FINAL NON-INTERVENTIONAL (NI)/LOW-INTERVENTIONAL STUDY TYPE 1 (LIS1) STUDY REPORT

PASS information

Title	An Open Label, Observational, Prospective Registry of Participants With Sickle Cell Disease (SCD) Treated With Oxbryta® (voxelotor)
Protocol number	GBT440-4R2 (C5341019)
Version identifier of the study report	1.0
Date	06 March 2025
European Union (EU) Post Authorization Study (PAS) register number	EUPAS1000000170
Active substance	Oxbryta® (voxelotor) (B06AX03)
Medicinal product	Oxbryta® (voxelotor) tablets for oral use Oxbryta® (voxelotor) tablets for oral suspension
Product reference	EMEA/H/C/004869
Procedure number	Not applicable
Marketing Authorization Holder (MAH)	[redacted]
Joint PASS	No
Research question and objectives	• The primary objective was to gather long term data on Oxbryta® (voxelotor) in a real-world setting. The following are 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

[redacted]

	• Health-related quality of life (HRQoL), as assessed by participants, parents/caregivers, and clinicians • Assess the safety and tolerability of Oxbryta® (voxelotor)
Country(-ies) of study	United States
Author	[redacted]

Marketing Authorization Holder(s)

Marketing Authorization Holder(s)	[redacted]
MAH contact person	[redacted]

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES AND FIGURES

Annex 1. List of stand-alone documents

Appendix 1. SIGNATURES

Appendix 2.1 PROTOCOL

Appendix 2.2 Protocol administrative change letter (PACL)

Not applicable.

Appendix 3. INVESTIGATORS AND CORRESPONDING INDEPENDENT ETHICS COMMITTEES (IECs) OR INSTITUTIONAL REVIEW BOARDS (IRBs)

Appendix 3.1. List of Investigators by Country

Appendix 3.2. List of Institutional Review Board (IRB) and Corresponding Protocol Approval Dates

Appendix 4. STATISTICAL ANALYSIS PLAN

Appendix 5. SAMPLE CASE REPORT FORM (CRF) / DATA COLLECTION TOOL (DCT)

Appendix 6. SAMPLE STANDARD SUBJECT INFORMATION SHEET AND INFORMED CONSENT DOCUMENT (ICD)

Appendix 7. LIST OF SUBJECT DATA LISTINGS

Appendix 7.1 Withdrawn Subjects

Not applicable.

Appendix 7.2 Protocol Deviations

Appendix 7.3 Subjects Excluded from the Analysis

Not applicable

Appendix 7.4 Demographic Data

Not applicable.

Appendix 7.5 Medication/Treatment Data

Not applicable.

Appendix 7.6 Endpoint Data

Not applicable.

Appendix 7.7 Adverse Events

Not applicable.

Appendix 7.8 Laboratory Listings

Not applicable.

Appendix 8. ADDITIONAL DOCUMENTS

Not applicable.

[redacted]

1. ABSTRACT (STAND-ALONE DOCUMENT)

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
ACR	albumin-creatinine ratio
ACS	acute chest syndrome
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BID	twice daily
C-section	cesarean section
CGIC	Clinician Global Impression of Change
CHF	congestive heart failure
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
COVID-19	coronavirus disease 2019
CRF	case report form
CRO	contract research organization
CSR	clinical study report
DCT	data collection tool
DT	dispersible tablet
eCRF	electronic case report form
ED	emergency department
EDC	electronic data capture
EEIG	European economic interest grouping
eGFR	estimated glomerular filtration rate
EMEA	Europe, Middle East, and Africa
ESA	erythropoietin stimulating agents
EU	European Union
FCT	film-coated tablet
FDA	Food and Drug Administration
FAS	full analysis set
g/dL	grams per deciliter
GFR	glomerular filtration rate
Hb	hemoglobin
HbSβ0	hemoglobin S-beta-zero
HbSβ+	hemoglobin S-beta plus
HbSC	hemoglobin SC
Hb F%	percent of hemoglobin F
HbS	hemoglobin S

[redacted]

HbSS	hemoglobin SS
HCRU	healthcare resource utilization
HRQoL	health-related quality of life
HU	hydroxyurea
ICD	Informed consent document
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Institutional ethics committee
Inc.	incorporated
IR	incidence rate
IRB	institutional review board
IV	intravenous
LIS1	low-interventional study type 1
LLC	limited liability corporation
LPLV	last patient last visit
MAH	marketing authorization holder
MedDRA	Medical Dictionary for Regulatory Activities
mg/dL	milligrams per deciliter
min	minimum
max	maximum
MRI	magnetic resonance imaging
n	number (sample size)
N	number (population size)
N/A	not applicable
NI	non-interventional
NIS	non-interventional study
NPRS	numerical pain rating scale
NSAID	non-steroidal anti-inflammatory drug
O_2	molecular oxygen
oxyHb	oxyhemoglobin
PACL	protocol administrative change letter
PAS	Post Authorization Study
PASS	Post Authorization Safety Study
PGIC	Patient Global Impression of Change
PH	Pulmonary hypertension
PRO	patient reported outcome
PROMIS	Patient-Reported Outcomes Measurement Information System
PT	preferred term
Pt	patient
Q1	first quartile

Q3	third quartile
QD	once a day
QoL	quality of life
R2*MRI	rate of darkening magnetic resonance imaging
RBC	red blood cell
RWE	real world evidence
SAE	serious adverse events
SAP	statistical analysis plan
SAS	statistical analysis software; safety analysis set
SCD	sickle cell disease
SD	standard deviation
SoA	schedule of activities
SOC	standard of care; system organ class
T2	transverse relaxation time
TCD	transcranial doppler
TEAE	treatment-emergent adverse events
TIA	transient ischemic attack
TIBC	total iron-binding capacity
US	United States
USA	United States of America
USPI	United States Prescribing Information
VOC	vaso-oclusive crisis
VSD	ventricular septal defect

3. INVESTIGATORS

Principal Investigator(s) of the Protocol

Name, degree(s)	Title	Affiliation
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

The names, affiliations, and contact information of the investigators at each study site are listed in Appendix 3.1.

4. OTHER RESPONSIBLE PARTIES

Responsible Party Name and Affiliation	Role in the study
[redacted]	Data collection and analysis
[redacted]	Data collection
[redacted]	Steering Committee Chair
[redacted]	Steering Committee Member
[redacted]	Steering Committee Member
[redacted]	Steering Committee Member
[redacted]	Steering Committee Member
[redacted]	Steering Committee Member

[redacted]

Responsible Party Name and Affiliation	Role in the study
[redacted]	Steering Committee Member
[redacted]	Steering Committee Member

5. MILESTONES

Milestone	Planned date	Actual date	Comments
Date of independent ethics committee (IEC) or institutional review board (IRB) approval of protocol (original protocol first approval/protocol amendment 2 last approval)	Not applicable (N/A)	22 April 2021/ 23 July 2024	The IEC/IRB approval dates for the protocol and any amendments is provided in Appendix 3.2.
Start of data collection	02 February 2022	04 February 2022	Electronic data capture (EDC) was not operational as of the original planned date for start of data collection.
End of data collection The study was terminated on 25 September 2024.	31 January 2030	10 Oct 2024 (Last Patient Last Visit [LPLV]) 25 September 2024 (Study Termination Date)	The study was voluntarily terminated by the sponsor based on the totality of clinical data available for voxelotor.
Registration in the EU PAS register	22 May 2024	22 May 2024	This study was registered in EU PAS register upon integration of the study to [redacted] non-interventional study (NIS) processes.
Final report of study results	30 April 2030	06 March 2025	The study was terminated prior to initial planned end of data collection.

6. RATIONALE AND 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 (Nouraie et al, 2013; Gladwin et al, 2014). 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 et al, 2007). With improved survival in children living in high resource settings, 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 exert a high clinical burden in the aging adult, significantly impacting health-related quality of life (HRQoL) and overall functioning (Swanson et al, 2011).

Voxelotor (Oxbryta®; 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 Hb and allosterically increases HbS-oxygen (O_2) affinity, stabilizing the oxyhemoglobin (oxyHb) state and inhibiting the polymerization (Eaton et al, 1999; Oksenberg et al, 2016). The voxelotor binding site is distant from heme pockets and it can therefore increase O_2 affinity without sterically blocking the release of O_2 (Kato et al, 2007).

In November 2019, Oxbryta® (voxelotor) 500 mg film-coated tablet (FCT) was approved in the United States (US) by the Food and Drug Administration (FDA) for the treatment of SCD in adults and pediatric patients 12 years of age and older. The recommended dosage of voxelotor is 1500 mg taken orally once daily (QD) with or without food. This indication was approved under accelerated approval based on increase in Hb. In December 2021, the FDA approved the expanded indication of voxelotor to include children ≥ 4 years of age that also provided for use of 300 mg tablets for oral suspension (referred to as the dispersible tablet; DT) at a dose of 1500 mg or equivalent weight-based dosing. Marketing approval for Oxbryta 500 mg FCT was granted in the EU in November 2022 for the treatment of hemolytic anemia due to SCD in adults and pediatric patients 12 years of age and older as monotherapy or in combination with hydroxycarbamide. Since the first approval in 2019, voxelotor has been approved in over 35 countries globally.

Voxelotor continued 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 patients.

Information regarding nonclinical studies, clinical studies, and safety is available in the Oxbryta® (voxelotor) US prescribing information (Oxbryta® (voxelotor) USPI) (OXBRYTA (voxelotor) USPI, 2023).

This NIS was designated as a Post Authorization Safety Study (PASS) and was conducted voluntarily by [redacted] Inc. The study was voluntarily terminated by [redacted] on 25 September 2024 due to emerging clinical data and discontinuation of all ongoing

[redacted]

voxelotor clinical studies and early access and compassionate use programs and voluntary removal of voxelotor from the market.

This NIS abbreviated clinical study report (CSR) presents the final analyses as of the study termination date of all available safety data and select clinical outcomes as specified in the statistical analysis plan (SAP) (see details in Section 9.9).

The sponsor of the study was Global Blood Therapeutics Inc. Global Blood Therapeutics Inc. became a wholly owned subsidiary of [redacted] Inc. on 05 October 2022.

7. RESEARCH QUESTION AND OBJECTIVES

This registry was an observational study designed to evaluate the effect of voxelotor in individuals with SCD. This registry was intended to benefit and support interests of participants, clinicians, regulatory bodies, payers, and industry by obtaining longitudinal data on voxelotor.

The primary objective was to gather long term data on voxelotor in a real-world setting. The following table presents the primary objectives and outcome measures as presented in the final protocol (Appendix 2.1 Protocol Amendment 2).

Primary Objectives	Outcome Measures

• Clinical outcomes, as assessed by clinical and laboratory assessments of hematological parameters and end organ damage, and rate of significant clinical events	• Change from pre-voxelotor treatment period in the following hematologic parameters corresponding to treatment with voxelotor:
	  • 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* magnetic resonance imaging (T2*MRI)
	• Change from pre-voxelotor treatment period in renal function, as measured by the following:
	  • Creatinine (serum)
	  • Albuminuria (urine ACR)
	  • Hemoglobinuria (urine dipstick positive for blood +1 or greater and ≤2 RBC by high power field)
	  • Serum cystatin C

Primary Objectives	Outcome Measures
	• eGFR calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation • Rate of significant SCD-related clinical events, for example vaso-occlusive crisis (VOC)*, 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, erythropoietin stimulating agents (ESAs), non-steroidal anti-inflammatory drugs (NSAIDs), folic acid, and penicillin)
• Healthcare resource utilization (HCRU)	• Change from pre-voxelotor treatment period in HCRU: rates of outpatient visits (including infusion center, acute care, or telemedicine visit), emergency department (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
• Health-related quality of life, as assessed by participants, parents/caregivers, and clinicians	• Change from pre-voxelotor treatment period in the following HRQoL measures: • PROMIS Pediatric Profile-37 v2.0 or PROMIS-43 v2.1 • Patient Global Impression of Change (PGIC) • Clinical Global Impression of Change (CGIC) • Other measures (if assessed as part of usual care): acute pain intensity as measured by numerical pain rating scale (NPRS) and any objective measure of exercise tolerance
• Safety Objective: Assess the safety and tolerability of voxelotor	• Safety Measures: • Rate and severity of serious adverse events (SAEs) and adverse events (AEs) of interest

Primary Objectives	Outcome Measures
	• Rate of AEs leading to dose modification or discontinuation of voxelotor • Pregnancy outcomes and fertility

*Note that since VOC is a broad term and was not defined as a specific case report form (CRF) term in the final protocol, VOCs were captured as 'acute pain crisis' on the CRF (Appendix 5). Please see Section 9.9.1 for additional details on analyses performed and Section 11.2 for limitations of this study.

Certain protocol-specified primary objective outcome measures were not analyzed in this final abbreviated CSR, including HRQoL measures (except PGIC/CGIC), healthcare resource utilization measures (except RBC transfusions), and measures of iron overload (except ferritin). Since the CSR was designed to inform benefit-risk assessment of voxelotor, analyses were limited to all available safety data and select clinical outcomes specified in the SAP (Appendix 4 SAP Section 4.8.3) (see Section 9.9.1 statistical methods for more information).

[redacted]

8. AMENDMENTS AND UPDATES

Table 1. Amendments to the Protocol

Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment	Reason
1	12 January 2022	Both	Synopsis, 2.2.1 Effectiveness Outcome Measures, 4.1 Inclusion Criteria, Appendix 1 Schedule of Activities (SoA)	The protocol was updated to reflect the new expanded label indication (pediatric patients 4 years of age and older) and introduction of a new dosage form for the pediatric population. In addition, effectiveness endpoints were revised to add additional assessments and replace scales that were no longer considered validated. Furthermore, scope of safety data collection was expanded.	This amendment was to account for the expanded US label that now included patients down to 4 years of age
2	10 October 2023	Both	Entire protocol was updated to align to the [redacted] NI study template. Further study design changes were made in the following sections: • Study 9.1 Study Design • Section 9.3.1 Inclusion Criteria • Section 10.3.6.1.3 VOCs and ACS • Section 10.3.6.3.1 Patient-Reported Outcomes Measurement Information System (PROMIS) • Section 11 [redacted] Safety Reporting	The protocol was updated to change to the [redacted] NI study template, clarify inclusion criteria, revise the study schema to show how to enroll participants not on treatment at the time of consent, add 300 mg dose, update version of PROMIS form used, update the definition of VOC, and update the safety reporting section.	Study protocol was significantly revised to align with the [redacted] template for NI studies. Other changes were made based on sponsor decision and feedback from investigators

[redacted]

9. RESEARCH METHODS

In this CSR, the terms "participant," "subject," and "patient" are used interchangeably.

