Non-Interventional Study

C5341019

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

Statistical Analysis Plan

(SAP)

Version: <3>

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1. VERSION HISTORY AND LIST OF ABBREVIATIONS

Version history

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
2/ 21-Nov-2024	Original Protocol 10 October 2023	**Update to Section headers to provide clarity for the analysis and list of tables.**	Section 3.2: Updated SCD complications. Section 4.2.1: Added subgroup in this section Section 4.3: Modified age was based on the first dose of Oxbryta. Section 4.6: Added imputation rule for the end of study and treatment dates Section 4.7.1: Modified texts about post-Oxbryta Section 4.7.3: Modified SCD-related events Section 4.7.4: • Removed the sentence of SCD related events • Added an analysis period • Added SAE listings • Added 28 days to the TEAEs definition Section 4.7.5: • Modified the title to subgroup analyses • Added analysis for new added subgroup Appendices: • Removed 'Study Drug Administration and Dosage Changes Initiated by the Participant' table • Modified title for tables 15.2.5, 15.2.6, and 15.4 • Added table 15.2.5.1 'Summary of Transfusions' • Added table 15.2.6.1 'Annualized Incidence Rate of Transfusions)' • Updated table 15.3.3 title • Added table 15.3.7 • Added tables 15.5.1-15.5.4

3/ 24-Jan-2025	Original Protocol 10 October 2023	**Update to Section headers to provide clarity for the analysis and list of tables.**	Section 4.2: Modified analysis populations Section 4.7.3: Added texts to exclude lab values with the incorrect unit. Appendix 6.1: Modified the analysis population in the table title

List of abbreviations

Abbreviation	**Definition**
ACR	albumin/creatinine ratio
ACS	acute chest syndrome
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
CGIC	Clinical Global Impression of Change
CRF	case report form
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CSR	Clinical Study Report
ED	emergency department
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
ESA	erythropoietin-stimulating agent
FDA	(US) Food and Drug Administration
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
IRB	Institutional Review Board
LDH	lactate dehydrogenase
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for regulatory Activities
NPRS	Numerical Pain Rating Scale

NSAID	nonsteroidal anti-inflammatory drug
PGIC	Patient Global Impression of Change
PH	pulmonary hypertension
PROMIS	Patient-Reported Outcomes Measurement Information System
RBC	red blood cell
SAE	serious adverse event
SAP	statistical analysis plan
SCD	sickle cell disease
SD	standard deviation
SOC	standard of care
T2*MRI	T2-weighted magnetic resonance imaging
TCD	transcranial doppler
TIA	transient ischemic attack
US	United States
USPI	United States Prescribing Information
VOC	vaso-occlusive crisis
WBC	white blood cell

2. RATIONALE AND BACKGROUND

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in this study for the final clinical study report (CSR).

Sickle cell disease (SCD) is an inherited blood disorder caused by a mutation in the β globin gene, leading to the formation of sickle hemoglobin (HbS). This results in red blood cell (RBC) sickling, hemolytic anemia, vaso-occlusion, and progressive end-organ damage, causing life-long disability and early death. The disease's clinical course includes unpredictable vaso-occlusive pain episodes and systemic vasculopathy, leading to chronic tissue and organ injury. Improved survival in children has shifted SCD to a chronic disease affecting young and middle-aged adults, significantly impacting their health-related quality of life (HRQoL) and overall functioning.

Voxelotor (previously GBT440) is an HbS polymerization inhibitor that binds to HbS, increasing HbS-oxygen (O_2) affinity and stabilizing the oxyhemoglobin state, thus inhibiting polymerization. It binds covalently and reversibly to the N-terminal valine of one of the α chains of hemoglobin, increasing O_2 affinity without blocking O_2 release.

In November 2019, **Oxbryta® (Voxelotor)** was approved by the FDA for treating SCD in adults and pediatric patients aged 12 and older, under accelerated approval based on

increased Hb. In December 2021, the indication was expanded to include pediatric participants aged 4 and older, along with a new dosage form. Voxelotor was further valuated in clinical studies and expanded access programs for safety, tolerability, pharmacokinetics, pharmacodynamics, and treatment response in pediatric and adult participants with SCD, as well as in clinical pharmacology studies in healthy adults.

