Clinical Study Protocol

Study Number	**GBT440-029**
Study Title	**A Phase 2, Open Label, Multiple Dose Escalation Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Voxelotor in Patients with Sickle Cell Disease**
Investigational Product	Voxelotor (GBT440)
IND Number	121,691
EudraCT Number	2019-001838-34
Sponsor	Global Blood Therapeutics, Inc. 181 Oyster Point Blvd South San Francisco, CA 94080 United States of America
Study Director	Will Tappe, MD, Senior Medical Director Global Blood Therapeutics, Inc. 181 Oyster Point Blvd South San Francisco, CA 94080 United States of America Email: wtappe@gbt.com Telephone (707) 321-0745
Protocol Amendment 2.0	05 October 2020
Protocol Amendment 1.0	13 September 2019
Original Protocol	11 July 2019

CONFIDENTIAL

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

STATEMENT OF APPROVAL AND COMPLIANCE

An Open Label, Multiple Dose Escalation Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Voxelotor in Patients with Sickle Cell Disease

SPONSOR APPROVAL

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

Sponsor Representative (Print):	**Rajiv Patni, MD**
Signature:	DocuSigned by Rajiv Patni Rajiv Patni | I approve this document 05-Oct-2020 | 15:21 PDT 9E99A8FD66D84E979CDB6BD1017A274D
Date:	
Title:	**Chief Medical Officer**

INVESTIGATOR APPROVAL

The signature of the Investigator below constitutes approval of this protocol as written and reflects the Investigator's commitment to conduct the study in accordance with the protocol, the applicable laws and regulations, and in compliance with ICH GCP guidelines and Declaration of Helsinki. All data obtained during the study will be provided to GBT. GBT requires that any presentation or publication of study data by an Investigator be reviewed by GBT, before release.

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

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
BID	twice daily
CGI-C	Clinical Global Impression of Change
CRF	case report form
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
ECG	electrocardiogram
EDC	electronic data capture
EOS	End of Study
FDA	(US) Food and Drug Administration
GBT	Global Blood Therapeutics
GCP	Good Clinical Practice
Hb	hemoglobin
HbF	fetal hemoglobin
HbS	hemoglobin S
HIV	human immunodeficiency virus
HU	hydroxyurea
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IPF	idiopathic pulmonary fibrosis
IRB	Institutional Review Board
LDH	lactate dehydrogenase
MTD	maximum tolerated dose
NCI	National Cancer Institute
OxyHb	oxyhemoglobin
PD	pharmacodynamic
PE	physical examination

Abbreviation	Definition
PGI-C	Patient Global Impression of Change
PK	pharmacokinetic(s)
QTcF	QT interval corrected using Fridericia's formula
RBC	red blood cell
RSI	Reference Safety Information
SAE	serious adverse event
SCD	sickle cell disease
SMC	Safety Monitoring Committee
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
US	United States
VOC	vaso-occlusive crisis
WBC	white blood cells

PROTOCOL SYNOPSIS

Study Number	GBT440-029
Study Title	An Open Label, Multiple Dose Escalation Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Voxelotor in Patients with Sickle Cell Disease
Investigational Product	Voxelotor tablets, 500 mg tablets administered orally
Sponsor	Global Blood Therapeutics, Inc. 181 Oyster Point Blvd South San Francisco, CA 94080 United States of America
Number of Clinical Sites	The study will be conducted at up to approximately 10 clinical sites.
Number of Study Participants	Up to 40 participants.
Treatment	Voxelotor will be supplied as 500 mg tablets and will be administered at doses ranging from 1500 mg to up to 3000 mg.
Objectives	Primary Objective: • To evaluate the tolerability and safety of voxelotor at daily doses of > 1500 mg (2000 mg to 3000 mg) in participants with sickle cell disease (SCD) Secondary Objectives: • To evaluate the change in hemoglobin (Hb) and hemolysis measures • To evaluate the incidence rate of vaso-occlusive crises (VOCs) Exploratory Objectives: • To evaluate the PD properties (effect on Hb-oxygen equilibrium curve [OEC]) as measured by P50 and P20 • To assess voxelotor pharmacokinetics (PK) as evaluated by population PK analysis and % Hb occupancy • To evaluate the PK-PD relationship of voxelotor at daily doses of >1500 mg • To evaluate the effects of voxelotor on Clinical Global Impression of Change (CGI-C) and Patient Global Impression of Change (PGI-C)
Study Design	This is an open-label, sequential period, within-participant dose escalation study. Up to 40 participants with SCD (HbSS or $HbSB^0$) who are 18 to < 60 years of age, inclusive, will be enrolled.

Study Design (continued)	Study participants will undergo up to four periods of voxelotor administered orally at progressively higher dose levels from 1500 mg until either a maximum tolerated dose (MTD) or 3000 mg/day dose is reached, whichever occurs first: • Period 1: 1500 mg per day: 1500 mg once daily (3 × 500 mg tablets) for 3 weeks (± 3 days) • Period 2: 2000 mg per day: 1000 mg (2 × 500 mg) twice daily (BID) for 3 weeks (± 3 days) • Period 3: 2500 mg per day: 1500 mg (3 × 500 mg) in morning and 1000 mg (2 × 500 mg) in evening daily for 3 weeks (± 3 days) • Period 4: 3000 mg per day: 1500 mg (3 × 500 mg) BID for 3 weeks (± 3 days) • Observation Period: MTD or 3000 mg daily for 24 weeks • Safety Follow-up Period: from day of last dose to 28 days postdose. If at any time a dose level > 1500 mg is not tolerated by a participant, the dose may be reduced to a previous level for the participant, which will then be administered for 24 additional consecutive weeks as an observation period. Dose modifications are allowed during the observation period in consultation with the Sponsor's Medical Monitor. If 1500 mg daily is the MTD for a participant, then the participant may enter the observation period and continue to receive 1500 mg for up to 24 weeks until such time as they are able to roll over into the open-label extension study or receive commercial voxelotor, where available. If the participant discontinues early from the study, the participant will undergo an End of Study (EOS) visit approximately 28 days after the last dose and will not be eligible for the open-label extension study. The safety of study participants will be closely monitored by the study team. In addition, a Safety Monitoring Committee (SMC) will review safety, tolerability, and available PK and PD data at regular intervals. Blood draws for PK and PD (including Hb and hemolysis markers), routine chemistry and hematology laboratory tests, and 12-lead electrocardiograms (ECGs) in triplicate will be obtained periodically as listed in the Schedule of Assessments. Upon completion of the observation period for individual participants or after study termination, eligible participants will be given the option to enroll in an open-label extension study.
Duration of Study Participation	Study participation will be for up to 44 weeks, which includes up to 30 days in Screening Period; 21 days (3 weeks) each in Periods 1, 2, 3, and 4; 168 days (24 weeks) in the Observation Period; and 28 days in the Safety Follow-up Period.
Statistical Methods	<u>Primary Endpoints</u> • Treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs)

Statistical Methods (continued)	Secondary Endpoints • Change in Hb and clinical measures of hemolysis (unconjugated bilirubin, % reticulocyte, absolute reticulocyte, and lactate dehydrogenase [LDH]) from Baseline • Proportion of participants with an Hb increase > 1 g/dL compared to Baseline • Incidence rate of VOCs Exploratory Endpoints • P50 and P20 at 8 hours and 24 hours postdose • PK of voxelotor as assessed by population PK analysis using nonlinear mixed-effect modeling • % Hb occupancy at 8 hours and 24 hours postdose • CGI-C • PGI-C Sample Size As this is an exploratory study to provide descriptive information on the tolerability, safety and efficacy of voxelotor at dose levels >1500 mg daily, the sample size chosen was based on previous experience in exploratory studies to support the assessment of a MTD based on descriptive summaries of safety and PK data. The sample size of up to 40 participants takes into account the differential tolerance in participants, some potentially tolerating 3000 mg daily, while others only tolerating lower dose levels An effort will be made to enroll a number of subjects sufficient to ensure that at least 6 participants are treated at the study level MTD. Populations for Analysis Safety Population: All participants who receive at least one dose of study drug will be included in the safety population. PK Population: The PK population will consist of all participants who receive any amount of study drug and have at least one measured concentration at a scheduled PK time point after the start of dosing. Analyses TEAEs, defined as events that occur on or after Day 1 of study drug or the worsening of a pre-existing condition on or after Day 1 of study drug, will be classified according to the Medical Dictionary for Regulatory Activities (MedDRA). The incidence of TEAEs and relatedness to study drug, as assessed by the Investigator, will be summarized descriptively by maximum dose level tolerated. Clinical laboratory tests, ECGs, and vital signs over time will be summarized by maximum dose level tolerated using descriptive statistics. An Hb responder endpoint, defined as an increase in Hb of > 1 g/dL compared to Baseline, will be summarized. Additionally, change from baseline in Hb and clinical measures of hemolysis (unconjugated bilirubin, % reticulocyte, absolute reticulocyte, and LDH) will be summarized by maximum dose level tolerated using descriptive statistics. The incidence of VOCs will be summarized by maximum dose tolerated.

Statistical Methods (continued)	The CGI-C and PGI-C will be summarized by maximum dose level tolerated. Population PK analysis using nonlinear mixed-effect modeling will be performed to characterize voxelotor PK in plasma and whole blood.

1. INTRODUCTION

1.1. Disease Background

Sickle cell disease (SCD) is a rare and inherited disorder caused by a point mutation in the β-globin gene, leading to formation of hemoglobin S (HbS). It is a devastating and debilitating disease marked by the pathophysiologic features of hemolytic anemia, vaso-occlusion, and progressive end-organ damage, with a clinical course characterized by life-long disability and early death. A primary and obligatory event in the molecular pathogenesis of SCD is the polymerization of deoxygenated HbS, which leads to sickling of red blood cells (RBCs). The resulting hemolytic anemia is experienced to various degrees by all patients with SCD and is a defining and serious feature of the disease. Hemolytic anemia leads to reduced oxygen-carrying capacity, tissue hypoxia, and clinical manifestations of end-organ damage in patients with SCD. The disease course is also characterized by life-long pain and frequent healthcare interactions. Chronic hemolytic anemia, and its sequelae, have become the leading cause of mortality in adults with SCD and is recognized as a critical contributor to irreversible cumulative organ damage and dysfunction (Lanzkron, 2013; Vichinsky, 2018). Half of adult patients with SCD have irreversible organ damage, and presence of dysfunction in a single organ is an independent predictor of death and subsequent multiorgan dysfunction (Powars, 2005).

