27Oct2020

Re: Cover Letter for ClinicalTrials.gov NCT03036813 (Global Blood Therapeutics)

This Cover Letter accompanies Study Protocol for this trial NCT03036813 which completed.

Sincerely,

DocuSigned by Margaret Tonda

Margaret Tonda | I approve this document
27-Oct-2020 | 15:02 PDT

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CLINICAL STUDY PROTOCOL
GBT440-031

Study Number	GBT440-031
Study Title	A Phase 3, Double-blind, Randomized, Placebo-controlled, Multicenter Study of Voxelotor Administered Orally to Patients With Sickle Cell Disease
Investigational Product	Voxelotor, previously GBT440
IND Number	121,691
Sponsor	Global Blood Therapeutics, Inc. 171 Oyster Point Blvd, Suite 300 South San Francisco, CA 94080 United States of America

PROTOCOL SYNOPSIS

Protocol Title	A Phase 3, Double-blind, Randomized, Placebo-controlled, Multicenter Study of Voxelotor Administered Orally to Patients with Sickle Cell Disease
Study Drug	• GBT440 capsules or tablets, 300 mg each, administered orally • Matching placebo, administered orally
Number of Clinical Sites	The study will be conducted at approximately 100 international clinical sites.
Number of Study Participants	Approximately 370 total participants with Sickle Cell Disease (SCD), adults and adolescents (up to 435) will be enrolled, as follows: **Group 1:** Approximately 60 participants **Group 2:** Up to approximately 180 participants; enrollment begins with participant #61 and ends when the Group 3 dose has been selected from the Group 1 Analysis **Group 3:** At least 130 participants; enrollment begins when the Group 3 dose has been selected
Treatment	**Group 1:** Participants will be randomized in a 1:1:1 ratio to receive voxelotor 900 mg/day, voxelotor 1500 mg/day, or matching placebo **Group 2:** Participants will be randomized in a 1:1:1 ratio to receive voxelotor 900 mg/day, voxelotor 1500 mg/day, or matching placebo **Group 3:** Participants will be randomized in a 1:1 ratio to receive voxelotor (900 mg/day or 1500 mg/day), or matching placebo.
Objectives	**Primary** The primary objective is to assess the efficacy of voxelotor in adolescents and adults with SCD as measured by improvement in hemoglobin. **Secondary** The secondary objectives are to evaluate the effects of voxelotor compared to placebo on: • clinical measures of hemolysis • long term VOC incidence **Exploratory** The exploratory objectives are to evaluate the effects of voxelotor compared to placebo on. • Sickle Cell Disease Severity Measure (SCDSM) • EuroQol EQ-5D-5L health questionnaire (EQ-5D-5L™) • Clinical Global Impression of Change (CGIC)- Groups 1 and 2 only • Incidence and time to first RBC transfusion and post baseline onset of VOC • School and/or work attendance and the use of opioid during the treatment period as recorded via eDiary • Measures related to SCD pathophysiology and their utility as pharmacodynamic markers to evaluate including inflammatory biomarkers (Part 1 only), kidney function and RBC rheology • Measures predictive of response to voxelotor **Safety** The safety objectives are to assess the safety of voxelotor compared to placebo based on adverse events (AEs), clinical laboratory tests, physical

	examinations, and other clinical measures (eg, discontinuations due to AEs, dose reductions). **Pharmacokinetics** The pharmacokinetic (PK) objective is to assess the PK of voxeltor as evaluated by population PK analysis.
Study Design	**STUDY DESIGN** This study is a randomized, placebo-controlled, double -blind, parallel group, multicenter study of participants, age 12 to 65 years, with SCD (HbSS, HbSC, HbSβthalassemia or other sickle cell syndrome variants) conducted in three groups of study participants, Groups 1, 2, and 3. The key purposes for each group are: **Group 1:** • Evaluate safety and efficacy of voxelotor (900mg and 1500mg) compared to placebo. • Selection of voxelotor dose(s) for further study in Group 3. **Group 2:** • Enable a seamless transition from Group 1 to Group 3 by continuing enrollment and data collection until completion of Group 1 analysis. • If needed, data from Group 2 may be included in the Group 1 analysis to inform dose selection and potential study modification as appropriate. • Form the basis for the primary analysis of the study to establish the efficacy and safety of GBT440, in combination with Group 1. **Group 3:** Further investigate the effect of voxelotor at selected dose(s), eg, in participant subgroups as determined from the primary analysis of the study based on data from Group 1 and Group 2 combined. **Open Label Extension (under separate protocol)** Participants will be given the option to enroll in an open label extension study to receive voxelotor at the selected dose(s). The open label extension study will be available to eligible participants who: • Were included in the Group 1 Analysis regardless of the treatment arm to which they were randomized. • Were randomized in Group 2 to the dose not selected for Group 3 • Were randomized in Group 2 but unblinded and data combined with Group 1 data. • Were included in the Main Population (Group 3 and Group 2 placebo and selected dose) and completed through end of treatment. The Study Schematic is provided the Schedule of Assessments. **Adolescent Participants** Initially only adult participants will be randomized. Adolescent participants (12 to <18 years) will be included in screening/randomization when: 1) Single dose PK data and modeling from Study GBT440-007 are available to confirm the appropriate dose for adolescent participants, and 2) The Data Safety Monitoring Board (DSMB) has reviewed the safety data from at least 18 adults enrolled in this study of which at least 6

adults have received 1500 mg GBT440 for at least 4 weeks to confirm acceptable safety and tolerability before adolescents can be enrolled. Sites will be notified when adolescent participants can be enrolled in this study.

At the time that these criteria are met, adolescents may enter screening (as early as in Group 1); a minimum of 50 adolescents will be included inthis study.

SCREENING AND RANDOMIZATION

After signing the informed consent form (ICF), participant screening will include medical history, vital signs, electrocardiogram (ECG), complete physical exam (PE) including height and weight, blood chemistry including iron studies, hematology laboratory tests, serum pregnancy test for women, and urinalysis. The ePRO measure assessment must be completed for at least 75% of days of a 28-day Screening period. All screening procedures must be completed within 35 days before randomization. Laboratory tests will be performed by a central laboratory.

STUDY DRUG INFORMATION

Participants receiving 1500 mg voxelotor will receive five 300 mg capsules or tablets, administered orally, once daily; participants receiving 900 mg GBT440 will receive three 300 mg capsules or tablets, and 2 placebo capsules or tablets administered orally, once daily. Participants randomized to placebo will receive 5 placebo capsules or tablets administered orally, once daily. Study drug may be taken with or without food. Participants in Group 1 must take their study drug in the mornings and must avoid high fat meals for 4 hours before and 4 hours after taking study drug. Group 2 and Group 3 participants may take study drug in the morning or evening, preferably at same time each day throughout the study (Group 2 and Group 3 participants have no food restrictions/requirements).

DOSE MODIFICATIONS

Guidelines for dose modification are provided in Table 1 **Error! Reference source not found.**(study drug related AEs) and Table 2 **Error! Reference source not found.**(study drug related rash).

ANALYSIS GROUPS AND SPECIFICATIONS

Analysis will be conducted on populations:

- Group 1 analysis population
- The primary analysis (based on data from all Group 1 and 2 participants)
- Group 3 analysis population

Group 1: When the 60th participant reaches 12 weeks of treatment, data from the 60 participants will be unblinded, and an analysis of Group 1 will be conducted to inform the dose selection and other potential protocol modifications for Group 3 study conduct.

Group 2: Group 2 enrollment will begin with participant #61 and will end when the Group 3 dose(s) has been selected.

Group 3: Group 3 participants will be randomized in a 1:1 ratio to receive the voxeotory selected dose or placebo.

BLINDING

	This study is a double-blind study. The voxelotor and placebo capsules or tablets will be matched for shape, size, and color. To facilitate the Group 1 analyses, certain Sponsor representatives and Sponsor designees will be unblinded to treatment assignments prior to and during the data analysis (including the biostatistics contract research organization [CRO], Sponsor Biostatistics and Programming staff, and external groups for bioanalytical PK/PD). However, the rest of the Sponsor study team, including all study team members who have direct interactions with study sites, was not unblinded to individual treatment assignment. No site staff or study participants will be unblinded to randomization assignment. **Unblinding for Laboratory Test Assessment** Local laboratory tests including hematology laboratory tests may be used as needed per standard of care to manage AEs (such as hospitalization for VOC), and in these circumstances, the laboratory data may need to be unblinded. Because knowledge of certain laboratory assessments (Hb, hematocrit [Hct], RBC count, total and unconjugated bilirubin, and absolute and % reticulocyte count) may suggest the treatment assignment, these measurements will be redacted to the Investigator and monitored on a regular basis by the DSMB. Results of redacted laboratory tests will be communicated to the Investigator if a participant's absolute reticulocyte count declines to $<80 \times 10^9$/L or Hb declines to <5.0 g/dL or if the Hb declines $\geq$ 3 g/dL from screening (but this does not require breaking of the treatment assignment blind). This is to ensure participant safety by allowing the Investigator to monitor for potential bone marrow suppression, as described in hydroxyurea (HU) monitoring guidelines (NHLBI 2014) (National Heart, Lung, and Blood Institute; NHLBI; 2014). All other laboratory assessments (not redacted) will be available to the Investigator. Anonymized laboratory results will be available to the Sponsor. **Unblinding for Medical Need** If a medical condition should arise for which appropriate treatment cannot be decided without knowledge of the study treatment assignment, the Investigator may unblind a study participant. The investigator should promptly document and explain to the Sponsor any premature unblinding (eg, accidental unblinding, unblinding due to a serious adverse event) of the study participant. Pregnancy is considered a medical condition that requires unblinding. Unblinding procedures will be followed as outlined in the IWRS Manual and documented in the Investigator site file and the case report form (CRF). **DATA AND SAFETY MONITORING BOARD** An independent DSMB will monitor the safety and conduct of the trial. The DSMB will be comprised of medical and statistical representatives. The DSMB can provide recommendations to the Sponsor regarding stopping the study or discontinuing a treatment arm or otherwise modifying the study design or conduct.

