NONINTERVENTIONAL (NI) STUDY PROTOCOL

Study Information

Title	An Open Label, Observational, Prospective Registry of Participants With Sickle Cell Disease (SCD) Treated With Oxbryta® (Voxelotor)® (Voxelotor)
Protocol number	C5341019/GBT
Protocol version identifier	1.0
Date	10 October 2023
Eu Post Authorization Study (PAS) register number	TBD
Active substance	Oxbryta® (Voxelotor)®
Medicinal product	Oxbryta® (Voxelotor)® (voxelotor) tablets for oral use Oxbryta® (Voxelotor)® (voxelotor) tablets for oral suspension
Research question and objectives	The primary objective is 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 • Health-related quality of life (HRQoL), as assessed by participants, parents/caregivers, and clinicians • Assess the safety and tolerability of Oxbryta® (Voxelotor)®
Author	PPD MD PPD Pfizer, Inc. Telephone: PPD Email: PPD

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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
ACA	anterior cerebral artery
ACR	albumin/creatinine ratio
ACS	acute chest syndrome
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
CGIC	Clinical Global Impression of Change
CRO	Clinical Research Organization
CRF	case report form
CFR	Code of Federal Regulation
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
eCRF	electronic case report form
ED	emergency department
EDC	electronic data capture
eGFR	estimated glomerular filtration rat
HER	electronic health records
ESA	erythropoietin-stimulating agent
FDA	(US) Food and Drug Administration
GCP	Good Clinical Practice
Hb	hemoglobin

Abbreviation	Definition
HbF	fetal hemoglobin
HbS	sickle hemoglobin
HRQoL	health-related quality of life
ICA	internal carotid artery
ICF	Informed consent form
ICH	International Conference on Harmonization
ICU	intensive care unit
IID	Inactive Ingredient Database
IRB	Institutional Review Board
LDH	lactate dehydrogenase
MCA	middle cerebral artery
MCV	mean corpuscular volume
MCHC	mean corpuscular hemoglobin concentration
MedDRA	Medical Dictionary for regulatory Activities
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NPRS	Numerical Pain Rating Scale
NSAID	nonsteroidal anti-inflammatory drug
PI	Principal Investigator
PGIC	Patient Global Impression of Change
PH	pulmonary hypertension
PQC	Product Quality Complaint

Abbreviation	Definition
PROMIS	Patient-Reported Outcomes Measurement Information System
QoL	quality of life
RBC	red blood cell
SAE	serious adverse event
SCD	sickle cell disease
SOA	schedule of activities
SOC	standard of care
SpO2	pulse oximetry
SUSAR	serious unexpected adverse reaction
TAMMV	time-averaged maximum mean velocity
TIA	transient ischemic attack
T2*MRI	T2-weighted magnetic resonance imaging
TCD	transcranial doppler
TIBC	total iron binding capacity
US	United States
USPI	United States Prescribing Information
VOC	vaso-occlusive crisis
WBC	white blood cell

3. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

Name, Degree(s)	Job Title	Affiliation	Address
David Purdie, PhD	Senior Director, Rare Disease	Pfizer, Inc.	San Francisco, CA
Michelle Xu, MD	Medical Science Director	Pfizer, Inc.	San Francisco, CA

4. ABSTRACT

Study Number	GBT440-4R2
Study Title	An Open Label, Observational, Prospective Registry of Participants With Sickle Cell Disease (SCD) Treated With Oxbryta® (Voxelotor)® (Voxelotor)
Short Title	Oxbryta® (Voxelotor) Product Registry
Sponsor	Pfizer, Inc. New York, NY United States
Study Description	This registry is an observational study designed to evaluate the effect of Oxbryta® (Voxelotor) in individuals with SCD. This registry is intended to benefit and support interests of participants, clinicians, regulatory bodies, payers, and industry by obtaining longitudinal data on Oxbryta® (Voxelotor).
Number of Study Sites	The study will be conducted at approximately 35 sites in the US
Number of Participants	Approximately 500 eligible participants will be enrolled in this study
Treatment	This registry is an observational study to evaluate the effects of Oxbryta® (Voxelotor) in individuals with SCD. Participants will receive treatment with Oxbryta® (Voxelotor) as prescribed by their physician, as part of their usual care. Participants will be treated and evaluated per standard of care (SOC) and at the physician's discretion. There are no pre-defined treatment requirements.
Objectives	**Primary** The primary objective is to gather long term data on Oxbryta® (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 • Health-related quality of life (HRQoL), as assessed by participants, parents/caregivers, and clinicians • Safety and tolerability of Oxbryta® (Voxelotor)