For more information on nonclinical studies, clinical studies, and safety, refer to the Oxbryta® (Voxelotor) US prescribing information (Oxbryta® (Voxelotor)® USPI).

3. STUDY OBJECTIVES AND HYPOTHESES

3.1. Primary objectives

The primary objective is to gather long term data on Oxbryta® (Voxelotor) in a real-world setting. The following are outcome categories of interest in participants with SCD treated with Oxbryta® (Voxelotor):

- Clinical outcomes, as assessed by clinical and laboratory assessments of hematological parameters and end organ damage, and rate of significant clinical events
- Healthcare resource utilization (HCRU)
- Health-related quality of life (HRQoL), as assessed by participants, parents/caregivers, and clinicians
- Safety and tolerability of Oxbryta® (Voxelotor) Outcome Measures

3.2 Effectiveness Endpoint Measures

- Change from pre-Oxbryta® (Voxelotor) treatment period in the following hematologic parameters:
    - Hb
    - Hemolysis measures, including % reticulocytes, absolute reticulocytes, bilirubin (total, direct, and indirect)
    - Measures of iron overload, including ferritin, T2-weighted magnetic resonance imaging (T2*MRI)
- Change from pre-Oxbryta® (Voxelotor) treatment period in renal function, as measured by the following:
    - Creatinine (Serum)
    - 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 rate (eGFR) calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation
- Rate of significant SCD complications, for example acute pain crisis, acute chest syndrome (ACS), priapism, stroke, and transient ischemic attack (TIA), chronic or end stage kidney disease, iron overload, leg ulcers, cardiac malfunction, and pulmonary hypertension (PH)
- Treatment initiation or modification of SCD-related medications (eg, 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® (Voxelotor) treatment period in HCRU: rate of outpatient visits (including infusion center, acute care, or telemedicine visit), 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® (Voxelotor) treatment period in the following HRQoL measures:
    - Patient-Reported Outcomes Measurement Information System (PROMIS) 42 item (adults) and 39 item (children/ adolescents)
    - Patient Global Impression of Change (PGIC)
    - Clinical Global Impression of Change (CGIC)
    - Other measures: Acute pain intensity as measured by Numerical Pain Rating Scale (NPRS) and any objective measure of exercise tolerance.

3.3 Safety Endpoint Measures

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

4. RESEARCH METHODS

4.1. Study design

This registry is an observational study designed to evaluate the effect of Oxbryta® (Voxelotor) in individuals with SCD. This registry is intended to benefit and support interests of participants, clinicians, regulatory bodies, payers, and industry by obtaining longitudinal data on Oxbryta® (Voxelotor). Approximately 500 participants with SCD who are prescribed and treated with Oxbryta® (Voxelotor) will be enrolled. The study will be conducted at approximately 35 sites in the US.

Any participant who is currently taking Oxbryta® (Voxelotor) or has been prescribed and will initiate treatment with Oxbryta® (Voxelotor), is eligible to participate. Eligible participants will receive treatment with Oxbryta® (Voxelotor) as prescribed by their physicians, 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.

