REGISTRY PROTOCOL

Study Number	**GBT440-4R2**
Study Title	**An Open Label, Observational, Prospective Registry of Participants With Sickle Cell Disease (SCD) Treated With Oxbryta® (Voxelotor)**
Short Title	Oxbryta Product Registry
Drug Product	Oxbryta® (voxelotor) 500mg Tablets
Sponsor	Global Blood Therapeutics, Inc. [redacted] United States of America
Study Director	[redacted] Global Blood Therapeutics, Inc. [redacted]
Original Protocol Date	3 February 2021

CONFIDENTIAL

The information in this registry 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 participants. Once the protocol is signed, its terms are binding for all parties.

STATEMENT OF APPROVAL AND COMPLIANCE

STUDY TITLE: An Open Label, Observational, Prospective Registry of Participants With Sickle Cell Disease (SCD) Treated With Oxbryta® (Voxelotor)

SPONSOR APPROVAL

The signature of the Sponsor (Global Blood Therapeutics, Inc., "GBT") representative, below, signifies that the above-referenced registry 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 Jonathan Sorof | I approve this document 04-Feb-2021 | 17:51 PST 27FD75376AB94193BC2DC054593B8668
Date:	04-Feb-2021 | 17:51 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	GBT440-4R2
Study Title	An Open Label, Observational, Prospective Registry of Participants With Sickle Cell Disease (SCD) Treated With Oxbryta® (Voxelotor)
Short Title	Oxbryta Product Registry
Sponsor	[redacted] United States of America
Study Description	This registry is an observational study designed to evaluate the effect of Oxbryta in individuals with SCD. This registry is intended to benefit and support interests of patients, clinicians, regulatory bodies, payers, and industry by obtaining longitudinal data on Oxbryta.
Number of Study Sites	The study will be conducted at approximately 25 sites in the US.
Number of Participants	Approximately 750 eligible participants will be enrolled in this study.
Treatment	This registry is an observational study to evaluate the effects of Oxbryta in individuals with SCD. Participants will receive treatment with Oxbryta as prescribed by their physician, as part of their usual care. Participants will be treated and evaluated per standard of care (SOC) and at the physician's discretion. There are no pre-defined treatment requirements.
Objectives	**Primary** The primary objective is to gather long term data on Oxbryta in a real-world setting. The following are categories of interest in participants 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 participants, parents/caregivers, and clinicians **Safety** The safety objective is to assess the safety and tolerability of Oxbryta, including long-term safety.

Outcome Measures	**Effectiveness** • 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, 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: chronic and acute pain intensity (Visual Analog Scale for pain [VAS Pain]), Sheehan Disability Scale (SDS), Parent/Caregiver Productivity Questionnaire (PCPQ), and any objective measure of exercise tolerance **Safety** • 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	Any participant who is currently taking Oxbryta or has been prescribed and will initiate treatment with Oxbryta, is eligible to participate. Eligible participants will receive treatment with Oxbryta as prescribed by their physician, as part of their usual care. Participants will be treated and evaluated per standard of care (SOC) and at the physician's discretion. Participants will be introduced to the study by their health care team and will sign the informed consent form (ICF) or assent prior to any data collection for the study. This study will collect data that are recorded in the participants' medical records and other secondary data sources. Study data will be collected at regular intervals and entered in case report forms (CRFs) via an electronic data capture (EDC) system by the study staff. Participants will be considered to be on study for up to 5 years after their first dose of Oxbryta treatment, or until they withdraw their consent to participate, or are discontinued from the study. Treatment, including interruptions and restarting treatment, will continue at the discretion of the treating physician, and there are no pre-defined treatment requirements. Participants may receive any additional medications prescribed by their treating physician, or have any medical interventions that are deemed appropriate by the treating physician or study doctor. The participant or treating physician may discontinue Oxbryta at any time. Participants who discontinue treatment with Oxbryta earlier than 5 years will continue to be followed on study to collect clinical and quality of life (QoL) outcomes for up to 5 years after their first dose of Oxbryta treatment. Participant safety and tolerability will be assessed throughout the study data collection period by the study doctor and reported to the Sponsor.
Duration of Study Participation	The approximate duration of study participation for an individual participant includes an observation period of up to 60 months after the first dose of Oxbryta treatment.
End of Study	The end of study is defined as the date of the last data collection timepoint of the last participant being followed.
Study Population	**Inclusion Criteria**: Participants who meet all the following criteria will be eligible for enrollment: 1. Willing and able to provide written informed consent (ages ≥ 18 years) or parental/guardian consent and participant assent (age <18 years) per local regulations 2. Male or female participants with documented diagnosis of sickle cell disease (all genotypes) 3. Undergoing treatment with Oxbryta according to the Oxbryta USPI **Exclusion Criteria**: Participants meeting any of the following criteria will not be eligible for study enrollment: 1. Current participation or prior participation within ≤1 year before enrollment in an investigation clinical trial or expanded access program, in which the participant received voxelotor treatment 2. Medical, psychological, or behavioral condition that, in the opinion of the study doctor, would confound or interfere with evaluation of safety and/or effectiveness of the study drug, prevent compliance with the study protocol; preclude informed consent; or render the participant unable/unlikely to comply with the study procedures

