CLINICAL STUDY PROTOCOL

Study Number	GBT440-034 (C5341022)
Study Title	An Open Label Extension Study of Voxelotor (GBT440) Administered Orally to Participants with Sickle Cell Disease Who Have Participated in Voxelotor Clinical Trials
Investigational Product	Voxelotor (GBT440)
IND	121,691
EudraCT	2017-004045-25
Sponsor Legal Address	Global Blood Therapeutics, Inc., a wholly owned subsidiary of Pfizer Inc. 171 Oyster Point Boulevard, Suite 300 South San Francisco, CA 94080 United States of America
Amendment 3.0	18 December 2023
Amendment 2.0	19 December 2019
Amendment 1.0	14 June 2018
Original Version	09 October 2017
This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and IRBs/ECs and any protocol administrative change letter(s).	

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.

SUMMARY OF CHANGES

Amendment 3 (18 December 2023)

Overall Rationale for the Amendment:

- To incorporate changes previously implemented via protocol clarification memos
- To align the protocol with the Pfizer Protocol Template and Standard Operating Procedures
- Note: the changes below are not due to any increase in safety signals

Protocol Amendment Summary of Changes Table

Description of Change	Brief Rationale	Section # and Name
Non-substantial Modification(s)		
Removed name of Study Director	This section was removed because it contains personal protected data	Title Page
Removed Statement of Approval and Compliance	Statement of Approval and Compliance is not listed on Pfizer protocols per Pfizer SOPs	Approval page
Added language about identification of Single Reference Safety Document (SRSD)	To support Study transition to Pfizer procedures	1.3.1 Safety
Updated the list of examples of moderate and strong CYP3A4 inducers	To provide up-to-date guidance to Investigators per the latest list of examples provided by the FDA and align with other voxelotor clinical study protocols	5.5.3 Prohibited Medications
Added language regarding the maximum volume of blood to be collected in adolescents	For compliance with WHO guidelines	7.1.5 Laboratory Assessments
Added safety reporting clarifications	To support Study transition to Pfizer Pharmacovigilance processes and systems	7.2.2.1 General
Added language and a new appendix for reporting and follow-up assessments for potential drug-induced liver injury (DILI) events	To support study transition to Pfizer Pharmacovigilance processes and systems	7.2.2.3 Abnormal Laboratory Values Appendix 2 *(new appendix)*

Description of Change	Brief Rationale	Section # and Name
Added language for reporting AEs and SAEs after the end of AE/SAE active collection period	To support Study transition to Pfizer Pharmacovigilance processes and systems	7.2.3 Serious Adverse Events, Serious Adverse Drug Reactions, and Requirements for Immediate Reporting
Revised language on reporting overdose	To align with Pfizer's safety reporting process	7.2.4 Reporting Overdose
Added language regarding environmental and occupational exposure as well as exposure during pregnancy and breastfeeding. Previous section 8.2.4 Reporting Pregnancy has been replaced by the language in section 7.3	To support Study transition to Pfizer Pharmacovigilance processes and systems	7.3 Environmental Exposure, Exposure During Pregnancy or Breastfeeding, and Occupational Exposure (new section
Added language regarding the definition and reporting of medication errors	To support Study transition to Pfizer Pharmacovigilance processes and systems	7.4 Medication Errors (new section)
Added or revised language regarding access to medical monitor and regulatory obligations, dissemination of clinical study data, publication policy, data quality assurance, study and site start and closure, data protection, and informed consent	To support Study transition to Pfizer Protocol Template and Standard Operating Procedures	10.3 (Sponsor's Medically Qualified Individual) (new) 11. Regulatory, Ethical, Legal, and Oversight Obligations (includes several new subsections) 12. Data Handling and Record Keeping 13. Publication Policy
Inclusion of Pfizer study number	To support transition to Pfizer processes	At various points throughout the protocol
Minor clarifications and typo corrections across the protocol	For clarification purposes	At various points throughout the protocol

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PROTOCOL SYNOPSIS

PROTOCOL SYNOPSIS
PROTOCOL TITLE: An Open Label Extension Study of Voxelotor (GBT440) Administered Orally to Participants with Sickle Cell Disease Who Have Participated in Voxelotor Clinical Trials
PROTOCOL NUMBER: GBT440-034/C5341022
OBJECTIVES
The objective of this open-label extension (OLE) study is to assess the long-term safety and treatment effect of voxelotor in participants who have completed treatment in study GBT440-031, using the following parameters: 1. Safety based upon AEs, clinical laboratory tests, physical examinations (PE) and other clinical measures. 2. Frequency of sickle cell disease (SCD)-related complications. Hemolytic anemia as measured by hematological laboratory parameters (eg, hemoglobin, reticulocytes and unconjugated bilirubin).
ENDPOINTS
1. Safety endpoints include AEs, clinical laboratory tests, physical examinations and other clinical measures. 2. Frequency of SCD-related complications of long-term dosing with voxelotor. Hemolytic anemia as measured by hematological laboratory parameters (eg, hemoglobin, reticulocytes and unconjugated bilirubin).
STUDY DESIGN
This open label extension (OLE), multi-center study will be conducted at approximately 100 clinical sites globally and will be available to eligible participants from study GBT440-031. The study will enroll participants from GBT440-031 (approximately 435) under any of the following conditions: • Participant has completed 72 weeks of treatment regardless of dose selection for GBT440-031 • Dose selection has occurred for GBT440-031 and participant is on non-selected dose on GBT440-031 • GBT440-031 study interim data analysis and/or study modifications have occurred GBT440-031 study has completed

TREATMENT
All participants will receive daily voxelotor treatment. Participants may receive study drug as long they continue to receive clinical benefit which outweighs risk as determined by the Investigator and/or until the participant has access to voxelotor from an alternative source (i.e., commercialization or through a managed access program).

INCLUSION/EXCLUSION CRITERIA
Subject Inclusion Criteria 1. Male or female study participants with SCD who participated and received study treatment in study GBT440-031. *Note:* Participants in GBT440-031 who discontinued study drug due to an AE, but who remained on study may be eligible for treatment in this study provided the AE does not pose a risk for treatment with voxelotor. 2. Females of child-bearing potential are required to have a negative urine pregnancy test prior to dosing on Day 1. 3. Female participants of child-bearing potential must use highly effective methods of contraception to 30 days after the last dose of study drug. Male participants must use barrier methods of contraception to 30 days after the last dose of study drug. 4. Participant has provided written informed consent or assent (the ICF must be reviewed and signed by each participant; in the case of pediatric participants, both the consent of the participant's legal representative or legal guardian, and the participant's assent must be obtained). **Subject Exclusion Criteria** 1. Female who is breast-feeding or pregnant. 2. Participant withdrew consent from Study GBT440-031. 3. Participant was lost to follow-up from Study GBT440-031. 4. Participant requiring chronic dialysis. Any medical, psychological, safety, or behavioral conditions, which, in the opinion of the Investigator, may confound safety interpretation, interfere with compliance, or preclude informed consent.

STATISTICAL METHODS
Statistical programming and analyses will be performed using established statistical methods. Details of all planned analyses will be specified in a separate statistical analysis plan (SAP). The study data will be reported using summary tables, figures, and data listings. Continuous variables will be summarized using mean, standard deviation (SD), median, minimum, and maximum. Categorical variables will be summarized by presenting the number (frequency) and percentage in each category.

Study Endpoints

Safety

Safety data analysis will be performed on all participants enrolled in the study. A treatment-emergent adverse event (TEAE) is defined as an AE that emerges on or after initiation of study drug (having been absent pretreatment), or an AE that existed pretreatment and worsened on treatment (relative to the pretreatment state). The incidence of TEAEs will be tabulated by system organ class (SOC), preferred term, severity and relationship to study drug. AEs considered to be related by the Investigator will be summarized. AEs will be reported by severity and relatedness to study treatment and classified via the Medical Dictionary for Regulatory Activities (MedDRA).

Changes in clinical laboratory data (hematology, serum chemistry, CCI [redacted]) will be summarized.

