RETROSPECTIVE PROTOCOL

Study Number	**GBT440-4R1**
Study Title	**A Retrospective Data Collection and Analysis Study of Patients With Sickle Cell Disease (SCD) Who Have Been Treated With Oxbryta® (Voxelotor)**
Short Title	Retrospective Real World Oxbryta Data Collection and Analysis Study
Drug Product	Oxbryta® (voxelotor) 500-mg Tablets
Disease Under Study	Sickle cell disease
Sponsor	Global Blood Therapeutics, Inc. 181 Oyster Point Blvd South San Francisco, CA 94080 United States of America
Study Director	[redacted]
Original Protocol Date	22 January 2021

CONFIDENTIAL

The information in this study protocol is strictly confidential and is available for review to study doctors, 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 study patients. Once the protocol is signed, its terms are binding for all parties.

STATEMENT OF APPROVAL AND COMPLIANCE

STUDY TITLE: A Retrospective Data Collection and Analysis Study of Patients With Sickle Cell Disease (SCD) Who Have Been Treated With Oxbryta® (Voxelotor)

SPONSOR APPROVAL

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

Sponsor Representative:	[redacted]
Title:	**Senior Vice President of Medical Affairs**
Signature:	DocuSigned by Jonathan Sorof I approve this document [redacted] PST 27FD75376AB94193BC2DC054593B8668
Date:	26-Jan-2021 | 14:27 PST

INVESTIGATOR APPROVAL

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

Study Doctor:	
Title:	
Signature:	
Date:	

PROTOCOL SYNOPSIS

Study Number	GBT440-4R1
Study Title	A Retrospective Data Collection and Analysis Study of Patients With Sickle Cell Disease (SCD) Who Have Been Treated With Oxbryta® (Voxelotor)
Short Title	Retrospective Real World Oxbryta Data Collection and Analysis Study
Sponsor	Global Blood Therapeutics, Inc. 181 Oyster Point Blvd South San Francisco, CA 94080. United States of America
Study Description	The aim of this study is to collect and analyze retrospective data on Oxbryta in a real-world setting.
Number of Study Sites	The study will be conducted at approximately 10 sites in the US.
Number of Patients	Approximately 300 patients will be enrolled in this study.
Treatment	This is a retrospective data collection and analysis study. Patients will have received treatment with Oxbryta as prescribed by their physician at the approved dose per local prescribing information, as part of their usual care.
Objectives	**Primary** The following are categories of interest in patients with SCD treated with Oxbryta: • Clinical outcomes, as assessed by clinical and laboratory assessments of hematological parameters and end organ damage, and incidence of significant clinical events • Healthcare resource utilization • Health-related quality of life (HRQoL), as assessed by patient-reported outcome (PRO) measures and clinician-reported outcomes (ClinRO) **Safety** The safety objective is to assess the safety and tolerability of Oxbryta.
Outcome Measures	• Change from pre-Oxbryta treatment period in the following hematologic parameters corresponding to treatment with Oxbryta: o Hb o Hemolysis measures, including % reticulocytes, absolute reticulocytes, bilirubin (total, direct, and indirect) o Measures of iron overload, including ferritin, iron, total iron binding capacity (TIBC), T2-weighted magnetic resonance imaging (T2*MRI), and liver biopsy • Change from pre-Oxbryta treatment period in renal function, as measured by the following: o Albuminuria (urine albumin/creatinine ratio [ACR]) o Hemoglobinuria (urine dipstick positive for blood +1 or greater and ≤ 2 RBC by high power field) o Serum cystatin C o Estimated glomerular filtration rat (eGFR) calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation

	• Incidence of significant SCD-related clinical events, such as vaso-occlusive crisis (VOC), acute chest syndrome (ACS), priapism, cerebral infarcts, transient ischemic attack (TIA), leg ulcers, and measures of cardiac function and pulmonary hypertension (PH) • Treatment initiation or modification of SCD-related medications (e.g., hydroxyurea, crizanlizumab, L-glutamine, opioids [in daily morphine equivalents], iron chelating agents, erythropoiesis-stimulating agents [ESAs], nonsteroidal anti-inflammatory drugs [NSAIDs], folic acid, and penicillin) • Change from pre-Oxbryta treatment period in healthcare resource utilization: incidence of unplanned clinic visits, emergency department (ED) visits, hospitalizations (including total length of stay and time in intensive care unit [ICU], if applicable), acute and chronic RBC transfusions, home oxygen supplementation, and renal dialysis • Change from pre-Oxbryta treatment period in the following HRQoL measures: o Patient-Reported Outcomes Measurement Information System (PROMIS) o Patient Global Impression of Change (PGIC) o Clinical Global Impression of Change (CGIC) o Other measures (if assessed as part of usual care): chronic and acute pain intensity (Visual Analog Scale for pain [VAS Pain]), School Absence and Work Productivity, and any objective measure of exercise tolerance (e.g., Borg Scale of Perceived Exertion) **Safety Outcome Measures:** • Incidence and severity of serious adverse events (SAEs) and adverse events (AEs) of interest • Incidence of AEs leading to dose modification or discontinuation of Oxbryta • Pregnancy outcomes and fertility
Study Design	This is a multicenter, retrospective data collection and analysis study to characterize health outcomes in approximately 300 patients with SCD who have been treated with Oxbryta as part of their usual care. Any patient with SCD who received Oxbryta treatment for at least 2 weeks as part of their usual care according to the Oxbryta US Prescribing Information (USPI) is eligible to participate. Patients will be introduced to the study by their health care team and will sign the informed consent form (ICF) to allow their data to be collected and used for the study, if required by the Institutional Review Board (IRB), institution, or per local regulations. Only data that are available from the patient's medical records and other secondary data sources will be collected. Study data from 1 year before and up to 1 year after the first dose of Oxbryta will be entered in case report forms (CRFs) via an electronic data capture (EDC) system by the study staff.
Duration of Study Participation	Not applicable as this is a retrospective data collection study.
End of Study	The end of study is defined as the date when the last data point for the last patient is collected.