Statistical Methods	**Analysis Population** Effectiveness and safety analyses will primarily be based on the treated population, defined as all participants receiving at least one dose of Oxbryta. **Sample Size** The sample size is selected to provide an estimation of the relationship between change in Hb and significant clinical events, such as VOCs, cerebral infarcts, TIA, pulmonary hypertension, that participants experience over the 5 years of the study. The total sample size of approximately 750 participants is expected to support major subgroup analyses. **Effectiveness 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, measures of cardiac function and PH, and RBC transfusions 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 participants 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 in the 12 months prior to the first dose of Oxbryta treatment. Similar comparisons may be performed between the subgroup of participants who discontinue Oxbryta treatment but remain in the study and those participants who remain on Oxbryta. **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
CRO	Clinical Research Organization
CRF	case report form
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
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
PCPQ	Parent/Caregiver Productivity Questionnaire

Abbreviation	Description
PGIC	Patient Global Impression of Change
PH	pulmonary hypertension
PROMIS	Patient-Reported Outcomes Measurement Information System
QoL	quality of life
RBC	red blood cell
SAE	serious adverse event
SCD	sickle cell disease
SDS	Sheehan Disability Scale
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-Pain	Visual Analog Scale for Pain
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 α chain of hemoglobin (Hb) and allosterically increases HbS-oxygen (O_2) affinity (Eaton, 1999), stabilizing the oxyhemoglobin 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

The following objectives and outcome measures will be evaluated if the data are available.

2.1. Objectives

2.1.1. Primary Objective

The primary objective is to gather long term data on Oxbryta in a real-world setting. The following are categories of interest in participants 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 participants, parents/caregivers, and clinicians

2.1.2. Safety Objective

The safety objective is to assess the safety and tolerability of Oxbryta, including long-term safety.

2.2. Outcome Measures

2.2.1. Effectiveness 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, 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: chronic and acute pain intensity (Visual Analog Scale for Pain [VAS-Pain]), Sheehan Disability Scale (SDS), Parent/Caregiver Productivity Questionnaire (PCPQ), and any objective measure of exercise tolerance

2.2.2. 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 registry is an observational study designed to evaluate the effect of Oxbryta in individuals with SCD. This registry is intended to benefit and support interests of patients, clinicians, regulatory bodies, payers, and industry by obtaining longitudinal data on Oxbryta. Approximately 750 SCD participants who are prescribed and treated with Oxbryta will be enrolled. The study will be conducted at approximately 25 sites in the US.

Any participant who is currently taking Oxbryta or has been prescribed and will initiate treatment with Oxbryta, is eligible to participate. Eligible participants will receive treatment with Oxbryta as prescribed by their physician, as part of their usual care. Participants will be treated and evaluated per standard of care (SOC) and at the physician's discretion.

Participants will be introduced to the study by their health care team and will sign the informed consent form (ICF) or assent prior to any data collection for the study.