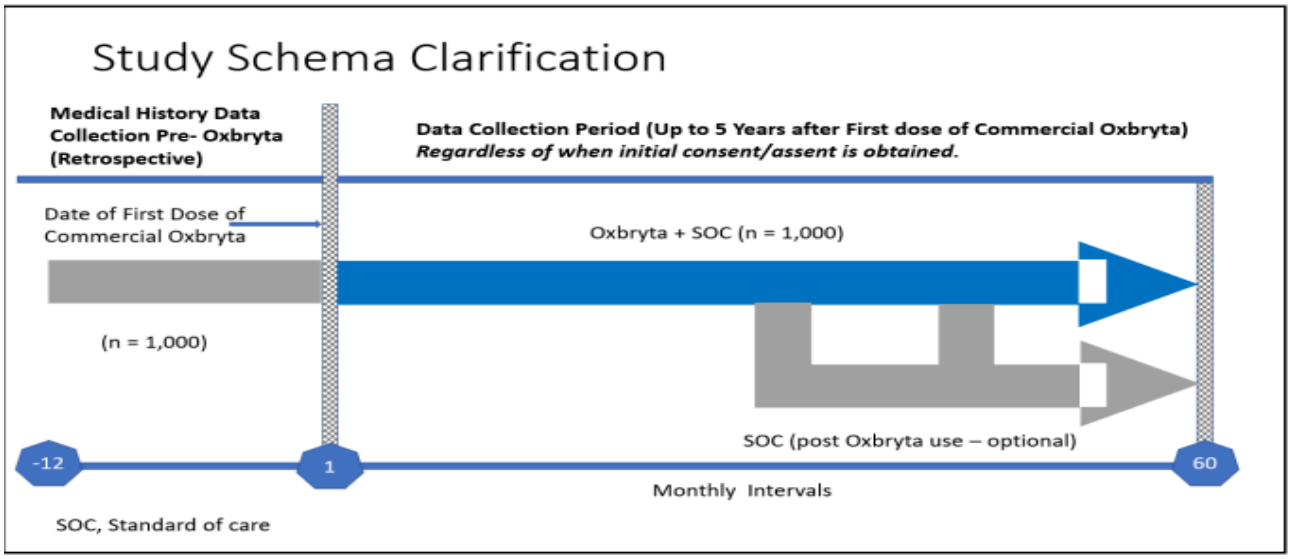
This study will collect data that are recorded in the participants' medical records and other secondary data sources such as Insurance and Pharmacy Claims. Study data will be collected at regular intervals (no more frequent than every 3 months) and entered in case report forms (CRFs) via an electronic data capture (EDC) system by the study staff.

Regardless of how long participants have been on Oxbryta® (Voxelotor) when they enroll in the study, participants will be followed for up to 5 years after their first dose of Oxbryta® (Voxelotor) 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® (Voxelotor) at any time. Participants who discontinue treatment with Oxbryta® (Voxelotor) earlier than 5 years will continue to be followed on study to collect clinical and health-related quality of life (HRQoL) outcomes for up to 5 years after their first dose of Oxbryta® (Voxelotor) 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 Clarification – Patient on Treatment at Time of Consent



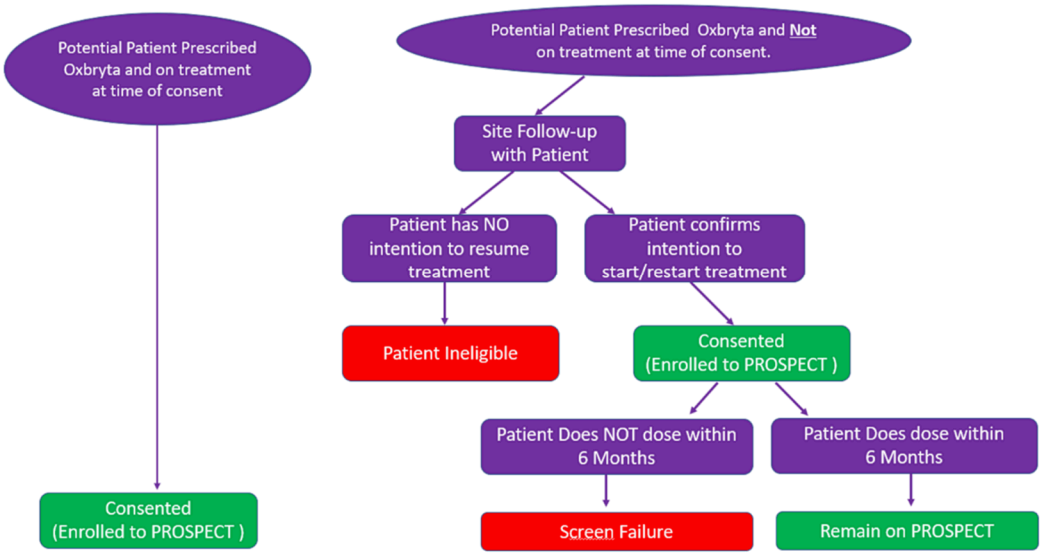
4.2. Study populations

All participants at each participating study site who have been treated with Oxbryta® (Voxelotor) or have been prescribed and will initiate treatment with Oxbryta® (Voxelotor) according to the Oxbryta® (Voxelotor) USPI will be considered for inclusion in this study.