Study Population	**Eligibility Criteria**: Patients who meet all the following criteria will be eligible for inclusion in this study: 1. Willing and able to provide written informed consent (ages ≥ 18 years) or parental/guardian consent and patient assent (age <18 years), as required by the IRB or institution or IRB, per local regulations 2. Male or female patients with documented diagnosis of SCD (all genotypes) 3. Have been treated with Oxbryta for at least 2 weeks, according to the Oxbryta USPI
Statistical Methods	**Analysis Population** Effectiveness and safety analyses will be based on the treated population, defined as all patients who received at least 2 weeks Oxbryta and meet all eligibility criteria and are included in this study. **Sample Size** The sample size is selected based on feasibility considerations and to provide descriptive summaries of outcomes of interest. **Analyses** Change from pre-Oxbryta treatment period in Hb, hemolysis measures, measures of iron overload, and renal function over time will be summarized descriptively. Annualized incidence rate of significant SCD-related clinical events, including VOC, ACS, priapism, cerebral infarcts, TIA, leg ulcers, and measures of cardiac function and PH will be calculated. The association between change in Hb and hemolysis marker and incidences of SCD-related clinical events will be evaluated. Incidences of unplanned clinic visits, ED visits, hospitalizations, acute and chronic RBC transfusions, home oxygen supplementation, and renal dialysis will be summarized with a similar approach as incidences of SCD-related clinical events. The total cost associated with clinical interventions will be summarized descriptively. HRQoL measures over time will be summarized descriptively. Proportions of patients with improved HRQoL measures will be calculated and the associated 95% confidence intervals will be constructed as appropriate. As appropriate, incidences of SCD-related clinical events, healthcare resource utilization, total cost associated with clinical interventions (if available) and HRQoL while on Oxbryta treatment will be compared qualitatively with the corresponding measures prior to the first dose of Oxbryta treatment. **Safety Analysis** SAEs and protocol-specified AEs will be classified according to Medical Dictionary for Regulatory Activities (MedDRA). The frequency of AEs will be tabulated by system organ class, preferred term, severity, and relationship to Oxbryta treatment.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Description
ACR	albumin/creatinine ratio
ACS	acute chest syndrome
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
CGIC	Clinical Global Impression of Change
ClinRO	clinician-reported outcome
CRO	Clinical Research Organization
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CRF	case report form
ED	emergency department
EDC	electronic data capture
eGFR	estimated glomerular filtration rat
ESA	erythropoietin-stimulating agent
FDA	(US) Food and Drug Administration
GBT	Global Blood Therapeutics, Inc.
GCP	Good Clinical Practice
Hb	hemoglobin
HbF	fetal hemoglobin
HbS	sickle hemoglobin
HRQoL	health-related quality of life
ICF	Informed consent form
ICH	International Conference on Harmonization
ICU	intensive care unit
IEC	Independent Ethics Committee
IID	Inactive Ingredient Database
IRB	Institutional Review Board
LDH	lactate dehydrogenase
MedDRA	Medical Dictionary for regulatory Activities
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NSAID	nonsteroidal anti-inflammatory drug

Abbreviation	Description
PGIC	Patient Global Impression of Change
PH	pulmonary hypertension
PRO	patient-reported outcome
PROMIS	Patient-Reported Outcomes Measurement Information System
QoL	quality of life
RBC	red blood cell
SAE	serious adverse event
SCD	sickle cell disease
SOA	schedule of activities
SOC	standard of care
SUSAR	serious unexpected adverse reaction
TIA	transient ischemic attack
US	United States
USPI	United States Prescribing Information
VAS	visual analog scale
VOC	vaso-occlusive crisis

1. INTRODUCTION

1.1. Disease Background

Sickle cell disease (SCD) is an inherited blood disorder caused by a point mutation in the β globin gene resulting in the formation of "sickle hemoglobin" (HbS), which polymerizes in the deoxygenated state and leads to red blood cell (RBC) sickling. The disease is 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 (Gladwin, 2014; Nouraie, 2013). In addition to unpredictable and recurrent vaso-occlusive pain episodes, hemolytic anemia directly damages blood vessels, resulting in a systemic vasculopathy that leads to chronic and progressive tissue and organ injury (Kato, 2007). With improved survival in children, the natural history of SCD has shifted from a disease of childhood to a chronic, debilitating disease of young and middle-aged adults. Cumulative injury to multiple organ systems from repeated episodes of RBC sickling, vaso-occlusion, and chronic hemolytic anemia exact a high clinical burden in the aging adult, significantly impacting quality of life (QoL) and overall functioning (Swanson, 2011).