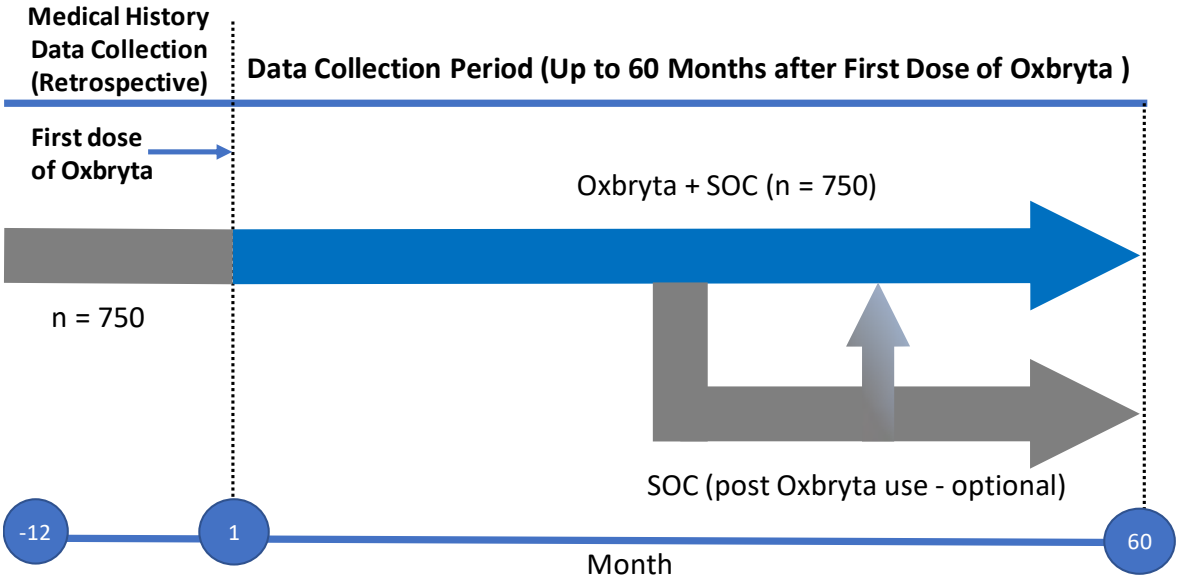
This study will collect data that are recorded in the participants' medical records and other secondary data sources. Study data will be collected at regular intervals and entered in case report forms (CRFs) via an electronic data capture (EDC) system by the study staff.

Regardless of how long participants have been on Oxbryta when they enroll in the study, participants will on study for up to 5 years after their first dose of Oxbryta treatment, or until they withdraw their consent to participate, or are discontinued from the study. Treatment, including interruptions and restarting treatment, will continue at the discretion of the treating physician, and there are no pre-defined treatment requirements. Participants may receive any additional medications prescribed by their treating physician, or have any medical interventions that are deemed appropriate by the treating physician or study doctor. The participant or treating physician may discontinue Oxbryta at any time. Participants who discontinue treatment with Oxbryta earlier than 5 years will continue to be followed on study to collect clinical and quality of life (QoL) outcomes for up to 5 years after their first dose of Oxbryta treatment.

Participant safety and tolerability will be assessed throughout the study data collection period by the study doctor and reported to the Sponsor.

The overall study design is illustrated in Figure 1.

Figure 1: Study Schema



SOC=standard of care.

3.2. Duration of Study Participation

The approximate duration of study participation for an individual participant includes an observation period of up to 60 months after the first dose of Oxbryta treatment.

3.3. End of Study

The end of study is defined as the date of the last data collection timepoint of the last participant being followed.

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. Inclusion Criteria

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

1. Willing and able to provide written informed consent (ages ≥ 18 years) or parental/guardian consent and participant assent (age <18 years) per local regulations
2. Male or female participants with documented diagnosis of sickle cell disease (all genotypes)
3. Undergoing treatment with Oxbryta according to the Oxbryta USPI

4.2. Exclusion Criteria

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

1. Current participation or prior participation within ≤1 year before enrollment in an investigation clinical trial or expanded access program, in which the participant received voxelotor treatment
2. Medical, psychological, or behavioral condition that, in the opinion of the study doctor, would confound or interfere with evaluation of safety and/or effectiveness of the study drug, prevent compliance with the study protocol; preclude informed consent; or render the participant unable/unlikely to comply with the study procedures

5. TREATMENT OF PARTICIPANTS

This registry is an observational study to evaluate the effects of Oxbryta in individuals with SCD. Participants will receive treatment with Oxbryta as prescribed by their physician, as part of their usual care. Participants will be treated and evaluated per SOC and at the physician's discretion. There are no pre-defined treatment requirements.

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.