Population	Description
Full analysis set	Participants met inclusion/exclusion criteria and signed the inform consent including screen failures (participants who did not receive Oxbryta within 6 months of the inform consent date).
Safety analysis set	Participants were in the Full analysis set and received at least one dose of Oxbryta includingparticipants who received at least one dose of Oxbryta in C5341018 (RETRO) study.

When participants have been prescribed Oxbryta® (Voxelotor) and deemed eligible to participate in the registry study based on the inclusion/exclusion criteria, they will be enrolled in the study regardless of whether they have started taking Oxbryta® (Voxelotor). After enrollment into the study, it is recommended that the site perform the pre-Oxbryta® (Voxelotor) participant assessments as soon as possible. Once the first dose of Oxbryta® (Voxelotor) treatment has been administered, the participants will be followed for up to 5 years. Patient enrollment process flow is shown in Figure 2.

Figure 2. Enrollment Process Flow



4.2.1. Subgroups

1) Chronic pain:

    a. Full analysis set for participants with chronic pain

    b. Full analysis set for participants without chronic pain

Participants with chronic pain are defined to have at least on one of following criteria during pre-Oxbryta or post-Oxbryta:

- SCD complications page: Avascular Necrosis, Chronic Pain; OR
- Non-SCD medical history page: Arthralgia, Arthritis, Neuralgia, Osteoarthritis, Osteonecrosis, Osteoarthritis, Rheumatoid arthritis, Spinal osteoarthritis; OR
- Concomitant medications page: BACLOFEN, GABAPENTIN, MELOXICAM, PREGABALIN, all “BUPRENORPHINE", DULOXETINE, DULOXETINE HYDROCHLORIDE, METHADONE, METHADONE HYDROCHLORIDE, PREGABALIN.

2) Maximum increase from Pre-Oxbryta in Hb

    a. Full analysis set for participants with > 1 g/dL maximum increase from Pre-Oxbryta in Hb during the study period

b. Full analysis set for participants with <= 1 g/dL maximum increase from Pre-Oxbryta in Hb during the study period

3) Full analysis set where participants had a non-missing Pre-Oxbryta SCD complication will be included in the analysis.

4) Full analysis set where participants who had a non-missing Pre-Oxbryta SCD complication or participants who had an adverse event reported in Pre-Oxbryta or Post-Oxbryta will be included in the analysis.

4.3. Variables

Variable	Role	Data source(s)	Operational definition
Index date	Study period	Case report form	Inform consent date
Index year	Study period	Case report form	Inform consent date
Pre-Oxbryta	Study period	Case report form	Baseline: any assessments within 12 months before receiving first dose of Oxbryta® (Voxelotor)
Post-Oxbryta	Study period	Case report form	Follow-up period for up to 5 years after the first dose of Oxbryta® (Voxelotor)
End of Treatment	Study period	Case report form	Captured from end of treatment form
End of Study	Study period	Case report form	Captured from end of study form
Age	Demographics	Case report form	Age at first dose of Oxbryta
Sex	Demographics	Case report form	Captured from the inform consent and eligibility form
Race/Ethnicity	Demographics	Case report form	Captured from the inform consent and eligibility form