	The DSMB will review: • The Group 1 Analysis and provide an assessment of the benefit to risk ratio of the 900 mg and 1500 mg doses. • Safety data from at least 18 adults enrolled in this study of which at least 6 adults have received 1500 mg voxelotor for at least 4 weeks to confirm acceptable safety and tolerability before adolescents can be enrolled. The sites will be notified when adolescent participants can be enrolled in this study. Additionally, this review of early safety and tolerability at 1500 mg must be satisfactory for dosing to continue to at this dose level. • 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 the DSMB Charter. **SAFETY ASSESSMENTS** Safety assessments will consist of recording all AEs and SAEs; protocol-specified hematology and clinical chemistry variables; measurement of protocol-specified vital signs; and the results from other protocol-specified tests that are deemed critical to the safety evaluation of voxelotor. **RESTRICTIONS REGARDING CONCOMITANT MEDICATIONS** GBT440 should be used with caution with CYP3A4 substrates with a narrow therapeutic index. The use of strong inducers of CYP2B6, CYP2C9, CYP2C19, and CYP3A4/CYP3A5 is prohibited. The use of herbal medications (eg, St. John's Wort) is not allowed.
Duration of Study Participation	**Duration of Treatment** **Group 1:** Minimum duration is 12 weeks, maximum duration is 72 weeks. **Group 2:** Minimum duration is 2 weeks, maximum duration is 72 weeks. **Group 3:** Minimum duration is 24 weeks, maximum duration is 72 weeks. **Duration of Study** The study will end when the Group 3 last participant last visit occurs which will be approximately 28 weeks after randomization for the last participant enrolled into Group 3. Duration of study for an individual participant includes Screening (at least 28 days, but up to 35 days to account for Screening window flexibility), treatment for a minimum of 2 weeks and a maximum of 72 weeks, and an End of Study (EOS) visit at 4 weeks (± 7 days) after the last dose of study drug. From Screening through follow-up, total participation in this study for an individual participant may last from approximately 10 weeks to up to 81weeks. The minimum study duration is approximately 10 weeks (for participants in Group 2 enrolled at a dose not selected for Group 3). Participants will continue to be followed for efficacy and safety through at least the endpoint visit (Week 12 for Group 1 and Week 24 for the Main Population) regardless of treatment discontinuation.
Study Population	**INCLUSION CRITERIA** 1. Male or female study participants with sickle cell disease

	• Documentation of SCD genotype (HbSS, HbSC, HbSβthalassemia or other sickle cell syndrome variants) may be based on history of laboratory testing or must be confirmed by laboratory testing during screening 2. Participants have had at least 1 episode of VOC in the past 12 months. For study eligibility, VOC is defined as a previously documented episode of ACS or acute painful crisis (for which there was no explanation other than VOC) which required prescription or healthcare professional-instructed use of analgesics for moderate to severe pain (documentation must exist in the patient medical record prior to Screening) 3. Age 12 to 65 years 4. Hemoglobin (Hb) ≥5.5 and ≤10.5 g/dL during Screening 5. For participants taking HU, the dose of HU (mg/kg) must be stable for at least 3 months prior to signing the ICF and with no anticipated need for dose adjustments during the study, in the opinion of the Investigator 6. Participants must demonstrate 75% compliance with ePRO measure completion to be randomized (participants will be given an ePRO device for at least 28 days during Screening). Participants who have <75% compliance may be rescreened up to two times for ePRO compliance 7. Participants, who if female and of child bearing potential, are using highly effective methods of contraception from study start to 30 days after the last dose of study drug, and who if male are willing to use barrier methods of contraception, from study start to 30 days after the last dose of study drug 8. Participant has provided documented informed consent or assent (the ICF must be reviewed and signed by each participant; in the case of pediatric participants, both the consent of the participant's legal representative or legal guardian, and the participant's assent must be obtained) **EXCLUSION CRITERIA** 1. More than 10 VOCs within the past 12 months that required a hospital, emergency room or clinic visit 2. Female who is breast feeding or pregnant 3. Participants who are receiving regularly scheduled blood (RBC) transfusion therapy (also termed chronic, prophylactic, or preventive transfusion) or have received a RBC transfusion for any reason within 60 days of signing the ICF or at any time during the screening period. 4. Hospitalized for sickle cell crisis or other vaso-occlusive event prior to 14 days of signing the ICF (ie, a vaso-occlusive event cannot be within 14 days prior to ICF) 5. Hepatic dysfunction characterized by alanine aminotransferase (ALT) >4 × ULN 6. Participants with clinically significant bacterial, fungal, parasitic or viral infection which require therapy:

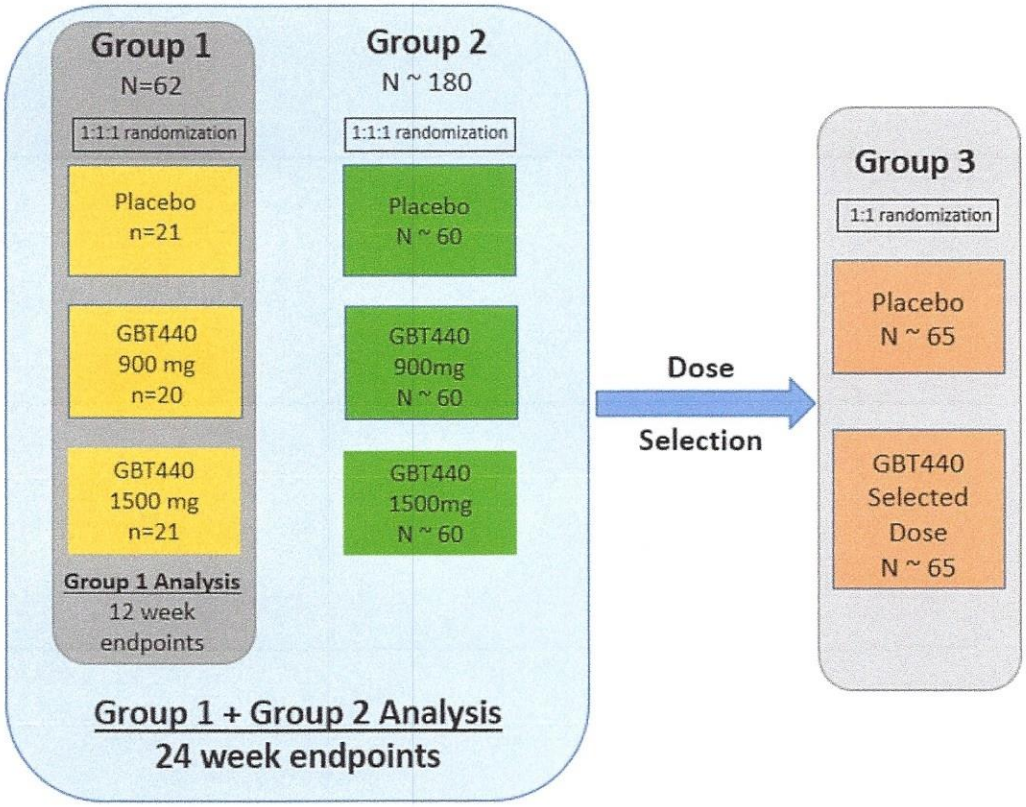
	• Participants with acute bacterial infection requiring antibiotic use should delay screening/enrollment until the course of antibiotic therapy has been completed. • Participants with known active hepatitis A, B, or C or who are known to be human immunodeficiency virus (HIV) positive 7. Severe renal dysfunction (estimated glomerular filtration rate at the Screening visit; calculated by the central laboratory) <30mL/min/1.73 m^2 or on chronic dialysis 8. 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). 9. History of unstable or deteriorating cardiac or pulmonary disease within 6 months prior to consent including but not limited to the following: • Unstable angina pectoris or myocardial infarction or elective coronary intervention • Congestive heart failure requiring hospitalization • Uncontrolled clinically significant arrhythmias 9. Any condition affecting drug absorption, such as major surgery involving the stomach or small intestine (prior cholecystectomy is acceptable). 10. Participated in another clinical trial of an investigational agent (or medical device) within 30 days or 5 half-lives of date of informed consent, whichever is longer, or is currently participating in another trial of an investigational agent (or medical device). 11. Inadequate venous access as determined by the Investigator/site staff. 12. Medical, psychological, or behavioral conditions, which, in the opinion of the Investigator, may preclude safe participation, confound study interpretation, interfere with compliance, or preclude informed consent. 13. Receipt of erythropoietin or other hematopoietic growth factor treatment within 28 days of signing ICF or anticipated need for such agents during the study
Statistical Methods	**STUDY ENDPOINTS** **Primary Endpoint** The primary efficacy measure is Hb response., defined as increase of Hb from baseline by > 1 g/dL at 24 weeks. Hb at 24 weeks is determined by the average value of Hb levels at Week 20 and Week 24. **Secondary Endpoints** The secondary efficacy endpoints are as follows: • Change from baseline in hemoglobin at Week 24 • Change and percent change from baseline in hemolysis measures, including unconjugated bilirubin, absolute reticulocyte, reticulocytes %, and LDH at Week 24 • Incidence of severe anemic episodes (Hb < 5.5 g/dL) • Annualized incidence rate of VOC **Exploratory Endpoints** • Change from baseline in hemoglobin at Week 48 and Week 72