5.2. Concomitant Medications

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

Pre-specified medications for SCD-related conditions taken by the participant from 12 months before screening through the end of study participation (60 months after the first dose of Oxbryta treatment or early discontinuation) will be recorded in the CRF.

Treating physicians may prescribe the participant any additional medications or perform medical interventions they deem appropriate.

Refer to the Oxbryta® USPI for details on concomitant medications and contraindications.

5.3. Discontinuation of Oxbryta and Participant Discontinuation

5.3.1. Withdrawal of Consent

Participants and/or their caregiver/legally authorized representative will be informed participation is voluntary and that they may discontinue Oxbryta treatment or withdraw from the study at any time and for any reason. Any participant who requests to be withdrawn or whose caregiver/legally authorized representative requests withdrawal will be withdrawn from the study by the study doctor.

5.3.2. Early Discontinuation of Oxbryta

Participants may be discontinued from Oxbryta treatment by the study doctor or treating physician at any time and for any reason.

Participants who are discontinued or withdraw from Oxbryta treatment will continue to be followed for up to 60 months after the first dose of Oxbryta treatment unless they withdraw consent for study participation.

5.3.3. Lost to Follow Up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for their routine visits per SOC for ≥1 year and is unable to be contacted by the study site.

6. STUDY DATA COLLECTION

Data on participants will be collected at regular intervals and entered into the EDC system by study personnel at the study site beginning with their first dose of commercial Oxbryta. Data collection will include those data that are recorded in the participant's medical records/other secondary data sources and based on assessments performed as part of the participant's SOC. Study data that are not available in medical records or other secondary data sources will not be solicited from participants. The data to be collected in this study and target timepoints for data collection and entry are specified in the schedule of activities (SOA) in Appendix 1.

6.1. Informed Consent/Assent

A signed and dated consent and/or assent form (age <18 years) will be obtained before any data collection for the study.

For pediatric participants, consent should be obtained from at least one parent (or both if it is required per study site policy) or the participant's legally authorized representative. Guidelines for the informed consent/assent process are outlined in Section 9.2.

6.2. Participant ID Number

Upon execution of consent/assent, all participants will be given a unique participant ID number. This number will be used to identify the participant throughout the study and must be used on all study documentation related to that participant.

6.3. Eligibility Assessment

Confirmation of eligibility (all inclusion/exclusion criteria) will be performed at pre-Oxbryta treatment period.

6.4. Medical History, Demographic Data, and Insurance Information

Medical history will be recorded for up to 12 months prior to the first dose of Oxbryta (retrospective data). 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 participant'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 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) and Acute Chest Syndrome (ACS)

VOC data as documented in the participant'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 measures will be collected. Data from the most recent assessment before each collection timepoint will be recorded in the CRF. The questionnaires are provided in Appendix 2.

6.6.3.1. Patient Reported Outcome Measurement Information System (PROMIS)

The National Institute of Health self-reported (or caregiver-reported) PROMIS 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.

If not performed as part of the participant's usual care, standardized PROMIS forms (PROMIS Pediatric Profile-37 v2.0 or PROMIS-43 v2.1) will be provided.

6.6.3.2. Patient Global Impression of Change (PGIC)

Data from the self-reported Patient Global Impression of Change (PGIC) will be collected. The PGIC is a single question that reflects a participant's or caregiver's belief about the effectiveness of treatment with Oxbryta. PGIC is a 7-point scale depicting a participant's rating of overall improvement. Participants/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.

If not performed as part of the participant's usual care, the questionnaire will be provided.

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

If not performed as part of the participant's usual care, the VAS-Pain scale will be provided.

6.6.3.4. School Absence, Work Productivity, and Caregiver Burden

Summaries of school absences, work productivity, and caregiver burden will be collected using the SDS and PCPQ. Data from the most recent assessment before each collection timepoint will be recorded in the CRF.

If not performed as part of the participant's usual care, the questionnaires will be provided.

6.6.3.5. 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 participant'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 participant's history, psychosocial circumstances, symptoms, behavior, and the impact of the symptoms on the participant's ability to function. CGIC will be collected, if it does not influence the participant's usual care.

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

If not performed as part of the participant's usual care, the CGIC will be provided.

6.6.3.6. Exercise Tolerance

Any objective measures or reports of exercise tolerance will be collected, if they were recorded as part of the participant'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 registry 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 participants who have experienced menarche will be collected. Data from the most recent assessment before each collection timepoint will be recorded in the CRF.