SCD genotype	SCD disease history	Case report form	Captured from SCD disease history form
Hydroxyurea use	SCD disease history	Case report form	Captured from SCD disease history form
Height	Baseline characteristics	Case report form	Captured from Physical examination form
Weight	Baseline characteristics	Case report form	Captured from Physical examination form
Pre-Oxbryta SCD complications	Medical history	Case report form	Captured from Pre-Oxbryta treatment form
Concomitant Medications	Concomitant Medications	Case report form	Captured from concomitant medications form
Hemoglobin	Effectiveness endpoint measures - Hematology	Case report form	Captured from laboratory assessment-Hematology form
Reticulocyte count (%)	Effectiveness endpoint measures – Hematology	Case report form	Captured from laboratory assessment-Hematology form
Reticulocyte count (absolute)	Effectiveness endpoint measures – Hematology	Case report form	Captured from laboratory assessment-Hematology form
White blood cells (WBC)	Effectiveness endpoint measures – Hematology	Case report form	Captured from laboratory assessment-Hematology form
Aspartate Aminotransferase (AST)	Effectiveness endpoint measures – Hematology	Case report form	Captured from laboratory assessment-Hematology form
Alanine Aminotransferase (ALT)	Effectiveness endpoint measures – Hematology	Case report form	Captured from laboratory assessment-Hematology form
Bilirubin (Total)	Effectiveness endpoint measures - Chemistry	Case report form	Captured from laboratory assessment-Chemistry form
Bilirubin (Direct)	Effectiveness endpoint measures - Chemistry	Case report form	Captured from laboratory assessment-Chemistry form

Bilirubin (Indirect)	Effectiveness endpoint measures - Chemistry	Case report form	Captured from laboratory assessment-Chemistry form
Ferritin	Effectiveness endpoint measures - Chemistry	Case report form	Captured from laboratory assessment-Chemistry form
Albumin Creatinine Ratio (ACR)	Effectiveness endpoint measures – Renal function	Case report form	Captured from laboratory assessment- Renal function form
GFR	Effectiveness endpoint measures – Renal function	Case report form	Captured from laboratory assessment- Renal function form
Creatinine (Serum)	Effectiveness endpoint measures – Renal function	Case report form	Captured from laboratory assessment- Renal function form
Serum cystatin C	Effectiveness endpoint measures – Renal function	Case report form	Captured from laboratory assessment- Renal function form
Estimated eGFR	Effectiveness endpoint measures – Renal function	Case report form	Captured from laboratory assessment- Renal function form
Transfusions	Safety endpoint measures	Case report form	Captured from transfusions form
Patient Global Impression of Change (PGI-C)	Effectiveness endpoint measures	Case report form	Captured from Patient Global Impression of Change (PGI-C) form
Clinical Global Impression of Change (CGI-C)	Effectiveness endpoint measures	Case report form	Captured from Clinical Global Impression of Change (CGI-C) form
Pregnancy Testing and Fertility	Safety endpoint measures	Case report form	Captured from Pregnancy Testing and Fertility form
SCD Complications/Adverse Events	Safety endpoint measures	Case report form	Captured from SCD Complications/Adverse Events Question form
Pregnancy	Safety endpoint measures	Case report form	Captured from Pregnancy Notification and Outcome forms
Oxbryta Physician Administration	Exposure measures	Case report form	Captured from Oxbryta Physician Administration form

4.4. Data sources

The main data source is through the electronic data capture in the study, while secondary data sources may include insurance claims, electronic medical records, hospital administrative data, and specific rare disease databases. Data from C5341018 (RETRO) being used for participants who transferred from RETRO to this study.

4.5. Sample size and power calculations

The sample size is selected based on feasibility considerations to provide an estimation of the relationship between change in Hb and significant clinical events, for example VOCs and stroke that participants experience over the 5 years of the study. The total sample size of approximately 500 participants is expected to be enrolled. There is no formal sample size calculation for this study.

4.6. Date Imputation

For the partial AE start dates, if month and day are missing, set to June 15. If day is missing, set to 15. If the imputed AE start date is after the AE end date, set AE start date to AE end date. If the AE start date is completely missing, no imputation will be done.

If the end of study date is missing, the last known visit date will be used. If the end of treatment date is partial (month and year is known), the last day of the month is used. If the end of treatment date is partial (only year is known) or is missing completely, the end of the study date is used.