	• Change from baseline in hemolysis measures: including unconjugated bilirubin, absolute reticulocytes, reticulocytes %, and LDH, at Week 48 and Week 72 • Time to first VOC. VOC is defined as: – A composite of acute painful crisis or ACS and includes the following: – Moderate to severe pain lasting at least 2 hours. – No explanation other than VOC. – Requires oral or parenteral opioids, ketorolac, or other analgesics prescribed or directed by a healthcare professional. – Must be documented in patient medical record that the patient was seen, or contacted the physician, within 1 business day of the event. The event may take place in a medical setting (hospital, clinic, emergency room). • Time to first ACS or pneumonia • Time to first RBC transfusion • Rate of opioid use as recorded in the eDiary • Sickle Cell Disease Severity Measure (SCDSM) • EuroQol EQ-5D-5L™ health questionnaire (EQ-5D-5L™) • Clinical Global Impression Scale (CGI) • School and/or work attendance as recorded via eDiary • **Safety Endpoint** • AEs, clinical laboratory tests, physical examinations, and vital signs **Pharmacokinetic Endpoint** • PK of voxelotor as evaluated by population PK analysis using nonlinear mixed effects modeling **SAMPLE SIZE** The sample size for the entire study, including Groups 1, 2 and 3, is estimated to be approximately 370 participants (up to a maximum of approximately 435 participants, depending on the dose[s] selected for the Group 3). Refer to the Study Schematic inFigure 1. For analysis purposes, data from all participants in Groups 1 and 2 will be combined to form the basis of the primary analysis of the study. **STRATIFICATION** At the time of randomization, participants will be stratified for HU use (yes/no), geographic region (North America, Europe, Other), and age (adolescent, 12 to <18 years, and adults, 18 to 65 years). **EFFICACY POPULATION AND ANALYSIS** For each population, efficacy analysis will be performed on the Intent to Treat (ITT) population which includes all randomized participants. **GROUP 1 AND MAIN POPULATION ANALYSIS** **Primary Endpoint:**

	Hb response rate will be analyzed using an exact Cochran-Mantel-Haenszel (CMH) general association test. Each voxelotor dose group (900 mg and 1500 mg) will be compared to placebo while stratifying for the randomization stratification factors as appropriate. The primary analysis of Hb response rate will be to compare voxelotor 1500 mg vs placebo. The test hypotheses are as follows: H_0: $p_v = p_c$ vs H_a: $p_v \neq p_c$ where p_v is the Hb response rate in voxelotor 1500 mg group and p_c is the Hb response rate in the placebo group. Change from baseline in Hb over time will be analyzed using a mixed effect for repeated measures (MMRM) model. The fixed effect terms include treatment, study visit, treatment by visit interaction, and randomization stratification factors as appropriate. Within-subject variability will be modeled using an unstructured covariance matrix. The adjusted mean (lsmean) change from baseline in Hb at each visit, estimated from the MMRM model, with the estimated standard error and 95% confidence interval (CI), will be presented. The difference in the adjusted means between treatment groups and the associated 95% CI of the difference will be provided. Hb worsening will summarized using a shift table for each treatment group. Incidenes of post-baseline Hb < 5.5 g/dL will be summarized by treatment group, as well as incidneces of Hb change from baseline < -2 g/dL. Proportion of subjects with Hb of ≥10 g/dL at Week 24 will explored. **Secondary Endpoints:** **Change from Baseline to Week 24 in Hemolysis Related Measures** Percent change from baseline over time in unconjugated bilirubin, absolute reticulocyte, reticulocytes %, and LDH will be analyzed with a similar MMRM model as for change from baseline to Week 24 in Hb. In addition, the absolute and percent changes from Baseline to Week 24 in each hemolysis measure, including absolute reticulocyte, reticulocytes %, and unconjugated bilirubin will be presented descriptively via tabulation of descriptive statistics by treatment group. **VOC up to Week 72** The number of VOC events will be modeled using a negative binomial model with the independent variable of treatment group and adjusted for the stratification factors used for randomization. Additional risk factors, including number of VOC occurrences during the 12 months prior to randomization, will also be explored. The mean cumulative function of VOC events will be presented using recurrent events analysis methods. Annualized incidence rate will be summarized for each treatment group. **Safety Population and Analysis** Safety analysis will be performed on all participants receiving at least one dose of study drug. A treatment-emergent adverse event (TEAE) is defined as an AE that emerges on or after initiation of study drug (having been absent

	pretreatment), or an AE that existed pretreatment and worsened on treatment (relative to the pretreatment state). The incidence of TEAEs will be tabulated by system organ class (SOC), preferred term, severity and relationship to study drug. AEs considered to be related by the Investigator will be summarized. Changes in laboratory parameters and vital signs over time will be summarized. Exposure-adjusted analyses may be performed to account for differences in exposure to study drug between treatment arms. AEs will be reported by severity and relatedness to study treatment and classified according to Medical Dictionary for Regulatory Activities (MedDRA). BPs, HR, and clinical laboratory data (hematology, serum biochemistry and coagulation) will be summarized. For the laboratory safety data, out of range values will be flagged in the data listings and a list of clinically significant abnormal values will be presented **Pharmacokinetics Population and Analysis** Population PK analyses using nonlinear mixed effects modeling will be performed to characterize voxelotor PK in plasma, if applicable, or whole blood. The influence of demographic covariates (such as body weight, age, gender) on voxelotor PK parameters (ie, clearance [CL] and volume of distribution) will be investigated. If appropriate, the voxelotor PK data may be pooled with PK data from other studies.

Figure 1 **Study Schematic**



1. STUDY OBJECTIVES

1.1. Primary Objective

The primary objective is to assess the effect of voxelotor compared to placebo on improvement in hemoglobin.

1.2. Secondary Objectives

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

- clinical measures of hemolysis
- long term VOC incidence

1.3. Exploratory Objectives

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

- Sickle Cell Disease Severity Measure (SCDSM)
- EuroQol EQ-5D-5L health questionnaire (EQ-5D-5L™)
- Clinical Global Impression of Change (CGIC)- Groups 1 and 2 only
- Incidence and time to first RBC transfusion and post baseline onset of VOC
- School and/or work attendance and the use of opioid during the treatment period as recorded via eDiary
- Measures related to SCD pathophysiology and their utility as pharmacodynamic markers to evaluate including inflammatory biomarkers (Part 1 only), kidney function and RBC rheology
- Measures predictive of response to voxelotor

1.4. Safety Objectives

The safety objectives are to assess the safety of voxelotor compared to placebo based on AEs, clinical laboratory tests, physical examinations, and other clinical measures (eg, discontinuations due to AEs, dose reductions).

1.5. Pharmacokinetic Objective

The PK objective is to assess the PK of voxelotor as evaluated by population PK analysis.

2. INVESTIGATIONAL PLAN

2.1. Study Design

This study is a randomized, placebo-controlled, double blind, parallel group, multicenter study of participants, age 12 to 65 years (refer to Section 2.1.1), with SCD (HbSS, HbSC, HbSβthalassemia, or other sickle cell syndrome variants). The study is composed of 3 groups as described below and in Figure 1.

Study procedures and assessments are outlined in Section 4. Dosage and treatment administration are outlined in Section 5. The Study Schematic is provided in Figure 1

The key purposes for each of the 3 study groups are:

Group 1:

- Evaluate safety and efficacy of voxelotor (900mg and 1500mg) compared to placebo.
- Selection of voxelotor dose(s) for further study in Group 3.

Group 2:

- Enable a seamless transition from Group 1 to Group 3 by continuing enrollment and data collection until completion of Group 1 analysis.
- If needed, data from Group 2 may be included in the Group 1 analysis to inform dose selection and potential study modification as appropriate.
- Form the basis for the primary analysis of the study to establish the efficacy and safety of voxelotor, in combination with Group 1.

Group 3: Further investigate the effect of voxelotor at selected dose(s), eg, in participant subgroups as determined from the primary analysis of the study based on data from Group 1 and Group 2 combined.

2.1.1. Adolescent Participants

Initially only adult participants will be enrolled. Adolescent participants (12 to <18 years) will be included in enrollment/randomization when:

1. Single dose PK data and modeling from a previous study are available to confirm the appropriate dose for adolescent participants, and
2. The DSMB has reviewed the safety data from at least 18 adults randomized in this study of which at least 6 adults have received 1500 mg voxelotor for at least 4 weeks to confirm acceptable safety and tolerability before adolescents can be enrolled. Sites will be notified when adolescent participants can be enrolled in this study.

At the time that these criteria are met, adolescents will begin to enroll (as early as Group 1); a minimum of 50 adolescents will be included in this study.

2.1.2. Study Conduct: Group 1

Approximately 60 participants will be randomized in Group 1 in a 1:1:1 ratio to receive voxelotor 900 mg, voxelotor 1500 mg, or matching placebo.

The randomization procedure and participant enrollment are discussed in Sections 5.3 and 6, respectively. Guidelines for enrollment of adolescents are outlined in Section 6.1.1. Details regarding study blinding are provided in Section 6.2.

When the 60th participant reaches 12 weeks of treatment, data from the 60 participants will be unblinded, and an analysis of Group 1 will be conducted to inform the dose selection and other potential protocol modifications for Group 3 study conduct. The voxelotor dose(s) for Group 3 will be determined from the unblinded analysis of efficacy and safety endpoints, and PK/PD.

2.1.3. Study Conduct: Group 2

Approximately 180 participants will be randomized in Group 2 in a 1:1:1 ratio to receive voxelotor 900 mg, voxelotor 1500 mg, or matching placebo. Group 2 enrollment will begin with participant #61 and will end when the Group 3 dose(s) has been selected.

2.1.4. Study Conduct: Group 3

Group 3 sample size (currently planned for approximately 65 participants per dose arm) will be evaluated when the voxelotor dose(s) is selected. Additional considerations (eg, selection of a dose other than those studied in Groups 1 and 2) may also be generated on the basis of findings from the analysis of Groups 1 and 2.

2.1.5. Open Label Extension Study (Under a Separate Protocol-)

Following completion of study treatment, eligible participants will be given the option to enroll in an open label extension study to receive voxelotor at the selected dose(s)

The open label extension study will be available to eligible participants who:

- Were included in the Group 1 Analysis regardless of the treatment arm to which they were randomized.
- Were randomized in Group 2 to the voxelotor dose not selected for Group 3.
- Were randomized in Group 2 and unblinded for data analysis combined with Group 1 data.
- Were included in Group 3 and Group 2 participants randomized to placebo or the selected dose(s) and completed through end of treatment.

2.1.6. Duration of Study

The study will end when the last participant's last visit occurs which is approximately 72 weeks after randomization of the last participant.

Duration of study for an individual participant includes Screening (at least 28 days, but up to 35 days to account for window flexibility), treatment for a minimum of 2 weeks and a maximum of 72 weeks, and an End of Study (EOS) visit at 4 weeks (± 7 days) after the last dose of study drug. From Screening through follow-up, total participation in this study for an individual participant may last from approximately 10 weeks to up to 81 weeks. Participants will continue to be followed for efficacy through at least the primary efficacy period regardless of treatment discontinuation.