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

Frequency of SCD-Related Complications

Over the course of the treatment period, the frequency of SCD complications for each participant will be recorded. SCD complications may include the following: VOC (Vaso-Occlusive Crisis), acute chest syndrome, hepatic sequestration, leg ulcers, priapism, pulmonary hypertension, retinopathy, scleral icterus, splenic sequestration, and stroke. The incidence and rate of each complication and the totality of all SCD-related complications will be computed and then compared to those observed in the GBT440-031 study.

Therapies Associated with VOC

During the treatment period, RBC (Red Blood Cell) transfusion and opioid usage will be recorded. The incidence and rate of these therapies will be calculated and compared to those observed in the GBT440-031 study.

Response in Hemolytic Anemia

At each scheduled laboratory assessment, hematology and serum chemistry will be measured to determine longitudinal durability of response with regards to hemolytic anemia. Of particular interest are hemoglobin, bilirubin, and reticulocyte counts. There will be two baseline values used to describe efficacy and durability: (1) Baseline derived from the pre-dose hematology measurements obtained during the GBT440-031 study and (2) Hematology measurements obtained via pre-dose on Day 1 in this study. Change from baseline, and percent change from baseline for the two aforementioned baseline values will be computed to determine trends over the duration of treatment.

1. BACKGROUND INFORMATION

Sickle Cell Disease (SCD) is a rare, devastating, and debilitating disease marked by the pathophysiologic features of hemolytic anemia, vaso-occlusion, and progressive end-organ damage, with a clinical course characterized by life-long disability and early death. In addition to unpredictable and recurrent episodes of severe pain, commonly referred to as painful crises, a systemic vasculopathy leads to chronic and progressive tissue injury across multiple organ systems. Multiple pathophysiologic mechanisms likely contribute to the systemic vasculopathy, including, importantly, chronic hemolytic anemia (Rother, 2005).

On 25 November 2019, the United States (US) Food and Drug Administration (FDA) approved the study drug voxelotor, now known by the trade name Oxbryta™. Oxbryta is indicated for the treatment of sickle cell disease in adults and pediatric patients 12 years of age and older.

In this trial, the Sponsor will be studying the risks and benefits of long-term treatment in participants previously treated in GBT440-031.

1.1. Name and Description of Investigational Product

Voxelotor is a small molecule allosteric modulator of hemoglobin (Hb) oxygen affinity, that was developed by Global Blood Therapeutics (GBT) for the treatment of sickle cell disease (SCD). Voxelotor is administered orally.

1.2. Summary of Findings from Relevant Nonclinical Trials

Information regarding nonclinical pharmacology (including safety pharmacology and metabolism) and toxicology is provided in the voxelotor Investigator's Brochure (IB), provided under separate cover.

1.3. Summary of the Voxelotor Clinical Program

The clinical activity, safety, and pharmacokinetics of voxelotor have been or are being assessed in 4 clinical studies in adults and pediatric participants with SCD (Table 1).

1.3.1. Safety

In the Phase 3 randomized controlled trial (GBT440-031) in adults and adolescents with SCD, the most frequently (>10%) reported TEAEs included: headache, diarrhea, nausea, arthralgia, abdominal pain, fatigue, rash, upper respiratory tract infection, pyrexia, pain in extremity, back pain, vomiting, pain, non-cardiac chest pain, and abdominal pain upper (Vichnisky 2019). The majority of these TEAEs were Grade 1 to Grade 2 in severity and resolved. Overall, the TEAEs were similar across all treatment groups (1500 mg voxelotor, 900 mg voxelotor, or placebo) except for diarrhea which is higher in the voxelotor treatment groups than placebo. The most common treatment-related TEAE was diarrhea.

Overall, the safety profile for TEAEs was similar between adolescents and adults.

Additional information on the safety of voxelotor is described in the current version of the voxelotor IB, which is the Single Reference Safety Document (SRSD) for this study.

1.3.2. Efficacy

Data from the Phase 3 randomized controlled trial (GBT440-031) demonstrated that administration of voxelotor in participants with SCD resulted in a statistically significant and clinically meaningful improvement in Hb (> 1 g/dL increase) at 24 weeks compared to placebo (Vichinsky, 2019). Concomitant with the improved anemia there was a reduction in laboratory measures of hemolysis, including reticulocytes, LDH (Lactate Dehydrogenase), and indirect bilirubin. Additionally, in the Phase 1/2 study (GBT440-001) and extension study (GBT440-024), treatment with voxelotor led to reductions in the percentage of sickled red cells in the peripheral blood (Howard, 2019).

Additional information on the efficacy of voxelotor is described in the current version of the voxelotor IB.

Table 1. Clinical Studies in SCD with Voxelotor

Study No./Phase	Sites/ Location	Study Type	Study Population	Voxelotor Doses Evaluated	Treatment Duration	No. of Subjects	Status of enrollment
GBT440-001/ Phase 1/2	1 Site/ United Kingdom	Single and multiple ascending dose, placebo-controlled, double blind (with PK sampling)	Adult healthy subjects	Single dose: 100, 400, 1000, 2000, and 2800 mg (Cohorts 1–5)	Single dose	40 (30 active/ 10 placebo)	Complete
				Multiple dose: 300, 600, and 900 mg (Cohorts 8–10)	Multiple dose × 15 days	24 (18 active/ 6 placebo)	
			Adult subjects with SCD	Single dose: 1000 mg (Cohort 7)	Single dose	8 (6 active/ 2 placebo)	
				Multiple dose: 500, 700, and 1000 mg (500 mg twice daily) (Cohorts 11, 12, 14)	Multiple dose × 28 days	38 (28 active/ 10 placebo)	
				Multiple dose: 600 mg (Cohort 15)	Multiple dose × 28 days	7 (6 active/ 1 placebo)	
				Multiple dose: 700 mg (Cohort 16) Multiple dose: 900 mg (Cohort 17)	Multiple dose × 90 days Multiple dose × 90 days	8 (6 active/ 2 placebo) 8 (6 active/ 2 placebo)	
GBT440-024 Phase 2a	1 Site/ United Kingdom	Open label, multiple-dose (expansion study for subjects who participated in GBT440-001 Cohort 15 and Cohort 17)	Adult subjects with SCD	900 mg	6 months (Total duration including exposure from GBT440-001)	5	Complete

Table 1. Clinical Studies in SCD with Voxelotor (Continued)

Study No./Phase	Sites/ Location	Study Type	Study Population	Voxelotor Doses Evaluated	Treatment Duration	No. of Subjects	Status of enrollment
GBT440-007 Phase 2a	15 Sites/ United States and Lebanon	Open-label, single- and multiple-dose, PK, safety, and treatment effect	Pediatric subjects with SCD	Part A: 600 mg Part B: 900 and 1500 mg Part C: 1500 mg or 1500 mg equivalent Part D: 1500 mg equivalent	Part A: Single Dose Part B: Multiple dose Up to 24 weeks Part C: Multiple dose Up to 48 weeks (pediatric population aged 4 to 17 years) Part D: Multiple dose Up to 48 weeks (pediatric population aged 9 months to < 4 years)	**Part A:** -6 to< 12 years: 6 -12 to< 18 years: 7 Complete **Part B:** -12 to<18 years: 25 enrolled at 900 mg -15 enrolled at 1500 mg Complete Part C: 42 enrolled* Part D: Not started	Ongoing
GBT440-031 Phase 3 (HOPE Study)	100 Inter-national sites	Double-blind, randomized, placebo-controlled	Adults and adolescents with SCD	voxelotor 900 mg or voxelotor 1500 mg or placebo	Up to 72 weeks	*Approximately 370-435 planned:* 271 participants have been randomized and dosed	Complete

PK = pharmacokinetics; SCD = sickle cell disease
*Enrollment as of 05 November 2019.

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

Voxelotor is only available in oral form and is intended for once daily administration. See Section 5 for additional information regarding voxelotor. The voxelotor dose administered in this trial will be determined from study GBT440-031.

1.5. Trial Conduct

See Section 11 for details regarding the conduct of this trial.

1.6. Description of the Population to be Studied

This trial is limited to participants with SCD who were enrolled and treated in GBT440-031. See Section 4 for additional information regarding participants for this trial.