4.7. Statistical methodology and analyses

The following general analysis will be followed for this study, unless otherwise specified.

Unless otherwise specified, continuous/quantitative variables will be summarized using descriptive statistics which will include the number of participants with data to be summarized (n), mean, standard deviation (SD), median, first and third quartile (Q1, Q3), minimum, maximum, and the number of missing observations. Minimum and maximum will be reported with the same number of decimal places as collected in raw data, while mean, median, Q1, Q3 will be reported with one extra decimal place, and SD will be reported with two extra decimal places. Descriptive statistics for categorical/qualitative variables will be presented with number of participants and percentage (%) of participants in each category.

Percentages will not include the missing category and will be calculated over the number of participants with available (non-missing) data. A category with a zero count will be presented as "0" and a category with a 100 percentage will be displayed as "100".

The annualized incidence rate is defined as total numbers of a given event for all participants divided by the total patient-year where the total patient-year is defined as the sum of total duration (years) as defined in the Section 4.7.1 for all participants.

4.7.1. Index date and follow-up

The index date is defined as the inform consent date. The Post Oxbryta period is from the first dose of Oxbryta to the date of end of treatment or end of study.

4.7.2. Risk window definitions

Not applicable.

4.7.3. Analyses for Effectiveness Endpoint Measures

Since this study was not designed as the efficacy study for different indications that contribute significant information about product safety, the analyses in the SAP are considered fit-for-purpose for an abbreviated clinical study report with data scope including 1) full safety data and 2) limited efficacy data to support the benefit-risk evaluation.
Given the reporting nature of the PROMIS items, the reported PRO response was sparse. Therefore, they were excluded from the planned CSR analyses.

The analyses for effectiveness endpoints are based on full analysis set (Section 4.2). The analyses for the abbreviated CSR focus on hematologic and renal function laboratory parameters and SCD-related clinical events.
Participant disposition, non-SCD medical history, concomitant medication, study drug administration (including dosage changes initiated by the participant and by the physician), demographics and baseline characteristics will be summarized descriptively based on full analysis set.

The descriptive statistics will be provided for the following medications:

- long-acting opioids
- Erythropoiesis-stimulating agents
- Other relevant pain meds (e.g. Gabapentin, Lyrica, Cymbalta)
- SCD disease modification agents (hydroxyurea, Adakveo/crizanlizumab, L-Glutamide/levoglutamide).

The study drug administration will be categorized as 1) < 1 month, 2) >=1, <2 months, 3) < 3 months, 4) >=3 months, < 6 months, 5) >=6 months, < 9 months, 6) >=9 months, < 12

months, 7) >=12 months, < 18 months, 8) >=18 months, < 24 months, 9) >=24 months, < 36 months, 10) >=36 months, < 48 months and 11) >=48 months.

The following effectiveness endpoints will be summarized descriptively:

- Change from pre-Oxbryta treatment period in the following hematologic parameters corresponding to treatment with Oxbryta® (Voxelotor):
  - Hb
  - Hemolysis measures, including % reticulocytes, absolute reticulocytes, bilirubin (total, direct, and indirect)
  - ALT and AST

  Analysis: Observed and change from pre-Oxbryta treatment period on Hb, Hemolysis measures will be summarized descriptively (Section 4.7) by visit

  If a queried hemolysis value remained greater than its threshold listed in the table below, the value would be deemed erroneous and excluded from the analysis,

Parameter	**Threshold**
Reticulocyte Count (absolute)	10,000 10^9/L
Ferritin	100,000 µg/L

- Change from pre-Oxbryta treatment period in the following Chemistry parameters corresponding to treatment with Oxbryta® (Voxelotor):
  - Ferritin

  Analysis: Observed and change from pre-Oxbryta treatment period on ferritin will be summarized descriptively (Section 4.7) by visit.