Hemoglobin (Hb) concentration is an important indicator of disease severity, indicating not only the degree of anemia but also the degree of hemolysis that occurs in patients with SCD, as evidenced by the strong inverse correlation between Hb and clinical measures of RBC destruction, such as indirect bilirubin, reticulocyte count, and lactate dehydrogenase (LDH), and the association of low Hb and elevated hemolysis with increased risk of mortality (Taylor, 2008). It is well established that low Hb levels are associated with an increased risk for end-organ complications in SCD, including stroke/silent cerebral infarction, chronic kidney disease, leg ulcers, and pulmonary hypertension (Powars, 1991; Ohene-Frempong, 1998; Gladwin, 2004; Ataga, 2018).

Therapies approved for the treatment of SCD in some regions include hydroxyurea (HU) (Smith, 2011), L-glutamine (Emmaus Medical, 2018), and crizanlizumab (Novartis, 2019). Hydroxyurea is an established therapeutic option that is indicated to reduce the frequency of painful crisis and the need for blood transfusions in patients with recurrent moderate-to-severe sickle cell crises (E.R. Squibb, 2018). L-glutamine is an approved therapy in the United States (US) that is indicated to treat the acute complications of SCD in adult patients and pediatric patients five years of age and older (Emmaus Medical, 2018). Although shown to decrease vaso-occlusive crises (VOCs), L-glutamine has no demonstrated effect on hemolytic anemia. Despite the current standard of care, patients with SCD continue to suffer serious morbidity and premature mortality (Steinberg, 2003). Crizanlizumab is approved in the US to reduce the frequency of VOCs in adults and pediatric patients aged 16 years and older with SCD (Novartis, 2019).

1.2. Voxelotor

Voxelotor (formerly known as GBT440) is an orally administered small molecule that inhibits HbS polymerization by allosterically modifying Hb-O_2 affinity and is being developed for the treatment of SCD. Voxelotor was designed to bind to HbS with preferential partitioning into RBCs. It binds covalently and reversibly via Schiff base to the N-terminal valine of the Hb

α chain (ie, a single voxelotor molecule binding per HbS tetramer in a 1:1 stoichiometry) and allosterically (Eaton, 1999) increases HbS-O_2 affinity (Oksenberg, 2016), stabilizing the oxyhemoglobin (oxyHb) state and inhibiting polymerization (Oksenberg, 2016). The voxelotor binding site is distant from heme pockets and therefore it can increase O_2 affinity without sterically blocking the release of O_2.

A primary and obligatory event in the molecular pathogenesis of SCD is the polymerization of deoxygenated HbS. Because oxyHb is a potent inhibitor of HbS polymerization, increasing the proportion of oxyHb in all RBCs with voxelotor can reduce HbS polymerization, decrease RBC membrane damage and destruction and has the potential to subsequently achieve long term disease modification. This principle is supported by the finding that in patients with sickle hereditary persistence of fetal hemoglobin (HbF), the dilution of HbS by 20% to 30% HbF in all RBCs is sufficient to inhibit HbS polymerization, preventing RBC damage and SCD clinical sequelae. This suggests that pharmacologically maintaining approximately 20% to 30% of Hb in the nonpolymerizing oxygenated state in all RBCs may be an effective approach for the treatment of SCD. This therapeutic effect was demonstrated in the pivotal Phase 3 study (GBT440-031) where 1500 mg of voxelotor, achieving Hb modification of 20% to 30%, administered daily orally for 24 weeks showed a significant and clinically meaningful increase in Hb, and decrease in hemolysis (Vichinsky, 2019).

In November 2019, the US Food and Drug Administration (FDA) approved voxelotor, now known by the trade name Oxbryta™, for the treatment of SCD in adults and pediatric patients 12 years of age and older. However, voxelotor remains an investigational drug outside of the US, and this study administers doses at and higher than the approved dose in the US.

1.3. Summary of Relevant Nonclinical Data and Clinical Data

1.3.1. Nonclinical Data

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

Collectively, these studies demonstrate that voxelotor increases Hb-O_2 affinity with high specificity of binding to Hb, stabilizes the oxy or R-state conformation of Hb, prevents HbS polymerization and RBC sickling in vitro, and improves sickle blood viscosity and deformability in vitro. In addition, voxelotor increases HbS-O_2 affinity and RBC half-life, while decreasing ex vivo sickling and reticulocyte count in a SCD mouse model.

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

1.3.2. Clinical Data

As of 05 November 2019, approximately 823 participants have received single or multiple doses of voxelotor in 23 clinical development studies (five studies in SCD, two studies in idiopathic pulmonary fibrosis [IPF], 15 clinical pharmacology studies, and one physiology study of healthy participants exercising in hypoxic conditions).

The 823 participants consist of:

- 379 participants with SCD (122 pediatric and 257 adult participants)
- 378 healthy participants (including participants with severe renal impairment [not on dialysis] and participants with hepatic impairment)
- 43 adult participants with IPF
- 23 participants from the expanded access program (6 adolescents and 17 adults)
  - 15 participants from the GBT-sponsored expanded access protocol
  - 8 participants from the single-patient Investigational New Drug (IND) program

Information regarding the safety, tolerability, and efficacy of voxelotor is provided in Section 1.4. and can be found in the Voxelotor IB.

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

Clinical data to date have shown that treatment with voxelotor results in a dose-dependent increase in Hb within 2 weeks that is maintained through 24 weeks, and with an associated decrease in clinical measures of hemolysis which correlates with drug exposure (Brown, 2018; Vichinsky, 2018). In a global, multicenter, Phase 3, double-blind, randomized, placebo-controlled trial of voxelotor in participants with SCD (Study GBT440-031), the percentage of participants achieving an Hb response (> 1 g/dL Hb increase from Baseline at Week 24) was dose dependent: 51.1% for the voxelotor 1500 mg group, 32.6% for the voxelotor 900 mg group, and 6.5% for the placebo group ($p < 0.001$ for each voxelotor dose vs placebo). In the 1500 mg group, the mean Hb increase at Week 24 was 1.14 g/dL and in placebo -0.08 g/dL. Consistent with the improvement in Hb, the reductions in hemolysis measures (indirect bilirubin, absolute reticulocytes, percent reticulocytes, and LDH) were observed with both voxelotor 1500 mg and 900 mg compared to placebo. These were significant for indirect bilirubin (-25.9%, $p < 0.001$) and percent reticulocytes (-24.5%, $p < 0.001$) (Vichinsky, 2019).

Based on available data, voxelotor has been well tolerated in adult and adolescent patients with SCD. The most common adverse reactions in participants with SCD ≥ 12 years old in ≥ 10% of participants treated with voxelotor 1500 mg with a difference of > 3% compared to placebo included headache, diarrhea, abdominal pain, nausea, fatigue, rash, and pyrexia. Other clinically relevant and less frequent adverse reactions included drug hypersensitivity (< 1%). There were no reported events of anaphylaxis or anaphylactoid reactions in the clinical development program. The majority of treatment-emergent adverse events (TEAEs) were Grade 1 to Grade 2 in severity, clinically manageable, and reversed or resolved. Overall, the safety profile was similar in participants who were or were not receiving HU concomitantly, and between adults and adolescents. In SCD studies with voxelotor, the incidence of VOCs was similar to placebo

regardless of the extent of Hb increase with voxelotor. No increase in incidence of VOC was observed following voxelotor discontinuation. In study participants with SCD, there has been no evidence of mechanism–related toxicity (ie, inadequate O_2 offloading from voxelotor-bound Hb) as indicated by clinical observations, vital signs, electrocardiograms (ECGs), hematologic changes, or cardiopulmonary exercise testing (Howard, 2019; Stewart, 2018).

Overall, no concerning safety findings have been identified in studies with voxelotor and there has been no pattern of adverse events (AEs) that would raise concerns or alter the benefit-risk profile of voxelotor.

Additional information regarding safety is available in the Voxelotor IB (provided separately).

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

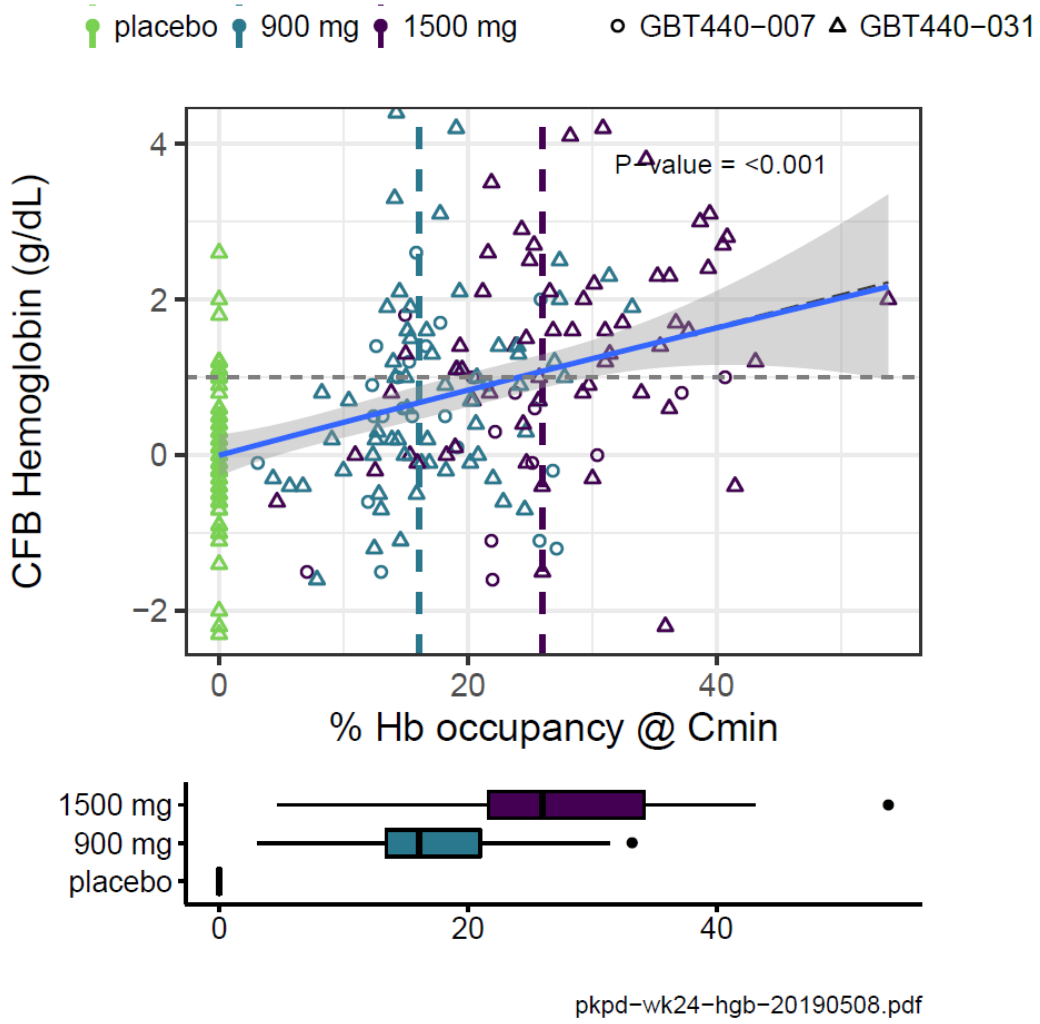
Voxelotor is available in an oral form and is intended for once daily administration. See below, and Section 3.2 and Section 5.1 for additional information regarding the dose to be used in this study.