1.2. Oxbryta® (Voxelotor)

Voxelotor (previously GBT440) is an HbS polymerization inhibitor that binds to HbS with a 1:1 stoichiometry and exhibits preferential partitioning to RBCs. Voxelotor binds covalently and reversibly to the N-terminal valine of one of the Hb α chain of Hb and allosterically increases HbS-oxygen (O_2) affinity (Eaton, 1999), stabilizing the oxyhemoglobin (oxyHb) state and inhibiting polymerization (Oksenberg, 2016). The voxelotor binding site (Kato, 2007) is distant from heme pockets and it can therefore increase O_2 affinity without sterically blocking the release of O_2.

In November 2019, Oxbryta® (voxelotor) was approved in the US by the Food and Drug Administration (FDA) for the treatment of SCD in adults and pediatric patients 12 years of age and older. This indication was approved under accelerated approval based on increase in Hb. Voxelotor continues to be evaluated in ongoing clinical studies/expanded access programs exploring the safety, tolerability, pharmacokinetics, pharmacodynamics, and treatment response in pediatric and adult participants with SCD as well as in clinical pharmacology studies in healthy adult participants.

Information regarding nonclinical studies, clinical studies, and safety is available in the Oxbryta US prescribing information (Oxbryta® USPI).

2. OBJECTIVES AND OUTCOMES

2.1. Objectives

The aim of this study is to collect and analyze retrospective data on Oxbryta in a real-world setting.

2.1.1. Primary Objectives

The following are categories of interest in patients with SCD treated with Oxbryta:

- Clinical outcomes, as assessed by clinical and laboratory assessments of hematological parameters and end organ damage, and incidence of significant clinical events
- Healthcare resource utilization
- Health-related quality of life (HRQoL), as assessed by patient-reported outcome (PRO) measures and clinician-reported outcomes (ClinRO)

2.1.2. Safety Objective

The safety objective is to assess the safety and tolerability of Oxbryta.

2.2. Outcome Measures

- Change from pre-Oxbryta treatment period in the following hematologic parameters corresponding to treatment with Oxbryta:
  - Hb
  - Hemolysis measures, including % reticulocytes, absolute reticulocytes, bilirubin (total, direct, and indirect)
  - Measures of iron overload, including ferritin, iron, total iron binding capacity (TIBC), T2-weighted magnetic resonance imaging (T2*MRI), and liver biopsy
- Change from pre-Oxbryta treatment period in renal function, as measured by the following:
  - Albuminuria (urine albumin/creatinine ratio [ACR])
  - Hemoglobinuria (urine dipstick positive for blood +1 or greater and ≤ 2 RBC by high power field)
  - Serum cystatin C
  - Estimated glomerular filtration rat (eGFR) calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation
- Incidence of significant SCD-related clinical events, such as vaso-occlusive crisis (VOC), acute chest syndrome (ACS), priapism, cerebral infarcts, transient ischemic attack (TIA), leg ulcers, and measures of cardiac function and pulmonary hypertension (PH)

- Treatment initiation or modification of SCD-related medications (e.g., hydroxyurea, crizanlizumab, L-glutamine, opioids [in daily morphine equivalents], iron chelating agents, erythropoiesis-stimulating agents [ESAs], nonsteroidal anti-inflammatory drugs [NSAIDs], folic acid, and penicillin)
- Change from pre-Oxbryta treatment period in healthcare resource utilization: incidence of unplanned clinic visits, emergency department (ED) visits, hospitalizations (including total length of stay and time in intensive care unit [ICU], if applicable), acute and chronic RBC transfusions, home oxygen supplementation, and renal dialysis
- Change from pre-Oxbryta treatment period in the following HRQoL measures:
  - Patient-Reported Outcomes Measurement Information System (PROMIS)
  - Patient Global Impression of Change (PGIC)
  - Clinical Global Impression of Change (CGIC)
  - Other measures (if assessed as part of usual care): chronic and acute pain intensity (Visual Analog Scale for pain [VAS Pain]), School Absence and Work Productivity, and any objective measure of exercise tolerance (e.g., Borg Scale of Perceived Exertion)

2.2.1. Safety Outcome Measures

- Incidence and severity of serious adverse events (SAEs) and adverse events (AEs) of interest
- Incidence of AEs leading to dose modification or discontinuation of Oxbryta
- Pregnancy outcomes and fertility

3. STUDY PLAN

3.1. Overall Study Design

This is a multicenter, retrospective data collection and analysis study to characterize health outcomes in approximately 300 patients with SCD who have been treated with Oxbryta as part of their usual care. Data will be collected at approximately 10 sites in the US.