Any participant 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 participant 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 participant 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 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 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 participant 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 registry, 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 participant'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 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 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 participant, 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 registry 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 participant 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 registry.

All SAEs, protocol-specified AEs of interest, and AEs that are assessed by the study doctor as related to Oxbryta 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
Non-serious AE that is assessed as related to Oxbryta	All related AEs	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		

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 doctor's site. Follow-up reports must be submitted within 24 hours of awareness, and participant 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 participant 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 participant or a participant's partner, while participating in this registry, 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 participant or a participant's partner consent for follow-up. The child born to a female participant or partner of a male participant 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 registry 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 primarily be based on the treated population, defined as all participants receiving at least one dose of Oxbryta.

8.2. Sample Size

The sample size is selected to provide an estimation of the relationship between change in Hb and significant clinical events, such as VOCs, cerebral infarcts, TIA, and PH, that participants experience over the 5 years of the study. The total sample size of approximately 750 participants is expected to support major subgroup analyses.

8.3. Effectiveness 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, 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 participants 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. Similar comparisons may be performed between the subgroup of participants who discontinue Oxbryta treatment but remain in the study and those participants who remain on Oxbryta.

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, Assent, USPI, 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 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 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 IRB/IEC requirements
- 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 study doctor or his/her representative will explain the nature of the study to the participant (or their legally authorized representative) and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants (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.

- Participants under 18 years of age (and their parent or legally authorized representative) will review the ICF and sign an Assent Form, according to local IRB/IEC guidelines. Participants 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 participant 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.
- Participants 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 participant (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.

Participants unable to sign the ICF may participate in the study if a legally authorized representative or witness provides the consent (in accordance with the procedures of ICH-GCP and local regulations) and the participant confirms his/her interest in study participation. The participant, parent, or legally authorized representative 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 legally authorized representative's responsibility to communicate this decision to the study doctor.

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

9.3. Data Protection

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant 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 participant who will be required to give consent for their data to be used as described in the informed consent.
- The participant 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 participant 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 participant 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 participant's medical records and other secondary data sources and collected as part of the participant's usual medical care.
- The study doctor must maintain accurate documentation (source data) that supports the information entered in the CRF.
- Study monitors will 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 participant 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 Recruitment

The study start date is the date on which the study is open for recruitment of participants.

The first act of recruitment 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 recruitment (evaluated after a reasonable amount of time) of participants by the study doctor
- Enrollment goal met earlier than expected

The study doctor shall inform the participant and the Independent Ethics Committees (IECs)/Institutional Review Boards (IRBs), 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.

Reasons for terminating the study may include, but are not limited to the following:

- Discontinuation of further Oxbryta development

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

The study doctor shall inform the participant and of any early termination of the study.

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 period	Study Data Collection Period											
Month Intervals	**–12 to 1**	**3**	**6**	**9**	**12**	**18**	**24**	**30**	**36**	**42**	**48**	**54**	**60**
Informed Consent/Assent [a]	X												
Review of eligibility [b]	X												
Medical history and SCD genotype [c]	X												
Clinical outcomes and interventions [d]	X	X	X	X	X	X	X	X	X	X	X	X	X
Health resource utilization [e]	X	X	X	X	X	X	X	X	X	X	X	X	X
HRQoL assessments (PROMIS, PGIC, VAS-Pain, SDS, PCPQ, CGIC, and exercise tolerance) [f]	X	X	X	X	X	X	X	X	X	X	X	X	X
SCD medications [g]	X	X	X	X	X	X	X	X	X	X	X	X	X
Safety data [h]	X	X	X	X	X	X	X	X	X	X	X	X	X

CGIC=Clinical Global Impression of Change; HRQoL=health-related quality of life; PGIC=Patient Global Impression of Change; PROMIS=Patient-Reported Outcomes Measurement Information System; VAS-Pain=Visual Analog Scale for Pain; SDS = Sheehan Disability Scale; PCPQ= Parent/Caregiver Productivity Questionnaire.

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 participant's standard-of-care; the data from these assessments will be collected at the timepoints indicated (if available) and will include all data available for the period between the timepoints.

[a] A signed and dated consent and/or assent form (age <18 years) will be obtained before any data collection for the study. For pediatric participants, consent should be obtained from at least one parent (or both if it is required per investigational site policy) or the participant's legally authorized representative.