1.5.1. Study Rationale

In the pivotal Phase 3 Study GBT440-031, voxelotor was shown to have a dose-dependent (1500 mg > 900 mg orally daily), and clinically meaningful increase in Hb, as well as concurrent reductions in clinical measures of hemolysis. Study GBT440-029, is designed to assess tolerability, safety, and PD of voxelotor dose levels higher than 1500 mg daily (the maximum dose in the pivotal Phase 3 study) and to compare these results to the 1500 mg dose. The rationale for this study is based on an exposure-response analysis from the pivotal Study GBT440-031, which showed a linear relationship between whole blood voxelotor and %Hb occupancy and efficacy as measured by improvement in Hb (see Figure 1 below) and hemolysis markers. The 1500 mg dose led to a mean Hb occupancy of 29% and led to a mean Hb increase of 1.1 g/dL. At 3000 mg of voxelotor, assuming a linear relationship, the mean Hb occupancy is projected to be 49.3% with a Hb increase of 2.04 g/dL. Furthermore, no dose level has been associated with exposure-related concerning safety signals, and a maximum tolerated dose (MTD) has not been defined. Treatment-related AEs were mostly grade 1/grade 2 gastrointestinal events. Given the predicted improved efficacy of higher doses, and lack of dose-limiting safety concerns, this study will investigate the potential for a greater benefit/risk for higher doses in patients with SCD.

In this study, baseline response will be characterized in participants receiving a 3-week treatment regimen with voxelotor 1500 mg and compared, within and across participants, to the response with the highest dose level tolerated at steady state. Dose escalation will be done in 3-week increments to assess tolerability at the escalated dose.

Figure 1: Relationships Between Change from Baseline in Hemoglobin at Week 24 and Percent Hemoglobin Occupancy



C_{min}, minimum plasma concentration at steady state; CFB, change from baseline; Hb, hemoglobin.
Note: The vertical dashed lines indicate the median of % Hb occupancy for each dose group. The box plots describe the distribution of % Hb occupancy in each dose group. The left and right edges of the box correspond to the 25th and 75th percentiles, and the vertical line inside the box indicates the median. The solid blue line and gray shaded area represent a second-degree polynomial regression and 95% confidence interval through the data. The p-value for the polynomial relationship compared with the null model (no relationship) is shown on the plot. The black dashed line is a linear regression line through the data.

1.5.2. Dose Rationale

The doses of voxelotor to be evaluated in this study are 1500 mg orally daily through 3000 mg administered by split dose twice daily (BID). This dose of voxelotor is supported by: 1) absence of concerning exposure-related safety findings with 1500 mg daily from the pivotal Phase 3 Study GBT440-031 in adults and adolescents with SCD; 2) demonstrating dose-dependent treatment effects of voxelotor on PD and efficacy measures; and 3) not yet achieving MTD with dose levels up to 2800 mg to date as a single dose in healthy volunteers and 1500 mg daily for multiple doses in healthy volunteers and participants with SCD. A conservative dose-escalation approach is undertaken with increments of 500 mg at a time, representing 33% increase at the lowest dose level and 20% increase at the highest, with careful monitoring and assessments prior to escalation to the next dose level. It is perceived, based on prior data, that voxelotor administration twice rather than once daily may result in favorable gastrointestinal tolerability.

See the IB for additional details.

2. STUDY OBJECTIVES

See Section 3 for details regarding the investigational plan.

2.1. Primary Objective

- To evaluate the tolerability and safety of voxelotor at daily doses of > 1500 mg (2000 mg to 3000 mg) in participants with SCD

2.2. Secondary Objectives

- To evaluate the change in Hb and hemolysis measures
- To evaluate the incidence of VOCs

2.3. Exploratory Objectives

- To evaluate the PD properties (effect on Hb-oxygen equilibrium curve [OEC]) as measured by P50 and P20
- To assess voxelotor pharmacokinetics (PK) as evaluated by population PK analysis and % Hb occupancy
- To evaluate the PK-PD relationship of voxelotor at daily doses of >1500 mg
- To evaluate the effects of voxelotor on Clinical Global Impression of Change (CGI-C) and Patient Global Impression of Change (PGI-C)

3. INVESTIGATIONAL PLAN

This study is an open-label, Phase 2 study of the tolerability and safety of voxelotor 2000, 2500, and 3000 mg in adult participants with SCD ≥ 18 to < 60 years of age.

3.1. Study Endpoints

Study endpoints are described in Section 10.

3.2. Study Design

This is an open-label, sequential period, within-participant dose escalation study. Up to 40 participants with SCD (HbSS or $HbSB^0$) who are 18 to < 60 years of age, inclusive, will be enrolled.

Study participants will undergo up to four periods of voxelotor administration at progressively higher dose levels from 1500 mg until either a MTD or 3000 mg daily dose is reached, whichever occurs first (Figure 2):

- Period 1: 1500 mg per day: 1500 mg once daily (3 × 500 mg tablets) for 3 weeks (± 3 days)
- Period 2: 2000 mg per day: 1000 mg (2 × 500 mg) BID for 3 weeks (± 3 days)
- Period 3: 2500 mg per day: 1500 mg (3 × 500 mg) in morning and 1000 mg (2 × 500 mg) in evening daily for 3 weeks (± 3 days)
- Period 4: 3000 mg per day: 1500 mg (3 × 500 mg) BID for 3 weeks (± 3 days)
- Observation Period: MTD or 3000 mg daily for 24 weeks
- Safety Follow-up Period: from day of last dose to 28 days postdose.

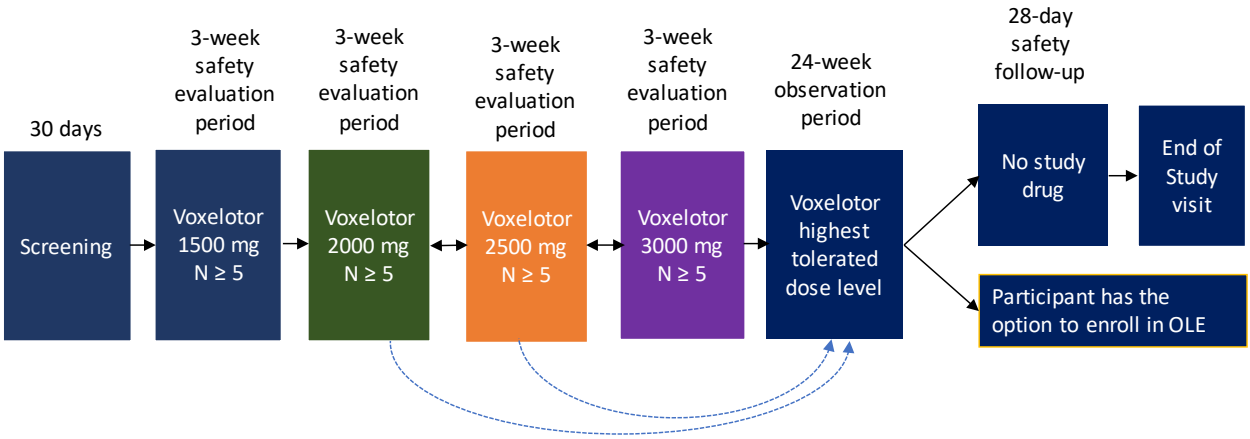
If at any time a dose level > 1500 mg is not tolerated by a participant in the dose escalation period, the dose may be reduced to a previous level for the participant, which will then be administered for 24 additional consecutive weeks as an observation period. Dose modifications are allowed during the observation period in consultation with the Sponsor's Medical Monitor (Appendix C).

If 1500 mg daily is the MTD for a participant, then the participant may enter the observation period and continue to receive 1500 mg, for up to 24 weeks or until they are able to roll over into the open-label extension or receive commercial voxelotor, where available. If the participant discontinues early from the study, the participant will undergo an End of Study (EOS) visit approximately 28 days after the last dose and will not be eligible for the open-label extension study.

The safety of study participants will be closely monitored by the study team. In addition, a Safety Monitoring Committee (SMC) will review safety, tolerability, and available PK and PD data at regular intervals (Section 3.4). Blood draws for PK and PD (including Hb and hemolysis markers), routine chemistry and hematology laboratory tests, and 12-lead ECGs in triplicate will be obtained periodically, as listed in the Schedule of Assessments (Appendix A, Appendix B).

Individual stopping rules are specified in Section 3.7. Upon completion of the observation period for individual participants or after study termination, eligible participants will be given the option to enroll in an open-label extension study.