A full description of the research methods is described in the final protocol (Appendix 2.1 Study GBT440-4R2 Protocol [dated 10 Oct 2023]).

9.1. Study design

The study was designed to enable robust and systematic data collection on product use in a real-world setting and provide details on measures such as care pattern, long term efficacy and safety which required long term follow-up and large number of patients.

Approximately 500 SCD participants who were prescribed and treated with voxelotor were planned to be enrolled. The study was planned to be conducted at approximately 45 sites in the US.

Eligible participants took voxelotor, or had been prescribed and initiated treatment with voxelotor within 6 months of consenting to participate, as prescribed by their physicians, as part of their usual care. Participants were treated and evaluated per standard of care (SOC) and at the physician's discretion.

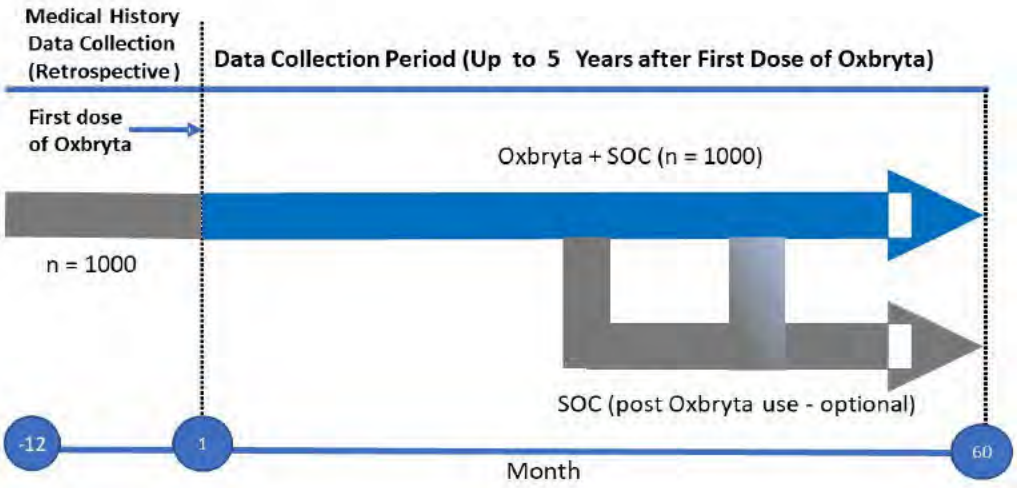
This study collected data recorded in the participants' medical records. Study data was collected at regular intervals and entered in CRFs via an EDC system by the study staff.

Regardless of how long participants had been on voxelotor when they enrolled in the study, participants were planned to be followed for up to 5 years after their first dose of voxelotor treatment, or until they withdrew their consent to participate, or were discontinued from the study.

Participant safety and voxelotor tolerability were assessed throughout the study data collection period by the study doctor and was reported to the sponsor.

The overall study design is illustrated in Figure 1.

Figure 1: Study Schema



Additional details regarding the study design are presented in Appendix 2.1 Study GBT440-4R2 Protocol (dated 10 Oct 2023) Section 9.

Clinical Outcome Measures

Certain protocol-specified primary objective clinical outcome measures were not analyzed for this final abbreviated CSR due to their irrelevance to the benefit-risk assessment of voxelotor. Results for the following clinical outcome measures specified in the SAP (Appendix 4 SAP Section 3.2) are presented in this CSR.

- Change from pre-voxelotor treatment period in the following hematologic parameters corresponding to treatment with voxelotor:
  - Hb
  - Hemolysis measures, including % reticulocytes, absolute reticulocytes, bilirubin (total, direct, and indirect)
  - Measure of iron overload (ferritin)
- Change from pre-voxelotor treatment period in renal function, as measured by the following:
  - Creatinine (Serum)
  - urine ACR
  - Hemoglobinuria (urine dipstick positive for blood +1 or greater and ≤2 RBC by high power field)

  - Serum cystatin C
  - eGFR calculated using the CKD-EPI equation
- Rate of significant SCD-related clinical events, for example acute pain crisis, ACS, priapism, stroke, chronic or end stage kidney disease, iron overload, leg ulcers, cardiac malfunction, and PH
- Treatment initiation or modification of SCD-related medications (eg, hydroxyurea, crizanlizumab, L-glutamine, opioids [in daily morphine equivalents], iron chelating agents, ESAs, NSAIDs, folic acid, and penicillin)
  - Due to limited data, only data on the following medications was analyzed:
    - Long-acting opioids
    - Erythropoiesis-stimulating agents
    - Other relevant pain meds (eg, gabapentin, pregabalin, duloxetine)
    - SCD-disease modification agents (eg, hydroxyurea, Adakveo /crizanlizumab, L-Glutamine/levoglutamine)
- Change from pre-voxelotor treatment period in healthcare resource utilization:
  - acute and chronic RBC transfusions
- Change from pre-voxelotor treatment period in the following HRQoL measures:
  - PGIC
  - CGIC

A full list of protocol-specified clinical outcome measures is presented in Appendix 2.1 Study GBT440-4R2 Protocol (dated 10 Oct 2023) Section 8.

Safety Outcome Measures

All protocol-specified safety outcome measures below were analyzed per SAP and results are presented in this CSR.

  - Rate and severity of SAEs and AEs of interest
  - Rate of AEs leading to dose modification or discontinuation of voxelotor
  - Pregnancy outcomes and fertility

9.2. Setting

This study was conducted at 24 clinical sites in the US (Appendix 3.1).

The approximate duration of study participation for an individual participant was planned to include an observation period of up to 5 years after the first dose of voxelotor treatment.

The start of the study period was 04 February 2022 (date of when the study was open for patient inclusion), and the end of study was defined by the study termination date (25 September 2024).

9.3. Subjects

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

All participants (≥4 years old) at each participating study site who had been treated with voxelotor or had been prescribed and had initiated treatment with voxelotor according to the voxelotor USPI were considered for inclusion in this study (OXBRYTA (voxelotor) USPI, 2023).

The participant enrollment process flow is presented in Appendix 2.1 Study GBT440-4R2 Protocol (dated 10 Oct 2023) Figure 2.

9.3.1. Inclusion Criteria

Participants who met all the following criteria were eligible for enrollment in this study:

1. Willing and able to provide written informed consent (aged ≥ 18 years), parental/guardian consent and participant assent (aged ≥12 to <18 years) per local regulations, or pediatric participants (aged 4 to <12 years) with parental/guardian consent per IRB policy and requirements, consistent with ICH guidelines

2. Male or female participants with documented diagnosis of sickle cell disease (all genotypes)

3. Participants who were currently taking voxelotor or had been prescribed and initiated treatment with voxelotor according to the voxelotor USPI

9.3.2. Exclusion Criteria

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

1. Current participation in an investigational clinical trial or expanded access program, in which the participant may have been receiving voxelotor.

2. Medical, psychological, or behavioral condition that, in the opinion of the study doctor, would have confounded or interfered with evaluation of safety and/or effectiveness of the

study drug, prevented compliance with the study protocol; precluded informed consent; or rendered the participant unable/unlikely to comply with the study procedures.

9.4. Variables

Variables collected and recorded on the CRF from the medical records of patients who had been treated with voxelotor, and corresponding operational definitions, that were summarized for this abbreviated CSR are presented in the SAP (Appendix 4 SAP Section 4.3).

The complete list of protocol-specified variables is presented in Appendix 2.1 Study GBT440-4R2 Protocol (dated 10 Oct 2023) Section 9.4.

9.5. Data sources and measurement

The main data source was through the EDC by the study sites. Data from Study GBT440-4R1 (C5341018; RETRO) were augmented for participants who transferred from RETRO into this study, such as baseline values before initiating voxelotor were collected from RETRO. A sample CRF is provided in Appendix 5.

Data on participants was collected at regular intervals and entered into the EDC system by study personnel at the study site beginning with their first dose of commercial voxelotor. Data collection included those data that were recorded in the participant's medical records and based on assessments performed as part of the participant's SOC. Study data that were not available in medical records or other secondary data sources were not solicited from participants. The data collected in this study and target timepoints for data collection and entry were specified in the protocol SoA (Appendix 2.1 Study GBT440-4R2 Protocol (dated 10 Oct 2023) Appendix 1). There were not any required study procedures or assessments beyond the SOC.

Note that laboratory values that were collected from participants' medical records might have been taken at any time including those collected during routine care, acute visits (eg, emergency room, hospitalization, infusion center) or right after complications.

Additional details regarding study data collection and assessments are presented in Appendix 2.1 Study GBT440-4R2 Protocol (dated 10 Oct 2023) Section 9.7.

9.6. Bias

Due to the observational study design, limitations include reliance on data included in participants' medical records, limited monitoring and quality control for data collection, patient population and SOC that vary among study sites, and susceptibility to multiple sources of bias for comparing outcomes. Potential sources of bias include:

- The data in patient medical records were not originally intended for research purposes; therefore, some information might be missing, incomplete, or could be inaccurate. Mitigations against missing and inaccurate data were employed throughout the research process. This included choosing qualified sites, site training, site monitoring, data review, reconciliation, and querying.

- AEs were captured from patient medical records; however, it is possible that not all AEs experienced by a patient were captured in the patient's medical record. Reported AEs were likely those deemed clinically significant or required to be captured in the medical records for other reasons. Evaluation of safety results was interpreted within this context.

9.7. Study Size

The sample size was selected to provide an estimation of the relationship between change in Hb and significant clinical events, for example acute pain crises and stroke that participants experience over the 5 years of the study. A total sample size of approximately 500 participants was expected to be enrolled.

9.8. Data transformations

Study data was collected at regular intervals and entered in CRFs via an EDC system. All data management and data analysis were performed by UBC using statistical software SAS®, SAS Institute Inc., Cary, NC, USA.

Detailed methodology for data transformations, particularly complex transformations (eg, multiple source variables used to derive an analytic variable), are documented in the SAP, which is dated, filed and maintained by the sponsor (Appendix 4 SAP Section 4.7).

9.9. Statistical methods

At the time of study termination, all statistical methods were detailed in the study protocol (Appendix 2.1 Study GBT440-4R2 Protocol (dated 10 Oct 2023) Section 9). Following study termination and LPLV, the statistical methods and analyses planned for this abbreviated CSR were summarized in the initial SAP that was approved prior to the database lock date (13 January 2025). The initial SAP was amended 2 times: once on 21 November 2024, before the database lock date, and a second time on 24 January 2025 after the database lock date. Details and rationale for each SAP amendment are provided in Section 9.9.5.

Since the study was not designed as an efficacy study, the analyses specified in the SAP focus on the full safety analyses as pre-specified in the study protocol and provided relevant exploratory clinical outcomes analyses to support the benefit-risk evaluation for voxelotor (Appendix 4 SAP Section 4.7.3 (clinical outcomes analyses) and Section 4.7.4 (safety analyses)). Per the SAP, analyses for selected clinical outcomes (including select HRQoL, HRCU, and clinical outcomes endpoints) were not conducted based on the sponsor's judgement of data relevance, completeness and exploratory nature of outcomes.

The analysis data sets (FAS and SAS) are described in Section 9.9.2.

9.9.1. Main summary measures

In general, continuous/quantitative variables were summarized using descriptive statistics and summary of categorical/quantitative variables were presented with the number of participants and percentage of participants in each category.

The annualized incidence rate was defined as total numbers of a given event for all participants divided by the total patient-year, which is defined as the sum of total duration (years) for all participants. The number of pre-voxelotor SCD complications of a given event

for each participant was computed by the sum of the event counts from pre-Oxbryta SCD complication and SCD AE forms.

The total duration of follow-up was defined as the period from the first dose of voxelotor through the end of study/treatment date for each participant.

Participant disposition, non-SCD medical history, demographics and baseline characteristics were summarized descriptively based on the FAS. Study drug administration and concomitant medication (ie, long-acting opioids, erythropoiesis-stimulating agents, other relevant pain medications, and SCD-disease modifying agents) was summarized descriptively based on the SAS. **Analyses of Clinical Outcomes:**

The analyses for the abbreviated CSR focus on hematologic and renal function laboratory parameters and SCD-related clinical events (SCD complications). The analyses for clinical outcomes are based on the FAS, except for analyses of SCD-related clinical events, which were based on the SAS.

- Observed and change from pre-voxelotor treatment period on hematologic, chemistry, and renal function laboratory parameters were summarized descriptively by visit period. The pre-voxelotor value was the latest measurement on or prior to the first dose of voxelotor. If there were multiple measurements at the same post-voxelotor visit period, the average of measurements was used for the visit period. The maximum change from pre-voxelotor through the treatment is defined as the maximum post-voxelotor value minus the pre-voxelotor value. The descriptive statistics (mean, standard deviation (SD), median, minimum and maximum) were summarized for the maximum change of all participants.
    - If queried hemolysis parameter values for reticulocyte count (absolute) or ferritin were greater than its threshold below, the values were deemed erroneous and excluded from the analysis.
        - Threshold for reticulocyte count (absolute): 10,000 10^9/L
        - Threshold for ferritin: 100,000 µg/L
- The number and percentage of participants with SCD-related clinical events were summarized by SOC and preferred term (PT) throughout the treatment period.
- The annualized incidence rate of SCD-related clinical events was summarized by SOC and PT throughout the treatment period based on the SAS.
- PGIC and CGIC were summarized as numbers and percentages by visit for each response category.

Safety Analyses:

All safety analyses were conducted on the SAS.