Outcome Measures	**Effectiveness**
	• Change from pre-Oxbryta® (Voxelotor) treatment period in the following hematologic parameters corresponding to treatment with Oxbryta® (Voxelotor):
	  • Hemoglobin (Hb)
	  • Hemolysis measures, including % reticulocytes, absolute reticulocytes, bilirubin (total, direct, and indirect)
	• Measures of iron overload, including ferritin, iron, total iron binding capacity (TIBC), T2-weighted magnetic resonance imaging (T2*MRI)
	• Change from pre-Oxbryta® (Voxelotor) treatment period in renal function, as measured by the following:
	  • Creatinine (Serum)
	  • Albuminuria (urine albumin/creatinine ratio [ACR])
	  • Hemoglobinuria (urine dipstick positive for blood +1 or greater and ≤ 2 RBC by high power field)
	  • Serum cystatin C
	  • Estimated glomerular filtration rat (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, erythropoiesis-stimulating agents [ESAs], nonsteroidal anti-inflammatory drugs [NSAIDs], folic acid, and penicillin)
	• Change from pre-Oxbryta® (Voxelotor) treatment period in healthcare resource utilization: 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 intensive care unit [ICU], if applicable), acute and chronic RBC transfusions, home oxygen supplementation, and renal dialysis
	
	• Change from pre-Oxbryta® (Voxelotor) treatment period in the following HRQoL measures:
	
	  • Patient-Reported Outcomes Measurement Information System (PROMIS Pediatric-37 v2.0-Profile; Parent Proxy v2.0 Profile-37 and 49 v2.1 Profile)
	
	  • Patient Global Impression of Change (PGIC)
	
	  • Clinical Global Impression of Change (CGIC)
	
	  • Other measures: Acute pain intensity as measured by Numerical Pain Rating Scale (NPRS) and any objective measure of exercise tolerance
	
	Safety
	• Rate and severity of serious adverse events (SAEs) and adverse events (AEs) of interest
	
	• Rate of AEs leading to dose modification or discontinuation of Oxbryta® (Voxelotor)
	
	• Pregnancy outcomes and fertility

Study Design	Any participant who is currently taking Oxbryta® (Voxelotor) or has been prescribed and will initiate treatment with Oxbryta® (Voxelotor), is eligible to participate. Eligible participants will receive treatment with Oxbryta® (Voxelotor) as prescribed by their physician, as part of their usual care. Participants will be treated and evaluated per SOC and at the physician's discretion. Participants will be introduced to the study by their health care team and will sign the informed consent form (ICF) or assent prior to any data collection for the study. This study will collect data that are recorded in the participants' medical records and other secondary data sources such as Insurance and Pharmacy Claims. Study data will be collected at regular intervals and entered in case report forms (CRFs) via an electronic data capture (EDC) system by the study staff. Participants will be followed for up to 5 years after their first dose of Oxbryta® (Voxelotor) treatment, or until they withdraw their consent to

	participate, or are discontinued from the study. Treatment, including interruptions and restarting treatment, will continue at the discretion of the treating physician, and there are no pre-defined treatment requirements. Participants may receive any additional medications prescribed by their treating physician or have any medical interventions that are deemed appropriate by the treating physician or study doctor. The participant or treating physician may discontinue Oxbryta® (Voxelotor) at any time. Participants who discontinue treatment with Oxbryta® (Voxelotor) earlier than 5 years will continue to be followed on study to collect clinical and health-related quality of life (HRQoL) outcomes for up to 5 years after their first dose of Oxbryta® (Voxelotor) treatment. Participant safety and tolerability will be assessed throughout the study data collection period by the study doctor and reported to the Sponsor.
Duration of Study Participation	The approximate duration of study participation for an individual participant includes an observation period of up to 5 years after the first dose of Oxbryta® (Voxelotor) treatment.
End of Study	The end of study is defined as the date of the last data collection timepoint of the last participant being followed.
Study Population	**Inclusion Criteria:** Participants who meet all the following criteria will be eligible for enrollment: 1. Willing and able to provide written informed consent (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 Institutional Review Board (IRB) policy and requirements, consistent with ICH guidelines 2. Male or female participants with documented diagnosis of sickle cell disease (all genotypes) 3. Undergoing treatment with Oxbryta® (Voxelotor) according to the Oxbryta® (Voxelotor) USPI **Exclusion Criteria:** Participants meeting any of the following criteria will not be eligible for study enrollment: 1. Current participation in an investigational clinical trial or expanded access program, in which the participant may be receiving voxelotor treatment 2. Medical, psychological, or behavioral condition that, in the opinion of the study doctor, would confound or interfere with evaluation of safety and/or effectiveness of the study drug, prevent compliance with the study protocol; preclude informed consent; or render the