Figure 2: Study Schema



OLE, open-label extension.

3.3. Assessments

Assessments and procedures are described in Section 8, Appendix A, and Appendix B.

3.4. Safety Monitoring Committee

The SMC will closely monitor the safety of the study participants throughout the duration of study. The SMC will review the totality of safety, tolerability, and available PK and PD data to monitor safety.

The SMC will be composed of the Principal Investigator or designee and Sponsor representatives, including the Study Director/Medical Monitor, Clinician with disease expertise, Biostatistician, and Safety Scientist. Details of the scope, responsibilities, and frequency of the SMC will be provided in the SMC Charter.

3.5. Treatment

See Section 5 for voxelotor information.

3.6. Duration of Study Participation and of the Study

Study participation will be up to 44 weeks in duration, which includes up to 30 days in the Screening Period; 21 days (3 weeks) each in Periods 1, 2, 3, and 4; 168 days (24 weeks) in the Observation Period; and 28 days in the Safety Follow-up Period. See Section 3.2 for additional information regarding the study periods for this study.

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

3.7. Stopping Rules

3.7.1. Early Discontinuation of the Study/Study Stopping Rules

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

The study will be put on hold immediately with the first fatal case reported in participants (at any dose level greater than 1500 mg/day) considered to be related to study drug, until SMC reviews the data and determines whether it is reasonable to proceed.

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

3.7.2. Cohort Dose Escalation Stopping Rules

- If ≥3 participants at a given dose level experience similar and related serious adverse events (SAEs), dose escalation will be paused until the SMC assesses the safety data and makes a recommendation.
- Progression to the next higher dose level can also be stopped if the SMC recommends discontinuation of dose escalation based on the totality of safety data.

3.7.3. Early Discontinuation of Individual Participants

3.7.3.1. Individual Dose-limiting Toxicity Definition: Dose Escalation Period

Criteria for individual dose-limiting toxicity at doses beyond 1500 mg/day include, but are not limited to, the following:

- Any AE Grade ≥ 3 not clearly resulting from the underlying disease and deemed by the Investigator and/or Medical Monitor to be related to study drug.
- Worsening of an ongoing, treatment-related AE by ≥ 1 grade as per Investigator assessment
- Grade 3 nausea, vomiting, or diarrhea (deemed related to study drug) requiring hospitalization and/or intravenous fluids and parenteral tube feeding, total parenteral nutrition
- Study drug-related SAE

If any of these criteria is met, the Investigator should consider temporary dose reduction and/or study drug discontinuation for the individual participant after discussing with the Sponsor. If a subject discontinues early due to AEs, the subject will not be eligible for the open-label extension study.

3.7.3.2. Individual Early Discontinuation of Study Drug

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

- Participant is lost to follow-up
- Discretion of the Investigator
- Participant is noncompliant
- Pregnancy
- Withdrawal of consent (participants are free to discontinue treatment or withdraw from the study at any time and for any reason. The Investigator must withdraw participants from the study who request to be withdrawn).

The participant should return to the study site for an EOS visit approximately 28 days after the last dose of study drug as indicated in Section 8.16. Subjects who discontinue study drug early will not be eligible for the open-label extension study.

4. SELECTION OF STUDY POPULATION

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

4.1. Inclusion Criteria

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

1. Male or female with SCD
2. Documentation of SCD genotype HbSS or $HbSB^0$
3. Age 18 to < 60 years, inclusive
4. Hemoglobin ≥ 5.5 and ≤ 10.5 g/dL during Screening, and considered stable and close to Baseline by the Investigator
5. For participants taking HU, the dose in mg/kg must be stable for at least 90 days prior to signing the informed consent form (ICF) and with no anticipated need for dose adjustments during the study, in the opinion of the Investigator.
6. Participants, who if female and of child-bearing potential, agree to use highly effective methods of contraception or practicing abstinence from study start to 30 days after the last dose of study drug, and who if male, agree to use barrier methods of contraception or practice abstinence from study start to 30 days after the last dose of study drug
7. Participant has provided documented informed consent

4.2. Exclusion Criteria

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

1. More than 10 VOCs within 12 months of screening that required a hospital, emergency room, or clinic visit
2. Female participant who is breast feeding or pregnant
3. Receiving regularly scheduled blood (RBC) transfusion therapy (also termed chronic, prophylactic, or preventive transfusion) or have received an 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 30 days prior to dosing (ie, a vaso-occlusive event cannot be within 30 days prior to dosing)
5. Screening laboratory test of alanine aminotransferase (ALT) > 4 × upper level of normal (ULN)
6. Clinically significant bacterial, fungal, parasitic, or viral infection which requires therapy, including acute bacterial infection requiring antibiotics

7. Known to be COVID-19 positive from within 3 weeks of screening through Day 1
8. Participants with active hepatitis A, B, or C or who are known to be human immunodeficiency virus (HIV) positive
9. Severe renal dysfunction (estimated glomerular filtration rate < 30 mL/min/1.73 m^2 at the Screening visit; calculated by the local laboratory to assess safety) or is on chronic dialysis
10. 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)
11. History of unstable or deteriorating cardiac or pulmonary disease within 6 months prior to consent including but not limited to the following:
    a. Unstable angina pectoris or myocardial infarction or elective coronary intervention
    b. Congestive heart failure requiring hospitalization
    c. Uncontrolled clinically significant arrhythmias
    d. Pulmonary hypertension
12. Criteria related to ECG parameters:
    a. PR interval > 220 msec in any participant
    b. QRS interval > 120 msec or QT interval corrected using Fridericia's formula (QTcF) > 480 msec (both genders) in participants without bundle branch block
    c. QRS interval > 120 msec in participants with newly (within 3 months) emerged bundle branch block
    d. A participant with stable bundle branch block with or without stable cardiac disease may be enrolled; QRS interval > 120 msec and QTcF interval > 480 msec are acceptable in these participants.
13. Any condition affecting drug absorption, such as major surgery involving the stomach or small intestine (prior cholecystectomy is acceptable)
14. 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
15. Inadequate venous access as determined by the Investigator/site staff
16. 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
17. Received erythropoietin or other hematopoietic growth factor treatment within 28 days of signing ICF or is anticipated to require such agents during the study
18. Ongoing or recent (within 2 years) substance abuse
19. Known allergy to voxelotor
20. Use of herbal medications (eg, St. John's Wort), sensitive cytochrome P450 (CYP) 3A4 substrates with a narrow therapeutic index, strong CYP3A4 inhibitors, fluconazole, or moderate or strong CYP3A4 inducers.

5. TREATMENTS ADMINISTERED

5.1. Treatments Administered

Participants will receive voxelotor as 500 mg tablets. Detailed instructions will be provided to participants prior to the first dose of study drug.

5.2. Dose Frequency

Participants will receive voxelotor tablets administered orally, once or twice daily, as outlined in Section 3.2. If a participant misses a dose, the participant should resume normal dosing the next day (ie, the dose, on the day after the day of a missed dose, should not be increased or decreased).

5.3. Physical Description of Voxelotor

Voxelotor is a synthetic small molecule bearing the chemical name 2-hydroxy-6-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)benzaldehyde. The chemical formula is $C_{19}H_{19}N_3O_3$ and the molecular weight is 337.4 g/mol.

5.4. Formulation

Voxelotor will be supplied as 500 mg tablets.

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

5.5. Packaging and Labeling

Voxelotor drug product will be supplied to clinical sites in high-density polyethylene bottles with induction sealed polypropylene child-resistant caps. At each visit (except for End of Treatment and EOS), participants will be supplied a sufficient quantity of study drug to ensure continuous dosing through to the next clinic visit. All study drug packaging must be returned at each visit, regardless if they are empty or contain unused study drug.

5.6. Investigational Product Supply

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

5.7. Storage and Handling Procedure

All study medications will be stored at controlled room temperature between 15°C to 25°C (59°F to 77°F), in the storage area of the investigational site pharmacy, which is a secure, temperature controlled, locked environment with restricted access. The Sponsor or its representatives will be permitted upon request to audit the supplies, storage, dispensing procedures, and records.

5.8. Concomitant and Prohibited Medications

5.8.1. Prior and Concomitant Medications

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

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

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

5.8.2. Hydroxyurea Therapy

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

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

5.8.3. Transfusion

Participants who require chronic transfusion will be discontinued from study drug and 28 days later undergo the EOS visit.

5.8.4. Other Therapies

Penicillin prophylaxis and vaccinations are allowed as per standard of care.

Other concomitant medications are allowed, unless the restrictions in Section 5.8.5 and Section 5.8.6 apply. Permitted concomitant medications include folic acid, L-glutamine, over-the-counter analgesics, and opioids.

The use of erythropoietin is prohibited during the study.

5.8.5. Concomitant Medications to Be Used with Caution

Voxelotor may increase the plasma concentrations of CYP3A4 substrates with a narrow therapeutic index and should be used with caution with these medications. See Table 1 for examples.

Table 1: CYP Substrates with Narrow Therapeutic Range

CYP Enzymes	Substrates with Narrow Therapeutic Range
CYP3A4	Alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, and tacrolimus,

CYP, cytochrome P450; FDA, Food and Drug Administration.
Note that this is not an exhaustive list; country specific lists may be used if available. Decision can be made in consultation with the Sponsor's Medical Monitor.
Substrates with a "narrow therapeutic range" refers to drugs whose exposure-response relationship indicates that small increases in their exposure levels by the concomitant use of CYP inhibitors may lead to serious safety concerns. Adapted from: FDA DRAFT Guidance for Industry: Drug Interactions Studies-Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations. February 2012. Restrictions.

5.8.6. Prohibited Concomitant Medications

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

Voxelotor is a moderate CYP3A4 inhibitor and should not be coadministered with sensitive CYP3A4 substrates with a narrow therapeutic index (refer to Table 2 for examples).

Table 2: Sensitive CYP3A4 Substrates with Narrow Therapeutic Range

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

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

Voxelotor should not be coadministered with strong CYP3A4 inhibitors (refer to Table 3 for examples) or fluconazole.