SAEs and protocol-specified AEs were classified according to MedDRA version 27.0.

[redacted]

    - The frequency of SCD-related and non-SCD related AEs were tabulated by system organ class, PT, severity, and relationship to voxelotor treatment.

- The following safety outcomes were provided as listings:
    - Pregnancy and fertility
    - Death
    - SAEs
    - Any events (including death) leading to discontinuation.

Subgroup Analyses:

The subgroup analyses were not pre-specified in the protocol, but they were specified in the SAP (see Appendix 4 SAP Section 4.7.5).

Annualized incidence rate (per patient year) of acute pain crisis for pre-voxelotor and post-voxelotor were reported for the following analysis subgroups:

- participants **with** chronic pain
- participants **without** chronic pain
- participants **with >1 grams per deciliter (g/dL) maximum increase in Hb** (baseline to highest post-voxelotor value)
- participants **with ≤1 g/dL maximum increase in Hb** (baseline to highest post-voxelotor value)

Participants with chronic pain were defined to have at least one of the following criteria during pre-voxelotor or post-voxelotor periods:

- SCD complications page: Avascular Necrosis, Chronic Pain; or
- Non-SCD medical history page: Arthralgia, Arthritis, Neuralgia, Osteonecrosis, Osteoarthritis, Rheumatoid arthritis, Spinal osteoarthritis; or
- Concomitant medications page: Baclofen, Gabapentin, Meloxicam, Pregabalin, all “Buprenorphine", Duloxetine, Duloxetine hydrochloride, Methadone, Methadone hydrochloride.

The VOC event definitions for pre- and post-voxelotor treatment are provided in Appendix 4 SAP Section 4.7.5.

9.9.2. Main statistical methods

Analyses were conducted using the following populations:

[redacted]

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

9.9.3. Missing values

When missing data occur, no imputation was made, and all statistics were calculated with non-missing values. Counts and percentages of missing values were presented in the tables where applicable.

For partial AE start dates, if month and day were missing, the AE start date was set to June 15 (ie, imputation of month as June, mid-point of the year, and imputation of date as 15th, mid-point of the month). If only the day was missing, the AE start day was set to the 15th of the month. If the imputed AE start date was after the AE end date, the AE start date was set to the AE end date. If the AE start date is completely missing, no data imputation was performed.

If the end of study date was missing or partial (only year), the last known visit date was used. If the end of study date was partial (year and month), then it was imputed to the last day of the month. If the end of treatment date was partial (month and year was known), the last day of the month was used. If the end of treatment date was partial (only year was known) or missing completely, the end of the study date was used.

9.9.4. Sensitivity analyses

None.

9.9.5. Amendments to the statistical analysis plan

The initial SAP was amended 2 times: once on 21 November 2024, before the database lock date, and a second time on 24 January 2025 after the database lock date. Each SAP amendment is summarized below and further detailed in Appendix 4 SAP Section 1:

- **SAP Amendment 1 (Version 2 dated 21 November 2024):** The SAP was amended prior to database lock to clarify the analyses specified in the original version, specify new subgroup analyses for analyses of annualized incidence rate of 'acute pain crisis', and update the list of outputs to be generated according to the changes made in amendment.
- **SAP Amendment 2 (Version 3 dated 24 January 2025):** The SAP was amended following database lock to establish a threshold for exclusion of physically

implausible outliers in laboratory data (specifically reticulocyte count [absolute] and ferritin) probably due to data entry errors. In addition, minor clarifications to analyses and editorial updates were made to the table shells to be generated prior to the final analyses.

9.10. Quality control

- This study involves secondary data collection with the following practices: All participant data relating to the study was recorded in the CRF. The study doctor was responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- Source documents provided evidence for the existence of the participant and substantiated the integrity of the data collected. Source documents were filed at the study site.
- For this study, source data included data recorded in the participant's medical records collected as part of the participant's usual medical care.
- Data entered into the CRF was source data verified, cleaned, reconciled and released according to the Data Review Plan and Site Monitoring Plan.

All tables and listings were generated by the contract research organization (CRO) using their quality procedures and underwent secondary quality control procedures by the sponsor.

9.11. Protection of human subjects

Subject information and consent

Written informed consent (see Appendix 6) was obtained prior to the subject entering the study (before initiation of study protocol-specified procedures) by study personnel; the nature, purpose, and duration of the study was explained to each subject. Each subject was informed that he/she could withdraw from the study at any time and for any reason. Each subject was given sufficient time to consider the implications of the study before deciding whether to participate. Subjects who chose to participate signed an informed consent document.

Independent Ethics Committee (IEC)/Institutional Review Board (IRB)

The final protocol, any amendments, and informed consent documentation were reviewed and approved by an IRB(s) and/or IEC(s) for each site participating in the study.

Ethical conduct of the study

The study was conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and followed generally accepted research practices described in ICH guidelines.

10. RESULTS

The study was terminated on 25 September 2024. Certain protocol-specified primary objective clinical outcome measures were not analyzed for this final abbreviated CSR due to limitations in the available data sources at the time of study termination, which may impact the overall interpretation of the study findings.

10.1. Participants

10.1.1. The study was conducted at 24 sites in the United States (Appendix 3.1). Disposition

The disposition of study participants is summarized in Table 2.

As of the study termination date, a total of 265 participants with SCD (all genotypes) aged ≥5 years were enrolled.

The FAS included 265 participants.

The SAS included 260 participants.

The 5 participants who were included in the FAS but not the SAS due to the following reasons: 4 participants did not take voxelotor prior to enrollment and did not start taking voxelotor within 6 months after enrollment, and 1 participant enrolled immediately prior to study termination and did not receive voxelotor.

There were 19 participants who enrolled in PROSPECT from the RETRO study. For these participants, the index date was defined as the date of voxelotor initiation in RETRO and their pre-voxelotor data came from the 12-month data prior to voxelotor initiation in RETRO. It should be noted that 1 site participated in both the RETRO and PROSPECT studies and it de-identified RETRO participants per request from the IRB; therefore, it is possible that additional PROSPECT participants were RETRO participants, but they were not identifiable.

Participant enrollment by site is provided in Appendix 3.1.

Of the enrolled participants:

- The mean (SD) duration of the study was 34.01 (14.758) months.
- No participants completed the study prior to study termination. 245 participants (92.5%) discontinued the study early due to study termination by sponsor.
    - Screen failure (8/265 participants; 3.0%), Adverse Event (7/265 participants; 2.6%), and Other (2/265 participants, 0.8%) were the next most common primary reasons for early discontinuation from the study.
- 256 participants (96.6%) discontinued study treatment early with study terminated by sponsor reported as the most common primary reason for early discontinuation (217/265 participants; 81.9%)

[redacted]

- Other (11/265 participants; 4.2%), Adverse Event (8/265 participants; 3.0%), and Physician Decision (8/265 participants, 3.0%) were the next most common primary reasons for early treatment discontinuation.
    - The "other" reasons for early treatment discontinuation included treatment adherence, insurance issues, lost to follow-up, and difficulty delivering treatment to participants.

Table 2. Summary of Participant Disposition - All Enrolled Participants

	Participants (N=265)
Participants Enrolled	265 (100)
Full Analysis Set	265 (100)
Safety Analysis Set	260 (98.1)
Early Treatment Discontinuation	256 (96.6)
Primary Reason for Treatment Discontinuation	
Adverse Event	8 (3.0)
Lost to Follow-Up	1 (0.4)
Physician Decision	8 (3.0)
Lack of Efficacy	5 (1.9)
Pregnancy	1 (0.4)
Protocol Deviation	0
Study Terminated by Sponsor	217 (81.9)
Withdrawal by Participant	5 (1.9)
Withdrawal by Parent/Guardian	0
Other	11 (4.2)
Completed Study	0
Early Discontinuation from Study	265 (100)
Primary Reason for Study Discontinuation	
Adverse Event	7 (2.6)
Lost to Follow-Up	1 (0.4)
Physician Decision	1 (0.4)
Lack of Efficacy	1 (0.4)
Pregnancy	0
Protocol Deviation	0
Study Terminated by Sponsor	245 (92.5)
Withdrawal by Participant	0
Withdrawal by Parent/Guardian	0
Screen Failure[a]	8 (3.0)
Other	2 (0.8)
Duration of study (months)	
Mean (SD)	34.01 (14.758)
Median (range)	33.37 (4.6, 57.3)
Duration of study category	
<1 Month	0
1 - <2 Months	0
2 - <3 Months	0
3 - <6 Months	5 (1.9)
6 - <9 Months	5 (1.9)
9 - <12 Months	6 (2.3)
12 - <18 Months	31 (11.7)
18 - <24 Months	32 (12.1)
24 - <30 Months	35 (13.2)
30 - <36 Months	24 (9.1)

[redacted]

Table 2. Summary of Participant Disposition - All Enrolled Participants

	Participants (N=265)
36 - <42 Months	24 (9.1)
42 - <48 Months	34 (12.8)
≥48 Months	64 (24.2)

All percentages are of the column heading N.
Study Duration was derived starting from the date of first Oxbryta treatment through to the end of study date.
[a] Screen Failure was defined as participants who did not start or restart Oxbryta within six months of informed consent. Screen failed participants met eligibility criteria and were included in the Full Analysis Set (N=8) and took/prescribed at least one dose of Oxbryta were included Safety Analysis Set (N=4).
Data source: ADSL
Final Database Locked: 13JAN2025
Program Source: TDS.SAS
04FEB2025:11:21:17
Source: Table 15.1.1 is for [redacted] internal use only.

10.1.2. Important protocol deviations

There were 3 important protocol deviations related to late SAE reporting. All protocol deviations are listed by site in Appendix 7.2.

10.2. Descriptive data

10.2.1. Demographics and baseline characteristics

Baseline characteristics of the FAS population (N=265) are presented in Table 3 and summarized below:

- The mean (SD) age of participants at enrollment was 32.0 (14.78) years, with most of the participants in the 18 - <45 years old age group (57.7% [153/265 participants]).
- Adolescent (12 - <18 years) and pediatric (4 - <12 years) participants made up 12.5% (33/265) and 8.7% (23/265) of participants, respectively.
- 58.1% (154/265) of participants were female.
- Most participants were Black or African American (92.8%; 246/265 participants) and Not Hispanic or Latino 90.6% (240/265).
- 82.6% (219/265) of participants had hemoglobin SS (HbSS) genotype and 65.3% (173/265) of participants were receiving concurrent hydroxyurea (HU) (pre-voxelotor).
- The mean (SD) Hb level at baseline was 7.81 g/dL (1.356); 66.8% (117/265) of participants had a baseline Hb value between 7 to 10.5 g/dL. Note that baseline Hb was determined using the most recent value prior to initiation of voxelotor treatment.

Table 3. Demographics and Baseline Characteristics - Full Analysis Set

	Participants (N=265)
Age (years) at Index Date[a]	
N	265
[redacted]	

[redacted]

Table 3. Demographics and Baseline Characteristics - Full Analysis Set

	Participants (N=265)
Mean (SD)	32.0 (14.78)
Median	32.0
Q1, Q3	20.0, 42.0
Min, Max	5, 66
Age Groups, Index Date[a], n (%)	
4 - <12 years	23 (8.7)
12 - <18 years	33 (12.5)
18 - <45 years	153 (57.7)
45 - <65 years	54 (20.4)
≥65 years	2 (0.8)
Age (years) at date of first Oxbryta treatment	
N	260
Mean (SD)	30.3 (14.44)
Median	30.0
Q1, Q3	18.0, 40.0
Min, Max	5, 64
Age Groups, date of first Oxbryta treatment, n (%)	
4 - <12 years	24 (9.1)
12 - <18 years	38 (14.3)
18 - <45 years	150 (56.6)
45 - <65 years	48 (18.1)
≥65 years	0
Missing	5 (1.9)
HbS Genotypes, n (%)	
HbSS	219 (82.6)
HbSBeta0 Thalassemia	11 (4.2)
HbSC	4 (1.5)
HbSß+	2 (0.8)
Other: Essential Thrombocythemia	1 (0.4)
Other: Hb F%	1 (0.4)
Missing	27 (10.2)
Gender, n (%)	
Male	111 (41.9)
Female	154 (58.1)
Race[b], n (%)	
Asian	0
American Indian or Alaska Native	2 (0.8)
Black or African American	246 (92.8)
Native Hawaiian or Other Pacific Islander	0
White	6 (2.3)
Other	11 (4.2)
Race: multiracial and other races specified [b] [c], n (%)	
Other: Not documented	1 (0.4)
Other: Not recorded/Unknown	8 (3.0)
Other: Other not specified in record	2 (0.8)
Ethnicity, n (%)	
Hispanic or Latino	21 (7.9)
Not Hispanic or Latino	240 (90.6)
Not Reported	2 (0.8)
Unknown	2 (0.8)
Participant Health Insurance, n (%)	
Private	83 (31.3)

[redacted]

Table 3. Demographics and Baseline Characteristics - Full Analysis Set

	Participants (N=265)
Medicaid	118 (44.5)
Medicare	43 (16.2)
Medicaid and Medicare	20 (7.5)
Self-Insured	0
Does not have insurance	1 (0.4)
Currently Taking Hydroxyurea (pre-Oxbryta)?, n (%)	
Yes	173 (65.3)
No	65 (24.5)
Missing	27 (10.2)
Baseline Hemoglobin (g/dL)	
N	252
Mean (SD)	7.81 (1.356)
Median	7.75
Q1, Q3	6.90, 8.60
Min, Max	4.5, 13.5
Baseline Hemoglobin (g/dL) Groups, n (%)	
< 7 g/dL	67 (25.3)
7 to 10.5 g/dL	177 (66.8)
> 10.5 g/dL	8 (3.0)
Missing	13 (4.9)

[a] Index date was the date of informed consent.
[b] Participant checking more than one race were classified as Other
[c] This analysis was limited to the 11 participants who are in the 'Other' category for the above 'Race' analysis.
Data Source: ADSL
Final Database Locked: 13JAN2025
Program Source: TDM.SAS
04FEB2025:11:21:11
Source: Table 15.1.2 for [redacted] internal use only.