1.7. Rationale for this Study

This open label extension study is being conducted to assess long-term safety and treatment effect of voxelotor by providing participants from the GBT440-031 study continued access to treatment with voxelotor after their participation in GBT440-031 and prior to the product potentially being available commercially. All participants enrolled into this study will receive voxelotor.

2. TRIAL OBJECTIVES AND PURPOSE

The objective of this open-label extension (OLE) study is to assess the long-term safety and treatment effect of voxelotor in participants who have completed treatment in study GBT440-031, using the following parameters:

- Safety based upon AEs, clinical laboratory tests, physical examinations (PE) and other clinical measures.
- Frequency of sickle cell disease-related complications
- Hemolytic anemia as measured by hematological laboratory parameters (eg, hemoglobin, reticulocytes and unconjugated bilirubin).

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design

3.1.1. Endpoints

3.1.1.1. Safety

Safety endpoints include AEs, clinical laboratory tests, physical examinations and other clinical measures.

3.1.1.2. Sickle Cell Disease (SCD)-Related Complications

Frequency of SCD-related complications of long-term dosing with voxelotor.

3.1.1.3. Treatment Effect

Hemolytic anemia as measured by hematological laboratory parameters (eg, hemoglobin, reticulocytes and unconjugated bilirubin).

3.1.2. Design

This open label extension (OLE), multi-center study will be conducted at approximately 100 clinical sites globally and will be available to eligible participants from study GBT440-031.

The study will enroll participants from GBT440-031 under any of the following conditions:

- Participant has completed 72 weeks of treatment regardless of dose selection for GBT440-031
- Dose selection has occurred for GBT440-031 and participant is on the non-selected dose on GBT440-031
- GBT440-031 study interim data analysis and/or study modifications have occurred
- GBT440-031 study has completed

3.2. Number of Subjects

All participants (approximately 435 or the maximum number of participants in GBT440-031) who received treatment in study GBT440-031 and who meet the eligibility criteria for this study may be enrolled.

3.3. Treatment Assignment

This is an open-label trial; all participants will receive daily voxelotor treatment.

3.4. Criteria for Study Termination

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

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

4. SELECTION AND WITHDRAWAL OF SUBJECTS

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

A participant will be considered enrolled upon the signing of the ICF and/or signing the assent (for participants between 12 to < 18 years of age) for this study. Informed consent/assent must be properly executed prior to the performance of any protocol-required assessment or procedure.

4.1. Subject Inclusion Criteria

1. Male or female study participants with SCD who participated and received study treatment in GBT440-031.

   Note: Participants in GBT440-031 who discontinued study drug due to an AE, but who remained on study may be eligible for treatment in this study provided the AE does not pose a risk for treatment with voxelotor.

2. Females of child-bearing potential are required to have a negative urine pregnancy test prior to dosing on Day 1.
3. Female participants of child-bearing potential must use highly effective methods of contraception to 30 days after the last dose of study drug. Male participants must use barrier methods of contraception to 30 days after the last dose of study drug.
4. Participant has provided written informed consent or assent (the ICF must be reviewed and signed by each participant; in the case of pediatric participants, both the consent of the participant's legal representative or legal guardian, and the participant's assent must be obtained).

4.2. Subject Exclusion Criteria

1. Female who is breast-feeding or pregnant.
2. Participant withdrew consent from Study GBT440-031.
3. Participant was lost to follow-up from Study GBT440-031.
4. Participant requiring chronic dialysis.
5. Any medical, psychological, safety, or behavioral conditions, which, in the opinion of the Investigator, may confound safety interpretation, interfere with compliance, or preclude informed consent.

4.3. Subject Withdrawal Criteria

Participants will be informed that they are free to withdraw from the study at any time and for any reason. If a participant withdraws from this study, the date and reason for withdrawal will be documented on the case report form (CRF).

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

- Adverse event

- Use of a prohibited therapy (Section 5.5.3)
- Withdrawal of consent/assent
- Discretion of the Investigator
- Participant is lost to follow-up
- Participant is noncompliant
- Pregnancy

The End of Study (EOS) visit should be conducted within 28-35 days after last dose of study drug for participants who withdraw from the study early.

5. TREATMENT OF SUBJECTS

Participants who complete 72 weeks of treatment on GBT440-031, regardless of a dose selection for GBT440-031, will receive voxelotor at the highest dose (either 900 or 1500-mg) deemed safe for continued assessment on the GBT440-031 study by the Data Safety Monitoring Board (DSMB).

Once a dose is selected for study GBT440-031, all GBT440-031 participants on the non-selected dose will be eligible to enroll into this OLE study at the selected dose. All participants already enrolled in this OLE study at the time of the dose selection will be administered the selected dose at their next scheduled assessment.

Participants may be eligible to enroll in this OLE study prior to GBT440-031 study completion based on interim data results and/or subsequent study modifications on GBT440-031. If this occurs, sites will be notified which participants are eligible.

When study GBT440-031 has completed, participants will be eligible to enroll in this study.

If a participant was on a reduced dose of voxelotor due to an AE in GBT440-031 or on this study prior to a dose selection on GBT440-031, dosing in this study may be continued at the reduced dose if deemed clinically appropriate by the Investigator. The original dose may be resumed if deemed clinically appropriate by the Investigator.

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

The EOS visit can occur any time after participants obtains commercial voxelotor for participants who complete study per protocol. Participants should remain on study drug until EOS visit is completed.

5.1. Study Drug Information

Voxelotor is 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 C19H19N3O3 and the molecular weight is 337.38.

Voxelotor 300 mg or 500 mg tablets contain GBT440 drug substance along with several formulation excipients. All the excipients used for the formulation are compliant with European regulations and are listed in the Food and Drug Administration (FDA) Inactive Ingredients Database (IID).

Voxelotor tablets will be supplied to clinical sites in high density polyethylene (HDPE) bottles with induction sealed polypropylene (PP) caps. Additional details are provided in the Pharmacy Manual.

All study medication will be stored at controlled room temperature between 15°C to 25°C, in the storage area of the investigational site pharmacy.

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

5.2. Study Drug Dispensation

Study Drug will be dispensed at the Day 1 visit and every 3 months thereafter. Participants will receive a 3-month (90 day) supply of study drug at each dispensation visit.

Participants should be instructed to take study drug once daily with water or other non-alcoholic beverage preferably at the same time each day. Study drug may be taken with or without food.

5.3. Drug Accountability and Retention

In accordance with Good Clinical Practice (GCP), the Investigational Site will account for all supplies of voxelotor. Details of receipt, storage, dispensation, and return will be recorded.

The Investigator must ensure that all drug supplies are kept in a secure locked area with access limited to those authorized by the Investigator.

The Investigator (or designee) will maintain an accurate record of the receipt of the investigational product as shipped by the Sponsor (or designee), including, but not limited to, the date received, storage conditions/location, lot number, amount received, and the disposition of all investigational product. A copy of the receipt will be returned to the Sponsor when the contents of the investigational product shipment have been verified.

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

At the completion of the study, the original drug accountability record will be available for review by the Sponsor upon request.

All unused supplies of voxelotor will either be destroyed by the investigational site or returned to the Sponsor in accordance with Sponsor instructions.

Additional details are provided in the Pharmacy Manual.

5.4. Dose Modification

Participants should adhere to the assigned dose. However, dose modification for management of adverse events should be considered as outlined below. Guidelines for reduction, interruption, or permanent discontinuation of study drug are provided below in Table 2 (study drug-related AEs) and Table 3 (study drug-related rash).

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

If a participant enrolled in this study is on a reduced dose due to an AE prior to dose selection on GBT440-031, dosing may be continued at the reduced dose if deemed clinically appropriate by the Investigator.