- Change from pre-Oxbryta® (Voxelotor) treatment period in renal function:
  - Creatinine (Serum)
  - 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 eGFR calculated using the CKD-EPI equation

  Analysis: Observed and change from pre-Oxbryta treatment period on Creatinine (Serum), Albuminuria, Hemoglobinuria, Serum cystatin C and eGFR will be summarized descriptively (Section 4.7) by visit

- Rate of SCD complications including acute pain crisis, acute chest syndrome

(ACS), priapism, stroke, and transient ischemic attack (TIA), chronic or end stage kidney disease, iron overload, leg ulcers, cardiac malfunction, and pulmonary hypertension (PH) and RBC transfusions.

Analysis:

The number and percentage of participants with SCD complications including acute pain crisis, ACS, priapism, stroke, chronic or end stage kidney disease iron overload, leg ulcers, cardiac malfunction and PH and RBC transfusions will be summarized by SOC and PT throughout the treatment period.

The annualized incidence rate of SCD complications including acute pain crisis, ACS, priapism, stroke, chronic or end stage kidney disease iron overload, leg ulcers, cardiac malfunction and PH and RBC transfusions will be summarized by SOC and PT throughout the treatment period.

- PGIC

  PGIC includes 7 response categories: Very much improved, much improved, minimally improved, no change, minimally worse, much worse and very much worse.

  Analysis: The PGIC will be summarized as numbers and percentages by visit for each response category.

- CGIC

  CGIC includes 7 response categories: Very much improved, much improved, minimally improved, no change, minimally worse, much worse and very much worse.

  Analysis: The CGIC will be summarized as numbers and percentages by visit for each response category.

4.7.4. Safety analysis

SCD complications are defined as 'Yes' to the question 'is this a SCD Complication' in the SCD complications/AE form while the other AEs are defined as 'No' to the question 'is this a SCD Complication' in the SCD complications/AE form.

All safety analyses will be based on safety analysis set (Section 4.2). The analysis period for Pre-Oxbryta is 12 months before the first dose of Oxbryta and the analysis period for post-Oxbryta is from the first dose of Oxbryta through end of the study or the date of dose pausing or treatment discontinuation if the date of end of study date is missing.

SAEs and protocol-specified AEs will be classified according to the Medical Dictionary for Regulatory Activities (MedDRA). The frequency of SCD complications and other AEs treatment-emergent adverse events (TEAEs) and treatment emergent SAEs will be tabulated by system organ class, preferred term, severity (and total), and relationship to Oxbryta® (Voxelotor) treatment. The pregnancy outcomes and fertility will be reposted as a listing. Any events (including deaths) leading to discontinuation of the study and SAEs will be listed.

A TEAE is defined as an AE that occurs during the effective duration of treatment defined as the time from the first dose of Oxbryta through end of treatment date or the end of study completion/discontinuation date (if the date of end of treatment is missing) +28 days.

On the AE case report form there is a question "Did AE start prior to first dose?"

- If the response is "Yes" or the adverse event start date is missing, and the end date is prior to the first dose of Oxbryta, then the AE is not considered a TEAE
- If the response is "No" or "Unknown", then the AE is considered a TEAE

4.7.5. Subgroup analyses

Analysis: The annualized incidence rate (per patient year) of rate of 'Acute Pain Crisis' (SCD Complications) will be performed by Pre-Oxbryta and Post-Oxbryta.

Analysis subgroups:

- Chronic pain
    a. participants with chronic pain
    b. participants without chronic pain
- Maximum increase from Pre-Oxbryta in Hb
    a. Full analysis set for participants with > 1 g/dL maximum increase from Pre-Oxbryta in Hb
    b. Full analysis set for participants with <= 1 g/dL maximum increase from Pre-Oxbryta in Hb

Analysis: Annualized incidence VOC rate for pre-Oxbryta and post-Oxbryta will be reported.

The VOC event for Pre-Oxbryta is defined as 1) SCD complication with 'Acute Pain Crisis' in the Pre-Oxbryta SCD complication page or 2) any qualifying complications from SCD AE prior to Treatment Start Date.

The VOC event for Post-Oxbryta is defined as any qualifying complications from SCD AE on or after the treatment start date.