Note: For the HbS genotypes parameter, "Other: Essential Thrombocythemia" and "Other: Hb F%" were verbatim entries into the CRF from the investigator.

10.2.2. Medical history

Participant medical history is summarized in Table 15.1.3.

In the FAS, 69.81% (185/265) of participants had at least one disease/syndrome prior to study entry.

10.2.3. Concomitant medications

Participant concomitant use of medications of interest consistent with SCD SOC is summarized in Table 15.4. In the SAS, 99.6% (259/260) of participants took at least 1 concomitant medication of interest one or more times.

The most commonly used (in >60% of participants) ATC level 2 class of concomitant medications were:

- Other hematological agents: 80.0% (208/260) of participants, with most participants being on hydroxycarbamide (75.4%, 196/260); all other medications used by <7% of participants.

- Analgesics: 70.0% (182/260) of participants, with paracetamol (70/260; 26.9%) and oxycodone (60/260; 23.1%) most commonly taken medication in this category; all other medications in the class were used by <17% of participants.

- Antianaemic preparations: 64.2% (167/260) of participants, with most participants being on folic acid (63.1%; 164/260); all other medications in the class were used by ≤5% of participants.

10.2.4. Exposure to voxelotor

10.2.4.1. Voxelotor treatment duration and administration

Details regarding study drug administration and exposure to voxelotor are presented in Table 4 and summarized below:

- The mean (SD) duration of voxelotor treatment was 143.18 (65.588) weeks; most participants were on voxelotor for ≥12 months with 22.7% (59/260) of participants having received voxelotor for ≥48 months.

- Most participants were initially prescribed voxelotor as 1500 mg QD (76.5%; 199/260 participants), in accordance with the USPI.

- Common reasons participants were prescribed voxelotor were reported as reduces anaemia (195 participants [75.0%]), reduces the frequency of VOCs (82 participants [31.5%]), reduces pain (77 participants [29.6%]), and reduces the need for blood transfusions (53 participants [20.4%]). All other reasons were reported for ≤10 participants each.

- Treatment was discontinued in 256/260 participants (the remaining 4 participants, considered screen failures, in the SAS took voxelotor prior to enrollment but did not re-start voxelotor after enrollment); most participants (83.5%, 217/260) discontinued from treatment due to study termination by the sponsor. The next most common reasons for treatment discontinuation were other (4.2%; 11/260), AEs (3.1%; 8/260) and physician decision (3.1%; 8/260). The mean (SD) duration of treatment for participants who discontinued treatment was 143.84 (65.880) weeks.

[redacted]

Table 4. Study Drug Administration - Safety Analysis Set

	Participants (N=260)
Duration of Treatment, weeks	
N	260
Mean (SD)	143.18 (65.588)
Median	137.00
Q1, Q3	92.36, 204.00
Min, Max	6.4, 249.0
Duration of Treatment, category	
1 - <2 Months	1 (0.4)
2 - <3 Months	2 (0.8)
3 - <6 Months	5 (1.9)
6 - <9 Months	6 (2.3)
9 - <12 Months	8 (3.1)
12 - <18 Months	32 (12.3)
18 - <24 Months	30 (11.5)
24 - <30 Months	38 (14.6)
30 - <36 Months	21 (8.1)
36 - <42 Months	24 (9.2)
42 - <48 Months	34 (13.1)
≥48 Months	59 (22.7)
Initial Prescribed Dose per day, n (%)	
4500 mg	1 (0.4)
1500 mg	210 (80.8)
1000 mg	16 (6.2)
900 mg	18 (6.9)
600 mg	5 (1.9)
500 mg	8 (3.1)
300 mg	2 (0.8)
Initial Prescribed Dose Strength & Frequency[a], n (%)	
1500 mg QD	199 (76.5)
900 mg QD	18 (6.9)
1000 mg QD	11 (4.2)
500 mg TID	11 (4.2)
500 mg QD	8 (3.1)
500 mg BID	5 (1.9)
600 mg QD	5 (1.9)
300 mg QD	2 (0.8)
1500 mg TID	1 (0.4)
Reported Reason(s) for Prescribing Oxbryta[b], n (%)	

[redacted]

Table 4. Study Drug Administration - Safety Analysis Set

	Participants (N=260)
Reduces anemia	195 (75.0)
Reduces the frequency of vaso-occulsive crises (VOCs)	82 (31.5)
Reduces pain	77 (29.6)
Reduces the need for blood transfusion	53 (20.4)
Other	47 (18.1)
Increase hemoglobin	10 (3.8)
Reduce hemolysis	7 (2.7)
Reduce SCD complications	5 (1.9)
Sickle cell disease management	5 (1.9)
Fatigue	3 (1.2)
Inadequate response to Hydroxyurea	3 (1.2)
Leg ulcer(s)	2 (0.8)
Reduces the need for blood transfusions	2 (0.8)
Adverse events from Hydroxyurea	1 (0.4)
Prevent SCD complications	1 (0.4)
Reduces pain	1 (0.4)
Reducing hypoxia	1 (0.4)
Refuse Hydroxyurea	1 (0.4)
Stabilize hemoglobin	1 (0.4)
Unspecified	5 (1.9)
Unknown, not specified	4 (1.5)
Treatment Discontinuation, n (%)	
Yes	256 (98.5)
Did not take Oxbryta	4 (1.5)
Duration of Treatment, weeks, for Participants who Discontinued Treatment	
N	256
Mean (SD)	143.84 (65.880)
Median	139.29
Q1, Q3	91.50, 204.71
Min, Max	6.4, 249.0
Duration of Treatment, category, for Participants who Discontinued Treatment, n (%)	
<1 Month	0
1 - <2 Months	1 (0.4)
2 - <3 Months	2 (0.8)
3 - <6 Months	5 (1.9)
6 - <9 Months	6 (2.3)
9 - <12 Months	8 (3.1)
12 - <18 Months	32 (12.3)
18 - <24 Months	28 (10.8)

Table 4. Study Drug Administration - Safety Analysis Set

	Participants (N=260)
24 - <30 Months	36 (13.8)
30 - <36 Months	21 (8.1)
36 - <42 Months	24 (9.2)
42 - <48 Months	34 (13.1)
≥48 Months	59 (22.7)
Reason for Treatment Discontinuation, n (%)	
Adverse Event	8 (3.1)
Lost to Follow-Up	1 (0.4)
Physician Decision (Specify)	8 (3.1)
Lack of Efficacy	5 (1.9)
Pregnancy	1 (0.4)
Study Terminated by Sponsor	217 (83.5)
Withdrawal by Participant (Specify)	5 (1.9)
Other	11 (4.2)
Reason for Treatment Discontinuation, n (% of participants who discontinued)	
Adverse Event	8 (3.1)
Lost to Follow-Up	1 (0.4)
Physician Decision (Specify)	8 (3.1)
Lack of Efficacy	5 (2.0)
Pregnancy	1 (0.4)
Study Terminated by Sponsor	217 (84.8)
Withdrawal by Participant (Specify)	5 (2.0)
Other	11 (4.3)
Other/Specified Reason for Treatment Discontinuation, n (% of participants who discontinued)	
Other (Specify): Hospitalization and insurance issues	1 (0.4)
Other (Specify): Lack of adherence and delivery of drug	1 (0.4)
Other (Specify): On 7-6-2023 visit, provider stated patient had poor adherence; Date Oxbryta last filled was March 2023, Patient has not been seen since 7-6-2023	1 (0.4)
Other (Specify): Patient did not believe medication was effective	1 (0.4)
Other (Specify): Patient did not want to continue taking 5 pills a day	1 (0.4)
Other (Specify): Patient is lost to follow-up unknown if he is still taking Oxbryta	1 (0.4)
Other (Specify): Patient stopped taking	1 (0.4)
Other (Specify): Pharmacy was unable to reach patient to deliver the Oxbryta.	1 (0.4)
Other (Specify): Source documentation doesn't support taking this medication as of 4/8/24	1 (0.4)
Other (Specify): Stopped due to insurance denial. Patient changed insurance and was denied again. Due to patient being on Transfusion Provider decided patient does not need to be on Oxb	1 (0.4)
Other (Specify): The participant stopped taking Oxbryta on 29 April 2024	1 (0.4)
Physician Decision (Specify): "Although patient demonstrates improvement on this medication, we are taking these precautions to avoid any potential risks based on the manufacturer's dec	1 (0.4)

Table 4. Study Drug Administration - Safety Analysis Set

	Participants (N=260)
Physician Decision (Specify): Discontinued on 2/22/24, started chronic transfusion therapy due to abnormal TCDs	1 (0.4)
Physician Decision (Specify): Elevated LFTs	1 (0.4)
Physician Decision (Specify): Not specified and not re-subscribed after 22MAR2024.	1 (0.4)
Physician Decision (Specify): Reason was not specified in chart.	1 (0.4)
Physician Decision (Specify): Started on a chronic transfusion therapy program	1 (0.4)
Physician Decision (Specify): The subject wanted to join a clinical trial and physician discontinued Oxbryta for the patient.	1 (0.4)
Physician Decision (Specify): Voxelotor discontinued; Started chronic blood transfusions due to abnormal TCD velocities	1 (0.4)
Withdrawal by Participant (Specify): It was not specified in the chart why the patient decided to stop taking.	1 (0.4)
Withdrawal by Participant (Specify): No reason was given. Pt said that they had stopped taking it, and the last time it was given was in the hospital.	1 (0.4)
Withdrawal by Participant (Specify): Patient did not like the size of the med and wanted to switch treatments	1 (0.4)
Withdrawal by Participant (Specify): Patient quit taking medication, poor adherence taking all meds	1 (0.4)
Withdrawal by Participant (Specify): Subject information physician that stopped taking awhile ago. Unclear what date of discontinuation would be.	1 (0.4)

Percentages are out of the number of participants unless otherwise stated.
Duration of treatment was derived starting from the date of first Oxbryta treatment through 1) the end of treatment date if available; 2) if the end of treatment date is missing, the end of study date is used.
[a] QD is once daily, TID is three times a day, BID is twice a day.
[b] Prescriber may have had more than one reason for prescribing Oxbryta.
Data Source: ADSL, ADEX
Final Database Locked: 13JAN2025
Program Source: TEX.SAS
04FEB2025:11:21:20
Source: Table 15.1.4 for [redacted] internal use only.

10.2.4.2. Voxelotor Dose Modification

Additional data regarding study drug administration and dosage changes initiated by the physician for participants are presented in Table 15.1.5 and summarized below:

- 21.2% (55/260) of participants had dosage changes initiated by the physician (15.0% [39/260] of participants had dose adjustment and 8.5% [22/260] of participants had dose interruption).
    - 48.7% (19/39) of the dose adjustments were decrease(s) only and 30.8% (12/39 dose adjustments) were both decrease(s) and increase(s).
        - AEs were the most common reason for physician-initiated dose decrease(s); the most common AE reported was Diarrhoea (16 [51.6%] decreases), followed by headache (3 [9.7%] decreases) and multiple/other AE (3 [9.7%] decreases). Other specific AEs were reported as the reason for 1 decrease (3.2%) each.
        - Of the reasons of physician-initiated dose decreases, 6 were categorized as "other"; the specific reason as entered by the investigator are provided in Table 15.1.5.
        - Of the reasons for physician-initiated dose increases, 17 were categorized as "other"; the specific reason as entered by the investigator are provided in Table 15.1.5.

10.3. Outcome data

The FAS included 265 participants, and the SAS included 260 participants. Further details of the participants included in the analyses presented in this CSR are provided in Section 10.1.

Study results are presented below in Section 10.4 through Section 10.6.

10.4. Main results

10.4.1. Clinical outcomes measures

10.4.1.1. Hematologic parameters

10.4.1.1.1. Change in Hb from pre-voxelotor treatment

Change in Hb (g/dL) from baseline (the most recent pre-voxelotor treatment value on or prior to initial voxelotor dose) over time (all available measures averaged in 3- or 6-month periods through 60 months) post-voxelotor treatment is presented in Table 5 and key results are summarized below:

- Over the follow-up period, mean Hb levels increased following voxelotor treatment.
    - An increase in mean (SD) Hb level from baseline was observed for the 3-months post-voxelotor treatment period and continued through the 4.5-years (54 months) post-treatment period. The mean (SD) Hb change from baseline at 3-months through 4 years post-voxelotor treatment period ranged between 0.4 (1.48) to 0.7 (1.47) g/dL (for time points with available data for at least 50 participants).

[redacted]

- The mean (SD) peak (maximum observed value of post-voxelotor assessments up through the Month 60 period) of Hb value was 9.8 g/dL (1.81) and mean (SD) increase from baseline was 2.0 g/dL (1.62) (N=251 participants).

