time that C_{max} was observed for whole blood and plasma
$AUC_{0\text{-last}}$	Area under the concentration-time curve from time 0 to the time of the last quantifiable concentration; calculated using the linear/log trapezoid rule for whole blood and plasma
$AUC_{0\text{-}24}$	Area under the concentration-time curve from time 0 to 24 hours for whole blood and plasma
$AUC_{0\text{-inf}}$	Area under the concentration-time curve from time 0 extrapolated to infinity; calculated as $AUC_t + C_t/\lambda_z$, where C_t is the last quantifiable concentration for whole blood and plasma
$t_{1/2}$	Terminal elimination half-life; calculated as $\ln(2)/\lambda_z$ for whole blood and plasma
Blood/Plasma Ratio	Ratio of blood $AUC_{0\text{-}24}$ to plasma $AUC_{0\text{-}24}$ at steady-state (Day 28)
RBC/Plasma Ratio	Ratio of RBC $AUC_{0\text{-}24}$ to plasma $AUC_{0\text{-}24}$ at steady-state (Day 28)
Accumulation Ratio	Ratio of $AUC_{0\text{-}24}$ at steady-state (Day 28) to $AUC_{0\text{-}24}$ on Day 1
%Hemoglobin Occupancy	Ratio of RBC concentration in mM at C_{max} on Day 28 multiplied by 20

The methodology for collection, handling, storage and shipping of whole blood and plasma PK samples will be provided in a separate laboratory manual.

5.8. Electronic Patient Reported Outcomes and eDiary (Part B only)

Section 5.8.1 and Section 5.8.2 describe the information that will be captured daily using the handheld study-specific device.

5.8.1. Electronic Patient Reported Outcome Sickle Cell Disease Severity Measure

A self-administered participant questionnaire of SCD core symptoms including pain severity, frequency and type as well as fatigue and mental acuity will be completed daily by participants in Part B (only) of the study.

5.8.2. eDiary of Study Drug Compliance

Participants in Part B (only) of the study will record whether or not they took their prescribed study drug daily.

5.9. Taste and Palatability Questionnaire (Part A Cohort 2, Part C, and Part D)

For Part A, Cohort 2: A Taste and Palatability Questionnaire will be provided and used to evaluate the pediatric participants' taste and palatability experience after taking the dose.

For Part C: For the dispersible tablets, a Taste and Palatability Questionnaire will be administered to the caregiver/legal guardian and/or children (≥ 6 years old) at Week 2 and Week 12 during the study.

For Part C: For the powder for oral suspension formulation, a Taste and Palatability Questionnaire will be administered to the caregiver/legal guardian and/or children (all ages) at the Transition Visit and at the next scheduled study visit.

For Part D: A Taste and Palatability Questionnaire will be administered to the caregiver/legal guardian at Week 2, Week 4, and Week 12 during the study.

5.10. Formulation Transition Visit (Part C)

A Transition Visit will be conducted to transition Part C participants who are receiving voxelotor as dispersible tablets to voxelotor powder for oral suspension, packaged as stick packs. A signed and dated updated informed parental/guardian consent and participant assent must be obtained at the Formulation Transition Visit if the participant has not signed the updated ICF for the transition visit. Assessments to be completed at this visit include the following: physical examination (as described in Section 5.4.6), weight, concomitant medication and AE review, PK sampling, in-clinic study drug dosing (powder for oral suspension), Taste and Palatability Questionnaire, and dispensing of study drug (packaged as stick packs).

This visit should occur within 30 days of Sponsor notification of availability of the powder for oral suspension formulation. Due to the COVID-19 impact on clinical sites, the transition visit may occur at a scheduled study visit.

A telephone follow-up visit should be conducted within 1 to 2 weeks after the transition to assess tolerability of the powder for oral suspension formulation.

5.11. 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. EARLY DISCONTINUATION OF TRIAL OR INDIVIDUAL PARTICIPANTS

6.1. Early Discontinuation of the Trial

The Sponsor has the right to terminate this study at any time and for any reason, including due to the incidence or severity of AEs in this or other studies indicating a potential health hazard to participants. Stopping rules are outlined in Section 3.6 of the protocol.

In any instance of early termination of the study, the Sponsor will notify, in writing, the Investigators and will specify the reason(s) for termination. The Investigator will inform the IRB or EC.

6.2. Early Discontinuation of Study Treatment

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

- Adverse Event(s)
- Withdrawal of consent
- Discretion of the Investigator
- Participant is lost to follow-up
- Participant is non-compliant
- Pregnancy

Participants will be informed that they are free to withdraw from the study at any time and for any reason. In addition, the Investigator may remove a participant from the study if, in the Investigator's opinion, it is not in the best medical interest of the participant to continue the study.

The date the participant is withdrawn from the study and the reason for withdrawal will be documented.

With the exceptions of 'withdrawal of consent' and 'lost to follow-up,' participants who are discontinued from study treatment for any of the aforementioned reasons will continue to participate in the study assessments. If a participant fails to return for scheduled visits, a documented effort (eg, at least 2 phone calls to the participant and a certified letter) must be made to determine the reason.

6.3. Early Discontinuation of Study Participation

Any participant (or his or her legally authorized representative) may withdraw their consent to participate in the study at any time without prejudice. The Investigator must withdraw from the study any participant who requests to be withdrawn. A participant's participation in the study may be discontinued at any time at the discretion of the Sponsor or the Investigator and in accordance with his or her clinical judgment. However, all efforts must be made to follow participants for the full duration of the study and to encourage all participants who ask to leave the study early to undergo the tests and evaluations listed for the early termination visit. If a

participant withdraws before completing the study, the reason for withdrawal is to be documented on the CRF.

6.4. Participant Replacement

Once dosed, participants who discontinue study drug due to an AE will not be replaced. Participants who discontinue study drug due to reasons other than an AE or who have non-evaluable PK samples may be replaced at the discretion of the Sponsor.

7. STUDY DRUG

7.1. Investigational Medicinal Product

7.1.1. Parts A and B

For participants who are ages 12 to 17 years old, the study may be performed with voxelotor common blend 300 mg capsules or voxelotor tablets. For participants who are ages 6 to 11 years old, the granulation from the voxelotor common blend capsules will be mixed with food and administered to the participant. Results are available from a relative bioavailability study which showed comparable PK of voxelotor 300 mg tablets with voxelotor capsules. These data show that the whole blood PK for voxelotor tablets and capsules are similar. The 90% confidence intervals for C_{max} and for AUC fall within the 80% to 125% (the acceptable range for bioequivalence).

7.1.2. Part C

Participants who are between 12 and 17 years of age will receive voxelotor, 1500 mg/day as dispersible tablets or powder for oral suspension.

Participants who are between 4 to 11 years of age will receive voxelotor, 1500 mg/day EQUIVALENT based on body weight as dispersible tablets or powder for oral suspension. The participant's weight at screening will be used to determine the initial treatment dose (Table 3).

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.

7.1.3. Part D

Participants who are 6 months to < 4 years of age will receive voxelotor 1500 mg/day EQUIVALENT based on body weight as powder for oral suspension. If powder for oral suspension is not available, dispersible tablets will be used. The participant's weight at screening will be used to determine the initial treatment dose (Table 3). The dose should be adjusted if the participant's weight increases or decreases and the investigator determines that the weight change is stable. The participant's weight will be measured according to the Schedule of Assessments (Appendix 7), and dose adjustments made as needed, as indicated in Table 8.

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.

7.1.4. Physical Description

Voxelotor is a synthetic small molecule bearing the chemical name 2-hydroxy-6-((2-(1-isopropyl-1H-pyrazol-5-yl) pyridin-3-yl) methoxy) benzaldehyde. The chemical formula is $C_{19}H_{19}N_3O_3$ and the molecular weight is 337.38.