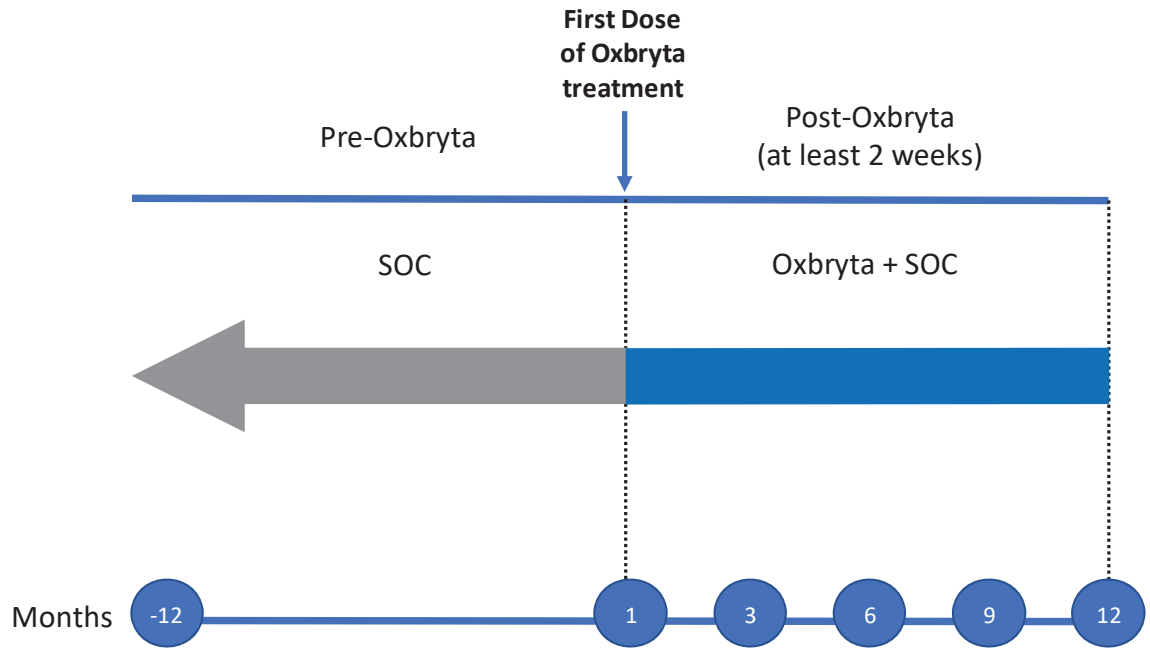
Any patient with SCD who received Oxbryta treatment for at least 2 weeks as part of their usual care according to the Oxbryta US Prescribing Information (USPI) is eligible to participate.

Patients will be introduced to the study by their health care team and will sign the informed consent form (ICF) to allow their data to be collected and used for the study, if required by the Institutional Review Board (IRB), or institution, per local regulations.

Only data that are available from the patient's medical records and other secondary data sources will be collected. Study data from 1 year before and up to 1 year after the first dose of Oxbryta will be entered in case report forms (CRFs) via an electronic data capture (EDC) system by the study staff.

The overall study design is illustrated in Figure 1.

Figure 1: Study Schema



SOC=standard of care.

3.2. Duration of Study Participation

Not applicable as this is a retrospective data collection study.

3.3. End of Study

The end of study is defined as the date when the last data point for the last patient is collected.

4. STUDY POPULATION

All patients at each participating study site who have been treated with Oxbryta will be considered for inclusion in this study.

4.1. Eligibility Criteria

Patients who meet all the following criteria will be eligible for inclusion in this study:

1. Willing and able to provide written informed consent (ages ≥ 18 years) or parental/guardian consent and patient assent (age <18 years), as required by the IRB, institution, or per local regulations
2. Male or female patients with documented diagnosis of SCD (all genotypes)
3. Have been treated with Oxbryta for at least 2 weeks, according to the Oxbryta USPI

5. TREATMENT OF PATIENTS

This is a retrospective data collection and analysis study to evaluate the effects of Oxbryta in individuals with SCD. Patients will have received treatment with Oxbryta as prescribed by their physician at the approved dose per local prescribing information, as part of their usual care. Treatment duration and patient evaluation are per SOC and at the physician's discretion.

5.1. Description of Oxbryta

Oxbryta (voxelotor) is a hemoglobin S polymerization inhibitor indicated for the treatment of SCD in adults and pediatric patients 12 years of age and older.

Refer to the Oxbryta US prescribing information (Oxbryta® USPI) for details on the formulation, packaging, storage, and handling of Oxbryta.

6. STUDY DATA COLLECTION

After informed consent/assent has been obtained (if required by the institution or IRB), the data listed below that are available at or around the timepoints indicated in the schedule of activities (SOA) in Appendix 1 will be collected and entered into the EDC by study personnel at the study site. Data collection will include only those data that are recorded in the patient's medical records and other secondary data sources, up to the timepoint when the data is extracted. Study data that are not available in medical records or other secondary data sources will not be solicited from patients.

6.1. Informed Consent/Assent

A signed and dated consent and/or assent form (ages 12-18 years) will be obtained before any data collection for the study, as required by the IRB or institution.

For pediatric patients, consent should be obtained (if required) from at least one parent (or both if it is required per study site policy) or the patient's legally authorized representative.

Patients and/or their caregiver/legal representative may withdraw consent to participate at any time and for any reason. Any data that was collected prior to patient withdrawal may still be analyzed for the study, unless the patient and/or their caregiver/legal representative specifically ask that the data not be used. However, any data that has already been analyzed will remain as part of the overall research data

6.2. Patient ID Number

After informed consent/assent is obtained (if required), all patients will be given a unique patient ID number. This number will be used to identify the patient on all study documentation related to that patient.

6.3. Eligibility Assessment

Confirmation of eligibility (all inclusion/exclusion criteria) will be performed after informed consent/assent (if required).

6.4. Medical History, Demographic Data, and Insurance Information

Medical history for up to 1 year before and after initiation of Oxbryta (retrospective data) will be recorded in the CRF. Medical history will include all available SCD genotype results and significant medical history, including hematological parameters.

Demographics (sex, race, ethnicity, and age) and SCD characteristics will be recorded at pre-Oxbryta treatment period, using the most recent data before enrollment.

Information on the patient's insurance payer will be also be collected (e.g., Medicaid, Medicare, dual eligible, private, or self-insured).