[b] Inclusion and exclusion criteria should be reviewed at the pre-Oxbryta treatment period to ensure participant 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 RBC transfusions, home oxygen supplementation, and renal dialysis occurring during the period between data collection timepoints.
[f] HRQoL assessments will include PROMIS, PGIC, VAS-Pain, SDS, PCPQ, CGIC, and exercise tolerance. Record data from the most recent assessment before each collection timepoint. If not performed as part of the participant's usual care, the questionnaires will be provided for the participant, parent/caregiver, or clinician to complete. See Section 6.6.3 for details. The questionnaires are provided in Appendix 2.
[g] 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 participant from 12 months before screening through the end of study participation (60 months after the first dose of Oxbryta treatment or early discontinuation).
[h] Record all serious adverse events, adverse events of interest, Oxbryta-related AEs, other 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.

APPENDIX 2. HEALTH-RELATED QUALITY OF LIFE MEASURES

Patient-Reported Outcomes Measurement Information System (PROMIS) – Adult

Patient-Reported Outcomes Measurement Information System (PROMIS) - Pediatric

Patient Global Impression of Change (PGIC)

Visual Analog Scale for Pain (VAS-Pain)

Sheehan Disability Scale (SDS)

Parent/Caregiver Productivity Questionnaire (PCPQ)

Clinical Global Impression of Change (CGIC)

Patient-Reported Outcomes Measurement Information System (PROMIS) - Adult

Please respond to each question of statement by marking one box per row.

Physical Function	Without any difficulty	With a little difficulty	With some difficulty	With much difficulty	Unable to do
Are you able to do chores such as vacuuming or yard work?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Are you able to go up and down stairs at a normal pace?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Are you able to go for a walk of at least 15 minutes?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Are you able to run errands and shop?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
	Not at all	**Very little**	**Somewhat**	**Quite a lot**	**Cannot do**
Does your health now limit you in doing two hours of physical labor?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Does your health now limit you in doing moderate work around the house like vacuuming, sweeping floors or carrying in groceries?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Anxiety **In the past 7 days…**	**Never**	**Rarely**	**Sometimes**	**Often**	**Always**
I felt fearful	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I found it hard to focus on anything other than my anxiety	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
My worries overwhelmed me	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I felt uneasy	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I felt nervous	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I felt like I needed help for my anxiety	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Depression **In the past 7 days...**	**Never**	**Rarely**	**Sometimes**	**Often**	**Always**
I felt worthless	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I felt helpless	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I felt depressed	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Depression

In the past 7 days...	Never	Rarely	Sometimes	Often	Always
I felt hopeless	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I felt like a failure	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I felt unhappy	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Fatigue

During the past 7 days…	Not at all	A little bit	Somewhat	Quite a bit	Very much
I feel fatigued	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I have trouble starting things because I am tired	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
In the past 7 days…					
How run-down did you feel on average?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
How fatigued were you on average?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
How much were you bothered by your fatigue on average?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
To what degree did your fatigue interfere with your physical functioning?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Sleep Disturbance

In the past 7 days…	Very poor	Poor	Fair	Good	Very good
My sleep quality was	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
In the past 7 days…	**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
My sleep was refreshing	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
I had a problem with my sleep	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I had difficulty falling asleep	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
My sleep was restless	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I tried hard to get to sleep	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Ability to Participate in Social Roles and Activities

	Never	Rarely	Sometimes	Usually	Always
I have trouble doing all of my regular leisure activities with others	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
I have trouble doing all of the family activities that I want to do	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
I have trouble doing all of my usual work (include work at home)	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
I have trouble doing all of the activities with friends that I want to do	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
I have to limit the things I do for fun with others	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
I have to limit my regular activities with friends	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

Pain Interference

In the past 7 days…	Not at all	A little bit	Somewhat	Quite a bit	Very much
How much did pain interfere with your day to day activities?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
How much did pain interfere with work around the home?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
How much did pain interfere with your ability to participate in social activities?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
How much did pain interfere with your household chores?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
How much did pain interfere with the things you usually do for fun?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
How much did pain interfere with your enjoyment of social activities?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Pain Intensity

In the past 7 days…											
How would you rate your pain on average?	☐ 0 No pain	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10 Worst pain imaginable

Patient-Reported Outcomes Measurement Information System (PROMIS) - Pediatric

Please respond to each question of statement by marking one box per row.