7.1.5. Formulation

Voxelotor Capsules: Voxelotor 300 mg capsules contain granulation consisting of voxelotor drug substance along with several formulation excipients in Swedish orange, opaque, size 0, Hypromellose capsules. All the excipients used for the formulation are GRAS (Generally recognized as safe) materials and are also FDA IIG (Inactive Ingredients Guide) listed.

Voxelotor Tablets: The voxelotor 300 mg tablets contain voxelotor drug substance along with several formulation excipients. All the excipients used for the formulation are FDA Inactive Ingredients Database (IID) listed and compliant with European Regulations.

Voxelotor Dispersible Tablets: Voxelotor will be supplied as 100 or 300 mg dispersible tablets.

Voxelotor Powder for Oral Suspension: Voxelotor will be supplied as 300-, 400-, 600-, or 900-mg powder for oral suspension packaged as stick packs.

7.1.6. Packaging and Labeling

For Part A and Part B: Voxelotor drug product will be supplied to clinical sites in 30-count bottles. Voxelotor capsules will be packaged in 100 cc high density polyethylene (HDPE) bottles with induction sealed polypropylene child-resistant caps. Voxelotor tablets will be packaged in 60 cc HDPE bottles with induction sealed PP CR caps.

For Part C: Voxelotor dispersible tablets will be supplied to clinical sites in HDPE bottles with induction sealed polypropylene child-resistant caps. Voxelotor also will be supplied to clinical sites in a tamper-sealed carton containing stick packs. Additional details are provided in the Pharmacy Manual.

For Part D: Voxelotor will be supplied to clinical sites in a tamper-sealed carton containing stick packs.

If powder for oral suspension is not available, dispersible tablets will be used . Voxelotor as dispersible tablets will also be supplied to clinical sites in HDPE bottles with induction sealed polypropylene child-resistant caps. Additional details are provided in the Pharmacy Manual.

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

GBT or their representative will supply the packaged and labeled drug product to the investigational sites.

7.1.7. Storage and Handling Procedure

All study medications will be stored at controlled room temperature between 15°C to 25°C protected from light in the storage area of the investigational site pharmacy, which must be a secure, temperature-controlled, locked environment with restricted access.

No special procedures for the safe handling of voxelotor are required. The Sponsor will be permitted upon request to audit the supplies, storage, dispensing procedures and records.

7.2. Drug Accountability and Retention

In accordance with GCP, the Investigational Site will account for all supplies of voxelotor. Details of receipt, storage, assembly and return will be recorded.

The lot numbers for the IMP will be provided to the site by the supplier/manufacturer as soon as available.

The Investigator (or designee) will maintain an accurate record of the receipt of the IMP as shipped by the Sponsor (or designee), including the date received and storage conditions/location. In addition, an accurate drug disposition record will be kept, specifying the following: amount dispensed to each participant, the date of dispensation, the date of return, the number of capsules/tablets/powder for oral suspension stick packs returned, and destruction records. Participants will be instructed to keep the used capsule shells for study drug accountability purposes.

The Investigator must maintain accurate records of the receipt of all IMP shipped by the Sponsor or their representative, including but not limited to the date received, storage conditions/location, lot number, amount received, and the disposition of the IMP. A copy of this record will be returned to the Sponsor when the contents and condition of the IMP shipment have been verified.

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

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

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

8. DOSAGE AND TREATMENT ADMINISTRATION

8.1. Treatment Regimen

In Part A, participants will receive a single oral dose of voxelotor 600 mg (two 300 mg capsules or tablets).

In Part B, participants will receive voxelotor administered each day for 24 weeks (168 days). Voxelotor will be administered as 300 mg capsules or tablets.

In Part C, participants will receive voxelotor administered each day for 48 weeks (336 days). Participants who are between 12 to 17 years of age will receive voxelotor, 1500 mg/day as dispersible tablets or powder for oral suspension. Participants who are between 4 to 11 years of age will receive voxelotor 1500 mg/day EQUIVALENT as dispersible tablets or powder for oral suspension based on body weight. Either dispersible tablets (100 or 300 mg) or powder for oral suspension (300, 400, 600, or 900 mg) will be used based on Table 3.

In Part D, participants will receive voxelotor administered each day for 48 weeks (336 days). Participants will receive voxelotor 1500 mg/day EQUIVALENT as powder for oral suspension based on body weight. Voxelotor powder for oral suspension (300, 400, 600, or 900 mg) will be used based on Table 3. If powder for oral suspension is not available, dispersible tablets will be used and will be supplied as 100 or 300 mg tablets.

Instructions for administration of study drug for capsules (Part B):

- Voxelotor will be self-administered by the participant in the morning. When necessary, a parent or guardian may be present to assist with this process.
  - except on study visit days when the participant must not take study drug at home. It will be administered at the site after completion of appropriate assessments.
- Participants should take voxelotor with water or other non-alcoholic beverage.

Instructions for administration of study drug as dispersible tablets or powder for oral suspension (Parts C and D):

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

Participants must be instructed not to take study drug the day of their scheduled visits (refer to Appendix 1 for Part A, Appendix 3 for Part B, Appendix 5 for Part C, and Appendix 7 for Part D). Study drug will be administered at the site on these days, after completion of all the assessments scheduled for that visit.

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

8.2. Dose Modification for Parts B, C, and D

Participants should adhere to their assigned dose level. However, dose modification may be considered if warranted and as outlined below in Section 8.2.1, Section 8.2.2, and Section 8.2.3.

All instances of study drug modification (dose reduction, interruption, increase, or discontinuation) are to be captured in the participant research record and on the CRF, and the Medical Monitor should be notified within 72 hours. If the conditions/event leading to a dose modification have resolved, the original dose level should be resumed, unless in the judgment of the Investigator, this cannot be done safely.

8.2.1. Dose Frequency

Part B: Participants receiving voxelotor 900 mg will receive three 300 mg capsules or tablets administered orally, once daily. Participants receiving voxelotor 1500 mg will receive five 300 mg capsules or tablets, administered orally, once daily. If a participant misses a dose, the participant should resume normal dosing the next day (ie, the dose on the day after a day of a missed dose should not be increased or decreased).

Part C: Participants ages 12 to 17 years of age receiving voxelotor 1500 mg will receive dispersible tablets or powder for oral suspension administered orally, once daily. Participants ages 4 to 11 years of age receiving voxelotor 1500 mg equivalent will receive dispersible tablets or powder for oral suspension, administered orally, once daily. If a participant misses a dose, the participant should resume normal dosing the next day (ie, the dose on the day after a day of a missed dose should not be increased or decreased).

Part D: Participants receiving voxelotor 1500 mg equivalent will receive powder for oral suspension, administered orally once daily. If powder for oral suspension is not available, dispersible tablets will be used. If a participant misses a dose, the participant should resume normal dosing the next day (ie, the dose on the day after a day of a missed dose should not be increased or decreased).

8.2.2. Dose Modification Guidelines Parts B and C for Participants Aged 12 to 17 Years

Guidelines for reduction, hold, or permanent discontinuation of study drug are provided above, in Table 6 (study drug related AEs) and Table 7 (study drug related rash). The Medical Monitor should be notified of all dose modifications within 72 hours.