6.5. SCD Genotype

SCD genotype (at pre-Oxbryta treatment period) only for medical diagnosis of SCD, if diagnosis is not documented in medical chart)

6.6. Effectiveness Data

6.6.1. Clinical Outcomes

6.6.1.1. Hematological Parameters

The following data from the most recent results from tests before each data collection timepoint will be recorded in the CRF.

- Results of local laboratory assessments for Hb (including % HbF)
- Hemolysis measures during treatment with Oxbryta, including % reticulocytes, absolute reticulocytes, bilirubin (total, direct, and indirect)
- Measures of iron overload (ferritin, iron, TIBC, T2*MRI, and liver biopsy)

6.6.1.2. Renal Function

Urine ACR and cystatin C are included as exploratory measures of renal function. Renal damage is a progressive complication of SCD that begins in childhood and may progress to renal failure. The following data from the most recent results from tests before each collection timepoint will be recorded in the CRF.

- Albuminuria (ACR)
- Hemoglobinuria (urine dipstick positive for blood +1 or greater and ≤ 2 RBC by high power field)
- Serum cystatin C
- eGFR calculated using CKD-EPI equation

6.6.1.3. Vaso-Occlusive Crises (VOCs)

VOC data as documented in the patient's medical record will be collected and will include data on VOC events, duration, intensity, and associated interventions.

Data related to any events of ACS will be collected.

The events may have occurred in a medical setting (hospital, clinic, emergency room) or at home.

All data from events occurring during the period since the last collection timepoint will be recorded in the CRF.

6.6.1.4. Priapism

Occurrence of priapism events will be collected. All data from events occurring during the period since the last collection timepoint will be recorded in the CRF.

6.6.1.5. Cerebral infarcts and Transient Ischemic Attack (TIA)

Data related to any events of cerebral infarcts or transient ischemic attack (TIA), identified via MRI or TCD (TAMMV measures in ICA, MCA, ACA), will be collected. All data from events occurring during the period since the last collection timepoint will be recorded in the CRF.

6.6.1.6. Leg Ulcers

Data on leg ulcer(s) assessments will be collected. All data from events occurring during the period since the last collection timepoint will be recorded in the CRF.

6.6.1.7. Measures of Cardiac Function and Pulmonary Hypertension

Cardiac function, as assessed by cardiac ECHO or cardiac catheterization will be collected.

Clinical indicators of PH (such as the 6-minute walk test, dyspnea on exertion, hepatic congestion, etc.) will also be collected.

All data from events occurring during the period since the last collection timepoint will be recorded in the CRF.

6.6.1.8. RBC Transfusion

The occurrence and number of RBC transfusions will be collected. All data from events occurring during the period since the last collection timepoint will be recorded in the CRF.

6.6.1.9. SCD-Related Medication Use

Administration of SCD-related medications, such as hydroxyurea, crizanlizumab, L-glutamine, opioids (in daily morphine equivalents), iron chelating agents, ESAs, NSAIDs, folic acid, and penicillin, will be collected. Data on any of these medications administered during the period since the last collection timepoint will be recorded in the CRF.

6.6.2. Healthcare Resource Utilization

Data on any unplanned clinic visits, ED visits, hospitalizations (including total length of stay and time in ICU, if applicable), acute and chronic RBC transfusions, home oxygen supplementation, and renal dialysis will be collected. All data from events occurring during the period since the last collection timepoint will be recorded in the CRF.

6.6.3. Health-Related Quality of Life (HRQoL)

Data on HRQoL, including PRO and ClinRO measures will be collected. Data from the most recent assessment before each collection timepoint will be recorded in the CRF.

6.6.3.1. Patient Reported Outcome Measurement Information System (PROMIS)

If assessed, the National Institute of Health self-reported (or caregiver-reported) PROMIS (PROMIS Pediatric Profile-37 v2.0 or PROMIS-43 v2.1) measures of function, symptoms, behaviors, and feelings, will be collected.

Data from the most recent assessment before each collection timepoint will be recorded in the CRF.

6.6.3.2. Patient Global Impression of Change (PGIC)

If assessed, data from the self-reported Patient Global Impression of Change (PGIC) will be collected. The PGIC is a single question that reflects a patient's or caregiver’s belief about the effectiveness of treatment with Oxbryta. PGIC is a 7-point scale depicting a patient's rating of

overall improvement. Patients/caregivers rate their change as “very much improved,” “much improved,” “minimally improved,” “no change,” “minimally worse,” “much worse,” or “very much worse.”

Data from the most recent assessment before each collection timepoint will be recorded in the CRF.

6.6.3.3. Visual Analog Scale for Pain (VAS Pain)

Data from the VAS Pain will be collected, if it was used to assess pain intensity for VOCs and the result was recorded as part of the patient’s SOC. Data from the most recent assessment before each collection timepoint will be recorded in the CRF.

6.6.4. Clinical Global Impression of Change (CGIC)

Data from the CGIC will be collected. The CGIC is a brief, stand-alone assessment of the clinician's view of the patient's global functioning prior to and after initiating Oxbryta. The CGI provides an overall clinician-determined summary measure that takes into account all available information, including a knowledge of the patient's history, psychosocial circumstances, symptoms, behavior, and the impact of the symptoms on the patient's ability to function.

Data from the most recent assessment before each collection timepoint will be recorded in the CRF.

6.6.4.1. School Absence and Work Productivity

Summaries of school absences or reports of work productivity will be collected, if collected as part of the patient’s SOC. Data from the most recent assessment before each collection timepoint will be recorded in the CRF.