Table 5. Change in Hematologic Laboratory - Hb Tests by Visit - Full Analysis Set

	Participants (N=265)	
	N	Mean (SD), Median, (Min, Max)
Hemoglobin (g/dL)		
Maximum Observed Value[a]		
Pre-Oxbryta	251	7.8 (1.36), 7.8, (4.5, 13.5)
Post-Oxbryta		9.8 (1.81), 9.7, (4.7, 17.5)
Change from Baseline		2.0 (1.62), 1.9, (-1.3, 9.3)
3 months Post-Oxbryta[b]		
Pre-Oxbryta	215	7.8 (1.35), 7.7, (4.6, 13.5)
Post-Oxbryta		8.3 (1.66), 8.2, (3.3, 13.1)
Change from Baseline		0.5 (1.33), 0.5, (-4.4, 4.0)
6 months Post-Oxbryta[b]		
Pre-Oxbryta	219	7.9 (1.37), 7.8, (4.5, 13.5)
Post-Oxbryta		8.5 (1.70), 8.3, (1.0, 13.0)
Change from Baseline		0.6 (1.47), 0.8, (-5.8, 4.4)
9 months Post-Oxbryta[b]		
Pre-Oxbryta	205	7.8 (1.37), 7.7, (4.5, 13.5)
Post-Oxbryta		8.3 (1.66), 8.3, (1.0, 14.7)
Change from Baseline		0.5 (1.45), 0.5, (-7.5, 3.8)
12 months Post-Oxbryta[b]		
Pre-Oxbryta	209	7.9 (1.34), 7.8, (4.6, 13.5)
Post-Oxbryta		8.5 (1.58), 8.4, (4.2, 14.7)
Change from Baseline		0.6 (1.36), 0.5, (-2.6, 5.5)
18 months Post-Oxbryta[b]		
Pre-Oxbryta	220	7.8 (1.34), 7.8, (4.5, 13.5)
Post-Oxbryta		8.4 (1.57), 8.3, (4.4, 12.9)
Change from Baseline		0.7 (1.35), 0.6, (-3.8, 4.3)
24 months Post-Oxbryta[b]		
Pre-Oxbryta	184	7.8 (1.42), 7.7, (4.5, 13.5)
Post-Oxbryta		8.4 (1.69), 8.4, (1.0, 13.3)
Change from Baseline		0.6 (1.46), 0.6, (-8.1, 4.2)
30 months Post-Oxbryta[b]		
Pre-Oxbryta	155	7.8 (1.42), 7.5, (4.7, 13.5)
Post-Oxbryta		8.2 (1.85), 8.3, (1.0, 15.2)
Change from Baseline		0.5 (1.62), 0.3, (-6.0, 9.1)
36 months Post-Oxbryta[b]		
Pre-Oxbryta	122	7.6 (1.53), 7.3, (4.5, 13.5)
Post-Oxbryta		8.2 (1.71), 8.0, (3.9, 13.0)
Change from Baseline		0.6 (1.62), 0.5, (-3.5, 5.9)
42 months Post-Oxbryta[b]		
Pre-Oxbryta	103	7.6 (1.56), 7.3, (4.5, 13.5)
Post-Oxbryta		8.0 (1.76), 7.8, (3.6, 13.1)
Change from Baseline		0.4 (1.48), 0.2, (-2.6, 4.1)

Table 5. Change in Hematologic Laboratory - Hb Tests by Visit - Full Analysis Set

	Participants (N=265)	
	N	Mean (SD), Median, (Min, Max)
48 months Post-Oxbryta[b]		
Pre-Oxbryta	77	7.6 (1.49), 7.2, (4.7, 13.5)
Post-Oxbryta		8.2 (1.74), 8.1, (4.6, 13.0)
Change from Baseline		0.7 (1.47), 0.6, (-3.0, 5.5)
54 months Post-Oxbryta[b]		
Pre-Oxbryta	41	7.8 (1.64), 7.4, (5.7, 13.5)
Post-Oxbryta		7.9 (1.73), 7.7, (3.9, 13.0)
Change from Baseline		0.1 (1.68), 0.2, (-6.5, 3.7)
60 months Post-Oxbryta[b]		
Pre-Oxbryta	8	8.5 (1.78), 8.3, (6.1, 11.5)
Post-Oxbryta		8.4 (1.74), 7.8, (7.1, 12.4)
Change from Baseline		-0.2 (1.36), 0.4, (-2.7, 1.0)

[a] Assessments up through Month 60 Visit.
[b] Pre-Oxbryta value was the latest visit on or prior to the first dose of Oxbryta. Post-Oxbryta, for multiple assessments at the same specific visit, the average was used.
Data Source: ADLB, ADSL
Final Database Locked: 13JAN2025
Program Source: TLBVISHG.SAS
07FEB2025:13:35:54
Source: Table 15.2.1.1 is for [redacted] internal use only.

10.4.1.1.2. Change in ALT and AST measures from pre-voxelotor treatment

Change in ALT and AST (U/L) from baseline (the most recent pre-voxelotor treatment value on or prior to initial voxelotor dose) over time (all available measures averaged in 3- or 6-month periods through 60 months) post-voxelotor treatment is presented in Table 15.2.1 and key results are summarized below:

- There were no clear trends in change in ALT and AST measurements from pre- to post-voxelotor treatment through the 60-month follow-up period; ALT and AST levels were generally similar pre- and post-voxelotor treatment but were highly variable.
- The mean (SD) peak (maximum observed value of post-voxelotor assessments up through the Month 60 period) of ALT value post-voxelotor was 53.1 U/L (40.53) and mean (SD) increase from baseline was 27.4 U/L (38.38) (reference range: 7 – 52 U/L (N=222 participants).
- The mean (SD) peak (maximum observed value of post-voxelotor assessments up through the Month 60 period) of AST value post-voxelotor was 72.1 U/L (46.25) and mean (SD) increase from baseline was 27.6 U/L (42.86) (reference range: 13 – 39 U/L (N=218 participants).

10.4.1.1.3. Change in hemolysis measures from pre-voxelotor treatment

Change in hemolysis measures, reticulocyte count (absolute, %) and bilirubin (total, direct, indirect), from baseline (the most recent pre-voxelotor treatment value on or prior to initial

voxelotor dose) over time (all available measures averaged in 3- or 6-month periods through 60 months) post-voxelotor treatment are presented in Table 15.2.2; key results are summarized below:

- Overall, there was a decrease from baseline in clinical measures of hemolysis post-voxelotor treatment; however, the interpretation of this data is limited by the small sample sizes of participants with data available in the latter half of the follow-up period, particularly beyond 30 months post-voxelotor treatment.

Reticulocytes

- **Reticulocyte Count (Absolute)**: mean (SD) reticulocyte count (absolute) levels were similar pre- and post-voxelotor treatment throughout the 60-month follow-up period; however, some fluctuations from baseline (pre-voxelotor) were noted post-voxelotor treatment. The mean (SD) minimum (post-voxelotor) observed value of assessments up through the Month 60 period of reticulocyte count (absolute) value was 127.0 x 10^9/L (102.31) and mean (SD) decrease from baseline was 128.0 x 10^9/L (168.47) (N=169 participants).

- **Reticulocyte Count (%)**: a decrease in mean (SD) reticulocyte count (%) level from baseline was observed by the 3-month (N=164 participants) post-voxelotor treatment period and continued through the 3.5 year (42 months; N=77 participants) post-treatment period. The mean (SD) minimum (post-voxelotor) observed value of assessments up through the Month 60 period of reticulocyte count (%) value was 5.8% (4.08) and mean (SD) decrease from baseline was 5.5% (5.88) (N=211 participants).

Bilirubin

- A reduction in total bilirubin level from baseline was observed by the 3-month (N=184) post-voxelotor treatment period and continued through the 5 year (60 months; N=6 participants) post-treatment period. The mean (SD) minimum (post-voxelotor) observed value of assessments up through the Month 60 period of total bilirubin levels was 1.9 milligrams per deciliter (mg/dL) (1.50) and mean (SD) decrease from baseline was 1.8 mg/dL (2.22) (N=236 participants).

- The mean (SD) minimum observed value of assessments up through the Month 60 post-treatment period of indirect bilirubin levels was 1.7 mg/dL (2.05) and mean (SD) decrease from baseline was 0.7 mg/dL (2.26) (N=50 participants).

- There was no trend in change from baseline in mean (SD) direct or indirect bilirubin levels throughout the post-voxelotor treatment follow-up period up to 60 months.

10.4.1.1.4. Change in ferritin levels from pre-voxelotor treatment

Change in ferritin levels from baseline (the most recent pre-voxelotor treatment value on or prior to initial voxelotor dose) over time (all available measures averaged in 3- or 6-month periods through 60 months) post-voxelotor treatment are presented in Table 15.2.3.

Less than a third of the FAS had ferritin values at each follow-up period. There was no trend in mean (SD) ferritin levels relative to baseline throughout the post-voxelotor treatment

follow-up period up to 60 months; mean ferritin levels fluctuated in the post-voxelotor period from baseline.

10.4.1.2. Renal function

Creatinine, serum cystatin C, and ACR laboratory values (Table 15.2.4) and hemoglobinuria and eGFR (calculated using CKD-EPI equation) laboratory values (Table 15.2.4.1) pre-voxelotor (the most recent treatment value on or prior to initial voxelotor dose) and post-voxelotor treatment were collected as measures of renal function; key results are presented below:

The post-voxelotor renal function, as assessed by creatinine, serum cystatin C, and urine ACR levels, showed no clear trend; however, interpretation of results is limited by sample size and high variability.

- Mean (SD) creatinine levels were similar pre- and post-voxelotor treatment throughout the 60-month follow-up period. The mean (SD) minimum (post-voxelotor) observed value of assessments up through the Month 60 period of creatinine levels was 0.7 mg/dL (0.51) and mean (SD) decrease from baseline was 0.1 mg/dL (0.35) (N=244 participants).

- The number of participants with available data for serum cystatin C and ACR measures was small, ranging from N=1 to 2 (baseline and 3- to 30-month visit periods, respectively) participants over the follow-up period for the serum cystatin C analysis and N=3 to 41 (54-month visit period and baseline, respectively) participants for the ACR analysis.

For hemoglobinuria and eGFR measures, of the participants with available data pre- and post-voxelotor treatment:

- Most participants were none/negative for hemoglobinuria at baseline and throughout the post-voxelotor period.

- Most participants had eGFR classified as G1 (≥ 90 mL/min per 1.73 m^2) at baseline and subsequent assessments through the Month 60 follow-up period. Note, eGFR values were summarized as input into the eCRF by the investigator; as such, the collected data and interpretation of results is limited.

10.4.1.3. Rate of significant SCD-related clinical events

Significant SCD-related clinical events (also referred to as SCD complications) included but not limited to, for example, acute pain crisis, ACS, priapism, stroke, chronic or end stage kidney disease, iron overload, leg ulcers, cardiac malfunction, and PH. Sickle cell anaemia was included as a pre-specified SCD complication on the SCD complications CRF. However, interpretation of this term is limited because selection of this complication on the CRF could have been attributed to the participant's diagnosis of SCD or an exacerbation of SCD by the reporter.

Since VOC is a broad term and was not defined as a specific CRF term in the final protocol, VOCs were captured as 'acute pain crisis' on the CRF (Appendix 5). The rates of SCD complications and transfusions are reported in the subsections below.

[redacted]

Subgroup analyses of Acute Pain Crisis SCD complications are presented in Section 10.5.2.

- Section 10.6.1 presents treatment emergent SCD complications (SCD-related treatment-emergent AEs [TEAEs]) for the SAS (N=260 participants).

10.4.1.3.1. SCD complications post-voxelotor treatment

Post-voxelotor SCD-complications through end of study are presented by PT in 6 for the SAS and summarized below.

- SCD complications were reported in 205/260 (78.8%) participants.
  - The most common SCD complications (reported in ≥6% participants) experienced were Acute pain crisis (71.9%; 187/260 participants), ACS (28.8%; 75/260 participants), Pneumonia (7.7%, 20/260 participants), and Avascular necrosis (6.2%; 16/260 participants).

Table 6. Summary of SCD Complications – Safety Analysis Set

	Participants (N=260) n (%)
Any SCD Complications	205 (78.8)
SCD Complications	
Acute Chest Syndrome	75 (28.8)
Acute Pain Crisis	187 (71.9)
Aplastic Crisis	1 (0.4)
Avascular Necrosis	16 (6.2)
Cardiac Malfunction	3 (1.2)
Cardiac Malfunction and Pulmonary Hypertension	3 (1.2)
Cerebral Infarct	2 (0.8)
Cholecystectomy	0
Cholelithiasis	6 (2.3)
Chronic or End Stage Kidney Disease (as defined by GFR <60 mL/min/1.73 m² for three or more months)	2 (0.8)
Chronic Pain	4 (1.5)
Dactylitis	0
Deep Vein Thrombosis	8 (3.1)
Hepatic Sequestration	0
Iron Overload	4 (1.5)
Iron Overload (as diagnosed by T2* MRI or R2* MRI)	1 (0.4)
Leg Ulcer	5 (1.9)
Pneumonia	20 (7.7)
Priapism	2 (0.8)
Pulmonary Hypertension	2 (0.8)
Retinopathy	3 (1.2)
Sickle Cell Anemia	15 (5.8)
Splenectomy	0
Splenic Sequestration	1 (0.4)
Splenomegaly	1 (0.4)
Transient Ischemic Attack	2 (0.8)
Other:	31 (11.9)
Abdominal pain[a]	2 (0.8)
Acute hemolysis	1 (0.4)
Acute kidney injury	1 (0.4)

Table 6. Summary of SCD Complications – Safety Analysis Set

	Participants (N=260) n (%)
Acute pyelonephritis	1 (0.4)
Anemia	2 (0.8)
Artery occlusion	1 (0.4)
Bacteremia	1 (0.4)
Blood in stool	1 (0.4)
Cerebral aneurysm	1 (0.4)
Covid-19[a]	3 (1.2)
Death[a]	1 (0.4)
Delayed hemolytic transfusion reaction	1 (0.4)
Dyspnea	1 (0.4)
Fatigue	1 (0.4)
Headache[a]	2 (0.8)
Hemolysis	1 (0.4)
Hyperbilirubinemia	1 (0.4)
Hypoxia	3 (1.2)
Jaundice	1 (0.4)
Leukocytosis	1 (0.4)
Mild pulmonary vascular congestion	1 (0.4)
Nonocclusive thrombus in svc	1 (0.4)
Normocytic anemia	1 (0.4)
Pain	3 (1.2)
Pancreatitis	1 (0.4)
Pancytopenia	1 (0.4)
Paraopthalmic opthalmic artery aneurysm.	1 (0.4)
Possible vascular compromise of left upper extremity	1 (0.4)
Potential thrombus in right atrium	1 (0.4)
Pulmonary emboli	1 (0.4)
Pyelonephritis	1 (0.4)
Respiratory abnormality (unknown)	1 (0.4)
Sepsis	1 (0.4)
Septic shock	1 (0.4)
Shortness of breath	1 (0.4)
Superficial vein thrombosis	1 (0.4)
Thrombocytopenia	1 (0.4)
Thrombocytosis	1 (0.4)
Vein occlusion	1 (0.4)
Vomiting[a]	1 (0.4)
Weakness	1 (0.4)

Multiple occurrences of same SCD Complications were counted once for each subject. Displayed percentages represent percentage of participants.
Only SCD Complications from date of first Oxbryta treatment through the end of study were included in the table.
[a] Site reported non-SCD adverse event on SCD Complication CRF.
Data Source: ADSL, ADSCD
Final Database Locked: 13JAN2025
Program Source: TSCD.SAS
04FEB2025:11:22:03
Source: Table 15.2.5 is for [redacted] internal use only.