Physical Function Mobility **In the past 7 days…**	**With no trouble**	**With a little trouble**	**With some trouble**	**With a lot of trouble**	**Not able to do**
I could do sports and exercise that other kids my age could do	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
I could get up from the floor	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
I could walk up stairs without holding on to anything	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
I have been physically able to do the activities I enjoy most	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
I could keep up when I played with other kids	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
I could stand up on my tiptoes	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Anxiety **In the past 7 days...**	**Never**	**Almost Never**	**Sometimes**	**Often**	**Almost Always**
I felt like something awful might happen	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I felt nervous	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I felt worried	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I worried when I was at home	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I felt scared	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I worried when I went to bed at night	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Depressive Symptoms **In the past 7 days...**	**Never**	**Almost Never**	**Sometimes**	**Often**	**Almost Always**
I felt everything in my life went wrong	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I felt lonely	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I felt sad	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Depressive Symptoms **In the past 7 days...**	Never	Almost Never	Sometimes	Often	Almost Always
It was hard for me to have fun	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I could not stop feeling sad	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I felt like I couldn't do anything right	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Fatigue **In the past 7 days…**	Never	Almost Never	Sometimes	Often	Almost Always
Being tired made it hard for me to keep up with my schoolwork	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I got tired easily	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I was too tired to do sports or exercise	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I was too tired to enjoy the things I like to do	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I felt weak	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I had trouble finishing things because I was too tired	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Peer Relationships **In the past 7 days…**	Never	Almost Never	Sometimes	Often	Almost Always
I felt accepted by other kids my age	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I was able to count on my friends	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
My friends and I helped each other out	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Other kids wanted to be my friend	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I was good at making friends	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Other kids wanted to be with me	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Pain Interference **In the past 7 days…**	Never	Almost Never	Sometimes	Often	Almost Always
I had trouble sleeping when I had pain	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
It was hard for me to pay attention when I had pain	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Pain Interference
In the past 7 days…

	Never	Almost Never	Sometimes	Often	Almost Always
It was hard for me to run when I had pain ...	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
It was hard for me to walk one block when I had pain	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
It was hard to have fun when I had pain.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
It was hard to stay standing when I had pain	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Pain Intensity
In the past 7 days…

How bad was your pain on average? ..	☐ 0 **No pain**	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10 **Worst pain you can think of**

Patient Global Impression of Change (PGIC)

Not Done	☐	
* Not Done, Reason		
* Date of assessment		(DD-MMM-YYYY)
* Compared to your condition at the start of the study, how much have you changed?	○ VERY MUCH IMPROVED ○ MUCH IMPROVED ○ MINIMALLY IMPROVED ○ NO CHANGE ○ MINIMALLY WORSE ○ MUCH WORSE ○ VERY MUCH WORSE	
How has this assessment been performed?	○ PARTICIPANT SELF-REPORT ○ PARENT PROXY	

Visual Analog Scale for Pain (VAS-Pain)

Not Done	☐	
* Not Done, Reason		
* Date of VAS		(DD-MMM-YYYY)
Please select the Pain Rating from the dropdown list		
* Result	○ 0-NO HURT ○ 2-HURTS LITTLE BIT ○ 4-HURTS LITTLE MORE ○ 6-HURTS EVEN MORE ○ 8-HURTS WHOLE LOT ○ 10 HURTS WORST	

Please refer to the 4-minute audio at the link below for instructions on usage:
https://wongbakerfaces.org/instructions-use/

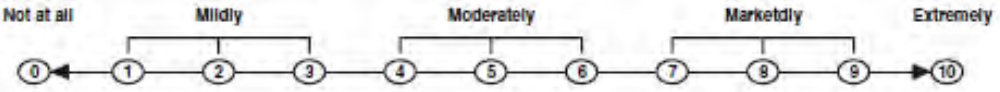
Sheehan Disability Scale (SDS)

A brief, patient rated, measure of disability and impairment.

Please mark ONE circle for each scale.