Table 2. Dose Modification Guidelines for Study Drug-Related Adverse Events

Dose Reduction	
Event	**Recommended Action**
Grade 2 or higher AE that is (1) study drug-related in the opinion of the Investigator AND (2) that precludes continued dosing at the current dose level due to safety concern or lack of tolerability (in the Investigator's judgment)	**Study drug**: May be reduced by one (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 may consider a dose interruption (hold), Maximum dose hold is 5 continuous days. If, in the opinion of the Investigator, a longer dose hold is clinically needed, the Medical Monitor should be contacted for discussion.
ALT ≥3x ULN if ALT WNL at baseline OR >3X ULN AND a ≥2-fold increase above baseline values if elevated ALT values at baseline In the absence of additional signs of compromised liver function such as elevated	**Study drug**: Confirm by repeat testing within 48 to 72 hours if possible, then repeat liver panel at least weekly until ALT levels improves. **Additional Actions**: If ALT levels continue to increase reduce by one tablet and notify the Medical Monitor

Table 2. Dose Modification Guidelines for Study Drug-Related Adverse Events

Dose Reduction	
Event	**Recommended Action**
PT, PTT, INR, elevated conjugated bilirubin, jaundice, or hepatic pain.	
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 test does not improve within 2 weeks of dose reduction, the Medical Monitor should be notified. If ALT continues to increase within 1 week after a dose reduction, dose should be interrupted, and the Medical Monitor should be notified.
Dose Interruption (Hold)	
Event	**Recommended Action**
Grade 3 or higher AE that is (1) study drug - related in the opinion of the Investigator AND (2) that precludes continued dosing at the current or at a reduced dose level due to safety concern or lack of tolerability in the Investigator's judgment	**Study drug**: Hold dose until ≤Grade 2, then resume study drug at original dose. If, in the opinion of the Investigator, dosing should be resumed at a lower dose, contact the Medical Monitor. If the AE recurs or worsens, reduce dose by one tablet. Maximum dose hold is 5 continuous days. If, in the opinion of the Investigator, a longer dose hold is clinically needed, the Medical Monitor should be contacted for discussion.

Table 2. Dose Modification Guidelines for Study Drug-Related Adverse Events (Continued)

Drug Discontinuation	
Event	**Recommended Action**
Grade 3 or higher, study drug-related SAE	**Study drug**: Discontinue study drug. If the Investigator considers that the participant would benefit from continuing treatment, the Medical Monitor should be contacted for discussion.
Grade 3 or higher study drug-related AE that, at the discretion of the Investigator, warrants discontinuation of study drug (eg, has not improved or resolved after dose hold)	**Study drug**: Discontinue study drug. If the Investigator considers that the participant would benefit from continuing treatment, the Medical Monitor should be contacted
Consider treatment discontinuation if:	**Study drug**: Hold dose, confirm by repeat testing within 48 to 72 hours if possible, and assess for

Table 2. Dose Modification Guidelines for Study Drug-Related Adverse Events (Continued)

Drug Discontinuation	
Event	**Recommended Action**
• **ALT >8× ULN** • **(1) ALT >3x ULN or (2) ALT≥3x AND ≥2-fold increase above baseline values if elevated ALT values at baseline** with additional signs of compromised liver function such as elevated PT, PTT, INR, elevated conjugated bilirubin, jaundice, or hepatic pain, appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia	potential reversible causes of liver function test abnormalities. Contact the Medical Monitor for discussion of study drug discontinuation.

Table 3. Dose Modification Guidelines for Study Drug-Related Rash

Dose Reduction	
Event	**Recommended Action**
Grade 1 or 2 study drug-related rash	**Management:** Consider antihistamines, topical steroids as clinically indicated. **Study drug**: If rash does not resolve or improve to Grade 1 within 4 days after oral antihistamines and/or topical steroids, the dose may be reduced by one (1) tablet. The dose may be reduced further by one tablet if the event does not resolve. If in the opinion of the Investigator, a Grade 2 AE has resolved to ≤Grade 1, participant may resume study drug at the original dose.
Dose Interruption (Hold)	
Event	**Recommended Action**
Grade 1 or 2 study drug-related rash that persists after dose reduction	**Management:** Consider antihistamines, topical steroids as clinically indicated. Consider a Dermatology Consult if clinically indicated. **Study drug**: If rash does not resolve or improve to Grade 1 on the lower dose, consider a dose hold until resolution or event returns to Grade 1 or Baseline. Once rash has resolved or improved to Grade 1, dosing may be resumed at the

Table 3. Dose Modification Guidelines for Study Drug-Related Rash

Dose Reduction	
	reduced level. Maximum dose hold is 5 continuous days. If, in the opinion of the Investigator, a longer dose hold is clinically needed, the Medical Monitor should be contacted for discussion. If, in the opinion of the Investigator, a Grade 2 AE has resolved to <Grade 1, participant may resume study drug at the original dose.
Drug Discontinuation	
Event	**Recommended Action**
Grade 3 or higher study drug-related rash	**Study drug**: Discontinue study drug. Consider a Dermatology Consult if clinically indicated. Notify Medical Monitor.

5.5. Concomitant Medications

A concomitant medication is defined as any prescription or over-the-counter preparation, including vitamins and supplements, as well as investigational products other than those under study in this trial.

5.5.1. Prior and Concomitant Medications

Except as noted below, 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. All administered concomitant medications from signing the ICF until 28 days after the participant's last dose of study drug must be recorded on the participants' CRF (medication, dose, treatment duration and indication).

5.5.2. Allowed Concomitant Medications

Permitted concomitant medications include penicillin, folic acid, and codeine, which are among the chronic medications commonly taken by SCD participants.

Hydroxyurea (HU), L-glutamine therapy and crizanlizumab, where available, are allowed.

5.5.3. Prohibited Medications

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

Voxelotor is a moderate CYP3A4 inhibitor and should not be co-administered with sensitive CYP3A4 substrates with a narrow therapeutic index. See Table 4 for examples.

Table 4. Sensitive CYP3A4 Substrates with Narrow Therapeutic Range

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

Please note the following: This is not an exhaustive list. Country-specific lists may be used if available.

Since CYP3A4 is a primary CYP (cytochrome P450) responsible for the metabolism of voxelotor, concomitant use of voxelotor and moderate or strong inducers of CYP3A4 is not allowed (refer to Table 5 for examples).

Table 5. Examples of Moderate and Strong CYP Inducers

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

Please note the following: This is not an exhaustive list. Country-specific lists may be used if available. For an updated list, refer to the following link: https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#table3-3. (last accessed 30 March 2023).

Medications listed in Table 6 are also prohibited.

Table 6. Additional Prohibited Medications

Prohibited Medications
Cisapride

This list of drugs prohibited for potential DDI concerns with the IMP may be revised during the course of the study with written notification from the sponsor to include or exclude specific drugs or drug categories for various reasons (eg, emerging DDI results for the IMP, availability of new information in literature on the DDI potential of other drugs) if the overall benefit/risk assessment is not impacted or if the changes do not significantly impact the safety of participants or the scientific value of the trial.

5.5.4. Management of Overdose

Based on the mechanism of action of voxelotor, an overdose might decrease O_2 delivery to tissues. Transfusion, exchange transfusion, and/or hyperbaric O_2 therapy may be administered in the event of a medical emergency due to a suspected voxelotor overdose.

5.6. Fertility/Contraceptive Requirements

There is no information about effects that voxelotor could have on the development of the fetus in humans. Therefore, all female participants of child-bearing potential (post menarche) should avoid pregnancy, and all active male participants should avoid fathering a child. Highly effective means of contraception are listed below in Section 5.6.4.

5.6.1. Instructions for Female Participants of Child-Bearing Potential

For female participants of child-bearing potential, 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. Pregnancy reporting requirements are outlined in Section 7.2.4.

5.6.2. Female Participants of Non-Child-Bearing Potential

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

5.6.3. Instructions for Male Participants

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 their last dose of voxelotor.

As a precaution, all male participants should avoid fathering a child by either abstinence or the use of barrier methods of contraception. As there is no information for voxelotor being secreted in the ejaculate, male participants (including men who have had vasectomies) whose partners are currently pregnant should use barrier methods for the duration of the study and for 30 days after the last dose of voxelotor.

5.6.4. Acceptable Forms of Contraception

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

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Intravaginal
  - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
  - Oral

  - Injectable
  - Implantable
- Hormonal contraception must be supplemented with a barrier method (preferably male condom)
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Sexual abstinence: Sexual abstinence is considered a highly effective method only if the participant is refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the participant.

For male participants with female partners capable of reproduction: barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository. The use of barrier contraceptives should always be supplemented with the use of a spermicide.