6.6.4.2. Exercise Tolerance

Any objective measures or reports of exercise tolerance (such as the Borg Scale of Perceived Exertion) will be collected, if they were recorded as part of the patient’s SOC. Data from the most recent assessment before each collection timepoint will be recorded in the CRF.

6.7. Safety Data

6.7.1. Adverse Events

See Section 7 for details regarding the AEs and safety events to be collected in this study as well as the AE reporting requirements. All events occurring during the period since the last collection timepoint will be recorded in the CRF.

6.7.2. Pregnancy Testing and Fertility Data

Results from pregnancy tests performed for female study patients who have experienced menarche will be collected. Data from the most recent assessment before each collection timepoint will be recorded in the CRF.

Any patient report of difficulty conceiving (i.e., infertility) will also be collected. All events occurring during the period since the last collection timepoint will be recorded in the CRF.

7. ADVERSE EVENTS

7.1. Definition of Adverse Events

7.1.1. Adverse Event (AE)

An AE is defined as any untoward medical occurrence in a patient administered a drug product during the course of a study. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a drug product, whether or not thought to be related to the drug product. In addition to new events, any increase in the severity or frequency of a pre-existing condition that occurs after the patient signs the ICF for participation 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 physician or Sponsor, places the patient 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 to be "unexpected" if it is not listed in the Reference Safety Information (RSI) section of the current USPI or is not listed at the specificity or severity that has been observed.

7.1.2. Serious Adverse Event (SAE)

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 physician or Sponsor, results in any of the following outcomes:

- Results in death
- It is immediately life-threatening
- It requires in-patient hospitalization or prolongation of existing hospitalization
- It results in persistent or significant disability or incapacity
- Results in a congenital abnormality or birth defect
- It is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above.

NOTE: Hospitalization planned prior to enrollment (eg, for elective surgeries) is not considered to be an SAE. Any complications arising from a planned hospitalization may be considered an adverse event and should be reported as applicable. Hospitalizations that occur for pre-existing conditions that are scheduled after enrollment are considered SAEs.

7.1.3. Adverse Events of Interest

For this retrospective study, the following are defined as AEs of interest:

- Rash
- Diarrhea
- Headache
- AEs leading to Oxbryta dose modification or discontinuation

7.2. Assessment of Relationship of Adverse Events to Oxbryta

The study doctor will assess each AE for seriousness and relationship to Oxbryta.

When assessing the relationship of an AE to Oxbryta, documentation should be in the patient's medical chart to support the relationship of Oxbryta using the following definitions:

- NOT RELATED: Evidence exists that the AE has an etiology other than the drug and/or the temporal relationship of the AE/SAE to the drug product administration makes the relationship unlikely. If an SAE is not considered to be related to Oxbryta, then an alternative explanation should be provided.
- RELATED: A temporal relationship exists between the event onset and the administration of the drug and makes a causal relationship possible or probable. It cannot be readily explained by the patient'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 judgment should be used for determining causal assessment.

7.3. Assessment of Intensity of Adverse Events

The study doctor will assess the intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the patient, causing minimal discomfort, and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort to interfere with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

Note: An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

7.4. Recording and Reporting of Adverse Events

This retrospective study does not impose a therapy protocol, diagnostic/therapeutic procedure, or a visit schedule.

This section describes the recording and reporting of AEs for Oxbryta. The source of AE data for this study will be secondary data from patients who have initiated treatment with Oxbryta.

Table 1 summarizes the requirements for recording safety events on the eCRF and for reporting safety events for this study.

All SAEs, protocol-specified AEs of interest, and safety events that occur after the first dose of Oxbryta will be recorded on the AE CRF in EDC. In addition, other safety events listed in Table 1, regardless of association with an AE will be reported. Identified SAEs will be reported within 24 hours of knowledge.

Table 1: Requirements for Recording and Reporting Safety Events for Oxbryta

Safety Event	Recorded in the CRF	Reporting Timelines in EDC
SAE	All	Within 24 hours of event knowledge
Non-serious AE of interest	Events listed in Section 7.1.3	Quarterly
Exposure during pregnancy, breast feeding	All events regardless of whether associated with an AE	Quarterly
Medication error		
Oxbryta overdose (accidental or intentional)		
Transmission of infectious agent		
Misuse		
Lack of efficacy		
Occupational exposure		

AE-adverse event; CRF=case report form; EDC=electronic data capture; SAE=serious adverse event.

7.4.1. Reporting Serious Adverse Events

All SAEs, regardless of causal attribution, must be reported by the study doctor or designee or site personnel within 24 hours of SAE awareness. The SAE will be reported by completing the AE CRF via EDC. If the EDC is unavailable, then paper SAE report forms should be completed and submitted via fax or emailed to the Sponsor or designee.

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

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

7.4.2. Reporting Pregnancy

If a patient or a partner pregnancy is identified during the course of the study (retrospective or prospective review) while taking Oxbryta, the pregnancy must be reported to the Sponsor or designee within timelines as noted in Table 1.