Table 6: Dose Modification Guidelines for Study Drug–Related Adverse Events (12-17 years)

Dose Reduction	
Event	**Recommended Action**
Grade 2 or higher AE that is (1) study drug related in the opinion of the Investigator, and (2) that 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 tablet If in the opinion of the Investigator, a Grade 2 AE has resolved to ≤ Grade 1, participant may resume study drug at the original dose. If, in the opinion of the Investigator, the AE poses a significant safety concern such that a dose hold is considered, the Investigator may consider a dose interruption (hold), 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
ALT ≥ 3x ULN if ALT WNL at baseline OR > 3 × ULN AND a ≥ 2-fold increase above baseline values if elevated ALT values at baseline In the absence of additional signs of compromised liver function such as elevated PT, PTT, INR, elevated conjugated bilirubin, jaundice, or hepatic pain.	**Study drug**: Confirm by repeat testing within 48-72 hours if possible, then repeat liver panel at least weekly until ALT levels improves. **Additional Actions**: If ALT levels continue to increase reduce by one tablet.and notify the Medical Monitor
ALT ≥ 5 × and < 8 × ULN (confirmed by repeat testing within 48-72 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 tablet. 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 test 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 or higher AE that is (1) study drug related in the opinion of the Investigator, and (2) that precludes continued dosing at the current 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. If the AE recurs or worsens, reduce dose by one tablet. Maximum dose hold is 5 continuous days. If, in the opinion of the Investigator, a longer dose hold is clinically needed, the Medical Monitor should be contacted for discussion.
Drug Discontinuation	
Event	**Recommended Action**
Grade 3 or higher study drug related SAE	**Study drug**: Discontinue study drug. If the Investigator considers that the participant would benefit from continuing treatment, the Medical Monitor should be contacted for discussion.
Grade 3 or higher study drug related AE that, at the discretion of the Investigator, warrants discontinuation of study drug (eg, has not improved or resolved after dose hold)	**Study drug**: Discontinue study drug. If the Investigator considers that the participant would benefit from continuing treatment, the Medical Monitor should be contacted for discussion.
Consider treatment discontinuation if: • **ALT > 8 ULN** **ALT > 3 × ULN or 2) ALT≥ 3x AND ≥ 2-fold increase above baseline values if elevated ALT values 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 48-72 hours if possible, and assess for 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; SAE, serious adverse event; ULN, upper limit of normal.

Table 7: Dose Modification Guidelines for Study Drug–Related Rash (12–17 years)

Dose Reduction	
Event	**Recommended Action**
Grade 1 or 2 Study Drug Related Rash	**Management:** Consider antihistamines, topical steroids as clinically indicated. **Study drug**: If rash does not resolve or improve to Grade 1 within 4 days after oral antihistamines and/or topical steroids, the dose may be reduced by one capsule/tablet (300 mg). The dose may be reduced further by one capsule/tablet (300 mg) if the event does not resolve. 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.
Dose Interruption (Hold)	
Event	**Recommended Action**
Grade 1 or 2 Study Drug Related Rash that Persists after Dose Reduction	**Management:** Consider antihistamines, topical steroids as clinically indicated. Consider a Dermatology Consult if clinically indicated. **Study drug**: If rash does not resolve or improve to Grade 1 on the lower dose, consider a dose hold until resolution or returns to Grade 1 or Baseline. Once rash has resolved or improved to Grade 1 dosing may be resumed at the reduced level. 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. 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.
Drug Discontinuation	
Event	**Recommended Action**
Grade 3 or Higher Study Drug Related Rash	**Study drug**: Discontinue study drug Consider a Dermatology Consult if clinically indicated

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; SAE, serious adverse event; ULN, upper limit of normal.

8.2.3. Dose Modification Guidelines for Part C Participants Aged 4 to 11 Years and for Part D Participants Aged 6 Months to < 4 Years

Participants should adhere to their dose level assigned at Day 1. However, dose modification will be conducted in accordance with the participants weight groups. If the participant gains or loses weight and moves from one weight-based dosing group to another during the study, adjustments in the drug dose will be made according to Table 8. Participant's weight will be checked as indicated in Appendix 5.

Table 8: Weight-Based Dose Groups

Weight	Voxelotor 1500 mg Dose Equivalent	Dose Reduction 1 - New Dose	Dose Reduction 2 - New Dose
5 to < 10 kg	400 mg	300 mg	200 mg [a]
10 to < 20 kg	600 mg	400 mg	300 mg
20 to < 40 kg	900 mg	600 mg	400 mg
≥ 40 kg	1500 mg	1200 mg	900 mg

[a] For participants who weigh 5 to < 10 kg and are taking voxelotor powder for oral suspension, only 1 dose reduction is possible.

Guidelines for reduction, hold, or permanent discontinuation of study drug are provided below, in Table 9 (study drug–related AEs) and Table 10 (study drug–related rash). The Medical Monitor should be notified of all dose modifications within 72 hours.

Table 9: Dose Modification Guidelines for Study Drug Related Adverse Events (6 Months–11 years)

Dose Reduction[a]	
Event	**Recommended Action**
Grade 2 or higher AE that is (1) study drug-related in the opinion of the Investigator AND (2) that 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, the 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 is WNL at baseline OR > 3× ULN AND a ≥ 2-fold increase above baseline values if elevated ALT values at baseline In the absence of additional signs of compromised liver function such as elevated PT, PTT, INR, elevated conjugated bilirubin, jaundice, or hepatic pain.	**Study drug**: May continue current dose until confirmed by repeat testing within 48-72 hours if possible, then repeat liver panel at least weekly until ALT levels improves. **Additional Actions**: If ALT levels continue to increase, reduce by one dose reduction and notify the Medical Monitor
ALT ≥ 5× and < 8× ULN (confirmed by repeat testing within 48-72 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 test 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 or higher AE that is (1) study drug -related in the opinion of the Investigator AND (2) that 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 AE resolves to ≤ 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. 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.
Drug Discontinuation	
Event	**Recommended Action**
Grade 3 or Higher, Study Drug-Related SAE	**Study Drug**: Discontinue study drug (see Section 6.2). If the Investigator considers that the participant would benefit from continuing treatment, the Medical Monitor should be contacted for discussion.
Grade 3 or higher study drug-Related AE that, at the discretion of the Investigator, warrants discontinuation of study drug (eg, has not improved or resolved after dose hold)	**Study drug**: Discontinue study drug (see Section 6.2). If the Investigator considers that the participant would benefit from continuing treatment, the Medical Monitor should be contacted.

Dose Reduction [a]	
Consider treatment discontinuation if: **ALT > 8× ULN** **ALT > 3× ULN or 2) ALT ≥ 3× AND ≥ 2-fold increase above baseline values if elevated ALT values 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 48-72 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; PT, prothrombin time; PTT, partial thromboplastin time; SAE, serious adverse event; ULN, upper limit of normal; WNL =within normal limits.
[a] For participants who weigh 5 to < 10 kg and are taking voxelotor powder for oral suspension, only 1 dose reduction is possible.

Table 10: Dose Modification Guidelines for Study Drug Related Rash (6 Months-11 years)

Dose Reduction [a]	
Event	**Recommended Action**
Grade 1 or 2 Study Drug Related Rash	**Management:** Consider antihistamines, topical steroids as clinically indicated. **Study drug**: If rash does not resolve or improve to Grade 1 within 4 days after oral antihistamines and/or topical steroids, the dose may be reduced by one dose reduction. The dose may be reduced by a second dose reduction if the event does not resolve. 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.
Dose Interruption (Hold)	
Event	**Recommended Action**
Grade 1 or 2 Study Drug Related Rash that Persists after Dose Reduction	**Management:** Consider antihistamines, topical steroids as clinically indicated. Consider a Dermatology Consult if clinically indicated. **Study drug**: If rash does not resolve or improve to Grade 1 following the second dose reduction, consider a dose hold until resolution or AE returns to Grade 1 or Baseline. Once rash has resolved or improved to Grade 1 dosing may be resumed at the reduced level (dose reduction 2 dose). 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. 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.
Drug Discontinuation	
Event	**Recommended Action**
Grade 3 or higher Study Drug Related Rash	**Study drug**: Discontinue study drug Consider a Dermatology Consult if clinically indicated

Abbreviations: AE, adverse event.
[a] For participants who weigh 5 to < 10 kg and are taking voxelotor powder for oral suspension, only 1 dose reduction is possible.

8.3. Treatment of Overdose

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

Guidelines for reporting a suspected treatment overdose are provided in Section 9.8.

8.4. 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 enrolled participants, all administered concomitant medications from signing the informed consent until 30 days after the participant's last dose of study drug, must be recorded in the participants' case report form (CRF) (medication, dose, treatment duration and indication).