5.7. Treatment Compliance

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

5.8. Randomization and Blinding

This is a non-randomized, open-label study of voxelotor.

6. ASSESSMENT OF TREATMENT EFFECT

The durability of the reduction of hemolysis will be assessed by hematological parameters. Hematology assessments for this trial are described in Section 7.1.5.1.

6.1. Hemolytic Anemia

Hb and hemolysis measures that will be summarized via descriptive statistics include mean change from Baseline in hemoglobin, % reticulocytes, and unconjugated bilirubin. Unconjugated bilirubin is a direct metabolic product of Hb derived from extravascular clearance (CL) of RBCs (85% of unconjugated bilirubin derives from Hb) and has been shown to correlate with RBC lifespan in SCD. The % reticulocyte count is the hemolysis measure that is most robustly correlated to RBC lifespan and reflects a physiologic bone marrow response to decreased RBC destruction (Hebbel, 2011).

There will be two baseline values used to describe durability of Hb and hemolysis responses: (1) Baseline derived from the pre-dose hematology measurements obtained during the GBT440-031 study and (2) hematology measurements obtained via pre-dose on Day 1 in this

study. Change from baseline, and percent change from baseline for the two aforementioned baseline values will be computed to determine trends over the duration of treatment.

7. ASSESSMENT OF SAFETY

7.1. Safety Parameters

Participant safety and tolerability will be monitored during the study using standard measures, including physical examinations, vital signs (including blood pressure [BP]), safety laboratory tests, concomitant medication usage and AE monitoring. Assessments will be performed at defined times during the study as indicated in the Schedule of Assessments (Appendix 1).

There are additional assessments (Week 4 and Week 8) during the first 8 weeks of this study for participants who transition from GBT440-031 and meet the following criteria:

- If the dose for this trial is 1500 mg, and the participant was randomized to either voxelotor 900 mg or placebo in GBT440-031.
- If the dose is 900 mg, and the participant was randomized to placebo in GBT440-031 study.
- If a participant received less than 12 weeks of treatment in GBT440-031.

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

7.1.1. Demographic/Medical History

Medical history will be recorded at the time of the physical examination on Day 1. The medical history will include information captured under Study GBT440-031 and new events that occurred since participating in GBT440-031 as clinically appropriate. Ongoing AEs in GBT440-031 will be recorded as new Medical History for this trial.

7.1.2. Vital Signs

Vital signs (heart rate [HR], BP) will be collected after a participant has rested for at least 5 minutes in the seated or supine position. A repeated measurement of HR and BP will be taken if the first reading is outside the normal range and deemed clinically significant.

7.1.3. Physical Examination

An abbreviated PE and a symptom directed examination will be completed at all visits.

An abbreviated PE will include at minimum general appearance, examination of eyes, skin, cardiovascular and respiratory systems, and an abdominal examination.

7.1.4. Electrocardiogram (ECG)

ECGs (12-lead) will be performed for participants from GBT440-031 who transitioned into this study and received:

- Voxelotor at a dose lower than the selected dose (eg, 900 mg for this trial)
- Placebo

ECGs will be performed after a participant has rested for at least 5 minutes in the seated or supine position. ECGs may be omitted pending a review of ECG data from GBT440-031 or ECG analyses from other clinical studies that indicate ECGs do not need to be collected in this trial. In this case, no study-specific ECGs would be required, but should still be performed as per standard of care.

Analysis from GBT440-0115, a dedicated TQT study in healthy subjects, indicated that voxelotor had no clinically significant ECG findings or no effect on the QT interval; therefore, ECG collection in this trial is no longer required as of 20Aug2019.

7.1.5. Laboratory Assessments

Central laboratory assessments will be performed for participants enrolled in the United States and Europe.

Local laboratory assessments will be performed by each site's local laboratory for participants enrolled outside of the United States or Europe.

The laboratory parameters listed in the sections below will be assessed. Additional laboratory assessments may be collected as indicated per standard of care for clinical management.

For adolescent participants, the total volume of blood collected for will not exceed the recommended blood sample volume limits outlined in 2010 WHO Guidelines. For this study, 12 years of age is the youngest age to be enrolled, thus total blood volume collection will not exceed 2.4 mL/kg in a given 4 week period, for any adolescent enrolled in the study.

7.1.5.1. Hematology (Day 1 through Week 48)

Hematology parameters for this trial are:

- RBC
- hematocrit (Hct)
- Hb
- platelets
- white blood cell (WBC)
- % reticulocytes
- absolute reticulocytes

- RBC distribution width (RDW)
- Mean corpuscular volume (MCV)
- Mean corpuscular hemoglobin concentration (MCHC)

7.1.5.2. Blood Chemistry (Day 1 through Week 48)

Serum chemistry parameters are:

- alanine aminotransferase (ALT)
- alkaline phosphatase (ALK)
- aspartate aminotransferase (AST)
- bicarbonate,
- blood urea nitrogen (BUN)
- creatinine
- lactate dehydrogenase (LDH)
- Sodium
- Potassium
- Bilirubin (total, direct, and indirect)

Assessment of hematology and serum chemistry after Week 48 but should be performed per standard of care.

After Week 48, local laboratory assessments for Hb and measures of hemolysis will be performed by each site's local laboratory for participants enrolled outside of the United States and Europe. (Every 24 weeks)

- Hemoglobin
- % reticulocytes
- absolute reticulocytes
- Bilirubin (total, direct, and indirect)

7.1.5.3. Exploratory Measures Related to SCD Pathophysiology (Day 1, Weeks 12, 24, and 48)

CCI [redacted] included as exploratory measures CCI [redacted] function. CCI [redacted] damage is a progressive complication of SCD that begins in childhood and may progress CCI [redacted] Assessments will be performed only for participants enrolled in the United States and Europe.

- CCI [redacted]
- [redacted]

7.1.5.4. Pregnancy Test (All visits)

Female study participants who have not experienced menarche will not undergo pregnancy testing. Should a female participant experience menarche during the course of the study, the participant will be considered a female of childbearing potential and will undergo pregnancy testing as per the Schedule of Assessments.

Female study participants of childbearing potential will have urine pregnancy tests at all visits. Female study participants with a positive pregnancy test at Day 1 will not be eligible to participate in the study.

If a urine pregnancy test is positive, the result must be confirmed per local standard of care (eg, ultrasound or serum pregnancy test). Female participants of child-bearing potential should be reminded to avoid pregnancy, and all active male participants should be reminded to avoid fathering a child. This discussion should be documented in the participant's medical record.

7.1.6. SCD-Related Complications

7.1.6.1. Vaso-Occlusive Crisis (VOC)

VOC must be documented in the participant's medical record that the participant was seen by, or in contact with the Investigator or health care provider. The event may take place in a medical setting (hospital, clinic, emergency room) or at home.

Acute chest syndrome (ACS) is defined as an acute illness characterized by fever and/or respiratory symptoms, accompanied by a new pulmonary infiltrate on a chest X-ray.

VOC during the treatment period is defined as:

A composite of acute painful crisis or ACS, and includes the following:

- Moderate to severe pain lasting at least 2 hours
- No explanation other than VOC
- Requires oral or parenteral opioids, ketorolac, or other analgesics prescribed or directed by a healthcare professional
- May include episodes of ACS

VOC events and associated therapies will be summarized via descriptive statistics. These endpoints include:

- Rate of VOC during treatment with voxelotor
- Rate of VOC hospitalization during treatment with voxelotor
- Rate of RBC transfusion during treatment with voxelotor
- Rate of opioid use during treatment with voxelotor

7.1.7. Other SCD-related Complications

SCD-related complications will be collected and assessed over the duration of the study.

7.2. 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.

All AEs will be recorded from the time the study participant signs the ICF until at least 28 days after last dose of study drug or EOS visit (per Appendix 1). The determination, evaluation, reporting, and follow-up of AEs will be performed as outlined in this section. At each visit, the study participant will be asked about any new or ongoing AE since the previous visit. Assessments of AEs will occur at each study visit.

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.

7.2.1. Adverse Events

7.2.1.1. 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, biopsies). 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 Pfizer, 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 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 Pfizer, 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 enrolment are considered SAEs.