The qualifying complications from SCD AE are those that met at least one of the following two conditions:

- AE preferred term (AEDECOD) to be 'Sickle cell anaemia crisis';
- type of complications (CMPTYP) is 'Acute Pain Crisis'

1) Analysis population: Safety analysis set where participants had a non-missing Pre-Oxbryta SCD complications will be included in the analysis.

2) Analysis population: Safety analysis set where participants who had a non-missing Pre-Oxbryta SCD complications or participants who had an adverse events reported in Pre-Oxbryta or Post-Oxbryta will be included in the analysis.

   Analysis: The annualized VOC incidence rate (per patient year) will be performed by Pre-Oxbryta and Post-Oxbryta.

5. REFERENCES

Not applicable

6. APPENDICES

6.1. Appendix A: List of tables

Table/Listing	Title	Endpoint
Table 15.1.1	Summary of Participant Disposition - Full Analysis Set	Disposition
Table 15.1.2	Demographics and Baseline Characteristics - Full Analysis Set	Baseline
Table 15.1.3	Medical History – Full Analysis Set	Medical history

Table 15.1.4	Study Drug Administration - Safety Analysis Set	Exposure
Table 15.1.5	Study Drug Administration and Dosage Changes Initiated by the Physician - Safety Analysis Set	Exposure
Table 15.2.1	Change in Hematologic Laboratory -Hb Tests by Visit - Full Analysis Set	Effectiveness
Table 15.2.2	Change in Hematologic Laboratory -Hemolysis measures by Visit - Full Analysis Set	Effectiveness
Table 15.2.3	Change in Chemistry Laboratory - Chemistry measures by Visit - Full Analysis Set	Effectiveness
Table 15.2.4	Change in Renal Function Laboratory Tests by Visit - Full Analysis Set	Effectiveness
Table 15.2.5	Summary of SCD Complications-Full Analysis Set	Effectiveness
Table 15.2.5.1	Summary of Transfusions -Full Analysis Set	Effectiveness
Table 15.2.6	Annualized Incidence Rate of SCD Complications - Safety Analysis Set	Effectiveness
Table 15.2.6.1	Annualized Incidence Rate of Transfusions - Safety Analysis Set	Effectiveness
Table 15.2.7	Summary of Patient Global Impression of Change (PGIC) – Full Analysis Set	HRQoL
Table 15.2.8	Summary of Clinical Global Impression of Change (CGIC) – Full Analysis Set	HRQoL
Table 15.3.1	Treatment Emergent Adverse Events by System Organ Class and Preferred Term by Severity - Safety Analysis Set	Safety
Table 15.3.2	Treatment Related Treatment Emergent Adverse Events by System Organ Class and Preferred Term by Severity- Safety Analysis Set	Safety

Table 15.3.3	Treatment Emergent Serious Adverse Events by System Organ Class and Preferred Term by Severity - Safety Analysis Set	Safety
Table 15.3.4	Pregnancy Outcomes and Fertility listings - Safety Analysis Set	Safety
Table 15.3.5	Individual Listings of Deaths- Safety Analysis Set	Safety
Table 15.3.6	Listing of AEs Leading to Discontinuation of the Study - Safety Analysis Set	Safety
Table 15.3.7	Individual Listing of SAEs - Safety Analysis Set	Safety
Table 15.4	Listing of Concomitant Medication - Safety Analysis Set	Concomitant Medication
Table 15.5.1	Annualized Incidence Rate of Acute Pain Crisis – Safety Analysis Set (With Chronic Pain)	Subgroup
Table 15.5.2	Annualized Incidence Rate of Acute Pain Crisis – Safety Analysis Set (Without Chronic Pain)	Subgroup
Table 15.5.3	Annualized Incidence Rate of Acute Pain Crisis – Safety Analysis Set (With > 1 g/dL Maximum Increase in Hb)	Subgroup
Table 15.5.4	Annualized Incidence Rate of Acute Pain Crisis – Safety Analysis Set (With <= 1 g/dL Maximum Increase in Hb)	Subgroup
Table 15.5.5	Annualized Incidence Rate of Acute Pain Crisis – Safety Analysis Set	ad-hoc