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

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

8.4.1. Restrictions Regarding Concomitant Medications

8.4.1.1. Hydroxyurea

- Parts A, B, and C: Concurrent treatment with HU is allowed if the dose and regimen have been stable for at least 3 months prior to signing the ICF and with no anticipated need for dose adjustments during the study and no sign of hematological toxicity.
- Part D: Concurrent treatment with HU is allowed if the dose and regimen have been stable for at least 1 month prior to signing the ICF. Titration to the MTD is allowed during the study.

8.4.1.2. Prohibited Concomitant Medications

Voxelotor is a moderate cytochrome P450 (CYP) 3A4 inhibitor and should be not be coadministered with sensitive CYP3A4 substrates with a narrow therapeutic index (refer to Table 11 for examples).

Table 11: Sensitive CYP3A4 Substrates with a Narrow Therapeutic Range

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

Concomitant use of strong inducers of CYP3A4 with voxelotor is not allowed (refer to Table 12 for examples).

Table 12: Examples of Strong CYP3A4 Inducers

CYP3A4 Inducer	Examples
Strong	Rifampin, mitotane, avasimbe, rifapentine, apalutamide, ivosidenib, phenytoin, carabamazepine, enzalutamide, St. John's wort extract, lumacaftor, phenobarbital

Please note the following: 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.

Any other experimental SCD therapy is not allowed during the entire study period. Any medication which is not approved for the indication of SCD and is not suggested in the current guidelines for the treatment of SCD is considered "experimental".

8.4.2. Other Restrictions

Participants must abstain from all alcohol from 2 days prior to Day 1 until the end of the study.

8.5. 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.

8.5.1. Instructions for Female Participants of Child-Bearing Potential

In 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 8.5.4. Pregnancy reporting requirements are outlined in Section 9.7.

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

8.5.2. Female Participants of Non-Child-Bearing Potential

Female participants of non-child-bearing potential are defined as those who have not started their menarche.

8.5.3. 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 GB440.

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.

8.5.4. Acceptable Forms of Contraception

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

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

For male participants with female partners capable of reproduction:

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

9. ADVERSE EVENTS

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

Participants will be monitored throughout the study for AEs, from the time informed consent is obtained through the EOS visit. AEs that are identified at the last assessment visit (or the early termination visit) as specified in the protocol must be recorded on the AE eCRF. All events that are ongoing at this time will be recorded as ongoing on the eCRF. 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. The Investigator should use his/her discretion in ordering additional tests as necessary to monitor the resolution of such events.

All reported AEs will be coded using the current version of the Medical Dictionary for Regulatory Activities (MedDRA).

The procedures specified in Section 9.5 are to be followed for reporting SAEs.

9.1. Recording Adverse Events

AEs are to be recorded on the AE page of the eCRF. The following information will be recorded:

- Assessment of whether or not the AE is an SAE (Section 9.2.1)
- Assessment of AE intensity (Section 9.2.2)
- Assessment of AE relationship to investigational product (Section 9.2.3)
- Action taken - categorized as none, investigational product discontinued, required concomitant medication, required procedure, or other
- Outcome - recorded as event resolved, resolved with sequelae, ongoing, or death

9.2. Assessment of Adverse Events

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

9.2.1. Serious Adverse Event

The Investigator is responsible for determining whether an AE meets the definition of an SAE. An SAE is any AE occurring from ICF signing through the EOS visit that results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization

- A persistent or significant disability or incapacity
- A congenital anomaly or birth defect
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, jeopardizes the participant and may require medical or surgical intervention to prevent any of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.
- Elective surgery, pre-planned surgery or hospitalization less than 24 hours will not be considered an SAE unless deemed by the Investigator to be a significant medical event as described above.

Note: SAEs require immediate reporting to the Contract Research Organization (CRO) Safety Department. Refer to "Reporting Serious Adverse Events" (Section 9.5) for details.

9.2.2. Intensity of Adverse Events

The intensity of an event describes the degree of impact upon the participant and/or the need for medical care necessary to treat the event. AEs reported for participants participating in this study will be graded primarily using the National Cancer Institute's (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 4.03.

For AEs not adequately addressed in the NCI-CTCAE Version 4.03, the following criteria should be used (Table 13).

Table 13: Grading for Adverse Events not Covered in the NCI-CTCAE

Severity	Description
Grade 1 – Mild	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2 – Moderate	Minimal, local or noninvasive intervention indicated; limited age-appropriate instrumental activities of daily living (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.

9.2.3. Relationship to Investigational Product

The relationship of an AE to the IMP 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 (such as a preexisting condition, underlying disease, intercurrent illness, or concomitant medication).
- **Possibly/Probably Related:** A temporal relationship exists between the event onset and administration of the study drug. It cannot be readily explained by the participant's clinical state or concomitant therapies and appears with some degree of certainty to be related based on the known therapeutic and pharmacologic actions of the drug. In case of cessation or reduction of the dose, the event abates or resolves and reappears upon rechallenge. It should be emphasized that ineffective treatment should not be considered as causally related in the context of AE reporting.

These criteria in addition to good clinical judgment should be used as a guide for determining the causal assessment. If it is felt that the event is not related to study drug therapy, then an alternative explanation should be provided.

9.2.4. Unexpected Adverse Reactions

An adverse reaction is 'unexpected' if its nature and severity are not consistent with the information about the medicinal product in question set out:

- In the case of a product with a marketing authorization, in the summary of product characteristics for that product;
- In the case of any other IMP, in the Investigator's Brochure relating to the trial in question.

9.3. Reporting Adverse Events

9.3.1. 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 as an AE or SAE on the eCRF. If a diagnosis is subsequently established, it should be reported as follow-up information.

9.3.2. Adverse Events Occurring Secondary to Other Events

In general, AEs occurring secondary to other events (eg, cascade events or clinical sequelae) should be identified by their primary cause. For example, if severe diarrhea is known to have resulted in dehydration, it is sufficient to record only diarrhea as an AE or SAE on the eCRF.

However, medically significant AEs occurring secondary to an initiating event that are separated in time should be recorded as independent events on the eCRF. For example, if a severe

gastrointestinal hemorrhage leads to renal failure, both events should be recorded separately on the eCRF.

9.3.3. Persistent or Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution between participant evaluation time points. Such events should only be recorded once in the eCRF unless their severity increases. If a persistent AE becomes more severe, it should be recorded again on an Adverse Event eCRF.

A recurrent AE is one that occurs and resolves between participant evaluation time points and subsequently recurs. All recurrent AEs should be recorded on an Adverse Event eCRF.

9.3.4. Abnormal Laboratory Values

Only clinically significant laboratory abnormalities that require active management will be recorded as AEs or SAEs on the eCRF (eg, abnormalities that require study drug dose modification, discontinuation of study treatment, more frequent follow-up assessments, further diagnostic investigation, etc.).

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

If the clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded as an AE or SAE on the eCRF. If the laboratory abnormality can be characterized by a precise clinical term, the clinical term should be recorded as the AE or SAE. 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 as AEs or SAEs on the Adverse Event eCRF, unless their severity, seriousness, or etiology changes.

9.4. Discontinuation due to Adverse Events

In addition to the dose modification and study stopping rules previously outlined in Section 6.2 and Section 8.2 and any participant who experiences an AE may be withdrawn at any time from the study at the discretion of the Investigator. Participants withdrawn from the study due to an AE, whether serious or nonserious, should be followed by the Investigator until the clinical outcome of the AE is determined, ie, the event has resolved or has stabilized. The AE(s) should be noted on the appropriate eCRFs, and the participant's progress should be followed until the AE is resolved or stabilized as determined by the Investigator. The Sponsor and the CRO Medical Monitors must be notified. If the AE relates to overdose of study treatment, the voxelotor IB should be consulted for details of any specific actions to be taken.