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

7.2.1.2. Severity of Adverse Events

Whenever possible, the severity of all AEs will be graded using the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.03.

For AEs not adequately addressed in the NCI CTCAE Version 4.03, the following criteria should be used (Table 7).

Table 7. 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

Table 7. Grading for Adverse Events Not Covered in the NCI CTCAE

Severity	Description
Grade 5 – Fatal	Death

Abbreviations: 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 a not synonymous, the following note of clarification is provided. The term "severe" is often used to describe the intensity (severity) of a specific event (i.e. mild, moderate, or severe); the event itself, however, may be of relatively minor medical significance (eg, severe headache). This is not the same as "serious" which is based on the study participant / event outcome or action criteria associated with events that post a threat to a participant's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

7.2.1.3. 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 probably. It cannot be readily explained by the participant's clinical state or concomitant therapies and may appear, with some degree of certainty, to be related based on the known therapeutic and pharmacologic actions of the drug. Good clinical judgement should be used for determining causal assessment.

7.2.1.4. Unexpected Adverse Reactions

An adverse event is 'unexpected' if its nature and severity are not consistent with the information about the study drug provided in the Reference Safety Information (RSI) in the voxelotor IB.

7.2.2. Adverse Event Reporting

7.2.2.1. General

For study participants transitioning from the primary study (GBT440-031), all AEs (both serious and nonserious) will be recorded from the time both informed consent is obtained for this extension study and End of Treatment (EoT) visit has been completed in the primary study (GBT440-031) until 28 days after last dose of study drug or End of Study visit in this study.

Before EoT visit is completed in the primary study (GBT440-031), study sites must continue to collect and report to Pfizer Safety, SAE through and including 28 calendar days after the last dose of the investigational product (IP) or EoT visit, in the primary study, even though the patient may have signed the informed consent (IC) or signed the IC and taken the first dose on the rollover study GBT440-034/C5341022. Study recording of adverse events in the case report form (CRF) must continue in the primary study until EoT visit is achieved.

Adverse events reported as ongoing at the completion of GBT440-031, will be recorded in the Medical History CRF in this study.

After End of Treatment visit in the study GBT440-031, reporting of all AEs and SAEs in the study GBT440-034/C5341022, must be promptly documented on the AE CRF via the EDC system. Requirements for immediate safety reporting will follow standard process as specified in section 7.2.3.

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.

When a clinically important AE remains ongoing at the end of the active collection period, follow-up by the investigator continues until the AE or SAE or its sequelae resolve or stabilize at a level acceptable to the investigator and Pfizer concurs with that assessment.

For participants who are screen failures, the active collection period ends when screen failure status is determined.

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

If a participant permanently discontinues or temporarily discontinues study intervention because of an AE or SAE, the AE or SAE must be recorded on the CRF and the SAE reported using PSSA. The Sponsor/Medical Monitor(s) must be notified of the study participant discontinuation.

Investigators are not obligated to actively seek information on AEs or SAEs after the participant has concluded study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has concluded study participation, and they consider the event to be reasonably related to the study intervention, the investigator must promptly report the SAE to Pfizer using PSSA.

7.2.2.2. 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.

7.2.2.3. Abnormal Laboratory Values

Only clinically significant laboratory abnormalities as assessed by the Investigator will be recorded on the AE CRF (eg, abnormalities that have clinical sequelae, require study drug dose modification, etc.). If the clinically significant laboratory abnormality is a sign of a disease or syndrome (eg, ALK and bilirubin 5x ULN associated with cholecystitis), only the diagnosis (eg, cholecystitis) should be recorded as an AE on the CRF.

If the clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself, characterized by precise clinical term, as possible, should be recorded on the CRF (eg, elevated potassium 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.

Note: Potential drug-induced liver injury (DILI; Hy's law) cases are to be reported as SAEs (Section 7.2.3). For suggested actions and follow-up assessments in the event of potential DILI, refer to Appendix 2. (This note is included to support Study transition to Pfizer Pharmacovigilance processes and systems.)

7.2.2.4. Preexisting Medical Conditions

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

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

7.2.2.5. Worsening of Sickle Cell Disease

Complications and symptoms of SCD should be recorded as an AE or SAE if judged by the Investigator to have worsened in severity and/or frequency or changed in nature during the study.

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

All SAEs, regardless of causal attribution, occurring on this study will be recorted on the AE eCRF and reported to Pfizer Safety via PSSA within 24 hours of the Investigator, designee, or site personnel's knowledge of the event. In the event that the EDC system is not available, paper SAE report forms will be used to report the SAE and faxed or emailed to Pfizer Safety.

The information reported on the paper SAE report form should be entered into PSSA once available.

The Sponsor may request additional information pertaining to the SAE from the investigational site. Follow-up reports 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 resolution of the SAE are performed.

7.2.3.1. Reporting Suspected Unexpected Serious Adverse Reactions (SUSARs) and Urgent Safety Issues

The Sponsor is responsible for reporting Suspected Unexpected Serious Adverse Reactions (SUSARs) to regulatory agencies, competent authorities, IRBs/ECs, and Investigators, as per local laws and regulations. Fatal and life-threatening SUSARs will be submitted no later than 7-calendar days of 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 first knowledge of the event. The Investigator is responsible for notifying the local IRB or local ECs of all SAEs that occur at his or her site as required by local regulations or IRB/EC policies, if this responsibility resides with the site.

Investigators are required to report any urgent safety matters to the Sponsor within 24 hours. The Sponsor will inform regulatory authorities, IRBs/ECs, and Investigators 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, as required, in accordance with applicable local laws and regulations. The reporting period for urgent safety issues is the period from signing the informed consent until 28 days after last dose of study drug or EOS visit on GBT440-034/C5341022.

7.2.4. Reporting Overdose

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

The Investigator will discuss the risks and concerns of investigational agent exposure with the participant. Parents, guardians or participants are to be instructed to contact their study site immediately if an overdose of study drug is suspected. An overdose with AEs must be followed until the adverse effects are resolved or stabilized, or until reasonable attempts to determine resolution of the event are exhausted.

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

- Contact the study Medical Monitor within 24 hours.

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

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

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

Any such exposures to voxelotor under study are reportable to Pfizer Safety within 24 hours of Investigator awareness.

7.3.1. Exposure During Pregnancy

An EDP occurs if:

- A female participant is found to be pregnant while receiving or after discontinuing voxelotor.
- A male participant who is receiving or has discontinued voxelotor inseminates a female partner.
- A female nonparticipant is found to be pregnant while being exposed or having been exposed to voxelotor because of environmental exposure. Below are examples of environmental EDP:
  - A female family member of healthcare provider reports that she is pregnant after having been exposed to voxelotor by all possible routes of exposure, eg, ingestion, inhalation, or skin contact.
  - A male family member or healthcare provider who has been exposed to voxelotor by all possible routes of exposure, eg, ingestion, inhalation, or skin contact, then inseminates his female partner prior to or around the time of conception.

The Investigator must report EDP to Pfizer Safety within 24 hours of the Investigator's awareness, irrespective of whether an SAE has occurred. The initial information submitted should include the anticipated date of delivery (see below of information related to termination of pregnancy).

- If EDP occurs in a participant/participant's partner, the Investigator must report this information to Pfizer Safety via PSSA regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of voxelotor and until at least 140 days after the last dose.
- If EDP occurs in the setting of environmental exposure, the Investigator must report information to Pfizer Safety via PSSA . Since the exposure information does not pertain to the participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed report is maintained in the Investigator site file.

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The Investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial report. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. The child born to a female participant or partner of a male participant exposed to study drug will be followed for 3 months after delivery. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

Abnormal pregnancy outcomes are considered SAEs. If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly in a live born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death), the Investigator should follow the procedures for reporting SAEs. Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

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

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

documents that the participant was given the Pregnant Partner Release of Information Form to provide to his partner.

7.3.2. Exposure During Breastfeeding

An EDB occurs if:

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

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

An EDB report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accordance with authorized use. However, if the infant experiences an SAE associated with such a drug, the SAE is reported together with the EDB.