WORK* / SCHOOL

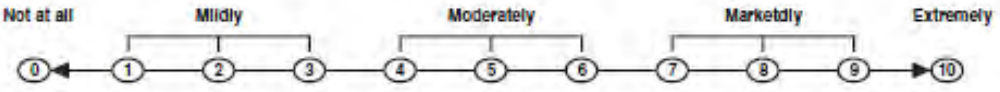
The symptoms have disrupted your work / school work:



☐ I have not worked / studied at all during the past week for reasons unrealted to the disorder.
* Work includes paid, unpaid volunteer work or training

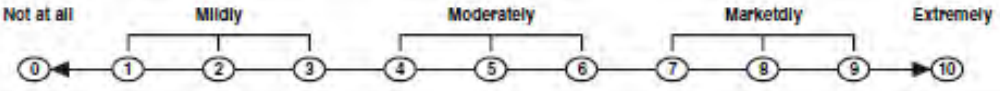
SOCIAL LIFE

The symptoms have disrupted your social life / leisure activities:



FAMILY LIFE / HOME RESPONSIBILITIES

The symptoms have disrupted your family life / home responsibilities:



Days Lost

On how many days in the last week did your symptoms cause you to miss school or work or leave you unable to carry out your normal daily responsibilities? _____

Days Unproductive

On how many days in the last week did you feel so impaired by your symptoms, that even though you went to school or work, your productivity was reduced? _____

Parent/Caregiver Productivity Questionnaire (PCPQ)

Parent/Caregiver Productivity

Are you the guardian/caregiver of this child? That is, is the child is in your care for 50% of the time or more of the week in general?

_____ NO _____ YES

If NO, check "NO" and STOP.

What is the relationship between you and this child?

_____*Father*
_____*Mother*
_____*Grandparent*
_____*Sibling*
_____*Other, specify:* _____

The following questions ask about the effect of your child's health problem(s) on your ability to work and perform regular activities. By health problem(s) we mean any physical or emotional problem or symptom. *Please place a check √ next to the best answer for each question.*

1) Are you currently employed (working for pay)? ____ NO ____ YES

2) Which of the following statements are true of you during the past four weeks (mark all that apply):

   _____ I had to work part-time rather than full time because of my child's health problem.

   _____ I was not able to work at all when I wanted to work full time because of my child's health problem.

   _____ My child's health problem kept me from working at all when I wanted to work part-time.

   _____ None of the above

   If answered "NO" to Question 1, skip to Question 8.

Please fill in the blanks.

3) **During the past four weeks,** how many days did you miss from work because of your child's health problems? Include days you missed on sick days, times you went in late, left early, etc., because of his/her health problems. Do not include time you missed due to your child's participation in this study.

   _____ DAYS

4) **During the past four weeks**, how many days did you go to work late or leave early because of your child's health problems? Do not include the days you went to work later or left early due to your child's participation in this study.

   _____ DAYS

5) **During the past four weeks,** how many days did you miss from work because of any other reason, such as vacation, holidays, and/or time off due to your child's participation in this study?

   _____ DAYS

6) **During the past four weeks,** how many days did you actually work?

   _____ DAYS *(If "0", skip to question 8.)*

7) Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual.

   During the past four weeks, how much did your child's health problems affect you while you were working?

   If your child's health problems affected your work only a little, choose a low number. Choose a high number if your child's health problems affected your work a great deal. Circle the number that best applies.

My child's health problems had no effect on my work	0	1	2	3	4	5	6	7	8	9	10	My child's health problems completely prevented me from working

8) Think about times you were limited in the amount or kind of activities you could do, and times you accomplished less than you would like.

During the past four weeks, how much did your child's health problems affect your ability to do your regular daily activities (such as work around the house, shopping, child care, studying, etc), other than work at a job?

If your child's health problems affected your activities only a little, choose a low number. Choose a high number if your child's health problems affected your activities a great deal. Circle the number that best applies.

My child's health problems had no effect on my daily activities	0	1	2	3	4	5	6	7	8	9	10	My child's health problems completely prevented me from doing my daily activities

Completed by: _____ Date: _____

Clinical Global Impression of Change (CGIC)

* Date of assessment	(DD-MMM-YYYY)
* Compared to the subject's condition prior to treatment, how much has the subject's condition changed?	○ NOT ASSESSED ○ VERY MUCH IMPROVED ○ MUCH IMPROVED ○ MINIMALLY IMPROVED ○ NO CHANGE ○ MINIMALLY WORSE ○ MUCH WORSE ○ VERY MUCH WORSE
* Rater initials	