2.1.7. Duration of Treatment

The duration of treatment for each of the 3 study groups is as follows:

Group 1:

Minimum duration is 12 weeks, maximum duration is 72 weeks.

Group 2:

Minimum duration is 2 weeks, maximum is duration 72 weeks.

Group 3:

Minimum duration is 24 weeks, maximum duration is 72 weeks.

2.2. Choice of Control Group

This study uses placebo as a comparator on the background of best clinical standard of care treatment. All approved therapies for SCD are allowed under this protocol, none are withheld. This includes pain control, hydroxyurea, L-glutamine and blood transfusions. Hydroxyurea (HU) dose should be stable for at least 90 days prior to signing the ICF to avoid confounding the interpretation of the safety and efficacy endpoint in this study. If HU is initiated after a participant has been randomized, the participant will be discontinued from the study.

Furthermore, the placebo group is needed to fully characterize the risks and benefits of voxelotor over the background of standard of care (HU), in particular for the key secondary electronic patient reported outcomes (ePRO) SCD Severity Measure (SCDSM) which requires a placebo group for interpretation for the meaningfulness of changes in symptoms.

Agreeing to placebo treatment does not place subjects at any increased risks because no standard of care therapies will be witheld as a result.

3. SELECTION OF STUDY POPULATION

3.1. Inclusion Criteria

All participants must meet the following inclusion criteria:

1. Male or female study participants with Sickle Cell Disease:
   - Documentation of SCD genotype (HbSS, HbSC, HbSβthalassemia or other sickle cell syndrome variants) may be based on history of laboratory testing or must be confirmed by laboratory testing during screening.
2. Participants have had at least 1 episode of VOC in the past 12 months. For study eligibility, VOC is defined as a previously documented episode of ACS or acute painful crisis (for which there was no explanation other than VOC) which required prescription or healthcare professional-instructed use of analgesics for moderate to severe pain (documentation must exist in the patient medical record prior to Screening).
3. Age 12 to 65 years (refer to Section 2.1.1).
4. Hemoglobin (Hb) ≥5.5 and ≤10.5 g/dL during screening.
5. For participants taking hydroxyurea (HU), the dose of HU (mg/kg) must be stable for at least 90 days prior to signing the ICF and with no anticipated need for dose adjustments or initiation during the study, in the opinion of the Investigator.
6. Participants must demonstrate 75% compliance with ePRO measure completion to be randomized (participants will be given an ePRO device for at least 28 days during Screening). Participants who have <75% compliance may be rescreened up to two times for ePRO compliance.
7. Participants, who if female and of child bearing potential, are using highly effective methods of contraception from study start to 30 days after the last dose of study drug, and who if male are willing to use barrier methods of contraception, from study start to 30 days after the last dose of study drug.
8. Participant has provided documented informed consent or assent (the informed consent form [ICF] must be reviewed and signed by each participant; in the case of pediatric participants, both the consent of the participant's legal representative or legal guardian, and the participant's assent must be obtained).

3.2. Exclusion Criteria

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

1. More than 10 VOCs within the past 12 months that required a hospital or emergency room or clinic visit.
2. Female who is breast feeding or pregnant.
3. Patients who are receiving regularly scheduled blood (RBC) transfusion therapy (also termed chronic, prophylactic, or preventive transfusion) or have received a RBC

transfusion for any reason within 60 days of signing the ICF or at any time during the screening period.

4. Hospitalized for sickle cell crisis or other vaso-occlusive event within 14 days prior to signing the ICF (ie, a vaso-occlusive event cannot be within 14 days prior to ICF).
5. Hepatic dysfunction characterized by alanine aminotransferase (ALT) >4 × ULN.
6. Participants with clinically significant bacterial, fungal, parasitic or viral infection which require therapy:
   - Participants with acute bacterial infection requiring antibiotic use should delay screening/enrollment until the course of antibiotic therapy has been completed.
   - Participants with known active hepatitis A, B, or C or who are known to be human immunodeficiency virus (HIV) positive.
7. Severe renal dysfunction (estimated glomerular filtration rate at the Screening visit; calculated by the central laboratory) <30mL/min/1.73^2 or on chronic dialysis.
8. 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).
9. History of unstable or deteriorating cardiac or pulmonary disease within 6 months prior to consent including but not limited to the following:
   - Unstable angina pectoris or myocardial infarction or elective coronary intervention.
   - Congestive heart failure requiring hospitalization.
   - Uncontrolled clinically significant arrhythmias.
10. Any condition affecting drug absorption, such as major surgery involving the stomach or small intestine (prior cholecystectomy is acceptable).
11. Participated in another clinical trial of an investigational agent (or medical device) within 30 days or 5 half-lives of date of informed consent, whichever is longer, or is currently participating in another trial of an investigational agent (or medical device)
12. Inadequate venous access as determined by the Investigator/site staff.
13. Medical, psychological, or behavioral conditions, which, in the opinion of the Investigator, may preclude safe participation, confound study interpretation, interfere with compliance, or preclude informed consent.
14. Receipt of erythropoietin or other hematopoietic growth factors within 28 days of signing ICF or anticipated need for such agents during the study.

4. STUDY PROCEDURES AND EVALUATIONS

Procedures that are to occur during Screening and study visits are summarized in Sections 4.2 through 4.12. The screening period for a particular participant commences at the point at which the participant undergoes the first study-specific screening assessment. All screening assessments must be completed within 35 days before randomization. The IXRS user manual contains the information needed for registering participant status (eg, assigning participant numbers, indicating screen failure, temporary suspension of treatment, and End of Treatment [EOT]). Study visits may be conducted ± 2 days of the scheduled visit through Week 8, ± 5 days for visits through Week 24, and ± 7 days for the subsequent visits.

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

4.1. Informed Consent

A signed and dated ICF will be obtained before any screening procedures or study-specific tests may be performed. Evaluations obtained as part of routine medical care and performed during Screening 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.

4.2. ePRO Screening

Participants will be given an ePRO device for at least 28 days during Screening. Participants must demonstrate 75% compliance with ePRO completion to be randomized (participants will be given an ePRO device for at least 28 days during Screening). Participants who have <75% compliance may be rescreened up to two times for ePRO compliance.

4.3. Medical History

Medical history and medication history will be recorded at the time of the physical examination (PE).

4.4. Physical Examination, Height, and Weight

The PE will be a complete PE at Screening, 24 weeks, 48 weeks, 72 weeks, and at the Follow-up Visit; and may be an abbreviated PE at all other visits. Height will only be collected at Screening for adults, but will be collected more frequently for participants that are <18 years of age; weight will be collected at the same visits for all participants.

- Complete PE should include at a minimum: Examination of HEENT, skin, cardiovascular and respiratory systems, abdominal examination, musculoskeletal and symptom directed examination.

- Abbreviated PE should include at a minimum: Examination of eyes, skin, cardiovascular and respiratory systems, abdominal examination, and symptom directed examination.

4.4.1. Vital Signs

Vital signs data to be collected include supine or recumbent systolic and diastolic blood pressure (BP) and pulse rate. 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.

4.4.2. Electrocardiograms

Electrocardiograms (ECGs) (12-lead) will be recorded after a participant has rested for at least 5 minutes in the supine position. At the visits that an ECG is conducted, a single 12-lead ECG will be conducted.

4.5. Eligibility Assessment

Eligibility assessment will be conducted during Screening and also prior to randomization on treatment Day 1. If a participant is found to meet inclusion/ exclusion criteria at screening, but then has a clinically significant change in status prior to randomization, for example is hospitalized for sickle cell crisis and has a change in hemoglobin $\geq$ 1 g/dL (from their screening value), the participant should be withdrawn from Screening and not randomized. If a participant is hospitalized for any reason during screening the Investigator should discuss suitability for randomization with the medical monitor. 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.

Treatment Day 1 should occur on the same day as randomization.

4.6. Randomization Assignment

The randomization will be carried out centrally through an IXRS (additional information is provided in Section 5.3). Permuted blocks within randomization strata will be used. Eligibility should be confirmed prior to randomization.

4.7. Study Drug Dispensation

Study drug will be dispensed as outlined in Section **Error! Reference source not found.**~~1.1.1~~.

4.8. Study Drug Administration

Study drug will be administered in accordance with Section 5.

4.9. Adverse Events

AEs will be recorded throughout the study at time points during the study.

4.10. Laboratory Assessments

Refer to the Schedule of Assessments (Error! Reference source not found.~~Appendix 1~~) for the specific timing that laboratory tests need to occur.

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

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

4.10.1. Hematology

Hematology assessments will be performed through a central laboratory and will include the following:

- RBCs
- Hematocrit (Hct)
- Hemoglobin (Hb)
- Platelets
- White blood cells (WBCs) with differential (basophils, eosinophils, neutrophils, monocytes, and lymphocytes)
- % and absolute reticulocytes
- % dense cells (hyperchromic RBCs)
- RBC distribution width (RDW)
- Hb distribution width (HDW)
- Cell Hb concentration mean (CHCM)
- Mean corpuscular volume (MCV)
- Mean corpuscular hemoglobin concentration (MCHC)

4.10.2. Serum Chemistry

Screening chemistry assessments will be performed through a central laboratory, and will include the following:

- Alanine aminotransferase (ALT)
- Albumin
- Alkaline phosphatase (ALK)
- Aspartate aminotransferase (AST)
- Bicarbonate
- Blood urea nitrogen (BUN)
- Chloride
- Calcium
- Creatinine
- Glucose
- LDH
- Sodium
- Potassium
- Magnesium
- Phosphorus
- Unconjugated Bilirubin (total, direct and indirect)
- Creatine kinase (analyzed as clinically indicated)

Note: Calcium, Magnesium and Phosphorous will be performed at Screening and EOS at a central laboratory and on study as clinically indicated.