7.3.3. Occupational Exposure

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

7.4. Lack Of Efficacy

The investigator must report signs, symptoms, and/or clinical sequelae resulting from lack of efficacy. Lack of efficacy or failure of expected pharmacological action is reportable to Pfizer Safety **only if** associated **with an SAE.**

7.5. Medication Errors

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

Medication errors are recorded and reported as follows:

Table 8. Reporting of Medication Errors

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

Abbreviations: AE, adverse event; CRF, case report form; SAE, serious adverse event; PSSA: Pfizer's Serious AE Submission Assistant

Medication errors include:

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

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

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

Medication errors should be reported to Pfizer Safety within 24 hours using PSSA only when associated **with an SAE.**

7.6. Data and Safety Monitoring Board

Not applicable to this open label trial.

8. BIOSTATISTICS

8.1. Statistical Methods

Statistical programming and analyses will be performed using established statistical methods. Details of all planned analyses will be specified in a separate statistical analysis plan (SAP).

The study data will be reported using summary tables, figures, and data listings. Continuous variables will be summarized using mean, standard deviation (SD), median, minimum, and maximum. Categorical variables will be summarized by presenting the number (frequency) and percentage in each category.

8.1.1. Study Endpoints

8.1.1.1. Safety

Safety data analysis will be performed on all participants enrolled in the study.

A treatment-emergent adverse event (TEAE) is defined as an AE that emerges on or after initiation of study drug (having been absent pretreatment), or an AE that existed pretreatment and worsened on treatment (relative to the pretreatment state). The incidence of TEAEs will be tabulated by system organ class (SOC), preferred term, severity and relationship to study drug. AEs considered to be related by the Investigator will be summarized. AEs will be reported by severity and relatedness to study treatment and classified via the Medical Dictionary for Regulatory Activities (MedDRA).

Changes in clinical laboratory data (hematology, serum chemistry, CCI [redacted]) will be summarized.

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

8.1.1.2. Frequency of SCD-Related Complications

Over the course of the treatment period, the frequency of SCD complications for each participant will be recorded. SCD complications may include the following: VOC, acute chest syndrome, hepatic sequestration, leg ulcers, priapism, pulmonary hypertension, retinopathy, scleral icterus, splenic sequestration, and stroke. The incidence and rate of each complication and the totality of all SCD-related complications will be computed and then compared to those observed in the GBT440-031 study.

8.1.1.2.1. Therapies Associated with VOC

During the treatment period, RBC transfusion and opioid usage will be recorded. The incidence and rate of these therapies will be calculated and compared to those observed in the GBT440-031 study.

8.1.1.3. Response in Hemolytic Anemia

At each scheduled laboratory assessment, hematology and serum chemistry will be measured to determine longitudinal durability of response with regards to hemolytic anemia. Of particular interest are hemoglobin, bilirubin, and reticulocyte counts. There will be two baseline values used to describe efficacy and durability: (1) Baseline derived from the pre-dose hematology measurements obtained during the GBT440-031 study and (2) Hematology measurements obtained via pre-dose on Day 1 in this study. Change from baseline, and percent change from baseline for the two aforementioned baseline values will be computed to determine trends over the duration of treatment.

8.2. Sample Size

The sample size for this study will not exceed the total enrollment of the GBT440-031 study.

8.3. Level of Significance

All statistical analyses conducted will be descriptive and no formal statistical tests will be performed.

8.4. Statistical Criteria for Termination of the Trial

No formal statistical criteria will be used for termination of the trial.

8.5. Missing, Unused, or Spurious Data

Data will be summarized as observed with no imputation for missing values, excepting partially missing dates. Full details of how missing date data will be handled will be described in the SAP.

8.6. Deviation from the Statistical Analysis Plan

Deviations from the SAP will be described in either an updated SAP or in the Clinical Study Report.

8.7. Analysis Population

All participants who sign the ICF and receive voxelotor treatment in this study will be included in the analyses. Participants will be assigned to cohorts based upon the treatment received during the GBT440-031 study, these cohorts are as follows:

1. Participants treated with placebo during GBT440-031 who transition into the OLE
2. Participants treated with the dose not selected during GBT440-031 who transition into the OLE.
3. Participants treated with the selected dose during GBT440-031 who transition into the OLE.

9. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

9.1. Source Data

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

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

9.2. Data Collection

The Investigator will be responsible for maintaining accurate and adequate case records (source documents) from which data will be transcribed (or if EDC source data, transferred) to CRFs designed to record data pertinent to this study. All relevant observations and data related to the study will be so 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. 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 CRF.

9.3. Essential Documentation Requirements

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

10. QUALITY CONTROL AND QUALITY ASSURANCE

10.1. Monitoring

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

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

10.2. Laboratory Accreditation

The laboratory facility used for analysis of clinical laboratory samples must provide evidence of adequate licensure or accreditation. Copies of laboratory certification, licensure, and reference ranges (as appropriate) will be supplied to the Sponsor prior to study initiation. The

Sponsor or designee should be notified of any changes in reference range values or certification/license renewal during the course of the study.

10.3. Sponsor's Medically Qualified Individual

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

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

The ECC is intended to augment, not replace, the established communication pathways between the participant and their Investigator and site staff, and between the Investigator and Sponsor study team. The ECC is only to be used by healthcare professionals not involved in the research study, as a means of reaching the Investigator or site staff related to the care of a participant. The Pfizer Call Center number is to be used when the investigator and site staff are unavailable. The Pfizer Call Center number is not for use by the participant directly; if a participant calls that number directly, they will be directed back to the investigator site.

11. REGULATORY, ETHICAL, LEGAL, AND OVERSIGHT OBLIGATIONS

11.1. Regulatory and Ethical Considerations

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

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

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

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

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

The investigator will be responsible for the following:

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

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

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

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

11.3. Informed Consent and Assent Process

11.3.1. Informed Consent

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

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

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

The participant (or their legally authorized representative) must be informed that their personal study-related data will be used by the Sponsor in accordance with local data

protection law. The level of disclosure must also be explained to the participant (or their legally authorized representative).

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

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

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

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

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

11.3.2. Informed Assent

The investigator or their representative will explain the nature of the study to the participant and their parent(s)/legal guardian and answer all questions regarding the study. The participant and their parent(s)/legal guardian should be given sufficient time and opportunity to ask questions and to decide whether or not to participate in the trial.

When consent is obtained from a participant's parent(s)/legal guardian, the participant's assent (affirmative agreement) must be subsequently obtained when the participant has the capacity to provide assent, as determined by the IRB/EC. If the investigator determines that a participant's decisional capacity is so limited they cannot reasonably be consulted, then, as permitted by the IRB/EC and consistent with local regulatory and legal requirements, the participant's assent may be waived with source documentation of the reason assent was not obtained. If the study participant does not provide their own assent, the source documents must record why the participant did not provide assent (for example, the child is not of assenting age per local regulations or policies), how the investigator determined that the person signing the consent was the participant's parent(s)/legal guardian, the consent signer's relationship to the study participant, and that the participant's assent was obtained or waived. If assent is obtained verbally, it must be documented in the source documents.

If study participants are minors who reach the age of majority or if a child reaches the age of assent (per local IRB/EC requirements) during the study, as recognized under local law, the child or adolescent must then provide the appropriate assent or consent to document their willingness to continue in the study. For an adolescent who reaches the age of consent,

parental consent would no longer be valid. If the enrollment of emancipated minors is permitted by the IRB/EC and local law, the participant must provide documentation of legal status to give consent without the permission of a legally authorized representative.

Participants and their parent(s)/legal guardian must be informed that their participation is voluntary. The participant's parent(s)/legal guardian will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements, where applicable, and the IRB/EC or study center.

The investigator must ensure that each study participant's parent(s)/legal guardian and the study participant as applicable are fully informed about the nature and objectives of the study, the sharing of data related to the study, and possible risks associated with participation, including the risks associated with the processing of the participant's personal data.

The participant's parent(s)/legal guardian must be informed that the participant's personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant's parent(s)/legal guardian.

The participant's parent(s)/legal guardian must be informed that the participant's medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/EC members, and by inspectors from regulatory authorities.

The investigator further must ensure that each study participant's parent(s)/legal guardian is fully informed about their right to access and correct their child's personal data and to withdraw consent for the processing of their child's personal data, keeping in mind the privacy rights that may restrict access of older adolescents' medical records by their parent(s)/legal guardian in certain regions.