Table 3: Examples of Strong CYP3A4 Inhibitors

CYP	Strong Inhibitors
CYP3A4	Boceprevir, ceritinib, clarithromycin, cobicistat, conivaptan, danoprevir/ritonavir, elvitegravir/ritonavir, grapefruit juice, idelalisib, indinavir/ritonavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, mifepristone, nefazodone, nelfinavir, posaconazole, ribociclib, ritonavir, saquinavir/ritonavir, telaprevir, telithromycin, tipranavir/ritonavir, troleandomycin, Viekira Pak®, voriconazole

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

Since CYP3A4 is a primary CYP responsible for the metabolism of voxelotor, concomitant use of voxelotor and moderate or strong inducers of CYP3A4 is not allowed (refer to Table 4 for examples).

Table 4: Examples of Moderate and Strong CYP Inducers

CYP3A4	Examples
Moderate CYP3A4 inducers	Efavirenz, bosentan, etravirine, phenobarbital, and primidone
Strong CYP3A4 inducers	Rifampin, apalutamide, phenytoin, carbamazepine, enzalutamide, St John's wort, and mitotane

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

Additional prohibited medications are shown in Table 5.

Table 5: Additional Prohibited Medications

Prohibited Medications
Astemizole, cisapride, terfenadine, crizanlizumab

6. FERTILITY/CONTRACEPTIVE REQUIREMENTS

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

6.1. Instructions for Female Participants of Child-Bearing Potential

For female participants of child-bearing potential (post menarche) and sexually active, pregnancy should be avoided by either abstinence from sex/sexual intercourse or the use of highly effective means of contraception for the duration of the study, and for a total period of 30 days after the participant has taken her last dose of voxelotor. Highly effective means of contraception are listed below in Section 6.4. Pregnancy reporting requirements are outlined in Section 9.4.

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

6.2. Female Participants of Non-Child-Bearing Potential

Female participants of non-child-bearing potential are defined as: bilateral oophorectomy/ hysterectomy/postmenopausal females being amenorrheic for greater than 2 years with an appropriate clinical profile, eg, age appropriate, history of vasomotor symptoms.

6.3. Instructions for Male Participants Capable of Fathering a Child

There is no information about effects that voxelotor could have on the development of the fetus in humans. Therefore, it is important that the partners of male participants do not become pregnant during the study and for a total period of 30 days after the male participant has taken the last dose of voxelotor.

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

6.4. Acceptable Forms of Contraception for Sexually Active Participants

For female participants:

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

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

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

2. Intrauterine device (IUD)
3. Intrauterine hormone-releasing system (IUS)
4. Bilateral tubal occlusion
5. Sexual abstinence:

   Sexual abstinence is considered a highly effective method only if the participant is refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the participant.

For male participants with female partners capable of reproduction:

Barrier methods of contraception:

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

7. ASSESSMENT OF TREATMENT COMPLIANCE

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

Compliance will be determined by returned tablet count.

8. STUDY PROCEDURES AND EVALUATIONS

The Screening Period for a participant commences at the point at which the participant undergoes the first study-specific screening assessment. All screening assessments must be completed within 30 days before the first dose of study drug.

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

8.1. Informed Consent

A signed and dated consent form will be obtained before any protocol-specified screening procedures are performed.

Guidelines for the informed consent process are outlined in Section 13.6.

8.2. Participant Study Number

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

8.3. Demographics and Medical and Medication History

Demographic and baseline characteristics of sex, race, ethnicity, age, weight, and height of the participant will be collected at the time of Screening.

Medical history includes clinically significant diseases, surgeries, all medications (eg, prescription drugs, over-the-counter drugs, herbal/homeopathic remedies, nutritional supplements) used by the participant within 30 days prior to the first dose will be recorded.

8.4. Physical Examination

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

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

8.5. Vital Signs

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

8.6. Body Mass Index

Height and weight will be measured, and body mass index (BMI) will be calculated.

8.7. Electrocardiograms

Electrocardiograms (12-lead) will be recorded after 10 minutes of rest in the supine position. ECGs recorded at Screening, on Days 1 and 7 of each period, and Day 21 in Period 4 will be recorded in triplicate for evaluation at a central ECG laboratory (refer to the Schedule of Assessments, Appendix A, Appendix B). Other ECGs will be recorded as singles.

8.8. Eligibility Assessment, Inclusion/Exclusion Review

Eligibility assessments will be conducted during screening and prior to receiving study drug on treatment Day 1. If a participant is found to meet the inclusion/exclusion criteria, but then has a clinically significant change in status prior to administration of the first dose of study drug (eg, is hospitalized for sickle cell crisis), the participant should be considered a screen failure. Participants who have not been enrolled or dosed may be rescreened once at the Investigator's discretion and in consultation with the Sponsor. Participants who rescreen will have all SCREENING assessments redone, except for Hb genotyping.

8.9. Adverse Events and Concomitant Medications

AEs and concomitant medications will be recorded throughout the study. See Section 9.2 for details regarding AE reporting period for this study.

8.10. Clinical Global Impression of Change

Investigator's assessment of change in the overall health condition of the participant. The CGI-C assessment will be performed using a 7-point scale to assess how much the participant's SCD has improved or worsened relative to Baseline.

8.11. Patient Global Impression of Change

The participant's assessment of change in their overall health condition. The PGI-C assessment will be performed using a 7-point scale to assess how much the participant's SCD has improved or worsened relative to Baseline.

8.12. Safety Laboratory Assessments

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

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

8.12.1. Screening

In addition to screening laboratory tests that are also conducted throughout the study, the following laboratory assessments will be conducted at Screening only:

- Follicle-stimulating hormone (FSH) (postmenopausal females only)
- Coagulation panel (prothrombin time [PT], partial thromboplastin time [PTT], international normalized ratio [INR])
- Serology panel: Serum virology (hepatitis A, B, C, and, if clinically indicated, HIV)
- Hemoglobin genotyping (only if no documentation of hemoglobin genotype is available)
- Fetal hemoglobin
- 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, and occult blood. Microscopic analysis (RBCs, white blood cells [WBCs], bacteria, and casts) will be collected as clinically indicated.

8.12.2. Hematology

Hematology assessments include the following:

- RBCs
- Hematocrit
- Hb
- Platelets
- WBCs with differential (basophils, eosinophils, neutrophils, monocytes, and lymphocytes)
- Percent and absolute reticulocytes
- Mean corpuscular volume (MCV)
- Mean corpuscular hemoglobin concentration (MCHC)

8.12.3. Serum Chemistry

Chemistry assessments include the following:

- ALT
- Albumin
- Alkaline phosphatase (ALP)
- Aspartate aminotransferase (AST)

- Bicarbonate
- Blood urea
- Chloride
- Calcium
- Creatinine
- Glucose
- LDH
- Sodium
- Potassium
- Bilirubin (total, direct, and indirect)

8.13. Other Laboratory Assessments

8.13.1. Effect on Hemoglobin Oxygen Equilibrium Curve

Assessments of P50 and P20 will be conducted by hemoximetry as indicated in the Schedule of Assessments (Appendix A, Appendix B).

8.13.2. Hemoglobin Genotype

Unless documented in their medical record, participants will be tested for hemoglobin genotype at Screening.

8.13.3. Serum Erythropoietin

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

8.13.4. Red Blood Cell Deformability and Dense Cells

Assessments will be conducted as indicated in the Schedule of Assessments (Appendix A, Appendix B).

8.13.4.1. Pregnancy Test

Pregnancy tests will be performed on female participants who are post menarche; a serum pregnancy test (human chorionic gonadotropin in serum) will be performed at Screening. Urine pregnancy tests will be performed in females who are post menarche as outlined in the Schedule of Assessments (Appendix A and Appendix B). If a urine test is positive, the result must be confirmed with a serum pregnancy test.

Information regarding fertility and contraceptive requirements is provided in Section 6; highly effective means of contraception are listed in Section 6.4. Instructions for reporting pregnancy are provided in Section 9.4.

8.13.5. Pharmacokinetic Sample Collection

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

8.14. Phone Call

Follow-up phone calls will be conducted on Day 3 of each study period (Appendix A, Appendix B). These phone calls will be used to confirm compliance, ask for concomitant medications, and check for participant wellbeing by asking open ended questions (eg, How are you feeling?).

8.15. Missed Assessments

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

8.16. End of Study Visit

The EOS is defined as the visit that occurs 28 days after the last dose of study drug. Assessments for this visit are outlined in the Schedule of Assessments (Appendix A, Appendix B).

If the participant terminates study drug early, every effort should be made to collect the Day 168/End-of-Treatment assessments. The participant should also be asked to attend the Safety Follow-up visit 28 days later.

8.17. Participant Discontinuation from the Study

The reasons for a participant's discontinuation from the study may include but are not limited to the following:

- Patient withdrawal of consent
- Study termination
- Adverse event
- Loss to follow-up
- Participant non-compliance, defined as failure to comply with protocol requirements, as determined by the Investigator or Sponsor

If a participant requests to be withdrawn from the study, this information should be documented and signed by the Investigator. No further data will be collected from the signed date onwards.

8.18. Order of Assessments

Visits should take place in the morning. Participants are instructed to hold study drug until a predose blood sample for PK is obtained at the investigational site.

For procedures scheduled to be performed at the same timepoint, the order of assessments is as follows: vital signs, PK sample collection, blood draw for PD/safety laboratory assessments, ECGs. If times are delayed due to technical difficulties, this will be noted but not considered a protocol violation.

The predose PK sample should be collected within 30 min prior to dosing.

On Day 1 in Period 1:

- Triplicate ECGs should be recorded at 3 timepoints prior to dosing (-45 min, -30 min, -15 min).
- Postdose triplicate ECGs (after the morning dose) should be recorded within 15 min following the 2-hour PK sample collection.

On Day 1 in Periods 2, 3, and 4, on Day 7 in all periods, and on Day 21 in Period 4:

- Predose triplicate ECGs should be recorded within 15 min following the predose PK sample collection.
- Postdose triplicate ECGs (after the morning dose) should be recorded within 15 min following the 2-hour PK sample collection.

All PD assessments should be performed after the PK assessments. RBC deformability and dense cells will be tested, if feasible, by the local or collaborating lab at the time of collection.