4.10.3. Urinalysis

Urine will be assessed for color and appearance. Dipstick analysis will be conducted for: Specific gravity, pH, protein, glucose, ketones, leucocytes, bilirubin, urobilinogen, nitrite, creatinine, and occult blood. Microscopic analysis (RBCs, WBCs, microalbumin, bacteria, and casts) collected as clinically indicated.

Urinalysis will be performed at Screening at a central laboratory and on study.

4.10.4. Erythropoietin

Erythropoietin levels will be evaluated through a central laboratory.

4.10.5. Coagulation

Coagulation (panel) will be conducted at Screening and as clinically indicated, and will include: Prothrombin time (PT), partial thromboplastin (PTT), and international normalized ratio (INR).

4.10.6. Exploratory Assessments

Exploratory assessments that will be performed through a central laboratory and will include:

- Carboxyhemoglobin (Group 1 only)
- Serum Cystatin C
- Soluble P-selectin, VCAM, ICAM, E-Selectin, and other exploratory measures that may be related to disease activity (Group 1 only)
- Hemoglobin fetal (HbF)
- Urine albumin to creatinine ratio
- Pharmacogenomic sample (to be analyzed for markers predictive of response to voxelotor)

Exploratory assessments will be conducted on a less frequent schedule that the standard laboratory tests and urinalysis listed above.

4.10.7. Serum Virology

Serum virology will be performed through a central laboratory and will include: Hepatitis B surface antigen (HBsAg), hepatitis A IgM, and hepatitis C virus (HCV); to be conducted at Screening only if clinically indicated.

4.10.8. Iron Studies

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

4.10.9. Pregnancy Test

In women of childbearing potential, a serum pregnancy test (HCG in serum) will be performed at Screening. Urine pregnancy tests will be performed as outlined in the Schedule of Assessments (refer to Appendix A). If a urine test is positive, the result must be confirmed with a serum pregnancy test.

4.10.10. Pharmacokinetic Sampling

Pre-dose blood samples for whole blood and plasma PK assessments will be collected on a pre-defined schedule. Additionally, Group 1 participants will have PK samples collected on a semi-intensive schedule. Whole blood and plasma concentrations of voxelotor will be measured using a validated liquid chromatography mass spectrometry (LCMS) assay.

4.10.11. Total Blood Volume

The total volume of blood samples (including all hematology and chemistry test samples, and PK samples) to be collected will be less than 100 mL in any 4 week period for adults. For adolescents, blood volume collections will not exceed 2.4 mL/kg in a given 4 week period. Specific blood specimens (eg, exploratory measures) may be omitted at the discretion of the Investigator if warranted such as in the context of blood loss associated with standard clinical

care, bleeding events, or if otherwise deemed appropriate. In this instance, the Site Operations Manual should be consulted for information regarding specimen priority.

4.11. ePRO and eDiary

Sections 4.11.1 through 4.11.4 describe the information that will be captured daily using the handheld study-specific device.

4.11.1. ePRO SCD Severity Measure

A self-administered patient questionnaire of SCD core symptoms including pain severity, frequency and type as well as fatigue and mental acuity will be completed daily.

4.11.2. eDiary of Study Drug Compliance

Participants will record whether or not they took their prescribed study drug daily.

4.11.3. eDiary of School/Work Attendance

Participants will record the days of school or work that were missed daily.

4.11.4. eDiary of Rescue Medications

At the Day 1 visit, this module will be customized by the site staff to reflect the medications/treatments that each participant routinely takes for pain and other symptoms related to their SCD. Both the type and the amount of medications/treatments will be recorded daily. The medication nomenclature captured in the database will be harmonized across geographies for ease of analysis.

4.12. EuroQol EQ-5D-5L Health Questionnaire

EQ-5D-5L™ is a standardized instrument for use as a measure of health outcome. EQ-5D-5L™ is applicable to a wide range of health conditions and treatments, and it provides a simple descriptive profile and a single index value for health status. Participants will complete the EQ-5D-5L™ at the start of the defined clinic visits using the handheld study-specific device.

4.12.1. Clinical Global Impression - Change (Groups 1 and 2 only)

The Invetigator will provide an assessments of the participants overall condition at the timepoints outlined in Appendix A.

4.13. 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.

In an effort to minimize missed assessments and increase patient retention, a third party nursing service may be employed to conduct at-home study visits at the written request of the site investigator. All nurses will be trained to the protocol prior to the first at-home visit, and a copy of qualifications and training records will be provided to and kept at the site. Examples of

at-home visit activities include blood draws, vital signs, and dispensation of study drug. All source documentation of the visit will be provided to and kept at the study site.

4.14. Permanent Study Discontinuation

4.14.1. Early Discontinuation of the Trial

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

In any instance of early termination of the study, the Sponsor will notify, in writing, the Investigators, regulatory authorities and ethics committees (ECs), and will specify the reason(s) for termination.

4.14.2. Early Discontinuation of Individual Participants

4.14.2.1. Early Discontinuation of Study Treatment

Participants may discontinue study treatment for any of the following reasons:

- Adverse Event
- Withdrawal of consent
- Discretion of the Investigator
- Participant is lost to follow-up
- Participant is noncompliant
- Pregnancy

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. A participant may be discontinued from study treatment at any time at the discretion of the Investigator in accordance with his or her clinical judgment.

4.14.2.2. Early Discontinuation of Study Participation

Participants will be informed that they are free to withdraw from the study at any time and for any reason. The Investigator must withdraw from the study any participant who requests to be withdrawn. However, all efforts must be made to follow participants who do not withdraw consent for the full duration of the study through the endpoint visit. For Group 1, the endpoint visit is Week 12. For Groups 2 and 3, the endpoint visit is Week 24. Participants who ask to leave the study early (withdraw consent) should be encouraged to undergo the tests and evaluations listed for the early termination visit (ie, early termination is intended for participants who withdraw consent). If a participant withdraws before completing the study, the date and reason for withdrawal is to be documented on the CRF.

5. DOSAGE AND TREATMENT ADMINISTRATION

5.1. Treatment Regimen

Participants in Group 1 will be randomized in a 1:1:1 ratio to receive voxelotor or placebo each day for a minimum of 12 weeks and a maximum of 72 weeks. Participants will receive voxelotor 900 mg, voxelotor 1500 mg, or matching placebo daily.

Group 2 participants will be randomized in a 1:1:1 ratio to receive voxelotor 900 mg, voxelotor 1500 mg, or matching placebo

After completion of the analysis of data from Groups 1 and 2 and dose(s) selection, participants may be enrolled into Group 3 and randomized equally to receive voxelotor or matching placebo

Participants randomized to placebo will receive placebo that matches voxelotor.

Voxelotor will be administered as 300 mg capsules or tablets orally once daily. Placebo will be provided in the matching form to either the 300 mg capsules or tablets orally once daily.

Each participant may receive doses that are all active, all placebo, or a combination of the two, depending upon the randomization coded to the participant.

Study participants are to be instructed to take study drug with water or other non-alcoholic beverage. Study drug may be taken with or without food. Participants in Group 1 must take their study drug in the mornings and must avoid high fat meals for 4 hours before and 4 hours after taking study drug. Group 2 and Group 3 participants may take study drug in the morning or evening, preferably at same time each day throughout the study (Group 2 and Group 3 participants have no food restrictions/requirements). Participants should be instructed to complete the daily ePRO and eDiary.

Eligible participants may be given the option to enter the open label extension study to receive voxelotor at the dose selected from the Group 1 Analysis (refer to Section 2.1.5).

5.2. Dose Modification

Participants should adhere to their assigned dose level. However, dose modification may be considered if warranted and as outlined below in Sections 5.2.1 and 5.2.2.

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

5.2.1. Dose Frequency

Participants receiving 1500 mg voxelotor will receive five 300 mg capsules or tablets, administered orally, once daily. Participants receiving 900 mg voxelotor will receive three 300 mg capsules or tablets, and 2 placebo capsules or tablets administered orally, once daily. Participants randomized to placebo will receive 5 placebo capsules or tablets administered orally, once daily. If a participant misses a dose, the participants should resume normal dosing the next day (ie, the dose on the day after a day of a missed dose should not be increased or decreased).

5.2.2. Dose Modification Guidelines

Guidelines for reduction, hold, or permanent discontinuation of study drug are provided in Table 1 (study drug related AEs) and Table 2 (study drug related rash).

Table 1 Dose Modification Guidelines for Study Drug Related Adverse Events

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 (1) tablet. If, in the opinion of the Investigator, a Grade 2 AE has resolved to ≤Grade 1, participant may resume study drug at the original dose. If, in the opinion of the Investigator, the AE poses a significant safety concern such that a dose hold is considered, the Investigator should contact the Medical Monitor.
ALT ≥ 3x ULN if ALT WNL at baseline OR >3X 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 or at a reduced dose level due to safety concern or lack of tolerability in the Investigator's judgment	**Study drug**: Hold dose until ≤Grade 2, then resume study drug at original dose. If, in the opinion of the Investigator, dosing should be resumed at a lower dose, contact the Medical Monitor. 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 4.14. If the Investigator considers that the participant would benefit from continuing treatment, the Medical Monitor should be contacted
Consider treatment discontinuation if: • **ALT >8× ULN** • **ALT >3x 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 potential reversible causes of liver function test abnormalities. Contact the Medical Monitor for discussion of study drug discontinuation.

Table 2 Dose Modification Guidelines for Study Drug Related Rash

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. Participant Enrollment and Randomization

5.3. Randomization Procedure

The randomization will be carried out centrally through an IXRS. Permuted blocks within randomization strata will be used. Eligibility should be confirmed prior to randomization on Study Day 1 (first day of dosing).

6. PARTICIPANT RANDOMIZATION

Male or female study participants with sickle cell disease (HbSC, HbSS, or HbS and HbS β0 thal or HbS β+ thal) who have had between 1 and 10 episodes of VOC (defined in Section 8.1.1) in the past year (the past 12 months) will be randomized within each of 3 separate study groups. Groups 1 and 2 will include 3 arms (2 voxelotor doses and placebo), Group 3 will include 2 or 3 arms (depending on voxelotor dose(s) selected for this Group).