9.5. Reporting Serious Adverse Events

SAEs occurring on this study will be reported to GBT Pharmacovigilance or designated CRO within 24 hours of the Investigator, designee, or site personnel's knowledge of the event. The SAE will be reported by completing the paper SAE report forms for Part A, B and C participants

or in the EDC for Part D participants and submitted to GBT Pharmacovigilance or designated CRO within 24 hours of becoming aware of the event. Follow-up reports must be submitted in a timely fashion as additional information becomes available.

The Investigator is responsible for notifying the IRB or EC in accordance with local regulations, of all SAEs. The Sponsor or designee may request additional source documentation pertaining to the SAE from the investigational site. If a participant is permanently withdrawn from the study due to a SAE, this information must be included in the initial or follow-up SAE report.

Properly anonymized and de-identified documents (eg, hospital discharge summaries, autopsy reports and/or death certificates) as available will be provided to GBT Pharmacovigilance or designated CRO for all reported SAEs.

9.6. Choosing Adverse Event Terms

Whenever possible, reported event terms for AEs (including SAEs) should be the names of medical events, not lists of symptoms or event outcomes. Below are some examples of terms to avoid and more accurate alternatives. Abbreviations are not permitted.

Examples of Terms to Avoid	Examples of More Accurate Terms
Death (this is an outcome)	Fatal myocardial infarction (best choice) Death due to unknown cause, autopsy results pending (if no other information is available)
Hospitalized (this is a serious criterion)	Myocardial infarction (best choice) Hospitalized with chest pain, rule out myocardial infarction (if no other information is available)
Chest pain, shortness of breath, diaphoresis, anxiety, left arm pain	Myocardial infarction (best choice) Hospitalized, rule out myocardial infarction (if no other information is available)

9.7. Reporting Pregnancy

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

Reported pregnancy of a participant or a participant's partner, while participating in this study, will be monitored for the full duration of the pregnancy and/or followed through a definitive outcome (ie, birth 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 9.5. Note that an elective abortion is not considered an SAE. Pregnancy and pregnancy outcomes must be reported on a Pregnancy Notification Form or

Pregnancy Outcome Form, respectively, and sent to the Sponsor or designee within 24 hours of the Investigator or site personnel learning of the pregnancy or pregnancy outcome.

The child born to a female participant or partner of a male participant exposed to study drug may be followed for 3 months after delivery if consent is provided. The outcome of any pregnancy and the presence or absence of any congenital abnormality will be recorded in the Pregnancy Outcome Form and reported to the Sponsor or designee. Any congenital abnormalities in the offspring will be reported as an SAE and must be reported as described in Section 9.5.

Information regarding pregnancy testing (including definition of females of childbearing potential) is provided in Section 8.5. Highly effective means of contraception are listed in Section 8.5.4.

9.8. Reporting Overdose

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

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

10. DATA ANALYSIS AND STATISTICAL PLANS

10.1. Sample Size

Part A: A cohort size of up to approximately 6 participants for each age group: 6 to 11 and 12 to 17 is based on a typical size for a single-dose PK study and is intended to balance the desire to minimize exposure of pediatric participants to a novel compound at this stage of voxelotor's development with the need to obtain PK, safety and tolerability data. No formal power or sample size calculations were performed to determine the cohort size.

Part B: Approximately 12 participants at 900 mg were selected to determine preliminary safety, tolerability, PK, laboratory effects and treatment response of voxelotor in pediatric participants with SCD. The number of participants may be increased to approximately 36 to further characterize the effect of multiple doses of voxelotor. Upon a favorable review by the DSMB, dosing of a minimum of 6 participants at 1500 mg may commence (dependent on how many participants were enrolled at 900 mg, ie, not to exceed a total study size of approximately 36).

The study with N = 12 for 900 mg is adequately powered for the primary endpoint of change from baseline to Week 24 in Hb. Power calculations assume normally distributed data, a mean treatment effect (change from baseline) of 0.8 g/dL, with a standard deviation (SD) of 0.6 g/dL. For a 2-sided alpha = 0.05 and N = 12, power exceeds 90% with a paired t-test to reject the null hypothesis of equality of post-treatment and baseline Hb means. The estimates of 0.8 and 0.6 g/dL for the mean and SD, respectively, are based on available Day 90 data from Cohorts 16 and (partial data) 17 from the GBT440-001 study.

Part C: Up to 50 pediatric participants who are 4 to 17 years of age with SCD will be enrolled. For the primary efficacy endpoint, change from baseline in TAMM TCD velocity at Week 48, a sample size of 30 participants achieves greater than 95% power to detect a mean difference of 15 cm/sec with an estimated sample standard deviation of 22 cm/sec using a paired t-test (2-sided) with a significance level (alpha) of 0.10.

Part D: Approximately 30 pediatric participants with SCD who are 6 months to < 4 years of age will be enrolled. The sample size was selected to provide descriptive assessment of safety, tolerability, and PK effects of voxelotor in this younger age group with no formal statistical assumptions.

10.2. Populations for Analysis

Two analysis populations will be defined:

- Safety population: all participants who receive any amount of study drug.
- PK population: all participants who receive any amount of study drug and who provide PK data from at least one postdose sample in plasma.

If any participants are found to be non-compliant 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.

10.3. Analyses

Details of all planned analyses will be specified in a separate Statistical Analysis Plan (SAP). The SAP will be finalized prior to final database lock. Data will be presented by each study part (Parts A and B) and dose level. For Part C, data will be presented by age group (4–11 years and 12–17 years). Part D data will be presented by age group (6 months to < 2 years and 2 to < 4 years).

Demographic and baseline characteristics, primary and secondary endpoints, and safety parameters will be summarized using descriptive statistics and presented in select individual listings.

10.3.1. Pharmacokinetic Data

For Part A, noncompartmental methods will be used for determination of PK parameters. All PK parameters will be presented by individual listings and summary statistics (eg, mean, geometric mean, median, standard deviation, 95% confidence interval, coefficients of variation, minimum and maximum, and number of participants). Preliminary metabolite profiling of plasma and/or whole blood may be conducted.

In Part B, RBC concentrations will be calculated from whole-blood and plasma concentrations. The following plasma, whole-blood, and RBC PK parameters will be calculated for voxelotor, as appropriate:

C_{max}, T_{max}, $AUC_{0\text{-}last}$, $AUC_{0\text{-}inf}$, area under the concentration-time curve from time zero (predose) to 24 hours ($AUC_{0\text{-}24}$) following the first and last day of dosing, accumulation ratio, blood/plasma ratio, RBC/plasma ratio, terminal half-life ($t_{1/2}$) and percent Hb occupancy.

In Parts C and D, population PK modeling will be used to determine the whole-blood and plasma PK parameters of voxelotor in the study population. The PK parameters to be determined will include C_{max}, AUC, $t_{1/2}$, and percent Hb occupancy.

10.3.2. Safety Data

All safety assessments will be conducted on the Safety population.

A TEAE is defined as an AE that emerges on or after initiation of study drug (having been absent pretreatment), or an AE that existed pretreatment and worsened on treatment (relative to the pretreatment state). The number and percentage of participants reporting TEAEs will be tabulated by MedDRA® (current version) system organ class and preferred term, severity and relationship to study medication. Serious TEAEs and TEAEs resulting in discontinuation of study drug will be summarized separately.

Concomitant medications will be mapped using the WHODRUG dictionary (current version). The number and percentage of participants taking each concomitant medication will be tabulated.

Analysis of laboratory results will be based on those reported by the local laboratory at each site. Continuous laboratory measurements will be descriptively summarized at each visit for observed values and changes from baseline.

Vital signs and ECG parameters (based on average of triplicate measurements) will be summarized at each visit for observed values and changes from baseline. In addition, QT and QTc intervals will be summarized categorically as number and percentage of participants with abnormal values or increases.