10.4.1.3.1.1. Annualized incidence rate of SCD complications

The annualized IRs encompass SCD complications that occurred 1 year prior to initial voxelotor dose (pre-voxelotor) and from initial voxelotor dose through the end of study or end of treatment +28 days (post-voxelotor).

[redacted]

The annualized IR (events per patient-year) of SCD complications pre- and post-initial voxelotor dose is summarized below:

- The annualized IR of SCD complications was 6.25 events/patient-year pre-voxelotor and 3.60 events/patient-year post-voxelotor (Table 7).
  - Acute pain crisis: 4.78 events/patient-year pre-voxelotor and 3.15 events/patient-year post-voxelotor (Table 8).
    - A post-hoc analysis using the estimated negative binomial analysis method is presented in Section 10.5.1.
    - Annualized IR of acute pain crisis was analyzed in the context of subgroups of participants with and without chronic pain and participants with >1 g/dL and ≤1 g/dL maximum increase from baseline in Hb (baseline to highest post-voxelotor value); subgroup results are presented in Section 10.5.2.
  - ACS: 0.29 events/patient-year pre-voxelotor and 0.19 events/patient-year post-voxelotor.

Table 7. Annualized Incidence Rate of SCD Complications – Safety Analysis Set

	Participants (N=260)			
	Pre-Oxbryta		Post-Oxbryta	
	Number of Events	Annualized Rate	Number of Events	Annualized Rate
Any SCD Complications	1624	6.25	2579	3.60
SCD Complications				
Aplastic Crisis	2	<0.01	1	<0.01
Acute Chest Syndrome	76	0.29	136	0.19
Acute Pain Crisis	1243	4.78	2258	3.15
Avascular Necrosis	23	0.09	24	0.03
Cardiac Malfunction	0	0.00	3	<0.01
Cardiac Malfunction and Pulmonary Hypertension	7	0.03	3	<0.01
Cerebral Infarct	1	<0.01	1	<0.01
Cholecystectomy	3	0.01	0	0.00
Cholelithiasis	4	0.02	8	0.01
Chronic or End Stage Kidney Disease (as defined by GFR <60 mL/min/1.73 m² for three or more months)	7	0.03	2	<0.01
Chronic Pain	76	0.29	7	<0.01
Dactylitis	0	0.00	0	0.00
Deep Vein Thrombosis	9	0.03	7	<0.01
Hepatic Sequestration	2	<0.01	0	0.00
Iron Overload	15	0.06	4	<0.01
Iron Overload (as diagnosed by T2* MRI or R2* MRI)	5	0.02	1	<0.01
Leg Ulcer	28	0.11	7	<0.01

Table 7. Annualized Incidence Rate of SCD Complications – Safety Analysis Set

	Participants (N=260)			
	Pre-Oxbryta		Post-Oxbryta	
	Number of Events	Annualized Rate	Number of Events	Annualized Rate
Pneumonia	17	0.07	26	0.04
Priapism	4	0.02	1	<0.01
Pulmonary Hypertension	5	0.02	1	<0.01
Retinopathy	7	0.03	3	<0.01
Sickle Cell Anemia	74	0.28	35	0.05
Splenectomy	3	0.01	0	0.00
Splenic Sequestration	3	0.01	1	<0.01
Splenomegaly	5	0.02	1	<0.01
Transient Ischemic Attack	3	0.01	1	<0.01
Other	2	<0.01	48	0.07

Displayed rates represent annualized incidence rates.
Pre-Oxbryta duration was set to 365 days. Post-Oxbryta duration was calculated as the earliest of (end of treatment date + 28 days, end of study date) - date of first Oxbryta treatment + 1.
Pre-Oxbryta was data from the Pre-Oxbryta SCD Complications CRF and SCD Complication AE CRFs. Post-Oxbryta was data from the SCD Complication AE CRF. Patient-years was calculated as duration/365 days. Annualized incidence rate was calculated as the total number of SCD Complications / total patient-years.
Data Source: ADSCD
Final Database Locked: 13JAN2025
Program Source: TSCDINCR.SAS
04FEB2025:11:22:08
Source: Table 15.2.6 is for [redacted] internal use only.

Table 8. Annualized Incidence Rate of Acute Pain Crisis – Safety Analysis Set

Number of Patients	Number of Acute Pain Crisis Pre-Oxbryta	Patient-Years Pre-Oxbryta	Number of Acute Pain Crisis Pre-Oxbryta per Patient-Year	Number of Acute Pain Crisis Post-Oxbryta	Patient-Years Post-Oxbryta	Number of Acute Pain Crisis Post-Oxbryta per Patient-Year
260	1243	260.00	4.78	2258	716.13	3.15

Pre-Oxbryta duration was set to 365 days. Post-Oxbryta duration was calculated as the earliest of (end of treatment date + 28 days, end of study date) - date of first Oxbryta treatment + 1.
Number of Acute Pain Crisis Pre-Oxbryta was data from the Pre-Oxbryta SCD Complications and SCD Complication AE CRFs. Number of Acute Pain Crisis Post-Oxbryta was data from the SCD Complication AE CRF.
Patient-years was calculated as duration/365 days.
Data Source: ADPAIN
Final Database Locked: 13JAN2025
Program Source: TPAINANRT.SAS
04FEB2025:11:21:55
Source: Table 15.5.5 is for [redacted] internal use only.

10.4.1.3.2. RBC transfusions

RBC transfusions post-voxelotor were reported in 172/260 (66.2%) participants (Table 15.2.5.1).

The annualized IR of RBC transfusions was 1.83 transfusions/patient-years pre-voxelotor and 2.39 transfusions/patient-years post-voxelotor (Table 15.2.6.1).

10.4.1.4. HRQoL measures

The following HRQoL measures were collected and analyzed:

- PGIC
- CGIC

The PGIC is a single question that reflects a participant's or caregiver's belief about the effectiveness of study treatment since the start of the study. The CGIC is a brief, stand-alone assessment of the clinician's view of the patient's global functioning after initiating study treatment.

Responses from the most recent assessment before each visit window were recorded. Results for PGIC and CGIC are presented in Table 15.2.7 and Table 15.2.8, respectively.

Since Health-Related Quality of Life Measures are not commonly conducted as SOC, to allow important health-related quality of life data to be gathered in the registry, questionnaires were provided to the sites and participants; it was recommended (but not required) for the sites to perform these assessments. As such, interpretation of the results from HRQoL measures (PGIC and CGIC) are limited by small sample sizes of participants with available data.

The sample size for PGIC was N=10 to 48 (3-month and 42-month visit window, respectively). The sample size for CGIC was N=4 to 30 (3-month and 42-month visit window, respectively).

- Compared with baseline, most (approximately 93% to 100%) participants and clinicians considered patient's symptoms have not worsened while on voxelotor treatment (excluding visits with sample size ≤10 participants). CGIC scores improved in 57% to 81% of participants and PGIC scores improved in 57% to 82% of participants (excluding visits with sample size ≤10 participants).

10.4.2. Given the reporting nature of the PROMIS measures pre-specified in the protocol, the reported patient reported outcome (PRO) response was sparse; therefore, these analyses were excluded from the planned CSR analyses (see Appendix 4 SAP). Safety measures

10.4.2.1. Rate and severity of SAEs and AEs of interest

SCD-related complications (SCD complications) post-voxelotor through end of study are presented in Section 10.4.1.3.1, and treatment-emergent SCD-related SAEs and AEs by SOC/PT with severity categories are presented in Section 10.6.1.

The rate and severity of non-SCD complication treatment-emergent SAEs and AEs are presented in Section 10.6.2.

10.4.2.2. Pregnancy testing and fertility

All positive pregnancy test cases and fertility complications cases are listed in Table 15.3.4. The listing also includes events that occurred prior to initial voxelotor dose; these events are not discussed further.

- A total of 7 positive pregnancy tests and no fertility complications were reported in 6 female participants while taking voxelotor; 4 of 6 participants continued to take voxelotor until the study termination date (25 September 2024). Further details for each pregnancy case are provided below:
  - [redacted] participant who began taking voxelotor on [redacted] had a positive pregnancy test on [redacted] ([redacted] and stopped taking voxelotor on the same day. She elected to voluntarily terminate the pregnancy with termination date of [redacted].
  - [redacted] participant who began taking voxelotor on [redacted] had positive pregnancy tests on [redacted] and [redacted] and stopped taking voxelotor in [redacted] (at ~7 weeks gestation) when she found out she was pregnant with a home pregnancy test. On [redacted], the baby was delivered full-term with no complications. On an unknown date in [redacted], the infant was noted to have 2 small mid-muscular ventricular septal defects (VSDs). The VSDs spontaneously closed and did not require further evaluation. It was unknown whether the participant re-stared voxelotor prior to discontinuation from the study early on [redacted]
  - A [redacted] participant who began taking voxelotor on [redacted] had a positive pregnancy test on [redacted] [redacted] She interrupted voxelotor on [redacted] due to the pregnancy but elected to have a voluntary termination which occurred on [redacted]. Voxelotor was restarted on an unknown date, and she continued to take voxelotor until study termination.
  - A [redacted] participant who began taking voxelotor on [redacted] had a positive pregnancy test on [redacted] [redacted] and continued to take voxelotor until study termination. No information concerning the pregnancy outcome was reported.
  - A [redacted] participant who began taking voxelotor on [redacted] had a positive pregnancy test on [redacted] ([redacted]; she discontinued voxelotor on [redacted] due to the pregnancy. She had delivery of a baby by C-section on [redacted] with no other details provided. She resumed voxelotor on an unknown date and continued to take voxelotor until study termination.
  - A [redacted] participant who began taking voxelotor on [redacted] had a positive pregnancy test on [redacted] ([redacted] and

[redacted]

continued to take voxelotor until study termination. The participant elected to have a voluntary termination that occurred on an unknown date.

10.5. Other analyses

10.5.1. Post-hoc analysis of annualized IR of acute pain crisis

In order to account for potential over-dispersed count data for Acute pain crisis events, the negative binomial analysis method was used to determine the annualized IR of Acute pain crisis (Table 15.5.7).

- The estimated negative binomial annualized IR of Acute pain crisis was 4.784 events/patient-year pre-voxelotor (95% CI: 3.525-6.492) and 3.018 events/patient-year post-voxelotor (95% CI: 2.356-3.865).
- The estimated negative binomial IR ratio (post-voxelotor to pre-voxelotor) was 0.631 (95% CI: 0.460-0.865), which means a 37% reduction in the event rate for post-voxelotor compared to pre-voxelotor.

10.5.2. Subgroup analyses of annualized IR of acute pain crisis

The annualized IR of acute pain crisis is presented in Table 8.

Acute pain crisis was analyzed in the context of participants with and without chronic pain and participants with >1 g/dL and ≤1 g/dL maximum increase from baseline in Hb (baseline to highest post-voxelotor value) as outlined in the SAP; The 'Acute pain crisis' event definitions for pre-voxelotor and post-voxelotor are provided in Appendix 4 SAP Section 4.7.5.

10.5.2.1. Chronic pain

The annualized IR (per patient-year) of Acute pain crisis pre- and post-voxelotor in participants with and without chronic pain (as defined in the SAP; Appendix 4 Section 4.2.1) is presented in Table 9 and Table 10, respectively.

In 102 participants **with** chronic pain, the annualized incidence of Acute pain crisis was 7.62 events/patient-year pre-voxelotor treatment and 4.01 events/patient-year post-voxelotor treatment.

In 158 participants **without** chronic pain, the annualized incidence of Acute pain crisis was 2.95 events/patient-year pre-voxelotor treatment and 2.51 events/patient-year post-voxelotor treatment.

The annualized IR of Acute pain crises pre- and post-voxelotor was higher in participants with chronic pain compared to participants without chronic pain.

Table 9. Annualized Incidence Rate of Acute Pain Crisis – Safety Analysis Set (With Chronic Pain)

Number of Patients	Number of Acute Pain Crisis Pre-Oxbryta	Patient-Years Pre-Oxbryta	Number of Acute Pain Crisis Pre-Oxbryta per Patient-Year	Number of Acute Pain Crisis Post-Oxbryta	Patient-Years Post-Oxbryta	Number of Acute Pain Crisis Post-Oxbryta per Patient-Year
102	777	102.00	7.62	1227	305.61	4.01

Pre-Oxbryta duration was set to 365 days. Post-Oxbryta duration was calculated as the earliest of (end of treatment date + 28 days, end of study date) - date of first Oxbryta treatment + 1.
Number of Acute Pain Crisis Pre-Oxbryta was data from the Pre-Oxbryta SCD Complications and SCD Complication AE CRFs. Number of Acute Pain Crisis Post-Oxbryta was data from the SCD Complication AE CRF.
Patient-years was calculated as duration/365 days.
Data Source: ADVOC
Final Database Locked: 13JAN2025
Program Source: TVOCANRT.SAS
04FEB2025:11:22:16
Source: Table 15.5.1 is for [redacted] internal use only.

Table 10. Annualized Incidence Rate of Acute Pain Crisis – Safety Analysis Set (Without Chronic Pain)

Number of Patients	Number of Acute Pain Crisis Pre-Oxbryta	Patient-Years Pre-Oxbryta	Number of Acute Pain Crisis Pre-Oxbryta per Patient-Year	Number of Acute Pain Crisis Post-Oxbryta	Patient-Years Post-Oxbryta	Number of Acute Pain Crisis Post-Oxbryta per Patient-Year
158	466	158.00	2.95	1031	410.52	2.51

Pre-Oxbryta duration was set to 365 days. Post-Oxbryta duration was calculated as the earliest of (end of treatment date + 28 days, end of study date) - date of first Oxbryta treatment + 1.
Number of Acute Pain Crisis Pre-Oxbryta was data from the Pre-Oxbryta SCD Complications and SCD Complication AE CRFs. Number of Acute Pain Crisis Post-Oxbryta was data from the SCD Complication AE CRF.
Patient-years was calculated as duration/365 days.
Data Source: ADVOC
Final Database Locked: 13JAN2025
Program Source: TVOCANRT.SAS
04FEB2025:11:22:16
Source: Table 15.5.2 is for [redacted] internal use only.