9. ADVERSE AND SERIOUS ADVERSE EVENTS

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

The determination, evaluation, reporting, and follow-up of AEs will be performed as outlined in Section 9.1. At each visit, the study participant or participant caregiver will be asked about any new or ongoing AE since the previous visit. Assessments of AEs will occur at each study visit. See Section 9.2 for details regarding the required time periods for AE reporting.

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

9.1. Adverse Events

9.1.1. Definition of Adverse Events

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

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

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

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

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

- Death
- A life-threatening AE
- Inpatient hospitalization or prolongation of existing hospitalization

- Persistent or significant incapacity or disability (substantial disruption of the ability to conduct normal life functions)
- A congenital anomaly/birth defect
- Important medical events (IME) that may not result in death, be immediately life-threatening, or require hospitalization may be considered serious when based upon medical judgement, they may jeopardize the study participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

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

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

9.1.2. Severity of Adverse Events

Whenever possible, the severity of all AEs will be graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0.

For AEs not adequately addressed in the NCI CTCAE Version 5.0, the following criteria should be used (Table 6).

Table 6: Grading for Adverse Events Not Covered in the NCI CTCAE

Severity	Description
Grade 1 – Mild	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2 – Moderate	Minimal, local or non-invasive intervention indicated; limited age appropriate instrumental activities of daily living (ADL)
Grade 3 – Severe	Medically significant but not immediately life threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
Grade 4 – Life threatening	Life threatening consequences; urgent intervention indicated
Grade 5 – Fatal	Death

NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events.

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

9.1.3. Relationship to Investigational Product

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

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

9.1.4. Unexpected Adverse Reactions

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

9.2. Adverse Event Reporting

9.2.1. General

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

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

9.2.2. Diagnosis Versus Signs and Symptoms

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

9.2.3. Abnormal Laboratory Values

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

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

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

9.2.4. Pre-existing Medical Conditions

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

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

9.2.5. Worsening of Sickle Cell Disease

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

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

All SAEs, regardless of causal attribution, occurring on this study will be reported to the Sponsor's designated CRO's Drug Safety Department within 24 hours of the Investigator, designee, or site personnel's knowledge of the event. The SAE will be reported via the EDC system. If the EDC system is not available, paper SAE report forms will be used to report the SAE and faxed or emailed to GBT Pharmacovigilance or CRO designee. The information reported on the paper SAE report form should be entered into the EDC once available.

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

Follow-up SAE information must be submitted within 24 hours of awareness as additional information becomes available. All SAEs, regardless of causal attribution, must be followed to resolution, stabilization or until reasonable attempts to determine that resolution of the SAEs are performed.

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

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

Investigators are required to report any urgent safety matters to the Sponsor or its designee within 24 hours of awareness. The Sponsor or its designee will inform regulatory authorities, IECs/IRBs, and Investigators, as applicable, of any events (eg, change to the safety profile of voxelotor, major safety findings that may place study participants at risk) that may occur during the clinical trial that do not fall within the definition of a SUSAR but may adversely affect the safety of study participants.

9.4. Reporting Pregnancy

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

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

An uncomplicated pregnancy will not be considered an AE or SAE. Pregnancy complications such as spontaneous abortion/miscarriage and congenital anomalies are considered SAEs and must be reported as described in Section 9.3. Note: an elective abortion is not considered an SAE. Pregnancy and pregnancy outcomes must be reported on a Pregnancy Notification or Pregnancy Outcome Form, respectively, and sent to the Sponsor or designated Drug Safety CRO within 24 hours of the Investigator, designee, or site personnel learning of the pregnancy or pregnancy outcome.

The child born to a female participant or participant's partner exposed to study drug will be followed for 3 months after delivery. The outcome of any pregnancy and the presence or absence

of any congenital abnormality will be recorded in the Pregnancy Outcome Form and reported to the Sponsor or designated Drug Safety CRO. Any congenital abnormalities in the offspring will be reported as an SAE and must be reported as described in Section 9.3.

Information regarding pregnancy testing (including definition of females of child-bearing potential) is provided in Section 6. Highly effective means of contraception are listed in Section 6.4.

9.5. Reporting Overdose

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

The Investigator will discuss the risks and concerns of investigational agent exposure with the participant. Participants are to be instructed to contact their study site immediately if an overdose of study drug is suspected. A suspected overdose with AEs should be reported to the Sponsor's designated CRO's Drug Safety Department within 24 hours of the Investigator, designee, or site personnel's knowledge of the event. An overdose with AEs must be followed until the adverse effects are resolved or stabilized, or until reasonable attempts to determine resolution of the event are exhausted.

9.6. Safety Monitoring Committee

See Section 3.4 for information regarding the SMC.

10. DATA ANALYSIS AND STATISTICAL PLANS

10.1. Endpoints

10.1.1. Primary Endpoint

The primary endpoints are:

- TEAEs and SAEs

10.1.2. Secondary Endpoints

The secondary endpoints are:

- Change in Hb and clinical measures of hemolysis (unconjugated bilirubin, % reticulocyte, absolute reticulocyte, and LDH) from Baseline
- Proportion of participants with an Hb increase > 1 g/dL compared to Baseline
- Incidence rate of VOCs

10.1.3. Exploratory Endpoints

The exploratory endpoints are:

- P50 and P20 at 8 hours and 24 hours postdose
- PK of voxelotor as assessed by population PK analysis using nonlinear mixed-effect modeling
- % Hb occupancy at 8 hours and 24 hours postdose
- CGI-C
- PGI-C

10.2. Determination of Sample Size

As this is an exploratory study to provide descriptive information on the tolerability, safety, and efficacy of voxelotor at dose levels > 1500 mg daily, the sample size chosen was based on previous experience in exploratory studies to support the assessment of a MTD based on descriptive summaries of safety and PK data. The sample size of up to 40 participants takes into account the differential tolerance in participants, some potentially tolerating 3000 mg daily, while others only tolerating lower dose levels. An effort will be made to enroll a number of subjects sufficient to ensure that at least 6 participants are treated at the study level MTD.

10.3. Populations for Analysis

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

Pharmacokinetic Population: The PK population will consist of all participants who receive any amount of study drug and have at least one measured concentration at a scheduled PK time point after the start of dosing.

10.4. Data Analysis

Data will be presented by maximum dose level.

A TEAE, defined as an event that occurs on or after Day 1 of study drug or the worsening of a pre-existing condition on or after Day 1 of study drug, will be classified according to the Medical Dictionary for Regulatory Activities (MedDRA). The incidence of TEAEs and relatedness to study drug, as assessed by the Investigator, will be summarized descriptively by maximum dose level tolerated.

Clinical laboratory tests, ECGs, and vital signs over time will be summarized by maximum dose level tolerated using descriptive statistics. Change from baseline in ECG intervals will be evaluated using descriptive statistics. If an effect on mean change from baseline in QTc interval exceeding 10 msec is observed, concentration-QTc analysis may be explored. Results from the diagnostic interpretation will be summarized by maximum dose tolerated.

An Hb responder endpoint, defined as an increase in Hb of > 1 g/dL compared to Baseline, will be summarized. Additionally, change from baseline in hemoglobin and clinical measures of hemolysis (unconjugated bilirubin, % reticulocyte, absolute reticulocyte, and LDH) will be summarized by maximum dose level tolerated using descriptive statistics.

The incidence of VOCs will be summarized by maximum dose tolerated.

The CGI-C and PGI-C will be summarized by maximum dose level tolerated.

Population PK analysis using nonlinear mixed-effect modeling will be performed to characterize voxelotor PK in plasma, and whole blood.

11. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

11.1. Source Data

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

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

11.2. Data Collection

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

Data for each participant will be recorded on the CRF unless transmitted to the sponsor or designee electronically, eg, laboratory data. A CRF must be completed for every participant enrolled in the study. When data are complete, the Investigator or medically qualified Sub-Investigator listed on Form FDA 1572 will apply his/her signature on the CRF indicating he/she has reviewed and approves of the data collected on the CRF.

11.3. Essential Documentation Requirements

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

12. QUALITY CONTROL AND QUALITY ASSURANCE

12.1. Monitoring

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

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

12.2. Quality Control and Quality Assurance

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

12.3. Laboratory Accreditation

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

13. REGULATORY, ETHICAL AND LEGAL OBLIGATIONS

13.1. Ethical Conduct of the Study

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

The Investigator is generally not to deviate from the protocol. In medical emergencies, the Investigator will use medical judgment and will remove the participant from immediate hazard. The Investigator will immediately notify the Sponsor and IEC/IRB regarding the nature of the emergency and the course of action taken. The Investigator is to notify the Sponsor of any inadvertent protocol deviations upon discovery and is to document the deviations appropriately in the study files or on the CRFs. The Sponsor assumes no responsibility or liability for any unapproved deviations. Major changes in the protocol initiated by the Sponsor will be provided as an amendment and will be approved by the IEC/IRB prior to implementation (refer to Section 13.4).

13.2. Good Clinical Practice

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

13.3. Written Informed Consent

Each individual will be provided with oral and written information describing the nature, purpose and duration of the study, participation/termination conditions, and risks and benefits. Prior to initiation of any study-related procedures, participants will sign and date the ICF to participate in the study. In the event of a pregnancy in the female partner of a male participant, a pregnancy consent form will be provided to allow the follow-up of the pregnancy.

13.4. Independent Ethics Committee, Institutional Review Board, and Regulatory Approval

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

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

The Investigator will be responsible for ensuring that an annual update is sent to the EC to facilitate their continuing review of the study (if needed) and that the IEC/IRB is informed about the end of the study. Copies of the update, subsequent approvals, and final letter must be sent to the Sponsor. The Investigator will inform the IEC/IRB of any reportable AEs.

13.5. 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.

13.6. Informed Consent

13.6.1. Participant

Each participant will be provided with oral and written information describing the nature, purpose and duration of the study, participation/termination conditions, and risks and benefits. Prior to initiation of any study-related procedures, participants will sign and date the ICF to participate in the study.

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 they can freely withdraw consent and stop participation in the study at any time with no prejudice post study care.