Groups 1, 2, and 3 will be randomized in a sequential manner, as follows:

Group 1: Initially, participants will be randomized in a 1:1:1 ratio to receive oral voxelotor 900 mg, oral voxelotor 1500 mg, or matching placebo. When approximately the 60th participant reaches 12 weeks of treatment, data from the 60 participants will be unblinded for the Group 1 Analysis that will inform the dose(s) selection and other modifications for Group 3.

Group 2

Randomization into Group 2 will begin with participant #61 and will end when the Group 3 dose has been selected. It is anticipated that approximately 180 participantsmay be randomized, or until the doses(s) are selected for Group 3 (which ever occurs first), in a 1:1:1 ratio into Group 2.

Group 3

Randomization into Group 3 will begin after selection of the voxelotor dose(s), and completion of any necessary study design modifications. participants will be randomized equally into dose arms to receive oral voxelotor or matching placebo. Group 3, pending Groups 1 and 2 data analysis is currently expected to enroll at least 130 participants.

6.1.1. Adolescent Participant Enrollment

A minimum of 50 adolescents will be included in the study. Refer to Section 2.1.1 for information regarding enrollment of adolescent participants.

6.1.2. Stratification Factors

At the time of randomization, participants will be stratified for HU use (yes/no), geographic region (North America, Europe, Other), and age (adolescent, 12 to <18 years, and adults, 18 to 65 years).

6.2. Blinding

This study is a double-blind study. The voxelotor and placebo capsules or tablets will be matched for shape, size, and color.

With the exception of those noted below in Section 8.3.1.1 Unblinding for Analysis, all individuals involved in the conduct of the study (ie, site staff and participants, Investigator, CRO

personnel, Sponsor personnel) will be blinded to randomized treatment assignment. Drug Supply personnel will remain unblinded throughout the study. Other sponsor and CRO personnel may be unblinded as required per Regulatory reporting requirements of SUSARS.

6.2.1. Events Necessitating Unblinding

Study data will be unblinded for the planned analyses. Section 6.2.1.1 describes the process to support Group 1 analysis. Events that may necessitate unblinding during the conduct of the study, and specific individuals that may be unblinded to manage these events, are outlined below in 6.2.1.2, and 6.2.1.3.

6.2.1.1. Unblinding for Group 1 Analysis

To facilitate the Group 1 analyses, certain Sponsor representatives and Sponsor designees will be unblinded to treatment assignments prior to and during the data analysis (including the biostatistics contract research organization [CRO], Sponsor Biostatistics and Programming staff, and external groups for bioanalytical PK/PD). However, the rest of the Sponsor study team, including all study team members who have direct interactions with study sites, was not unblinded to individual treatment assignment. No site staff or study participants will be unblinded to randomization assignment.

6.2.1.2. Unblinding for Laboratory Test Assessment

Local laboratory tests including hematology laboratory tests may be used as needed per standard of care to manage AEs (such as hospitalization for VOC), and in these circumstances, the laboratory data may need to be unblinded.

Because knowledge of certain laboratory assessments (Hb, hematocrit [Hct], RBC count, total and unconjugated bilirubin, and absolute and % reticulocyte count) may suggest the treatment assignment, these measurements will be redacted to the Investigator and monitored on a regular basis by the DSMB. Results of redacted laboratory tests will be communicated to the Investigator if a participant's absolute reticulocyte count declines to $<80 \times 10^9$/L or Hb declines to <5.0 g/dL or if the Hb declines $\geq$ 3 g/dL from screening. (but this does not require breaking of the treatment assignment blind). This is to ensure participant safety by allowing the Investigator to monitor for potential bone marrow suppression, as described in hydroxyurea (HU) monitoring guidelines (NHLBI 2014) (National Heart, Lung, and Blood Institute; NHLBI, 2014). All other laboratory assessments (not redacted) will be available to the Investigator. Anonymized laboratory results will be available to the Sponsor.

6.2.1.3. Unblinding for Medical Need

If a medical condition should arise for which appropriate treatment cannot be decided without knowledge of the treatment assignment, the Investigator may unblind a study participant. The investigator should promptly document and explain to the Sponsor any premature unblinding (eg, accidental unblinding, unblinding due to a serious adverse event) of the study participant. Pregnancy is considered a medical condition that requires unblinding. Unblinding procedures will be followed as outlined in the IWRS Manual and documented in the Investigator site file and the CRF.

7. ASSESSMENT OF SAFETY

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

7.1. Data and Safety Monitoring Board

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

The DSMB will review:

- The Group 1 Analysis and provide an assessment of the benefit to risk ratio of the 900 mg and 1500 mg doses.
- Safety data from at least 18 adults enrolled in this study of which at least 6 adults have received 1500 mg voxelotor for at least 4 weeks to confirm acceptable safety and tolerability before adolescents can be enrolled. The sites will be notified when adolescent participants can be enrolled in this study. Additionally, this review of early safety and tolerability at 1500 mg must be satisfactory for dosing to continue to at this dose level.
- 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 the DSMB Charter.

8. DATA ANALYSIS AND STATISTICAL PLANS

Statistical programming and analyses will be performed using established statistical methods. Details of all planned analyses will be specified in the statistical analysis plan (SAP). The SAP will be finalized prior to study unblinding. All statistical tests will be conducted at a two sided alpha level of 0.05 unless otherwise stated.

The number of participants will be shown by visit for the duration of the treatment period. Where applicable, Baseline measurements for efficacy assessments will be the average of pre-treatment values. The study data will be reported using tables, figures, and data listings. Continuous variables will be descriptively summarized using mean, standard deviation (SD), coefficient of variation (CV%, as appropriate), median, minimum, maximum, and, as appropriate, geometric mean. Categorical variables will be descriptively summarized by presenting the number (frequency) and percentage in each category. Time to event data will be displayed as Kaplan-Meier curves. Data for participants who provide diary data, but discontinue treatment but continue in the study will be included in the analysis. Descriptive statistics for healthcare utilization will be summarized in a separate report. Where applicable, additional specifications as delineated in the SAP will supersede related descriptions in the protocol.

8.1. Endpoints

8.1.1. Primary Endpoints

The primary efficacy measure is Hb response., defined as increase of Hb from baseline by > 1 g/dL at 24 weeks. Hb at 24 weeks is determined by the average value of Hb levels at Week 20 and Week 24. If Hb assessment is missing at Week 20 or Week 24, the calculation will use the non-missing Hb level.

8.1.2. Secondary Endpoints:

The secondary efficacy endpoints are as follows:

- Change from baseline in hemoglobin at Week 24
- Change and percent change from baseline in hemolysis measures, including unconjugated bilirubin, absolute reticulocyte, reticulocytes %, and LDH at Week 24
- Incidence of severe anemic episodes (Hb < 5.5 g/dL)
- Annualized incidence rate of VOC

8.1.3. Exploratory Endpoints:

- Change from baseline in hemoglobin at Week 48 and Week 72
- Change from baseline in hemolysis measures: including unconjugated bilirubin, absolute reticulocytes, reticulocytes %, and LDH, at Week 48 and Week 72
- Time to first VOC. VOC is defined as:
  - A composite of acute painful crisis or ACS and includes the following:
  - Moderate to severe pain lasting at least 2 hours.

- No explanation other than VOC.
- Requires oral or parenteral opioids, ketorolac, or other analgesics prescribed or directed by a healthcare professional.
- Must be documented in patient medical record that the patient was seen, or contacted the physician, within 1 business day of the event. The event may take place in a medical setting (hospital, clinic, emergency room).

- Time to first ACS or pneumonia
- Time to first RBC transfusion
- Rate of opioid use as recorded in the eDiary
- Sickle Cell Disease Severity Measure (SCDSM)
- EuroQol EQ-5D-5L™ health questionnaire (EQ-5D-5L™)
- Clinical Global Impression Scale (CGI)
- School and/or work attendance as recorded via eDiary

8.1.4. Pharmacokinetic Endpoint

- PK of voxelotor as evaluated by population PK analysis using nonlinear mixed effects modeling.

8.2. Sample Size

The sample size for the entire study, including Groups 1, 2 and 3, is estimated to be approximately 370 participants (up to a maximum of approximately 435 participants, depending on the dose[s] selected for the Group 3). Refer to the Study Schematic in Figure 1 and Section 2.1.

For analysis purposes, data from all participants in Groups 1 and 2 will be combined to form the basis of the primary analysis of the study.

8.2.1. Group 1

The primary efficacy measure, Hb, will be evaluated as 2 endpoints:

- as change from Week 12 to Baseline
- as a responder endpoint (change from Week 12 to Baseline >1 g/dL)

For the endpoint of change from Baseline in Hb, power calculations assume a mean treatment effect of 0.8 g/dL (voxelotor at either dose, minus placebo), the placebo change from Baseline is equal to 0, a per-group SD of 0.6 g/dL. With N = 20 participants per arm, the power exceeds 95% of detecting a treatment difference between either voxelotor dose (900 mg or 1500 mg) versus placebo. Power is calculated for the t-test and assumes that the data are normally distributed. The estimates of 0.8 g/dL and 0.6 g/dL for the treatment effect and SD, respectively, are based on data at Day 90 from Cohorts 16 and 17 from a previous study.

For the responder endpoint at Week 12, the voxelotor doses will be pooled. Assuming responder proportions of 35% and 5% for N = 40 after pooling data from the 900 and 1500 mg groups and placebo (N = 20), respectively, the power with Fisher's exact test at a two-sided alpha = 0.05 is 80%.

8.2.2. Group 2

Group 2 is designed to allow continued enrollment between Group 1 and Group 3 while the Group 1 data collection and analysis with a minimum of 12 weeks of follow up and until decision is made on voxelotor dose selection for Group 3. Group 2 sample size was estimated based on these considerations and no formal statistical assessment was performed.

Based on the results from Group 1 analysis (62 participants), and a second analysis which included 94 subjects from Group 2 (total of 156 participants) with a minimum of 24 weeks of follow up, it was decided that the combination of Group 1 and all Group 2 participants, for a total of 274 randomized subjects, would constitute the basis for the primary analysis of the study.