The source documentation must include a statement that written informed consent, and as applicable, assent was obtained before the participant was enrolled in the study and the date the written consent/assent was obtained. The authorized person obtaining the informed consent must also sign the ICD.

Parent(s)/legal guardian and the participant must be reconsented to the most current version of the ICD(s)/assent during their participation in the study as required per local regulations.

A copy of the ICD(s) and assent, if written, must be provided to the parent(s)/legal guardian and the participant.

11.4. Data Protection

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

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

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

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

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

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

12. DATA HANDLING AND RECORDKEEPING

12.1. Inspection of Records

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

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

12.2. Retention of Records

The Investigator will maintain adequate records, including participants' medical records, laboratory reports, signed consent forms, drug accountability records, safety reports, information regarding participants who discontinued the protocol, and any other pertinent

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

The Investigators must retain protocols, amendments, IRB/IEC approvals, copies of the Form FDA 1572, 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.

12.3. Disclosure of Information

Participants' medical information obtained as a result of this study is considered confidential, and disclosure to third parties other than those noted in this protocol is prohibited. Subject to applicable authorization(s), reports and communications relating to participants in this study will identify those participants only by number and/or initials. Participant's medical information resulting from this study may be given to the participant's personal physician, other authorized parties, or to the appropriate medical personnel responsible for the participant with regard to this clinical trial. Data generated in this study will be available for inspection on request by the FDA or other government regulatory agency auditors, the sponsor, the sponsor's Medical Monitor (or designee), and their designated representatives, the IRB/EC, and other authorized parties. All information concerning the study medication and the sponsor's operations (such as patent applications, formulas, manufacturing processes, basic scientific data, or other information supplied by the Sponsor and not previously published) are considered confidential and shall remain the sole property of the Sponsor. The Investigator agrees to use this information only in conducting this study and to not use it for other purposes without the Sponsor's prior written consent. The information developed in this clinical study will be used by the Sponsor in the clinical development of voxelotor and therefore, may be disclosed by the Sponsor as required, to authorized parties (including its corporate partners for the study drug, if any, and their designated representatives), other clinical Investigators, pharmaceutical companies, the FDA, and other government agencies. Any information, inventions, discoveries (whether patentable or not), innovations, suggestions, ideas, and reports made or developed by the Investigator(s) as a result of conducting this study shall be promptly disclosed to the Sponsor and shall be the sole

property of the Sponsor. The Investigator agrees, upon the Sponsor's request and at the Sponsor's expense, to execute such documents and to take such other actions as the sponsor deems necessary or appropriate to obtain patents in the sponsor's name covering any of the foregoing.

12.4. Dissemination of Clinical Study Data

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

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

www.clinicaltrials.gov

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

EudraCT/CTIS

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

www.pfizer.com

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

Documents within marketing applications

The Sponsor complies with applicable local laws/regulations to publish clinical documents included in marketing applications. Clinical documents include summary documents and CSRs including the protocol and protocol amendments, sample CRFs, and SAPs. Clinical documents will have personally identifiable information anonymized.

Data sharing

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

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

12.5. Data Quality Assurance

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

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

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

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

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

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

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during

the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the Sponsor. The Investigator must ensure that the records continue to be stored securely for as long as they are maintained.

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

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

12.6. Study and Site Start and Closure

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

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

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

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

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

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

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

13. PUBLICATION POLICY

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

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

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

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

14. REFERENCES

1. Hebbel RP. Reconstructing sickle cell disease: a data-based analysis of the "hyperhemolysis paradigm" for pulmonary hypertension from the perspective of evidence-based medicine. Am J Hematol. 2011;86:123-154
2. 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):1865-1875.
3. Rother RP, Bell L, Hillmen, P and Gladwin MT. The clinical sequelae of intravascular hemolysis and extracellular plasma hemoglobin. JAMA 2005, 293:1653-1662.
4. Vichinsky E, Hoppe CC, 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;381:509-519.

15. APPENDICES

Appendix 1. Schedule of assessments

Assessments	Treatment Period									End of Study[i]
Study Day(s)	Day 1[a]	W4* ± 5 days	W8* ± 5 days	W12 ± 5 days	W24 ± 10 days	W36 ± 10 days	W48 ± 10 days	Q12 Wks ± 10 days	Q24 Wks ± 10 days	
Informed Consent/Assent	X									
Eligibility Assessment	X									
Medical History	X									
Physical Examination [b]	X	X	X	X	X		X		X	X
Vital Signs [c]	X	X	X	X	X		X			X
Adverse Events	X	X	X	X	X		X		X	X
Concomitant Medications	X	X	X	X	X		X		X	X
Hematology/Chemistry analyzed by Central Laboratory (US and Europe only) [d]	X	X	X	X	X		X			X
Hematology/Chemistry analyzed by Local Laboratory (ex-US and ex-Europe only) [d, e]	X[a]	X	X	X	X		X		X[f]	X
Exploratory Laboratory [redacted] (US and Europe Only)	X			X	X		X			
Urine Pregnancy Test [g]	X	X	X	X	X		X		X	X
Drug Dispensing and Accountability [h]	X			X	X	X	X	X	X	X

Assessments	Treatment Period									End of Study[i]
Study Day(s)	Day 1[a]	W4* ± 5 days	W8* ± 5 days	W12 ± 5 days	W24 ± 10 days	W36 ± 10 days	W48 ± 10 days	Q12 Wks ± 10 days	Q24 Wks ± 10 days	

Abbreviations: Q = every; W = week; Wks = weeks

* Participants from GBT440-031 who received GBT440 900 mg or placebo, or who received voxelotor for less than 12 weeks will have additional assessments at Week 4 and Week 8.

a. Eligibility assessments will be determined on Day 1 prior to dosing. If labs were done for GBT440-031 or this study within 7 days of Day 1, they do not need to be repeated on Day 1.

b. Abbreviated Physical Exam which includes: general appearance, examination of eyes, skin, cardiovascular and respiratory systems, an abdominal examination and a symptom directed examination.

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

d. Hematology assessments will include: red blood cell (RBC), hematocrit (Hct), hemoglobin (Hb), platelets, white blood cell (WBC), % reticulocytes, absolute reticulocytes, RBC distribution width (RDW), mean corpuscular volume (MCV) and mean corpuscular hemoglobin concentration (MCHC). After Week 48, hematology assessments should only be performed per standard of care.

e. Serum chemistries will include: Alanine aminotransferase (ALT), alkaline phosphatase (ALK), aspartate aminotransferase (AST), bicarbonate, BUN, creatinine, LDH, sodium, potassium, bilirubin (total, direct, and indirect). After Week 48, serum chemistries should only be performed per standard of care.

f. After Week 48 (for participants enrolled outside of the United States and Europe), laboratory values for measures of hemolysis such as hemoglobin, % reticulocytes, absolute reticulocytes, and bilirubin (total, direct, and indirect) will be collected every 24 weeks.

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

h. Voxelotor will be dispensed in 12-week (~90 day) intervals with instruction to participants to return any used/unused bottles to clinic.

i. The End of Study (EOS) visit should be conducted within 28-35 days after last dose of study drug for participants who withdraw from the study early.

The EOS visit can occur any time after participants obtains commercial voxelotor for participants who complete study per protocol. Participants who complete study per protocol should remain on study drug until EOS visit is completed.

Appendix 2. LIVER SAFETY: SUGGESTED ACTIONS AND FOLLOW UP ASSESSMENTS

Potential Cases of Drug Induced Liver Injury

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

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

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

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

- Participants with AST/ALT and total bilirubin values within the normal range who subsequently present with AST/ALT values ≥ 3 × ULN AND a total bilirubin value ≥ 2 × ULN with no evidence of hemolysis and an alkaline phosphatase value < 2 × ULN or not available.
- For participants with baseline AST OR ALT OR total bilirubin values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:
  - Preexisting AST/ALT baseline values above the normal range: AST/ALT values ≥ 2 times the baseline values AND ≥ 3 × ULN; or ≥ 8 × ULN (whichever is smaller).

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

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

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

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

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

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

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