13.6.2. Investigator Responsibilities

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 risks of the study and before any study procedures are commenced. The participant should be given a copy of the ICF in their native language. The informed consent processes should be recorded in the source documentation. The original copies of the signed and dated informed consent must be retained in the institution's records and are subject to inspection by representatives of the Sponsor, or representatives from regulatory agencies.

13.7. 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 IECs/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.

13.8. Regulatory, Ethical and Legal Obligations

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

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

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

13.9. Study Documentation and Data Storage

The Investigator must retain a comprehensive and centralized filing system of all study-related documentation that is suitable for inspection by the Sponsor and representatives of regulatory authorities.

The Investigator must retain essential documents as detailed in Section 14.2. Participant files and other source data (including copies of protocols, original reports of test results, investigational agent dispensing logs, correspondence, records of informed consent, and other documents pertaining to the conduct of the study) must be kept for the maximum period of time permitted by the institution. Documents should be stored in such a way that they can be accessed/data retrieved at a later date. Consideration should be given to security and env**iron**mental risks.

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

14. DATA HANDLING AND RECORDKEEPING

14.1. Inspection of Records

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

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

14.2. Retention of Records

The Investigator will maintain adequate records, including participants' medical records, laboratory reports, signed consent forms, drug accountability records, safety reports, information regarding participants who discontinued the protocol, and any other pertinent data. All study records must be retained for at least 2 years after the last approval of a marketing application in the US or an ICH region and until (1) there are no pending or contemplated marketing applications in the US or an ICH region or (2) at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product under study.
The Investigator/institution should retain participant identifiers for at least 15 years after the completion or discontinuation of the 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 if 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, IEC/IRB approvals, copies of the Form FDA 1572, signed and dated consent forms, medical records, CRFs, drug accountability records, all correspondence and any other documents pertaining to the conduct of the study.

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

14.3. Disclosure of Information

Participants' medical information obtained as a result of this study is considered confidential, and disclosure to third parties, other than those noted in this protocol, is prohibited. Subject to any applicable authorization(s), all reports and communications relating to participants in this study will identify participants only by initials and number. Medical information resulting from a participant's participation in this study may be given to the participant's personal physician, other authorized parties, or to the appropriate medical personnel responsible for the participant's

participation in this clinical study. Data generated in this study will be available for inspection on request by the FDA or other governmental regulatory agency auditors, the Sponsor, the Sponsor's Medical Monitor (or designee), and their designated representatives, the IEC/IRB, and other authorized parties. All information concerning the study medication and the Sponsor's operations (such as patent applications, formulas, manufacturing processes, basic scientific data, or other information supplied by the Sponsor and not previously published) are considered confidential and shall remain the sole property of the Sponsor. The Investigator agrees to use this information only in conducting this study and to not use it for other purposes without the Sponsor's prior written consent. The information developed in this clinical study will be used by the Sponsor in the clinical development of voxelotor and, therefore, may be disclosed by the Sponsor as required, to authorized parties (including its corporate partners for the study drug, if any, and their designated representatives), other clinical Investigators, pharmaceutical companies, the FDA, and other governmental agencies. Any information, inventions, discoveries (whether patentable or not), innovations, suggestions, ideas, and reports made or developed by the Investigator(s) as a result of conducting this study shall be promptly disclosed to the Sponsor and shall be the sole property of the Sponsor. The Investigator agrees, upon the Sponsor's request and at the Sponsor's expense, to execute such documents and to take such other actions as the Sponsor deems necessary or appropriate to obtain patents in the Sponsor's name covering any of the foregoing.

15. PUBLICATION POLICY

The Sponsor intends to publish the results of the study once all participants have completed the study and the study has been analyzed.

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

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

16. FINANCING AND INSURANCE

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.

17. REFERENCES

1. Ataga KI. New and experimental agents for sickle cell disease. Clin Adv Hematol Oncol. 2018;16(7):476-9.
2. Brown C, Hoppe C, Inati A, Abboud MR, Wang W, Liem R, et al. Efficacy and safety of 1500 mg voxelotor in a Phase 2a study (GBT440-007) in adolescents with sickle cell disease. Blood. 2018;132(Suppl 1):509.
3. Dufu K, Patel M, Oksenberg D, Cabrales P. GBT440 improves red blood cell deformability and reduces viscosity of sickle cell blood under deoxygenated conditions. Clin Hemorheol Microcirc. 2018;70(1):95-105.
4. E.R. Squibb & Sons, L.L.C. (2018). Droxia® (hydroxyurea) Prescribing Information. Plainsboro, NJ.
5. Eaton WA, Henry ER, Hofrichter J, Mozzarelli A. Is cooperative oxygen binding by hemoglobin really understood? Nat Struct Biol. 1999;6(4):351-8.
6. Emmaus Medical Inc (2018). ENDARI™ (L-glutamine oral powder) Prescribing Information. Torrance, CA.
7. Gladwin MT, Sachdev V, Jison ML, Shizukuda Y, Plehn JF, Minter K, et al. Pulmonary hypertension as a risk factor for death in patients with sickle cell disease. N Engl J Med. 2004;350(9):886-95.
8. Howard J, Hemmaway CJ, Telfer P, Layton DM, Porter J, Awogbade M, et al. A phase 1/2 ascending dose study and open-label extension study of voxelotor in patients with sickle cell disease. Blood. 2019;133(17):1865-75.
9. Kato GJ, Piel FB, Reid CD, Gaston MH, Ohene-Frempong K, Krishnamurti L, et al. Sickle cell disease. Nat Rev Dis Primers. 2018;15(4):18010.
10. Lanzkron S, Carroll CP, Haywood C Jr. Mortality rates and age at death from sickle cell disease: U.S., 1979-2005. Public Health Rep. 2013;128(2):110-6.
11. Novartis (2019). Advakeo® (crizanlizumab) Prescribing Information. East Hanover, NJ.
12. Ohene-Frempong K, Weiner SJ, Sleeper LA, Miller ST, Embury S, Moohr JW, et al. Cerebrovascular accidents in sickle cell disease: rates and risk factors. Blood. 1998;91:288-94.
13. Oksenberg D, Dufu K, Patel MP, Chuang C, Li Z, Xu Q, et al. GBT440 increases hemoglobin oxygen affinity, reduces sickling and prolongs RBC half-life in a murine model of sickle cell disease. Br J Haematol. 2016;175(1):141-53.
14. Powars DR, Chan LS, Hiti A, Ramicone E, Johnson C. Outcome of sickle cell anemia: a 4-decade observational study of 1056 patients. Medicine (Baltimore). 2005;84(6):363-76.
15. Powars DR, Elliott-Mills DD, Chan L, Niland J, Hiti AL, Opas LM, et al. Chronic renal failure in sickle cell disease: risk factors, clinical course, and mortality. Ann Intern Med. 1991;115(8):614-20.
16. Smith WR, Jordan LB, Hassell KL. Frequently asked questions by hospitalists managing pain in adults with sickle cell disease. J Hosp Med. 2011;6(5):297-303.

17. Steinberg MH, Barton F, Castro O, Pegelow CH, Ballas SK, Kutlar A, et al. Effect of hydroxyurea on mortality and morbidity in adult sickle cell anemia: risks and benefits up to 9 years of treatment. JAMA. 2003;289(13):1645-51.

18. Stewart G, Chase S, Cross T, Ziegler B, Joyner M, Curry T, et al. Effect of GBT440, an R-state stabilizer of hemoglobin, on hypoxic maximal exercise. Am J Respir Crit Care Med. 2018;197:A2367.

19. Taylor JG, Nolan VG, Mendelsohn L, Kato GJ, Gladwin MT, Steinberg MH. Chronic hyper-hemolysis in sickle cell anemia: Association of vascular complications and mortality with less frequent vasoocclusive pain. PLoS One. 2008;3(5):e2095.

20. Vichinsky E, Hoppe C, Ataga KI, Ware RE, Nduba V, El-Beshlawy A, et al. A phase 3 randomized trial of voxelotor in sickle cell disease. N Engl J Med. 2019;381(6):509-19.

21. Vichinsky E, Hoppe C, Howard J, Ataga KI, Nduba V, El-Beshlawy A, et al. Results from Part A of the Hemoglobin Oxygen Affinity Modulation to Inhibit HbS Polymerization (HOPE) Trial (GBT440-031), a placebo-controlled randomized study evaluating voxelotor (GBT440) in adults and adolescents with sickle cell disease. Blood. 2018;132(Suppl 1):505.

APPENDIX A. SCHEDULE OF ASSESSMENTS: DOSE ESCALATION PHASE

	Screening	Periods 1, 2, 3, and 4					Period 4 Only
Visit (days)	**Day -21 to Day -1**	**Day 1**	**Day 2**	**Day 3**	**Day 7 ± 1**	**Day 14 ± 2**	**Day 21**
Visit to investigational site	X	X	X		X	X	X
Phone call				X			
Informed consent	X						
Review inclusion/exclusion criteria	X	X					
Medication and medical history	X	X					
Height[a]/weight/BMI	X	X					X
Vital signs[b]	X	X	X			X	
ECG (12-lead) in triplicate[c]	X	X			X		X
Physical examination[d]	X	X					
Serum pregnancy test (females of child-bearing potential only)	X						
Urine pregnancy test (females of child-bearing potential only)[e]		X					
FSH (postmenopausal females only)	X						
Coagulation panel (PT, PTT, INR)	X						
Serology panel (Hepatitis A, B, C, and HIV[f])	X						
Blood for hematology and chemistry	X	X	X			X	X
Hemoglobin genotype testing (if not already available)	X						
Fetal hemoglobin	X						
Urinalysis	X						
Erythropoietin		X					
RBC deformability, dense cells (if feasible)		X					
Hemoximetry (P50 and P20)[g]		X	X		X		X
Study drug administration[h,i]		→					
Blood for PK assessment[j]		X	X		X		X
CGI-C and PGI-C		X[k]					X

Visit (days)	Screening	Periods 1, 2, 3, and 4					Period 4 Only
	Day -21 to Day -1	Day 1	Day 2	Day 3	Day 7 ± 1	Day 14 ± 2	Day 21
Concomitant medications	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X

BID, twice daily; BMI, body mass index; CGI-C, Clinical Global Impression of Change; ECG, electrocardiogram; FSH, follicle-stimulating hormone; HIV, human immunodeficiency virus; INR, international normalized ratio; P20, partial pressure at which hemoglobin is 20% saturated with oxygen; P50, partial pressure at which hemoglobin is 50% saturated with oxygen; PGI-C, Patient Global Impression of Change; PK, pharmacokinetic; PT, prothrombin time; PTT, partial thromboplastin time; RBC, red blood cell.