For the primary analysis of hemoglobin response rate comparing voxelotor 1500 mg to placebo, assuming a 10% Hb response rate in placebo, the study with approximately 90 subjects per treatment group will have >95% power to detect a targeted difference of 30%, using Fisher's exact test with a two-sided alpha of 0.0481 (Section 8.4.3).

8.2.3. Group 3

Group 3 sample size will be determined when the voxelotor dose(s) is selected. Additional considerations may also be generated on the basis of key findings in the primary analysis from Groups 1 and 2.

8.3. Populations for Analysis

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

- Safety Population: All participants who receive any amount of study medication will be included in the Safety Population. Participants will be analyzed based on medication received. This is the primary population for demography and safety data.
- Intent to Treat (ITT) Population: Efficacy analyses will be performed on the ITT population which includes all randomized participants.
- Modified Intent-to-Treat (mIIT) Population: mITT population incudes all randomized patients who received at least one dose of study treatment.
- PK Population: The PK Population will consist of all participants who receive active study drug and have at least one measured concentration at a scheduled PK time point after the start of dosing. If any participants are found to be noncompliant with respect to dosing or have incomplete data, protocol violations, or clinical events that affect PK, a decision will be made on a case-by-case basis as to their inclusion in the analysis. Participants in this population will be used for all PK summaries.

8.4. Analysis

The primary analyses (based on data from all Group 1 and 2 participants) will adjust for the randomization stratification factors. For the Group 1 population, due to the smaller sample size, adjustment will be made only for a single stratification factor. The factor that will be selected will be the one for which the imbalance between the largest and smallest strata level is the smallest. If both voxelotor dose groups are selected in the primary analysis, the comparisons will be of each voxelotor dose versus placebo, and will be adjusted for multiplicity.

8.4.1. Efficacy Analysis

8.4.1.1. Primary Endpoint

Hb response rate will be analyzed using an exact Cochran-Mantel-Haenszel (CMH) general association test. Each voxelotor dose group (900 mg and 1500 mg) will be compared to placebo while stratifying for the randomization stratification factors as appropriate. The primary analysis of Hb response rate will be to compare voxelotor 1500 mg vs placebo. The test hypotheses are as follows:

$H_0: p_v = p_c$ vs $H_a: p_v \neq p_c$

where p_v is the Hb response rate in voxelotor 1500 mg group and p_c is the Hb response rate in the placebo group.

Change from baseline in Hb over time will be analyzed using a mixed effect for repeated measures (MMRM) model. The fixed effect terms include treatment, study visit, treatment by visit interaction, and randomization stratification factors as appropriate. Within-subject variability will be modeled using an unstructured covariance matrix.

The adjusted mean (lsmean) change from baseline in Hb at each visit, estimated from the MMRM model, with the estimated standard error and 95% confidence interval (CI), will be presented. The difference in the adjusted means between treatment groups and the associated 95% CI of the difference will be provided.

Hb worsening will summarized using a shift table for each treatment group. Incidenes of post-baseline Hb < 5.5 g/dL will be summarized by treatment group, as well as incidneces of Hb change from baseline < -2 g/dL.

Proportion of subjects with Hb of ≥10 g/dL at Week 24 will explored.

All analyses specified above will be based on data with imputation for RBC transfusion, and VOC and VOC hospitalization as applicable. The analysis of Hb response rate will also be repeated using observed data without imputation to assess the robustness of the data.

8.4.1.2. Secondary Endpoints

8.4.1.2.1. Change from Baseline to Week 24 in Hemolysis Related Measures

Percent change from baseline over time in unconjugated bilirubin, absolute reticulocyte, reticulocytes %, and LDH will be analyzed with a similar MMRM model as for change from baseline to Week 24 in Hb.

In addition, the absolute and percent changes from Baseline to Week 24 in each hemolysis measure, including absolute reticulocyte, reticulocytes %, and unconjugated bilirubin will be presented descriptively via tabulation of descriptive statistics by treatment group.

8.4.1.2.2. VOC up to Week 72

The number of VOC events will be modeled using a negative binomial model with the independent variable of treatment group and adjusted for the stratification factors used for randomization. Additional risk factors, including number of VOC occurrences during the 12 months prior to randomization, will also be explored.

The mean cumulative function of VOC events will be presented using recurrent events analysis methods.

Annualized incidence rate will be summarized for each treatment group.

For Group 1 analysis, the proportion of days with SCD exacerbation will be analyzed by a fixed effects linear model. Change from Baseline in the TSS will be analyzed with an MMRMThe rate of VOC will be analyzed by the CMH row means scores test. Given the size and duration of the study at the time of the Group 1 Analysis, the recurrent event rate is expected to be low. However, negative binomial regression analyses will be performed if justified by the distribution of event rates.

8.4.1.3. Exploratory Endpoints

Kaplan Meier methods will be used to summarize time-to-event endpoints, including time to first VOC, time to first ACS and time to first RBC transfusion. Event rates will be estimated at landmark time points, eg, Week 12, Week 24, Week 48, as appropriate.

Rate of opioid use, and rate and reasons for RBC transfusion will be summarized descriptively by treatment group.

EQ-5D-L heath questionnaire, Clinical Global Impression (CGI), will be summarized descriptively by treatment group.

8.4.2. Handling of Missing Data and Data Post-Transfusion

Full details of how missing data will be handled will be described in the SAP. The general rule is assigning the most recent score for missing data due to VOC, hospitalization for VOC, and the most recent score for RBC transfusions regardless of whether or not data are missing. The general guidelines regarding how missing data will be handled are described below. It is anticipated the participant dropout rate will be less than 10%.

8.4.2.1. Hemoglobin Responder

- Missing endpoint visit data due to dropout, VOC, or VOC hospitalization: participant will be treated as a non-responder.
- RBC transfusions: For participants who receive a transfusion due to anemia on or 8 weeks (primary analysis) or 12 weeks (sensitivity analysis) before the endpoint visit, the participant will be treated as a non-responder.

8.4.2.2. Hemoglobin Change from Baseline

- Missing data due to participant dropout: For the primary method of analysis of this endpoint (MMRM), missing at random (MAR) will be assumed and no imputation will be done.
- Missing endpoint visit data due to VOC or VOC hospitalization: the most recent Hb measurement prior to hospitalization will be used.
- RBC transfusions: For participants who receive a transfusion on or 8 weeks (primary analysis) or 12 weeks (sensitivity analysis) before the endpoint visit, the most recent score prior to the transfusion will be used.

8.4.2.3. Total Symptom Score

- Missing data due to missing diary entries or participant dropout: If a participant has 7 or more missing diary entries unrelated to VOC or hospitalization due to VOC in a 4-week period, the TSS will be set to missing for that period. For the primary method of analysis of this endpoint (MMRM), missing at random (MAR) is assumed and no imputation will be done.
- Missing data due to VOC or hospitalization due to VOC: participant will be assigned the worst TSS score prior to the onset of the VOC or hospitalization due to VOC for each day that contributed to missing data.
- RBC transfusions: For the 8-week period (primary analysis) or 12-week period (sensitivity analysis) after the transfusion, the TSS from a 4-week period prior to transfusion will be used.

For the rate of VOC, the analyses will not make any adjustments due to missing data. Sensitivity analyses may be performed to test the robustness of inference to missing data. The imputation method will be informed by data from placebo participants with similar clinical status as those with missing data.

Additional details regarding handling of missing data will be described in the SAP.

8.4.3. Interim Efficacy Analysis

Two interim analyses (IA) are planned to inform voxelotor dose selection. The first IA was performed with Group 1 data (n=62), followed by the second IA with the combined Groups 1 and 2a (n=156).

The Main Analysis will be performed based on data from all randomized subjects in Group 1 and Group 2 (n=274). A Lan-DeMets alpha spending function with the O'Brien-Fleming boundary is used to determine the significance level for each IA and the Main Analysis, to maintain an overall type I error rate of 5% (two-sided), resulting in the following:

Analysis	Significance Level (two-sided)
IA #1 (n = 62)	0.000005
IA #2 (n = 156)	0.0059
Primary Analysis (n = 274)	0.0481

PASS Software (version 11) was used to calculate the alpha spending for each analysis (two-sample proportion).

8.4.4. Adjustment for Multiple Comparisons

A fixed sequence hierarchical test procedure will be used to formally evaluate voxelotor 1500 mg and 900 mg dose group in comparison to placebo. The analysis will be based on data from the ITT population (ie, all randomized subjects).

Primary Efficacy Analysis

The first hypothesis testing will be to compare Hb response rate in voxelotor 1500 mg vs placebo, as described in Section 8.4.1.1.

Secondary Efficacy Analyses

If the null hypothesis in the primary efficacy analysis is rejected at a two-sided significance level of 0.0481, the following hierarchically ordered statistical hypotheses will be tested in the order specified below, until the first non-rejection.

1. Change from baseline at Week 24 in Hb: voxelotor 1500 mg vs placebo
2. Percent change from baseline at Week 24 in unconjugated bilirubin: voxelotor 1500 mg vs. placebo
3. Percent change from baseline at Week 24 in reticulocyte %: voxelotor 1500 mg vs Placebo
4. Percent change from baseline at Week 24 in LDH: voxelotor 1500 mg vs placebo
5. Hb response rate at Week 24: voxelotor 900 mg vs placebo
6. Change from baseline at Week 24: voxelotor 900 mg vs placebo
7. Percent change from baseline at Week 24 in unconjugated bilirubin: voxelotor 900 mg vs Placebo
8. Percent change from baseline at Week 24 in reticulocyte %: voxelotor 900 mg vs placebo
9. Percent change from baseline at Week 24 in LDH: voxelotor 900 mg vs placebo

8.4.5. Subgroups

Subgroups defined by subject age group, (adolescent, 12 to <18 years; and adults, 18 to 65 years), geographic region (North America, Europe, Other), baseline HU use (yes, no), baseline VOC history (1, >1) will be analyzed to evaluate the internal consistency of the study outcomes. Subgroups defined by baseline Hb level will also be explored.