Reported pregnancy of a patient or a patient's partner, while participating in this study, will be monitored for the full duration of the pregnancy and/or followed through a definitive outcome (i.e., birth, or spontaneous or elective abortion), if patient or a patient's partner consent for follow-up. The child born to a female patient or partner of a male patient exposed to Oxbryta will be followed for 3 months after delivery

An uncomplicated pregnancy will not be considered an AE or SAE. Pregnancy complications such as spontaneous abortion/miscarriage and congenital anomalies are considered SAEs and must be reported as described in Table 1. Note that an elective abortion is not considered an SAE. Pregnancy and pregnancy outcomes must be reported on a Pregnancy Notification Form or Pregnancy Outcome Form, respectively, and sent to the Sponsor or designee within timelines as noted in Table 1.

The outcome of any pregnancy and the presence or absence of any congenital abnormality found retrospectively or prospectively will be recorded in the Pregnancy Outcome Form and reported to the Sponsor or designee. Any congenital abnormalities in the offspring will be reported as an SAE and must be reported as described in Table 1.

7.4.3. Product Complaint

Product Complaint is any complaint related to the drug component of the product. For a product this may include, but is not limited to, damaged/broken product or packaging, product appearance whose color/markings do not match the labeling, labeling discrepancies/inadequacies in the labeling/instructions (example: printing illegible), missing components/product, device not working properly, or packaging issues.

Product complaints concerning the product must be reported to the Sponsor within 24 hours of the site's knowledge of the event via paper SAE report forms, and submitted to the following email: gbtmedinfo.com. Product Complaints occurring during the study will be followed-up to a satisfactory conclusion. All follow-up information is to be reported to the Sponsor or designee and documented in source as required by the Sponsor. Product complaints associated with adverse events will be reported in the study summary. All other complaints will be monitored on an ongoing basis.

7.4.4. Regulatory Agency, Institutional Review Board, Independent Ethics Committee, and Site Reporting

The Sponsor and/or Clinical Research Organization (CRO) are responsible for notifying the relevant regulatory authorities, and central Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs), and study doctors of related, serious unexpected adverse reactions (SUSARs) as per local regulations. The study doctor is responsible for notifying the local IRBs/IECs of all SAEs that occur at his or her site as required by local regulations, if this responsibility resides with the study doctor.

8. STATISTICS

8.1. Analysis Population

Effectiveness and safety analyses will be based on the treated population, defined as all patients who received at least 2 weeks Oxbryta and meet all eligibility criteria and are included in this study.

8.2. Sample Size

The sample size is selected based on feasibility considerations and to provide descriptive summaries of outcomes of interest.

8.3. Analyses

Change from pre-Oxbryta treatment period in Hb, hemolysis measures, measures of iron overload, and renal function over time will be summarized descriptively.

Annualized incidence rate of significant SCD-related clinical events, including VOC, ACS, priapism, cerebral infarcts, TIA, leg ulcers, and measures of cardiac function and PH will be calculated. The association between change in Hb and hemolysis marker and incidences of SCD-related clinical events will be evaluated.

Incidences of unplanned clinic visits, ED visits, hospitalizations, acute and chronic RBC transfusions, home oxygen supplementation, and renal dialysis will be summarized with a similar approach as incidences of SCD-related clinical events. The total cost associated with clinical interventions will be summarized descriptively.

HRQoL measures over time will be summarized descriptively. Proportions of patients with improved HRQoL measures will be calculated and the associated 95% confidence intervals will be constructed as appropriate.

As appropriate, incidences of SCD-related clinical events, healthcare resource utilization, total cost associated with clinical interventions (if available) and HRQoL while on Oxbryta treatment will be compared qualitatively with the corresponding measures prior to the first dose of Oxbryta treatment.

8.4. Safety Analysis

SAEs and protocol-specified AEs will be classified according to Medical Dictionary for Regulatory Activities (MedDRA). The frequency of AEs will be tabulated by system organ class, preferred term, severity, and relationship to Oxbryta treatment.

9. REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

9.1. 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 Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable ICH Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations

The protocol, protocol amendments, ICF, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the study doctor and reviewed and approved by the IRB/IEC before the study is initiated.

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

The study doctor will be responsible for the following:

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

9.2. Informed Consent and Assent Process

The following process will apply if informed consent/assent is required by the site's IRB and/or local regulations to allow retrospective data collection:

- The study doctor or his/her representative will explain the nature of the study to the patient (or their legally authorized representative) and answer all questions regarding the study.
- Patients must be informed that their participation is voluntary. Patients (or their legally authorized representative) will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability, and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.

- Patients under 18 years of age (and their parent or legal guardian) will review the ICF and sign an Assent Form, according to local IRB/IEC guidelines. Patients who initially sign the assent form and subsequently legally become an adult while actively participating in the study (before the end of study) should be re-consented using the adult ICF soon after their status changes.
- The medical record must include a statement that written informed consent was obtained before the patient was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Patients must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the signed and dated ICF(s) must be provided to the patient (or their legally authorized representative).

The original copies of the signed and dated ICF (and assent form, if applicable), must be retained in the institution's records and are subject to inspection by representatives of the Sponsor, or representatives from regulatory agencies.

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

In the event of a pregnancy in the female partner of a male patient, a pregnancy consent form will be provided to allow the follow-up of the pregnancy.

9.3. Data Protection

- Patients will be assigned a unique identifier. Any patient records or datasets that are transferred to the Sponsor will contain the identifier only; patient names or any information which would make the patient identifiable will not be transferred.
- The patient must be informed that his/her 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 patient who will be required to give consent for their data to be used as described in the informed consent
- The patient must be informed that his/her medical records and secondary data sources may be examined by study auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

9.4. Dissemination of Study Data

This study and study results will be posted on the US National Institutes of Health's website www.Clinicaltrials.gov and other publicly-accessible sites.