Note: For procedures scheduled to be performed at the same timepoint, the order of assessments is as follows: vital signs, PK sample collection, blood draw for PD/safety laboratory assessments, ECGs. If times are delayed due to technical difficulties, this will be noted but not considered a protocol violation. RBC deformability and dense cells will be tested if feasible by the local or collaborating lab at the time of collection.

[a] Height to be assessed at Screening only.

[b] Vital signs (heart rate, blood pressure, and body temperature [only on Day 1] will be measured after a participant has rested for at least 5 minutes in the seated or supine position. While at the investigational site, vital signs will be obtained in the morning prior to dosing and other planned assessments.

[c] Triplicate ECGs should be recorded at screening. On Day 1 of Period 1 only, triplicate ECGs should be recorded at 3 timepoints prior to dosing (-45 min, -30 min, and -15 min); the predose PK sample should be collected immediately prior to the -30-minute ECGs; and postdose triplicate ECGs (after the morning dose) should be recorded within 15 min following the 2-hour PK sample collection. On Day 1 in Periods 2, 3, and 4, on Day 7 in all periods, and on Day 21 in Period 4, predose triplicate ECGs should be recorded within 15 minutes following the predose PK sample collection. Postdose triplicate ECGs (after the morning dose) should be recorded within 15 min following the 2-hour PK sample collection. All triplicate ECGs will be centrally read. Participants should rest supinely for at least 10 min prior to ECGs.

[d] A compete physical examination should be performed at the Screening visit; Physical examinations after the Screening visit may be abbreviated. Abbreviated physical examination should include at a minimum: Examination of skin, cardiovascular and respiratory systems, abdominal examination, and symptom-directed examination.

[e] If positive urine test, serum pregnancy test will be done to confirm result.

[f] A test for HIV will be performed only if clinically indicated.

[g] On Day 1, samples for hemoximetry will be obtained predose (within 30 minutes prior to dosing) and at 8 hours postdose. Samples will only be predose on all other scheduled days. The predose sample will be obtained prior to dosing at the investigational site.

[h] Visits should take place in the morning. Participants are instructed to hold study drug until a predose blood sample for PK is obtained at the investigational site.

[i] During Period 1 (1500 mg daily), study drug will be administered as 3 × 500 mg tablets once daily. During Periods 2, 3, and 4, study drug will be administered BID (Period 2: 2000 mg daily, 2 × 500 mg BID; Period 3: 2500 mg daily, 3 × 500 mg in morning and 2 × 500 mg in evening); Period 4: 3000 mg daily, 3 × 500 mg BID).

[j] On Day 1, blood samples for PK will be obtained predose (within 30 minutes prior to dosing) and at 2 hours (± 15 min) and 8 hours (± 15 min) postdose. On Day 2, blood samples for PK will be obtained predose only, and on Day 7, will be obtained predose and 2 hours postdose. The predose sample will be obtained prior to morning dosing at the investigational site.

[k] Periods 2, 3, and 4 only (equivalent to Day 21 for Periods 1, 2, and 3, respectively).

APPENDIX B. SCHEDULE OF ASSESSMENTS: OBSERVATION PERIOD AND SAFETY FOLLOW-UP

	Observation Period							Safety Follow-up[a]
Visit (weeks)	**Week 1**		**Week 3**	**Week 6**	**Week 12**	**Week 18**	**Week 24/ EOT**	**Week 28/ EOS**
Visit (days)	**Day 1[b]**	**Day 7**	**Day 21**	**Day 42**	**Day 84**	**Day 126**	**Day 168**	**Day 196**
Visit to investigational site	X	X	X	X	X	X	X	X
Weight/BMI							X	X
Vital signs[c]		X	X	X	X	X	X	X
ECG (12-lead) in triplicate[d]					X		X	X
Physical examination[e]							X	X
Urine pregnancy test (females of child-bearing potential only)[f]		X			X		X	
Blood for hematology and chemistry		X	X	X	X	X	X	X
Urinalysis							X	
Erythropoietin							X	
RBC deformability, dense cells (if feasible)					X		X	
Hemoximetry (P50 and P20)[g]		X	X		X		X	
Study drug administration[h,i]	→	→	→	→	→	→	→	
Blood for PK assessment[j]		X	X		X		X	
CGI-C and PGI-C					X		X	
Concomitant medications		X	X	X	X	X	X	X
Adverse events		X	X	X	X	X	X	X

BMI = body mass index; CGI-C, Clinical Global Impression of Change; ECG, electrocardiogram; EOS, End of Study; EOT, End of Treatment; P20, partial pressure at which hemoglobin is 20% saturated with oxygen; P50, partial pressure at which hemoglobin is 50% saturated with oxygen; PGI-C, Patient Global Impression of Change; PK, pharmacokinetic; RBC, red blood cell.

Note: For procedures scheduled to be performed at the same timepoint, the order of assessments is as follows: vital signs, PK sample collection, blood draw for PD/safety laboratory assessments, ECGs. If times are delayed due to technical difficulties, this will be noted but not considered a protocol violation. RBC deformability and dense cells will be tested if feasible by the local or collaborating lab at the time of collection.

[a] Safety Follow-up visit will take place 28 days post final dose.

[b] Day 1 of the observation period is the same as the last day of the dose escalation period. If the participant begins the observation period after a dose reduction, a Day 1 clinical visit is needed, which would collect the same assessments as the Day 21 visit in the Dose Escalation Period (Appendix A).

[c] Vital signs (heart rate and blood pressure) will be obtained in the morning prior to dosing and other planned assessments.

[d] Single safety ECG at Week 12, Week 24/ET, and Week 196 (EOS).
[e] Physical examinations may be abbreviated. Abbreviated physical examination should include at a minimum: Examination of skin, cardiovascular and respiratory systems, abdominal examination, and symptom-directed examination.
[f] If positive urine test, serum pregnancy test will be done to confirm result.
[g] Samples for hemoximetry will be obtained predose (within 30 minutes prior to dosing) at the investigational site.
[h] Visits should take place in the morning. Participants are instructed to hold study drug until a predose blood sample for PK is obtained at the investigational site.
[i] During the observation period, the participant will receive their maximum tolerated dose or 3000 mg daily.
[j] During the observation period, blood samples for PK will be obtained predose (within 30 minutes prior to dosing) at the investigational site.

APPENDIX C. DOSE MODIFICATION GUIDELINES FOR STUDY DRUG-RELATED ADVERSE EVENTS

Dose Reduction	
Event	**Recommended Action**
Grade ≥ 2 (NCI grading scale) AE deemed considered related to study drug by the Investigator AND Precludes continued dosing at the current dose level due to safety concern or lack of tolerability (in the Investigator's judgment)	**Study drug**: May be reduced by one (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 ≥ 3 × ULN if ALT within normal limits at baseline OR > 3 × ULN AND a ≥ 2-fold increase above baseline value if elevated ALT value at baseline in the absence of additional signs of compromised liver function such as elevated PT, PTT, INR, elevated conjugated bilirubin, jaundice, or hepatic pain	**Study drug**: Confirm by repeat testing within 48 to 72 hours if possible, then repeat liver panel at least weekly until ALT level improves. **Additional Actions**: If ALT level continues to increase, reduce dose by one tablet and notify the Medical Monitor.
ALT ≥ 5 × and < 8 × ULN (confirmed by repeat testing within 48 to 72 hours) in the absence of additional signs of compromised liver function such as elevated PT, PTT, elevated conjugated bilirubin, jaundice, or hepatic pain	**Study drug**: Reduce dose by one 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 does not improve within 2 weeks of dose reduction, the Medical Monitor should be notified. If ALT continues to increase within 1 week after a dose reduction, dose should be interrupted and the Medical Monitor should be notified.
Dose Interruption (Hold)	
Event	**Recommended Action**
Grade ≥ 3 (NCI grading scale) AE deemed considered related to study drug by the Investigator AND Precludes continued dosing at the current or at a reduced dose level due to safety concern or lack of tolerability in the Investigator's judgment	**Study drug**: Hold dose until ≤ Grade 2, then resume study drug at original dose. If, in the opinion of the Investigator, dosing should be resumed at a lower dose, contact the Medical Monitor for further discussion. If the AE recurs or worsens, reduce dose by one 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.

Dose Interruption (Hold) (continued)	
Event	**Recommended Action**
NOTE: Study drug-related rash Grade 2 study drug-related rash that persists after a dose reduction	Management: Consider antihistamines, topical steroids, as clinically indicated. **Study Drug**: If rash does not resolve or improve to Grade 1 after a dose reduction, consider a dose hold. Once the rash has resolved or improved, dosing may be resumed at the reduced level or if, in the opinion of the Investigator, participant may resume study drug at the original dose. The Medical Monitor may be contacted for further discussion. Maximum dose hold is 5 continuous days. If, in the opinion of the Investigator, a longer dose hold is clinically needed, the Medical Monitor should be contacted for discussion.
Drug Discontinuation	
Event	**Recommended Action**
Grade ≥ 3 study drug-related AE that, at the discretion of the Investigator, warrants discontinuation of study drug (eg, has not improved or resolved after dose hold).	**Study drug:** Discontinue study drug. If the Investigator considers that the participant would benefit from continuing treatment, the Medical Monitor should be contacted.
Consider drug discontinuation if: • **ALT > 8 × ULN** • **ALT > 3 × ULN or ≥ 2-fold increase above baseline value** if elevated ALT value at baseline with additional signs of compromised liver function such as elevated PT, PTT, INR, elevated conjugated bilirubin, jaundice, or hepatic pain, appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia.	**Study drug**: Hold dose, confirm by repeat testing within 48 to 72 hours if possible, and assess potential reversible causes of liver function test abnormalities. Contact the Medical Monitor for discussion of study drug discontinuation.

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