10.3.3. Efficacy Data

The laboratory parameters (Hb, reticulocyte count, erythropoietin, LDH and indirect bilirubin) and cerebral blood flow as measured by TAMM TCD velocity (Parts B and C only) will be listed and summarized at each visit for observed values and changes from baseline using appropriate descriptive statistics. Time to initial Hb response will be summarized descriptively (Parts C and D). The proportion of participants with normal TCD at 48 weeks will be summarized (Part C).

For Parts C and D, the incidence of stroke and annualized incidence of VOC will be summarized descriptively.

For Part B only, change from Baseline to Weeks 21–24 in the SCDSM TSS; for each participant, the TSS will be computed as follows: The Baseline TSS is the average of the score during the 35-day Screening period; during the treatment period, the TSS is the average score each 4-week period on treatment. The 4-week periods are Weeks 1–4, 5–8, 9–12, 13–16, 17–20 and 21–24 (and follows similarly for participants whose participation exceeds 24 weeks). Change from baseline in the TSS and the proportion of days with SCD symptom exacerbation will summarized using descriptive statistics (Part B).

10.3.4. Handling of Missing Data

Missing data will not be imputed. The details on efficacy analysis for participants that have been transfused will be detailed in the Statistical Analysis Plan.

11. REGULATORY, ETHICAL AND LEGAL OBLIGATIONS

11.1. Ethical Consideration

It is the responsibility of the Investigator to assure that the study is conducted in accordance with current country and local regulations, FDA, ICH GCP and the Declaration of Helsinki.

11.2. Institutional Review Board or Ethics Committee and Regulatory Approval

The Investigator must inform, and obtain approval from, the IRB/EC for the conduct of the study at named sites, for the protocol, the 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 drug.

Proposed amendments to the protocol and aforementioned documents must be discussed among the Sponsor and CRO, and then submitted to the IRB/EC for approval, as well as submitted to regulatory authorities prior to implementation. Amendments may be implemented only after a copy of the IRB/EC approval letter has been transmitted to the Sponsor. Amendments that are intended to eliminate an apparent immediate hazard to participants may be implemented prior to receiving Sponsor or IRB approval. However, in this case, approval must be obtained as soon as possible after implementation.

The Investigator will be responsible for ensuring that an annual update is sent to the IRB/EC to facilitate their continuing review of the trial (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.

11.3. 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.

11.4. Essential Documentation Requirements

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

11.5. Informed Consent and Assent

It is the Investigator's responsibility to obtain written informed consent/assent from the participant after adequate explanation of the objectives, methods, anticipated benefits, and potential risks of the study and before any study procedures are commenced. The participant should be given a copy of the ICF in their native language. The informed consent process should be recorded in the source documentation. The original copy of the signed and dated informed

consent must be retained in the institution's records, and is subject to inspection by representatives of the Sponsor, or representatives from regulatory agencies.

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

Participants who initially sign the Assent Form and subsequently legally become an adult while actively participating in the study (before the EOS visit) should be re-consented using the Adult ICF soon after their status changes.

11.6. Confidentiality

The Investigator must ensure that the participant's privacy is maintained. On the CRF or other documents submitted to the Sponsor, participants will be identified by a participant study number only. Documents that are not submitted to the Sponsor (eg, signed ICF) should be kept in a strictly confidential file by the Investigator.

The Investigator shall permit authorized representatives of the Sponsor, regulatory agencies and IRBs/ECs 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.

11.7. Regulatory, Ethical, and Legal Obligations

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

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

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

11.8. Trial Documentation and Data Storage

The Investigator must retain a comprehensive and centralized filing system of all essential trial-related documentation as outlined in ICH GCP Section 8. This Investigator Site File must be assembled and maintained in a timely manner in order to enable inspection by the Sponsor and representatives of regulatory authorities.

The Investigator must retain essential documents until at least 2 years after the last approval of a marketing application in any ICH region. Participant files and other source data (including copies of protocols, original reports of test results, investigational drug dispensing logs, correspondence, records of informed consent, and other documents pertaining to the conduct of the trial) 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 trial document will be destroyed without prior written agreement between the Sponsor and the Investigator. Should the Investigator wish to assign the trial records to another party or move them to another location, written agreement must be obtained from the Sponsor.

11.9. Study Record Retention

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 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. GBT must be notified should the Investigator/institution be unable to continue with the maintenance of study participant files for the full 15 years. All study records must be stored in a secure and safe facility.

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

If the Principal 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.

11.10. Disclosure of Information

Information concerning the study, patent applications, processes, scientific data or other pertinent information is confidential and remains the property of the Sponsor. The Investigator may use this information for the purposes of the study only.

It is understood by the Investigator that the Sponsor will use information developed in this clinical study in connection with the development of voxelotor and, therefore, may disclose it as required to other clinical investigators and to regulatory agencies. In order to allow the use of the information derived from this clinical study, the Investigator understands that he/she has an obligation to provide complete test results and all data developed during this study to the Sponsor.

Verbal or written discussion of results prior to study completion and full reporting should only be undertaken with written consent from the Sponsor.

11.11. Publication

It is intended to publish the results of the study as a whole once all participants have completed the study, the clinical database has been locked, 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 30 days in which to review and comment on the pre-publication manuscript.

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

12. ADMINISTRATIVE OBLIGATIONS

12.1. Source Data

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

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

12.2. Data Collection

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

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

12.3. Monitoring

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

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

The Investigator agrees to co-operate with the monitor to ensure that any problems detected during the course of these monitoring visits are resolved.

12.4. Quality Control, Quality Assurance and Regulatory Inspections

Quality Control will be performed according to Sponsor and CRO internal procedures. A Quality Assurance representative of the Sponsor and/or CRO may audit the study. In addition, the

investigative site may be inspected by a representative of a regulatory authority. The Investigator commits to making all necessary data/documents and key personnel available to support the inspection or audit.

13. STUDY REPORT

A clinical study report, compliant with the requirements of ICH E3, will be prepared by the Sponsor or designee.

14. REFERENCES

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APPENDIX 1. PART A SCHEDULE OF ASSESSMENTS

Procedure	Screening (Up to 28 Days Before Dosing)	Day 1[h]	Follow-up Period					Early Termination/ Withdrawal
			Day 2	Day 3	Day 5	Day 8	Day 15 (± 1 Day)	
Assent (if appropriate) & Informed Consent	X							
Review Inclusion/Exclusion Criteria	X	X						
Medication & Medical History	X	X						
Height[a]	X							
Body Weight	X	X					X	X
Vital Signs[b]	X	X	X	X			X	X
ECG[c]	X	X					X	X
Physical Examination[d]	X	X					X	X
Serum Pregnancy Test[e]	X							
Urine Pregnancy Test[e]		X					X	X
Hematology, Serum Chemistry, Liver Function, Urinalysis[f]	X	X		X			X	X
Coagulation Panel	X							
Voxelotor Drug Dosing		X						
PK Sampling (Plasma & Whole Blood)[g]		X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X
Taste & Palatability Questionnaire (only 6–11 years old)		X						

Abbreviations: ECG, electrocardiogram; PK, pharmacokinetics.

[a] Height will be recorded at Screening only.
[b] Vital signs (pulse rate (PR), blood pressure [BP], respiratory rate and body temperature) will be measured on Day 1 predose and at 8 and 24 hours postdose (Day 2). PR and BP will be measured after a participant has rested for at least 5 minutes in the seated or supine position.
[c] ECGs (12-lead) will be recorded after a participant has rested for at least 10 minutes in the supine position. ECGs will be collected in triplicate within a 5-minute timeframe. Triplicate ECGs will be collected on Day 1 both pre- and postdose. If the Screening triplicate ECGs are collected less than 24 hours before study drug dosing, the triplicate ECGs prior to dosing may be omitted. The ECG on Day 1 postdose may be collected between 1.5 and 2.5 hours relative to voxelotor administration.
[d] Physical examinations after the Screening Period may be abbreviated, focusing on abnormalities identified on the Screening examination and as related to adverse events
[e] Pregnancy tests will be performed on female participants who are of child-bearing potential.
[f] All labs to be done via local laboratories except PK draws.
[g] Blood samples for plasma and whole blood PK analysis of voxelotor will be collected as outlined in Appendix 2.
[h] Laboratory assessments, vital signs and physical examinations conducted on Day 1 predose may be conducted on Day -1.