10.5.2.2. Maximum increase from pre-voxelotor in Hb

The annualized IR (per patient-year) of Acute pain crisis pre- and post-voxelotor in participants with >1 g/dL and ≤1 g/dL maximum increase in Hb from pre-voxelotor (the most recent pre-voxelotor treatment value on or prior to initial voxelotor dose) is presented in Table 11 and Table 12, respectively.

In 182 participants **with >1 g/dL maximum increase in Hb from pre-voxelotor**, the annualized incidence of Acute pain crisis was 4.82 events/patient-year pre-voxelotor treatment and 3.47 events/patient-year post-voxelotor treatment.

In 69 participants **with ≤1 g/dL maximum increase in Hb from pre-voxelotor**, the annualized incidence of Acute pain crisis was 5.03 events/patient-year pre-voxelotor treatment and 2.45 events/patient-year post-voxelotor treatment.

[redacted]

Table 11. Annualized Incidence Rate of Acute Pain Crisis – Safety Analysis Set (with >1 g/dL maximum increase in Hb)

Number of Patients	Number of Acute Pain Crisis Pre-Oxbryta	Patient-Years Pre-Oxbryta	Number of Acute Pain Crisis Pre-Oxbryta per Patient-Year	Number of Acute Pain Crisis Post-Oxbryta	Patient-Years Post-Oxbryta	Number of Acute Pain Crisis Post-Oxbryta per Patient-Year
182	878	182.00	4.82	1846	532.75	3.47

Pre-Oxbryta duration was set to 365 days. Post-Oxbryta duration was calculated as the earliest of (end of treatment date + 28 days, end of study date) - date of first Oxbryta treatment + 1.
Number of Acute Pain Crisis Pre-Oxbryta was data from the Pre-Oxbryta SCD Complications and SCD Complication AE CRFs. Number of Acute Pain Crisis Post-Oxbryta was data from the SCD Complication AE CRF.
Patient-years was calculated as duration/365 days.
Data Source: ADVOC
Final Database Locked: 13JAN2025
Program Source: TVOCANRT.SAS
04FEB2025:11:22:16
Source: Table 15.5.3 for [redacted] internal use only.

Table 12. Annualized Incidence Rate of Acute Pain Crisis – Safety Analysis Set (with ≤1 g/dL maximum increase in Hb)

Number of Patients	Number of Acute Pain Crisis Pre-Oxbryta	Patient-Years Pre-Oxbryta	Number of Acute Pain Crisis Pre-Oxbryta per Patient-Year	Number of Acute Pain Crisis Post-Oxbryta	Patient-Years Post-Oxbryta	Number of Acute Pain Crisis Post-Oxbryta per Patient-Year
69	347	69.00	5.03	378	154.24	2.45

Pre-Oxbryta duration was set to 365 days. Post-Oxbryta duration was calculated as the earliest of (end of treatment date + 28 days, end of study date) - date of first Oxbryta treatment + 1.
Number of Acute Pain Crisis Pre-Oxbryta was data from the Pre-Oxbryta SCD Complications and SCD Complication AE CRFs. Number of Acute Pain Crisis Post-Oxbryta was data from the SCD Complication AE CRF.
Patient-years was calculated as duration/365 days.
Data Source: ADVOC
Final Database Locked: 13JAN2025
Program Source: TVOCANRT.SAS
04FEB2025:11:22:16
Source: Table 15.5.4 for [redacted] internal use only.

[redacted]

10.6. Adverse events / adverse reactions

A total of 210/260 (80.8%) participants experienced TEAEs during the study. An overview of all TEAEs by SOC and PT with severity categories is provided in Table 15.3.1.

A total of 150/260 (57.7%) participants experienced treatment-emergent SAEs. An overview of all SAEs by SOC and PT with severity categories is provided in Table 15.3.3. Note that all SAEs regardless of causality were reported during the study conducted under the original protocol (dated 3 Feb 2021) and after implementation of Protocol Amendment 1 (dated 12 Jan 2023) only treatment-related SAEs were reported (see Appendix 2.1).

A total of 6 deaths occurred in the study; the fatal cases are described in Section 10.6.4

Further details regarding AEs are separated into 2 categories:

- SCD Complication TEAEs (also referred to as SCD-related) results presented in Section 10.6.1 included, for example, Acute pain crisis, ACS, Priapism, Stroke, Chronic or End stage kidney disease, Iron overload, Leg ulcers, Cardiac malfunction, and PH.
- Non-SCD Complication TEAEs (also referred to as Other AEs), included all other TEAEs not characterized as SCD complications (results presented in Section 10.6.2).

Full results regarding TEAEs and SAEs, including severity and treatment-related TEAEs, are presented in the following tables:

Table 15.3.1 TEAEs by SOC and PT by Severity – Safety Analysis Set

Table 15.3.2 Treatment Related TEAEs by SOC and PT by Severity – Safety Analysis Set

Table 15.3.3 Treatment Emergent SAEs by SOC and PT by Severity – Safety Analysis Set

10.6.1. SCD complication TEAEs

10.6.1.1. TEAEs

A total of 203/260 (78.1%) participants experienced SCD complication TEAEs with severity levels of mild (24/260; 9.2%), moderate (86/260; 33.1%), and severe (93/260; 35.8%) (Table 15.3.1).

The most common SCD complication TEAEs by PT (>10% of participants [any severity]) were:

- Sickle cell anaemia with crisis (183/260; 70.4%) (by maximum severity: 9.2% [24/260] mild, 27.7% [72/260] moderate, and 33.5% [87/260] severe).
- Acute chest syndrome (74/260; 28.5%) (by maximum severity: 1.5% [4/260] mild, 11.9% [31/260] moderate, and 15.0% [39/260] severe).

Treatment-related SCD complication TEAEs by SOC and PT by severity are presented in Table 15.3.2 and summarized below:

- A total of 4/260 (1.5%) participants experienced treatment-related SCD-complication TEAEs that were considered related to voxelotor. The following PTs were reported for 1 participant (0.4%) each: Sickle cell anaemia with crisis (severe), Acute chest syndrome (severe), Thrombocytosis (moderate), and Headache (moderate).

10.6.1.2. SAEs

SCD complication SAEs are summarized by SOC and PT in Table 15.3.3 and listed by participant in Table 15.3.7.

SCD-complication SAEs were reported in 146/260 (56.2%) participants receiving voxelotor with maximum severity levels of mild (7/260; 2.7%), moderate (56/260; 21.5%), and severe (83/260; 31.9%).

The most common SCD-related SAEs (≥5% of participants) by PT were:

- Sickle cell anaemia with crisis (50.4%; 131/260 participants) (by maximum severity: 2.7% [7/260] mild, 18.5% [48/260] moderate, and 29.2% [76/260] severe).
- Acute chest syndrome (22.7%; 59/260 participants) (by maximum severity: 1.2% [3/260] mild, 8.1% [21/260] moderate, and 13.5% [35/260] severe).
- Pneumonia (5.0%; 13/260 participants) (by maximum severity: 0.4% [1/260] mild, 3.1% [8/260] moderate, and 1.5% [4/260] severe).

Full details for each SAE case are provided in the participant narratives presented in Section 15.3.12.

Additional details regarding SCD complications, including annualized incidence rates of SCD complications, are presented in Section 10.4.1.3.

10.6.2. Non-SCD complication TEAEs

TEAEs and SAEs that were not characterized as SCD complications were characterized as 'other' (referred to as 'non-SCD complications').

10.6.2.1. TEAEs

A total of 35.0% (91/260) of participants experienced non-SCD complication TEAEs with maximum severities of mild (31/260 participants; 11.9%), moderate (38/260 participants; 14.6%), and severe (22/260 participants; 8.5%) (Table 15.3.1 [Other AE]).

The most common non-SCD complications TEAEs (>10% of participants [any severity]) by PT were:

- Diarrhoea (18.5%; 48/260 participants) (by maximum severity: 13.1% [34/260] mild, 4.6% [12/260] moderate, and 0.8% [2/260] severe).
- Headache (15.8%; 41/260 participants) (by maximum severity: 10.8% [28/260] mild, 3.5% [9/260] moderate, and 1.5% [4/260] severe).

- Nausea (15.0%; 39/260 participants) (by maximum severity: 10.4% [27/260] mild, 3.8% [10/260] moderate, and 0.8% [2/260] severe).

- Abdominal pain (10.8%; 28/260 participants) (by maximum severity: 7.7% [20/260] mild, 2.7% [7/260] moderate, and 0.4% [1/260] severe).

Treatment-related non-SCD complication TEAEs by SOC and PT by severity are presented in Table 15.3.2 and summarized below:

- A total of 41/260 (15.8%) participants experienced treatment-related non-SCD complication TEAEs with maximum severities of mild (9.2%; 24/260 participants), moderate (4.2%; 11/260 participants), and severe (2.3%; 6/260 participants).

- The most common (>10% of participants [any severity]) non-SCD complications TEAEs by PT was Diarrhoea (11.2%; 29/260 participants) (by maximum severity: 7.3% [19/260] mild, 3.1% [8/260] moderate, and 0.8% [2/260] severe).

10.6.2.2. SAEs

Non-SCD complication SAEs are summarized in Table 15.3.3 [Other AE] and listed by participant in Table 15.3.7.

Non-SCD complication SAEs were reported in 43/260 (16.5%) participants receiving voxelotor with maximum severity levels of mild (4/260 participants; 1.5%), moderate (21/260 participants; 8.1%), and severe (18/260 participants; 6.9%).

The most common non-SCD-related SAEs (>2% of participants) by PT were:

- COVID-19 (2.3%; 6/260 participants) (by maximum severity: 0 mild, 1.9% [5/260] moderate, and 0.4% [1/260] severe).

- Pneumonia (2.3%; 6/260 participants) (by maximum severity: 0 mild, 1.9% [5/260] moderate, and 0.4% [1/260] severe).

Full details for each SAE case are provided in the participant narratives presented in Section 15.3.12.

10.6.3. AEs leading to drug administration changes and study discontinuation

A listing of all AEs for participants that discontinued the study due to AEs is provided in Table 15.3.6.

Few participants overall (N=7) had TEAEs that lead to voxelotor discontinuation.

- 6 participants had fatal events (see Section 10.6.4) that were the cause of permanent study discontinuation; none were considered related to voxelotor. Of these participants, 2 experienced prior TEAEs that led to study drug administration changes:

    - 1 participant experienced PT Sickle cell anaemia with crisis that led to voxelotor interruption; the TEAE was considered moderate in severity, not related to voxelotor, and resolved with sequelae.

[redacted]

  - 1 participant experienced PT Abdominal pain upper that led to dose reduction; the TEAE was considered moderate in severity, related to voxelotor, and resolved.

- 1 participant permanently discontinued voxelotor and the study in January 2024 due to PT Diarrhoea (AE onset date 29 May 2023; treatment day 636); the TEAE was considered mild, related to voxelotor, and recovered.

10.6.4. Deaths

A total of 6 deaths were reported; none of the deaths were considered related to voxelotor. A by participant listing of each death is provided in Table 15.3.5 and summarized below:

Three (3) participants were taking voxelotor at the onset of the fatal event:

- A [redacted] participant experienced a fatal event of Cardiac arrest while taking voxelotor (AE onset date: [redacted]; treatment day 1154); the event was considered not related to voxelotor. Voxelotor was permanently discontinued on [redacted]. The participant died on [redacted] and the cause of death was cardiac arrest. The participant had been hospitalized twice for VOC, pulmonary hypertension, ACS, pneumonia and experienced renal failure while outside of the hospital.

- A [redacted] participant experienced a fatal event of Sudden death (cause of death was unknown) on [redacted] (treatment day 1303); the last dose of voxelotor was on the same date. The event was considered not related to voxelotor. The participant went to work on the day prior and died during sleep.

- A [redacted] participant experienced a fatal event of Haemolytic anaemia while taking voxelotor on [redacted] (treatment day 1562) and died on [redacted]. The event was considered not related to voxelotor. The participant's last site encounter was 39 days prior to date of death.

Three (3) participants had a date of last dose of voxelotor 5 months to 2 years prior to date of death:

- A [redacted] participant who took their last dose of voxelotor on [redacted] experienced a fatal event of Death (cause of death was unknown) on [redacted] the event was considered not related to voxelotor. The participant had a history of CHF.

- A [redacted] participant who took their last dose of voxelotor on [redacted] was hospitalized for ACS and Pulmonary hypertension beginning on [redacted]. The participant died on [redacted] and the cause of death was acute hypoxic respiratory failure. The event was considered not related to voxelotor.

- A [redacted] participant who took their last dose of voxelotor on [redacted] experienced a fatal event of Death (cause of death was unknown) on [redacted] the event was considered not related to voxelotor. The participant had a history of stage 4 CKD, CHF, and cardiomyopathy.

Full details for each fatal case are provided in the participant narratives presented in Section 15.3.12.

[redacted]

10.6.5. Safety events after abrupt termination

AEs with onset dates after study termination (25 September 2024) were not recorded in the EDC database and were reported only to the [redacted] Safety Database. A search of the [redacted] Safety Database was conducted to identify all AEs with date of onset on or after 25 September 2024 for this study as of 09 January 2025. The search results are discussed below.