9.5. Data Quality Assurance

- All patient data relating to the study will be recorded in the CRF unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The study doctor 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 guideline.
- The study doctor must permit as needed study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details will be provided in the monitoring plan.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the study doctor for 2 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.

9.6. Source Documents

- Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the study site.
- For this study, source data includes data recorded in the patient's medical records and other secondary data sources and collected as part of the patient's usual medical care.
- The study doctor must maintain accurate documentation (source data) that supports the information entered in the CRF.
- Study monitors may perform minimal source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents.

9.7. Essential Documentation Requirements

The Sponsor or Sponsor's representative will collect from the study site the required essential regulatory documents per ICH guidance prior to enrollment of any patient in the study.

9.8. FINANCIAL DISCLOSURE

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

9.9. Study and Site Start and Closure

9.9.1. First Act of Inclusion

The study start date is the date on which the study is open for inclusion of patients.

The first act of data extraction is the first site open and will be the study start date.

9.9.2. Site Closure

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 Sponsor reserves the right to close the study site at any time for any reason at the sole discretion of the Sponsor. The study doctor may also initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

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

- Failure of the study doctor to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate or no patient data (evaluated after a reasonable amount of time) provided by the study doctor

The study doctor shall inform the patient and the IRB/IEC of any site closure.

9.9.3. Study Termination

The Sponsor reserves the right to terminate the study or close the study site at any time for any reason at the sole discretion of the Sponsor.

In any instance of early termination of the study, the Sponsor will notify, in writing, the study doctors, and the IRBs/IECs, and will specify the reason(s) for termination.

9.10. Publication Policy

It is intended to publish the results of the study at regular time intervals (e.g., yearly) over the course of the study. Authorship will be determined by the GBT Registry Steering Committee and in line with International Committee of Medical Journal Editors authorship requirements.

10. LIST OF REFERENCES

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APPENDIX 1. SCHEDULE OF ACTIVITIES

Data Collection/Procedure	Pre-Oxbryta Treatment	Study Data Collection			
Month Intervals	–12 to 1	3	6	9	12
Informed consent/assent (if required) [a]	X				
Review of eligibility [b]	X				
Medical history and SCD genotype [c]	X				
Clinical outcomes and interventions [d]	X	X	X	X	X
Health resource utilization [e]	X	X	X	X	X
PRO assessments (PROMIS, PGIC, VAS Pain) [f]	X	X	X	X	X
ClinRO assessments (GCIC, School Absence and Work Productivity, and exercise tolerance) [g]	X	X	X	X	X
SCD medications [h]	X	X	X	X	X
Safety data [i]	X	X	X	X	X

CGIC=Clinical Global Impression of Change; ClinRo=clinician-reported outcome; PGIC=Patient Global Impression of Change; PRO=patient-reported outcome; PROMIS=Patient-Reported Outcomes Measurement Information System; VAS-Pain=Visual Analog Scale for Pain.

NOTE: With the exception of informed consent/assent, all other data listed above are required to be collected if assessments are performed as part of the patient's standard-of-care; the data from these assessments will be collected at the timepoints indicated (if available).

[a] A signed and dated consent and/or assent form (age <18 years) will be obtained before any data collection for the study, if required by the Institutional Review Board (IRB) or local regulations. For pediatric patients, consent should be obtained from at least one parent (or both, as required by site's policy) or the patient's legally authorized representative.

[b] Inclusion and exclusion criteria should be reviewed at the pre-Oxbryta treatment period to ensure patient eligibility is met.

[c] Record available significant medical history for up to 12 months prior to the first dose of Oxbryta (retrospective data) in the CRF. Record demographics (sex, race, ethnicity, and age), and SCD characteristics (including hematological parameters), using the most recent data before enrollment. Record all available SCD genotype results.

[d] Record available clinical outcomes data including: hematological parameters, renal function, VOCs, ACS, priapism, cerebral infarcts, TIAs, leg ulcers, cardiac function, pulmonary hypertension, RBC transfusions, and SCD-related medication use (see Section 6.6.1 for details).

[e] Health resource utilization includes any unplanned clinic visits, ED visits, hospitalizations (including length of stay, if applicable), acute and chronic transfusions, home oxygen supplementation, and renal dialysis occurring during the period between data collection timepoints.

[f] PRO assessments will include PROMIS (PROMIS Pediatric Profile-37 v2.0 or PROMIS-43 v2.1), PGIC, and Visual Analog Scale (Pain). Record data from the most recent assessment before each collection timepoint. See Section 6.6.3 for details.

[h] ClinRO assessments will include CGIC, School Absence and Work Productivity, and any objective measures or reports of exercise tolerance (e.g., Borg Scale of Perceived Exertion). Record data from the most recent assessment before each collection timepoint. See Section 6.6.3 for details.

[h] Record medications for SCD-related conditions (e.g., hydroxyurea, crizanlizumab, L-glutamine, opioids, in daily morphine equivalents, iron chelating agents, ESAs, NSAIDs, folic acid, and penicillin) taken by the patient from 12 months before screening through the end of study participation (60 months after the first dose of Oxbryta treatment or early discontinuation).

[i] Record all serious adverse events, adverse events of interest, safety events, pregnancy test results, and reports of fertility issues occurring during the period since the last collection timepoint. See Section 7.1 for definitions and Section 7.4 for details on recoding and reporting AEs and safety events.