APPENDIX 2. DETAIL OF PART A BLOOD PK COLLECTIONS

Procedure	Sampling Time Points (Hours) Relative to Day 1								Early Termination/ Withdrawal
	Predose[a]	2[b]	8[c]	24[d] (Day 2)	48[e] (Day 3)	96[e] (Day 5)	168[e] (Day 8)	Day 15[f]	
PK Sampling (plasma & whole blood)	X	X	X	X	X	X	X	X	X

Note: For procedures scheduled to be performed at common times, priority is to be given to collection of the PK samples at the designated time.

[a] Can be collected up to an hour prior to dosing.
[b] Can be collected within ± 15 minutes of time point.
[c] Can be collected within ± 30 minutes of time point.
[d] Can be collected within ± 60 minutes of time point.
[e] Can be collected within ± 2 hours of time point.
[f] Can be collected within ± 1 day of time point.

APPENDIX 3. PART B SCHEDULE OF ASSESSMENTS

Procedure	Screening (Up to 35 Days Before Dosing)	Treatment Period									Follow-Up	Early Termination/ Withdrawal
		Day 1[i]	Day 2	Day 8	Week 2 (Day 14) (± 2 days)	Week 4 (Day 28) (± 3 days)	Week 8 (Day 56) (± 3 days)	Week 12 (Day 84) (± 3 days)	Week 16 (Day 112) & Week 20 (Day 140) (± 3 days)	Week 24 (Day 168) (± 3 days)	EOS (last dose + 4 Weeks) (± 2 days)	
Assent (if appropriate) & Informed Consent	X											
Review Inclusion/ Exclusion Criteria	X	X										
ePRO Screening (Part B only)	X											
Medication & Medical History	X	X										
Height[a]	X											
Body Weight	X	X				X	X	X	X	X	X	X
Vital Signs[b]	X	X	X	X	X	X	X	X	X	X	X	X
ECG[c]	X	X				X	X	X	X	X	X	X
Physical Examination	X	X				X	X	X	X	X	X	X
Serum Pregnancy Test[d]	X											
Urine Pregnancy Test[d]		X			X	X	X	X	X	X	X	X
Hemoglobin Electrophoresis	X											
Hematology, Serum Chemistry, Liver Function, Urinalysis[e]	X[f]	X		X	X	X	X	X	X	X	X	X
Serum Erythropoietin		X				X		X		X	X	X
Coagulation Panel	X											
Voxelotor Drug Dosing (daily from Day 1 to Week 24)[h]		X	X	X	X	X	X	X	X	X		
PK Sampling (plasma & whole blood)[g]		X	X		X	X	X	X	X	X	X	X
Transcranial Doppler	X	X						X		X	X	X

Procedure	Screening (Up to 35 Days Before Dosing)	Treatment Period								Follow-Up	Early Termination/ Withdrawal
		Day 1[i]	Day 2	Day 8	Week 2 (Day 14) (± 2 days)	Week 4 (Day 28) (± 3 days)	Week 8 (Day 56) (± 3 days)	Week 12 (Day 84) (± 3 days)	Week 16 (Day 112) & Week 20 (Day 140) (± 3 days)	Week 24 (Day 168) (± 3 days)	EOS (Last Dose + 4 Weeks) (± 2 days)	
Dispensing of Study Drug for Home Use		X				X	X	X	X			
Concomitant Medications	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
ePRO SCDS Measure	X	X	X	X	X	X	X	X	X	X	X	
eDiary		X	X	X	X	X	X	X	X	X		

Abbreviations: ECG, electrocardiogram; PK, pharmacokinetic; EOS, end of study; ePRO, electronic patient reported outcomes; SCDS, sickle cell disease severity.

[a] Height will be recorded at Screening only.

[b] Vital signs (pulse rate (PR), blood pressure [BP], respiratory rate and body temperature) will be measured on Day 1 predose and at 8 and 24 hours postdose (Day 2). PR and BP will be measured after a participant has rested for at least 5 minutes in the seated or supine position.

[c] ECGs (12-lead) will be recorded after a participant has rested for at least 10 minutes in the supine position. ECGs will be collected in triplicate within a 5-minute timeframe. Triplicate ECGs will be collected on Day 1 both pre- and postdose. If the Screening triplicate ECGs are collected less than 24 hours before study drug dosing, the triplicate ECGs prior to dosing may be omitted. The ECG on Day 1 postdose may be collected between 1.5 and 2.5 hours relative to voxelotor administration.

[d] Pregnancy tests will be performed on female participants who are of child-bearing potential.

[e] All labs to be done via local laboratories except PK draws.

[f] Iron studies at Screening only: Ferritin, transferrin, total iron binding capacity (TIBC) and serum iron.

[g] Blood samples for plasma (if applicable) and whole blood PK analysis of voxelotor will be collected as outlined in Appendix 4.

[h] Study drug administration on study visit days is to be postponed in order to enable administration in the clinical setting.

[i] Laboratory assessments, vital signs, physical examinations and Transcranial Doppler conducted on Day 1 predose may be conducted on Day -1.

APPENDIX 4. DETAIL OF PART B BLOOD PK COLLECTIONS

Procedure	Sampling Time Points (Hours) Relative to Day 1				Week 2 (Day 14)[f]	Sampling Time Points (Hours) Relative to Week 4 (Day 28)			Week 8 (Day 56)	Week 12 (Day 84)	Week 16 (Day 112)	Week 20 (Day 140)	Week 24 (Day 168)	Follow-Up	Early Termination/ Withdrawal
	Pre-dose[a]	2[c]	8[d]	24[e] (Day 2)		Pre dose[b]	1–4 Post-dose	6–8 Post-dose	Pre- or Post-Dose	Pre- or Post-Dose	Pre- or Post-Dose	Pre- or Post-Dose	Pre- or Post-Dose	EOS (Last Dose + 4 Weeks)	
PK Sampling (plasma & whole blood)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

[a] Can be collected up to an hour prior to dosing.
[a] Can be collected within 30 minutes prior to dosing.
[b] Can be collected within ± 15 minutes of time point.
[c] Can be collected within ± 30 minutes of time point.
[d] Can be collected within ± 60 minutes of time point.
[e] Can be collected pre or postdose, within ± 2 hours of the dose.

APPENDIX 5. PART C SCHEDULE OF ASSESSMENTS

Procedure	Screening (Up to 35 Days Before Dosing)	Day 1[a]	Treatment Period								Follow-Up	Formulation Transition Visit[b]	Early Termination/ Withdrawal
			Week 2 (Day 14) (± 2 days)	Week 4 (Day 28) (± 3 days)	Week 8 (Day 56) (± 3 days)	Week 12 (Day 84) (± 3 days)	Week 16 (Day 112) & Week 20 (Day 140) (± 5 days)	Week 24 (Day 168) (± 5 days)	Week 36 (Day 252) (± 5 days)	Week 48 (Day 336) (± 5 days)	EOS (last dose + 4 Weeks) (± 2 days)		
Assent (if appropriate) & Informed Consent	X											X[b]	
Review Inclusion/ Exclusion Criteria	X	X											
Medication & Medical History	X	X											
Height[c]	X												
Body Weight	X	X		X	X	X	X	X	X	X	X	X	X
Vital Signs	X	X	X	X	X	X	X	X	X	X	X		X
ECG[d]	X			X		X		X		X	X		X
Physical Examination	X	X		X	X	X	X	X	X	X	X	X	X
Serum Pregnancy Test[e]	X												
Urine Pregnancy Test[e]		X	X	X	X	X	X	X	X	X	X		X
Hemoglobin Electrophoresis	X												
Hematology, Serum Chemistry, Liver Function, Urinalysis[f]	X[g]	X	X	X	X	X	X	X	X	X	X		X
Serum Erythropoietin		X								X	X		
PK Sampling (plasma & whole blood)[h]		X		X	X	X	X	X	X	X			X
Voxelotor Drug Dosing in Clinic[i]		X		X	X	X	X	X	X	X		X	
Transcranial Doppler (without sedation)	X							X		X			X
Postdose Taste and Palatability Questionnaire[j]			X			X						X	