8.4.6. Safety and Tolerability Analyses

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

A treatment-emergent adverse event (TEAE) is defined as an AE that emerges on or after initiation of study drug (having been absent pretreatment), or an AE that existed pretreatment and worsened on treatment (relative to the pretreatment state). The incidence of TEAEs will be tabulated by system organ class (SOC), preferred term, severity and relationship to study drug.

AEs considered to be related by the Investigator will be summarized. Changes in laboratory parameters and vital signs over time will be summarized. Exposure-adjusted analyses may be performed to account for differences in exposure to study drug between treatment arms.

AEs will be reported by severity and relatedness to study treatment and classified according to Medical Dictionary for Regulatory Activities (MedDRA).

BPs, HR, and clinical laboratory data (hematology, serum biochemistry and coagulation) will be summarized.

For the laboratory safety data, out of range values will be flagged in the data listings and a list of clinically significant abnormal values will be presented.

8.5. Exploratory Analyses

Additional details regarding analysis methods for exploratory endpoints will be described in the SAP.

8.6. Pharmacokinetic Analyses

Population PK analyses using nonlinear mixed effects modeling will be performed to characterize voxelotor PK in plasma, if applicable, or whole blood. The influence of demographic covariates (such as body weight, age, gender) on voxelotor PK parameters (ie, clearance [CL] and volume of distribution) will be investigated. If appropriate, the voxelotor PK data may be pooled with PK data from other studies.

9. REGULATORY, ETHICAL AND LEGAL OBLIGATIONS

9.1. Ethical Consideration

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

9.2. Good Clinical Practice

The study will be conducted according to the protocol, guidelines established by the International Conference on Harmonization for Good Clinical Practice (ICH for GCP) in clinical trials, and country specific requirements as applicable.

9.3. Institutional Review Board and Regulatory Approval

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

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

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

9.4. 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.

9.5. Essential Documentation Requirements

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

9.6. Informed Consent

It is the Investigator's responsibility to obtain written informed consent from the participant after adequate explanation of the objectives, methods, anticipated benefits, and potential hazards 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 participant to inspection by representatives of the Sponsor, or representatives from regulatory agencies.

Participants unable to sign the ICF may participate in the study if a legal representative or witness provides the consent (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.

9.7. Confidentiality

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

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

9.8. Trial Documentation and Data Storage

The Investigator must retain a comprehensive and centralized filing system of all trial-related documentation that is suitable for 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. Participant files and other source data (including copies of protocols, original reports of test results, investigational agent dispensing logs, correspondence, records of informed consent, and other documents pertaining to the conduct of the 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.

9.9. 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 subject identifiers for at least 15 years after the completion or discontinuation of study. Study participant files and other resource data must be kept for the maximum period of time permitted by the hospital, institution but not less than 15 years. These documents should be retained for a longer period, if required by the applicable regulatory requirements or by the Sponsor. GBT must be notified with retention should the Investigator/institution are unable to continue with the maintenance of study participant files for the full 15 years. All study records must be stored in a secure and safe facility.

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

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

9.10. 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.

9.11. Publication

It is intended to publish the results of the study as a whole once all participants have completed the study and the study has been analyzed. In addition, results available prior to the primary analysis (participants from Group 1 and/or Group 2 who are not included in the primary analysis) may be published prior to completion of the study as a whole.

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

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

APPENDIX A. SCHEDULE OF ASSESSMENTS

Assessments	Screening	Treatment Period												Follow-Up
Study Day(s):	-35 to -1	D 1[a]	W 2[b]	W 4	W 6[b]	W 8	W 12	W16 & W20	W 24	W 36	W 48	W 60	W72[c] & EOT	EOS (last dose + 4 Wks)
Informed Consent	X													
ePRO Screening (at least 28 days)	X													
Eligibility Assessment	X	x												
Medication and Medical History	X	x												
Physical Examination[d]	X	x	x	x	x	x	x	x	x	x	x	x	x	x
Height[e]	X								x		x		x	x
Weight	X						x		x	x	x	x	x	x
Randomization Assignment		x												
Vital Signs[f]	X	x	x	x	x	x	x	x	x	x	x	x	x	x
ECG[g]	X	x		x		x	x	x	x	x	x	x	x	x
ePRO SCDS Measure		x	x	x	x	x	x	x	x					
EQ-5D-5L™[h]		x		x		x	x	x	x	x	x	x	x	x
Clinical Global Impression -Change (CGI-C; Groups 1 and 2 only)		x					x		x		x	x	x	
Adverse Events	~~X~~	x	x	x	x	x	x	x	x	x	x	x	x	x
Concomitant Medications		x	x	x	x	x	x	x	x	x	x	x	x	
eDiary		x	x	x	x	x	x	x	x	x	x	x	x	x
Hematology[i]	X	x	x	x	x	x	x	x	x	x	x	x	x	x
Erythropoietin		x					x		x	x	x	x	x	x
Exploratory Assessments[j]		x					x		x	x	x	x	x	x
HbF analysis		x					x		x				x	x
Blood Sample for Pharmacogenomic Analysis (if participant opted in on ICF)		x												
Serum Chemistry[k]	X	x	x	x	x	x	x	x	x	x	x	x	x	x
Urinalysis[l]	X													x

Assessments	Screening	Treatment Period												Follow-Up
Study Day(s):	-35 to -1	D 1[a]	W 2[b]	W 4	W 6[b]	W 8	W 12	W16 & W20	W 24	W 36	W 48	W 60	W72[c] & EOT	EOS (last dose + 4 Wks)
Coagulation [m]	X													
Serum Pregnancy Test [n]	X													
Urine Pregnancy Test [n]		x		x		x	x	x	x	x	x	x	x	x
Serum Virology [o]	X													
Iron Studies [p]	X													
Pharmacokinetic Sampling			x[q]			x[q]	x[q]		x	x	x	x	x	

Abbreviations: D = day; ECG = electrocardiogram; EOS = End of Study; EOT = End of Treatment; ePRO = electronic patient reported outcomes; EQ-5D-5L™ = EuroQol EQ-5D-5L™ health questionnaire; HbF = hemoglobin fetal; ICF = informed consent form; SCDS = sickle cell disease severity; W = week; Wks = weeks.

Note: Study visits must be conducted within ± 2 days of the scheduled visit through Week 8, and ± 5 days through Week 24, and ± 7 days for the subsequent visits through EOT; the EOS visit should be completed at 4 weeks (± 7 days) after last dose of study drug.

a Day 1 assessments should be performed at least 30 minutes prior to study drug administration and may be performed on Day -1.

b Visits at Week 2 and Week 6 may be removed for patients enrolled into Groups 2 and 3, pending data analysis from Group 1.

c Participants will complete a minimum of 24 weeks and a maximum of 72 weeks of treatment with study drug. Screening for participants will end when approximately 300 participants have been randomized.

d Physical examination (PE) will be a complete PE at Screening, Week 24, Week 48, Week 72, and at the Follow-up Visit; and may be abbreviated PE at all other visits.

e Adult participants (those who are 18 years of age and older) will only have height measured at Screening. Participants 12 to <18 will have height measured at Weeks 24, 48, 72, and EOS.

f Vital signs (blood pressure [BP] and pulse rate) will be measured after a participant has rested for at least 5 minutes in the supine or recumbent position. A repeated measurement of HR and BP will be taken within 5 minutes if the first reading is outside the normal range and deemed clinically significant.

g Electrocardiograms (ECG) (12-lead) will be recorded after a participant has rested for at least 5 minutes in the supine position.

h The EQ-5D-5L™ questionnaire will be implemented in each country when available (pending translation and cultural validation requirements).

i Hematology assessments will be performed through a central laboratory and will include: Red blood cell (RBC), hematocrit (Hct), hemoglobin (Hb), platelets, white blood cell (WBC) (with differential: basophils, eosinophils, neutrophils, monocytes, and lymphocytes), % reticulocytes, absolute reticulocytes, % dense cells (% hyperchomic RBCs), RBC distribution width (RDW), Hb distribution width (HDW), cell hemoglobin concentration mean (CHCM), mean corpuscular volume (MCV) and mean corpuscular hemoglobin concentration (MCHC).

j Exploratory assessments related to measures relevant to SCD pathophysiology and to evaluate measures predictive of response to voxelotor will be performed through a central laboratory and may include but not limited to:, serum cystatin C, urine albumin to creatinine ratio. carboxyhemoglobin, VCAM, ICAM, soluble P-selectin and E-selectin (and other exploratory measures that may be related to disease activity) will be completed for Group 1 only.

k Serum chemistries will be performed through a central laboratory and will include: Alanine aminotransferase (ALT), albumin, alkaline phosphatase (ALK), aspartate aminotransferase (AST), bicarbonate, blood urea nitrogen (BUN), chloride, calcium, creatinine, glucose, LDH, sodium, potassium, magnesium, phosphorus, unconjugated bilirubin (total, direct, and indirect), and creatine kinase (analyzed as clinically indicated). Calcium, magnesium, phosphorous collected at screening and EOS, and as clinically indicated.

l Urinalysis will include assessment for color and appearance and dipstick analysis for: Specific gravity, pH, protein, glucose, ketones, leucocytes, bilirubin, urobilinogen, nitrite, creatinine, and occult blood. Collected at screening, EOS and as clinically indicated. Microscopic analysis (RBCs, WBCs, microalbumin, bacteria, and casts) as clinically indicated.

m Coagulation will include: Prothrombin time (PT), partial thromboplastin (PTT), and international normalized ratio (INR).

n Serum pregnancy test will be performed during Screening for all female participants of child-bearing potential who are not post-menopausal or surgically sterile. Further pregnancy tests will be urine pregnancy tests. If a urine pregnancy test is positive, the result must be confirmed with a serum pregnancy test.

o Serum virology will be performed through a central laboratory and will include: Hepatitis B surface antigen (HBsAg), hepatitis A IgM, and hepatitis C virus (HCV) antibody (to be conducted at Screening only, if clinically indicated).

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

q Semi-intensive PK samples will be collected in the first 60 participants (Group 1) at Weeks 2, 8 and 12. Semi-intensive PK samples will be collected at predose, between 1 to 4 hours and between 6 to 8 hours. All other participants will have predose PK samples collected, regardless of participation in the semi-intensive PK schedule.