- 217 participants were on treatment as of 25 September 2024 (Table 2)
- As of 09 Jan 2025, no non-serious AEs and 5 SAEs with onset dates after 25 Sep 2024 were reported to the [redacted] Safety Database for 3 participants. Only 2 of the cases were possibly relevant to the abrupt termination of Oxbryta by the MAH:
  - One [redacted] participant was advised on 26 Sep 2024 to decrease their Oxbryta dose by one pill every 2 days (was receiving 3 X 100 mg tablets daily) until they were off drug. On [redacted] they were hospitalized for an SAE of Sickle cell anemia with crisis and received treatment with IV fluids, IV pain medications, and close cardiorespiratory monitoring. As of [redacted] (last contact date), the event was not resolved. The SAE was considered related to voxelotor by the investigator (related due to discontinuation per product recall) and possibly related by the MAH due to the temporal/chronological association with drug administration.
  - One [redacted] participant stopped treatment with Oxbryta on 13 October 2023 and was hospitalized for SAEs of Palpitations and Dyspnoea that started on 16 October 2024, approximately 1 year after the last dose of Oxbryta. Both SAEs were considered unrelated to voxelotor by the investigator and MAH and both events were resolved on 18 Oct 2024.
  - One [redacted] participant stopped treatment with Oxbryta sometime between [redacted] t to [redacted] (participant did not remember exactly) and was hospitalized for SAEs of Pain (described as “Pain crisis”) and Anaemia on [redacted]. Both events were considered recovered on [redacted].
    - the SAE of Pain (patient complained of total body aches) was considered related to voxelotor by the investigator and unrelated by the MAH.
    - the SAE of Anaemia (considered acute and likely hemolytic in nature given direct hyperbilirubinemia) was considered unrelated to voxelotor by both the investigator and the MAH.

10.6.6. Safety narratives

Narratives for participants who experienced death, SAEs, TEAEs leading to treatment discontinuation, and TEAEs leading to study discontinuation are provided in Section 15.3.12.

11. DISCUSSION

11.1. Key results

The mean (SD) duration of voxelotor treatment was 143.18 (65.588) weeks; most participants were on voxelotor for ≥12 months with 22.7% (59/260) of participants having received voxelotor for ≥48 months.

Clinical Laboratory Outcomes

Participants had increased Hb levels and decreased hemolytic markers following treatment with voxelotor.

- The mean (SD) Hb change from baseline at 3-months through 4 years post-voxelotor treatment period ranged between 0.4 (1.48) to 0.7 (1.47) g/dL (for time points with available data for at least 50 participants). The mean (SD) of the maximum change in Hb from baseline (pre-voxelotor) was 2.0 g/dL (1.62) (from 7.8 g/dL [SD 1.36] to 9.8 g/dL [SD 1.81]).

- The mean (SD) of the minimum change in observed reticulocyte count (%) and indirect bilirubin from baseline was -5.5% (5.88) and -0.7 mg/dL (2.26), respectively.

SCD Complication Clinical Events

Note that since VOC is a broad term and was not defined as a specific CRF term in the final protocol, VOCs were captured as 'acute pain crisis' on the CRF (Appendix 5).

- SCD complications were reported in 205/260 (78.8%) participants. The most common (≥6% participants) SCD complications were Acute pain crisis (71.9%; 187/260 participants), ACS (28.8%; 75/260 participants), Pneumonia (7.7%, 20/260 participants), and Avascular necrosis (6.2%; 16/260 participants).

The annualized IR of SCD complications was 6.25 events/patient-year pre-voxelotor and 3.60 events/patient-year post-voxelotor.

SCD Complication: Acute Pain Crisis

The annualized IR of Acute pain crisis was 4.78 events/patient-year pre-voxelotor and 3.15 events/patient-year post-voxelotor.

- In both participants with chronic pain (N=102) and without chronic pain (N=158), the annualized IR of Acute pain crisis was lower post-voxelotor (participants with chronic pain: 4.01 events/patient-year; participants without chronic pain: 2.51 events/patient) than pre-voxelotor (participants with chronic pain: 7.62 events/patient-year; participants without chronic pain: 2.95 events/patient). The annualized IR of Acute pain crises pre- and post-voxelotor was higher in participants with chronic pain compared to participants without chronic pain.

- In both participants with >1 g/dL maximum increase in Hb (N=182) and ≤1 g/dL maximum increase in Hb (N=69) from pre-voxelotor, the annualized IR of Acute pain crisis was lower post-voxelotor (participants with >1 g/dL in Hb: 3.47 events/patient-year;

participants with ≤1 g/dL in Hb: 2.45 events/patient-year) than pre-voxelotor (participants with >1 g/dL in Hb: 4.82 events/patient-year; participants with ≤1 g/dL in Hb: 5.03 events/patient-year).

Treatment-Emergent Adverse Events (TEAEs) and Serious Adverse Events (SAEs)

SCD Complications

A total of 203/260 (78.1%) participants experienced SCD complication TEAEs with severity levels of mild (24/260; 9.2%), moderate (86/260; 33.1%) and severe (93/260; 35.8%). The most common (>10% of participants) SCD complications TEAEs were Sickle cell anaemia with crisis (183/260; 70.4%) and ACS (74/260; 28.5%).

SCD-complication SAEs were reported in 146/260 (56.2%) participants receiving voxelotor; the most common SCD-related SAEs (≥5% of participants) were: Sickle cell anaemia with crisis (50.4%; 131/260 participants), ACS (22.7%; 59/260 participants), and Pneumonia (5.0%; 13/260 participants).

Non-SCD Complications

A total of 35.0% (91/260) of participants experienced non-SCD complication TEAEs with maximum severities of mild (31/260 participants; 11.9%), moderate (38/260 participants; 14.6%), and severe (22/260 participants; 8.5%) The most common non-SCD complication TEAEs (>10% of participants) were: Diarrhoea (18.5%; 48/260 participants), Headache (15.8%; 41/260 participants), Nausea (15.0%; 39/260 participants), and Abdominal pain (10.8%; 28/260 participants).

Non-SCD complication SAEs were reported in 43/260 (16.5%) participants receiving voxelotor; the most common non-SCD-related SAEs (>2% of participants) were COVID-19 and Pneumonia (each 2.3%; 6/260 participants).

Deaths

A total of 6 deaths were reported and occurred in participants between the ages of [redacted] None of the deaths were considered related to voxelotor. Three (3) participants were taking voxelotor at the onset of the fatal event. Causes of death for 2 of the 3 participants on voxelotor at the time of the fatal event included Cardiac arrest and Haemolytic anaemia (separately); the cause of death was unknown for the third participant. The other [redacted] participants reported a date of last dose of voxelotor 5 months to 2 years prior to the onset of the fatal event; the cause of death for one participant was acute hypoxic respiratory failure (PTs: ACS and PH) and unknown for 2 participants.

11.2. Limitations

Limitations inherent in observational studies include reliance on data from medical records, limited monitoring and quality control for data collection, variation in patient population, and differences among study sites in SOC, as well as susceptibility to multiple sources of bias for comparing outcomes. As there are no scheduled visits, the number of participants with data available for analysis at each point varies.

Several limitations of this study need to be considered when interpreting the results:

- The study was not designed to assess VOCs as a primary or secondary endpoint, which is defined as "acute pain crisis" in this study. There was no eligibility requirement for a minimum or maximum number of VOC episodes during the pre-voxelotor period. The VOC events were collected as patient-reported data and were entered by site staff into the EDC system based on what had been reported in the participants' medical records. Events that occurred in other settings (eg, home, hospital, other SCD clinics, emergency room) may not have been recorded in the medical record and, therefore, not captured in the study database. Additionally, most events were source verified, but none were adjudicated. Exacerbated chronic pain episodes or acute pain crisis events that lasted for several days could have been counted as distinctive VOC events.

- Following the initiation of voxelotor treatment, participants were followed prospectively and may have been followed more closely by healthcare providers, which could have resulted in more reported events, including VOCs, than the pre-voxelotor period.

- For observational studies, investigators provide standard care, and there is no close monitoring of the participants' drug compliance or changes in medications. Therefore, variability in compliance with voxelotor or change in other SCD-disease modifying medications such as hydroxyurea are potential confounders of the observed results.

- The laboratory values collected from participants' medical records may include those collected during acute visits (eg, emergency room, hospitalization, infusion center) or right after complications, which could have confounded the pre- and post-voxelotor values. Furthermore, as labs were only obtained as part of SOC and not following a schedule of assessments, some participants' data may not be included at each 3- or 6-month follow-up period.

11.3. Interpretation

Study C5341019 (PROSPECT/GBT440-4R2) (Andemariam et al, 2023) was a prospective, open-label, multi-center, registry study that collected data from the participants' medical records. Any participant who was taking voxelotor or had been prescribed and initiated treatment with voxelotor within 6 months of consenting to participate, was eligible. Eligible participants were prescribed voxelotor and treated and evaluated per SOC at the physician's discretion. When interpreting the results of this study, the inherent limitations as outlined in Section 11.2 need to be considered.

The PROSPECT study demonstrated increases in hemoglobin and improvements in hemolysis markers with voxelotor treatment in clinical practice.

Considering the limitations regarding VOC described above, the annualized IR of Acute pain crisis for all participants was lower following treatment with voxelotor than prior to voxelotor initiation. A stratified analysis by chronic pain status also showed lower rates of acute pain crises post-voxelotor treatment in those with and without chronic pain. A higher annualized IR of Acute pain crisis in both the pre- and post-voxelotor treatment period was found in participants with chronic pain compared to participants without chronic pain. The chronic pain subgroup was based on a broad set of criteria to encompass all possible chronic pain participants ensuring that those identified as not having chronic pain were accurately

classified. Since there is no adjudication of pain events, exacerbated chronic pain could be entered as acute pain crisis on the participant's medical record. Therefore, the acute pain crisis results for the chronic pain subgroup is difficult to interpret.

The most common SCD Complication TEAE was Sickle cell anaemia with crisis, in which 70.4% of participants experienced at least one acute pain crisis while on voxelotor. Similar to the annualized IR of acute pain crisis, this result is not unexpected in this real-world population.

None of the 6 deaths were considered related to voxelotor (refer to Section 10.6.4 for details).

11.4. Generalizability

Study C5341019 (PROSPECT) was a voluntary PASS conducted in the United States. The collected data represents human review of unstructured data from participant's medical records from routine clinical practice and survey of participants to assess HRQoL at sites in the US. Per the study design, participants had to have a documented diagnosis of SCD (any genotype), and currently taking or had to have been prescribed and would have initiated treatment with voxelotor.

To ensure a real-life setting, patient therapy was not decided by the study protocol but by current clinical practice, and a clinical decision was made to prescribe voxelotor for the treatment of SCD prior to enrollment. Voxelotor was used (dose, frequency) per the approved prescribing information at the treating physician's discretion. There were no restrictions regarding demographic characteristics or other known systematic factors that could affect the external validity of the results, where applied. The findings of this study are generalizable to US patients who are taking or will initiate treatment with voxelotor. However, findings from this analysis may not be generalizable to the SCD population in regions outside of the US because clinical practice, healthcare access, and the patient population may be different.

12. OTHER INFORMATION

Not applicable.

13. CONCLUSIONS

The PROSPECT study provides an insight to treatment patterns and clinical outcomes in SCD patients treated with voxelotor in a real-world setting. The dataset adds to evidence on the real-world impact of voxelotor treatment. The results indicate treatment with voxelotor increases Hb levels and decreases markers of hemolysis in clinical practice. The observed annualized incidence rate of acute pain crisis was 4.78 events/patient-year pre-voxelotor and 3.15 events/patient-year post-voxelotor. There was no evidence of voxelotor treatment leading to an increase of acute pain crisis frequency. Among the 260 participants who received voxelotor, 78.1% experienced SCD complication adverse events, primarily Sickle cell anaemia with crisis and ACS, while 35.0% reported non-SCD complication adverse events that were mostly mild or moderate in severity. Six deaths occurred, and none were related to voxelotor. The limitations of this real-world evidence study need to be considered when interpreting the findings, which may not be generalizable to the broader SCD population in regions outside of the US.

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15. LIST OF SOURCE TABLES AND FIGURES

15.1. Demographic data tables referred to but not included in the text

Table 15.1.3 Medical History – Full Analysis Set

Table 15.1.5 Study Drug Administration and Dosage Changes Initiated by the Physician - Safety Analysis Set

15.2. Endpoint data tables referred to but not included in the text

Table 15.2.1 Change in Hematologic Laboratory -Hb, ALT, AST Tests by Visit - Full Analysis Set

Table 15.2.2 Change in Hematologic Laboratory -Hemolysis Measures by Visit - Full Analysis Set

Table 15.2.3 Change in Chemistry Laboratory - Chemistry Measures by Visit - Full Analysis Set

Table 15.2.4 Change in Renal Function Laboratory Tests by Visit - Full Analysis Set

Table 15.2.4.1 Renal Function Laboratory Tests (Hemoglobinuria and eGFR) by Visit – Full Analysis Set

Table 15.2.5.1 Summary of Transfusions – Safety Analysis Set

Table 15.2.6.1 Annualized Incidence Rate of Transfusions - Safety Analysis Set

Table 15.2.7 Summary of Patient Global Impression of Change (PGIC) – Full Analysis Set

Table 15.2.8 Summary of Clinical Global Impression of Change (CGIC) – Full Analysis Set

Table 15.5.7 Negative Binomial Analysis of Pre-Oxbryta vs Post-Oxbryta Acute Pain Crisis Events – Safety Analysis Set

15.3. Safety data referred to but not included in the text

Table 15.3.1 Treatment Emergent Adverse Events by System Organ Class and Preferred Term by Severity - Safety Analysis Set

Table 15.3.2 Treatment Related Treatment Emergent Adverse Events by System Organ Class and Preferred Term by Severity- Safety Analysis Set

Table 15.3.3 Treatment Emergent Serious Adverse Events by System Organ Class and Preferred Term by Severity – Safety Analysis Set

Table 15.3.4 Pregnancy Outcomes and Fertility listings - Safety Analysis Set

Table 15.3.5 Individual Listings of Deaths- Safety Analysis Set

Table 15.3.6 Listing of All Adverse Events for Subjects that Discontinued Study Due to AE- Safety Analysis Set

Table 15.3.7 Individual Listing of SAEs - Safety Analysis Set

There are no sections numbered 15.3.1 through 15.3.11.

15.3.12. Safety narratives

C5341019 (GBT440-4R2) Safety Narratives

15.4. Medication data tables referred to but not included in the text

Table 15.4 Concomitant Medication - Full Analysis Set

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