Procedure	Screening (Up to 35 Days Before Dosing)	Treatment Period									Follow-Up	Formulation Transition Visit[b]	Early Termination/ Withdrawal
		Day 1[a]	Week 2 (Day 14) (± 2 days)	Week 4 (Day 28) (± 3 days)	Week 8 (Day 56) (± 3 days)	Week 12 (Day 84) (± 3 days)	Week 16 (Day 112) & Week 20 (Day 140) (± 5 days)	Week 24 (Day 168) (± 5 days)	Week 36 (Day 252) (± 5 days)	Week 48 (Day 336) (± 5 days)	EOS (last dose + 4 Weeks) (± 2 days)		
Dispensing of Study Drug for Home Use		X		X	X	X	X	X	X			X	
Concomitant Medications	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

Abbreviations: ECG, electrocardiogram; PK, pharmacokinetic; EOS, end of study; ePRO, electronic patient reported outcomes; SCDS, sickle cell disease severity.

[a] Laboratory assessments, vital signs, and physical examinations conducted on Day 1 predose may be conducted on Day -1.

[b] The Formulation Transition Visit should occur for all participants within 30 days of powder for oral suspension availability. A signed and dated updated informed parental/guardian consent and participant assent must be obtained at the Formulation Transition Visit if the participant has not signed the updated ICF for the transition visit. Due to the COVID-19 impact on clinical sites, the transiton visit may occur at a scheduled study visit. A telephone Follow-Up Visit should be conducted 1 to 2 weeks after this visit to assess tolerability of the new study drug formulation.

[c] Height will be recorded at Screening only.

[d] ECGs (12-lead) will be recorded after a participant has rested for at least 10 minutes in the supine position, as age appropriate. ECGs will be collected in triplicate within a 5-minute timeframe.

[e] Pregnancy tests will be performed for female participants who are of child-bearing potential.

[f] All clinical laboratory tests will be performed at the local laboratories except for analysis of PK samples.

[g] Iron studies will be performed at Screening only: ferritin, transferrin, total iron binding capacity (TIBC), and serum iron.

[h] Blood samples for plasma and whole blood PK analysis of voxelotor will be collected as outlined in Appendix 6.

[i] Study drug administration on study visit days will be postponed in order to enable administration in the clinic.

[j] The Postdose Taste and Palatability Questionnaire will be administered for both study drug formulations after in-clinic dosing. For the dispersible tablets, it will be administered to the caregiver/legal guardian and/or children (≥ 6 years old) at Week 2 and Week 12 (or any time after 3 months of study drug treatment). For the powder for oral suspension formulation, it will be administered to the caregiver/legal guardian and/or children (all ages) at the Formulation Transition Visit and at the next scheduled study visit.

APPENDIX 6. PART C PHARMACOKINETIC SAMPLING SCHEDULE

Procedure	Day 1	Week 4 Day 28 ± 3 days	Week 8 Day 56 ± 3 days	Week 12 Day 84 ± 3 days	Week 16 Day 112 ± 5 days	Week 20 Day 140 ± 5 days	Week 24 Day 168 ± 5 days	Week 36 Day 252 ± 5 days	Week 48 Day 336 ± 5 days	Early Termination/ Withdrawal
PK Sampling (Plasma and Whole Blood)	15 min to 2 h postdose	Predose[a]	Predose[a]	Predose[a]	Predose[a]	Predose[a]	Predose [a]	Predose[a]	Predose[a]	
	X	X	X	X	X	X	X	X	X	X

[a] Can be collected up to an hour prior to dosing.

APPENDIX 7. PART D SCHEDULE OF ASSESSMENTS

Procedure	Screening (Up to 35 Days Before Dosing)	Treatment Period									Follow-Up	Early Termination/ Withdrawal
		Day 1[a]	Week 2 (Day 14)	Week 4 (Day 28)	Week 8 (Day 56)	Week 12 (Day 84)	Week 16 (Day 112) and Week 20 (Day 140)	Week 24 (Day 168)	Week 36 (Day 252)	Week 48 (Day 336)	EOS (Last Dose + 28 days)	
			(± 3 days)			(± 5 days)					(+7 days)	
Assent (If Appropriate) and Informed Consent	X											
Review Inclusion/ Exclusion Criteria	X	X										
Medical History	X											
Height		X		X	X	X	X	X	X	X	X	X
Body Weight	X	X		X	X	X	X	X	X	X	X	X
Head Circumference		X				X		X	X	X		X
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X
ECG[b]	X											
Physical Examination	X	X	X	X	X	X	X	X	X	X	X	X
Hb Electrophoresis	X											
Hematology, Serum Chemistry, Liver Function[c]	X	X	X	X	X	X	X	X	X	X	X	X
Historical Hb Genotype	X											
Serum Erythropoietin		X						X		X	X	X
PK Sampling (Plasma and Whole Blood)[d]		See Appendix 8										
Voxelotor Drug Dosing in Clinic[e]		X	X	X	X	X	X	X	X	X		

Procedure	Screening (Up to 35 Days Before Dosing)	Treatment Period									Follow-Up	Early Termination/ Withdrawal
		Day 1[a]	Week 2 (Day 14) (± 3 days)	Week 4 (Day 28) (± 3 days)	Week 8 (Day 56) (± 3 days)	Week 12 (Day 84) (± 5 days)	Week 16 (Day 112) and Week 20 (Day 140) (± 5 days)	Week 24 (Day 168) (± 5 days)	Week 36 (Day 252) (± 5 days)	Week 48 (Day 336) (± 5 days)	EOS (Last Dose + 28 days) (+7 days)	
Postdose Taste and Palatability Questionnaire			X	X		X[f]						
Study Drug Dispensing		X				X		X	X			
Concomitant Medications	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

Abbreviations: ECG, electrocardiogram; Hb, hemoglobin; PK, pharmacokinetic.

[a] Laboratory assessments, vital signs, and physical examinations conducted on Day 1 predose may be conducted on Day -1.
[b] ECGs (12-lead) will be recorded after a participant has rested for at least 10 minutes in the supine position, as age appropriate. ECGs will be collected in triplicate within a 5-minute timeframe.
[c] All clinical laboratory tests will be performed at the local laboratories except for analysis of PK samples.
[d] Blood samples for plasma and whole blood PK analysis of voxelotor will be collected as outlined in Appendix 8.
[e] Study drug administration on study visit days will be postponed in order to enable administration in the clinic.
[f] May be performed any time after 3 months of treatment.

APPENDIX 8. PART D PHARMACOKINETIC SAMPLING SCHEDULE

Procedure	Day 1 Sample 1	Week 2 Day 14 ± 3 days	Week 8 Day 56 ± 3 days	Week 12 Day 84 ± 5 days	Week 16 Day 112 ± 5 days	Week 24 Day 168 ± 5 days	Week 36 Day 252 ± 5 days	Week 48 Day 336 ± 5 days	Early Termination/ Withdrawal
PK Sample (Plasma & Whole Blood)	15 min to 2 h postdose	Predose[a]	Predose[a]	Predose[a]	Predose[a]	Predose[a]	Predose[a]	Predose[a]	
	X	X	X	X	X	X	X	X	X

Abbreviation: PK, pharmacokinetic.
[a] Can be collected up to an hour prior to dosing.