	participant unable/unlikely to comply with the study procedures
Statistical Methods	**Analysis Population** Effectiveness and safety analyses will primarily be based on the treated population, defined as all participants receiving at least one dose of Oxbryta® (Voxelotor). **Sample Size** The sample size is selected to provide an estimation of the relationship between change in Hb and significant clinical events, for example VOCs, stroke, TIA, and PH that participants experience over the 5 years of the study. The total sample size of approximately 750 participants is expected to be enrolled in the study. **Effectiveness Analyses** Change from pre-Oxbryta® (Voxelotor) treatment period in Hb, hemolysis measures, measures of iron overload, and renal function over time will be summarized descriptively. Annualized rate of significant SCD-related clinical events, for example VOC, ACS, priapism, stroke, TIA, chronic or end stage kidney disease, iron overload, leg ulcers, cardiac malfunction, PH, and RBC transfusions will be calculated. The association between change in Hb and hemolysis marker and rates of SCD-related clinical events will be evaluated. Rates of outpatient visits (including infusion center, acute care, or telemedicine visit), ED visits, hospitalizations, acute and chronic RBC transfusions, home oxygen supplementation, and renal dialysis will be summarized with a similar approach as rate of SCD-related clinical events. The total cost associated with clinical interventions will be summarized descriptively. HRQoL measures over time will be summarized descriptively. Proportion of participants with improved HRQoL measures will be calculated and the associated 95% Clopper -Pearson Exact confidence intervals will be constructed as appropriate. As appropriate, rates of SCD-related clinical events, healthcare resource utilization, total cost associated with clinical interventions (if available) and HRQoL while on Oxbryta® (Voxelotor) treatment will be compared with the corresponding measures in the 12 months prior to the first dose of Oxbryta® (Voxelotor) treatment. Similar comparisons may be performed between the subgroup of participants who discontinue Oxbryta® (Voxelotor) treatment but remain in the study and those participants who remain on Oxbryta® (Voxelotor). **Safety Analysis** SAEs and protocol-specified AEs will be classified according to Medical Dictionary for Regulatory Activities (MedDRA). The total number with percentage and severity of AEs will be tabulated by system organ class and

	preferred term and by relationship to Oxbryta® (Voxelotor) treatment.

5. AMENDMENTS AND UPDATES

None.

6. MILESTONES

Milestone	Planned Date
Start of data collection	02 February 2022
End of data collection	31 January 2030
Final study report	30 April 2030

7. RATIONALE AND BACKGROUND

This noninterventional study is designated as a PASS and is conducted voluntarily by Pfizer.

7.1. Introduction

7.1.1. Disease Background

Sickle cell disease (SCD) is an inherited blood disorder caused by a point mutation in the β globin gene resulting in the formation of sickle hemoglobin (HbS), which polymerizes in the deoxygenated state and leads to red blood cell (RBC) sickling. The disease is marked by the pathophysiologic features of hemolytic anemia, vaso-occlusion, and progressive end-organ damage, with a clinical course characterized by life-long disability and early death.[2,4] 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.[3] With improved survival in children, the natural history of SCD has shifted from a disease of childhood to a chronic, debilitating disease of young and middle-aged adults. Cumulative injury to multiple organ systems from repeated episodes of RBC sickling, vaso-occlusion, and chronic hemolytic anemia exert a high clinical burden in the aging adult, significantly impacting quality of life (QoL) and overall functioning.[7]

7.1.2. Oxbryta® (Voxelotor)® (Voxelotor)

Voxelotor (previously GBT440) is an HbS polymerization inhibitor that binds to HbS with a 1:1 stoichiometry and exhibits preferential partitioning to RBCs. Voxelotor binds covalently and reversibly to the N-terminal valine of one of the α chain of hemoglobin (Hb) and allosterically increases HbS-oxygen (O_2) affinity,[1] stabilizing the oxyhemoglobin state and inhibiting polymerization.[5] The voxelotor binding site,[3] is distant from heme pockets and it can therefore increase O_2 affinity without sterically blocking the release of O_2.

In November 2019, Oxbryta® (Voxelotor)® was approved in the US by the Food and Drug Administration (FDA) for the treatment of SCD in adults and pediatric patients 12 years of age and older. This indication was approved under accelerated approval based on increase in Hb. In December 2021, the indication was expanded to include pediatric participants 4 years of age and older. This indication was an extension of the accelerated approval of Oxbryta® (Voxelotor) based on increase in Hb. In addition, a new dosage form was also approved for this patient population. Voxelotor continues to be evaluated in ongoing clinical studies/expanded access programs exploring the safety, tolerability, pharmacokinetics, pharmacodynamics, and treatment response in pediatric and adult participants with SCD as well as in clinical pharmacology studies in healthy adult patients.

Information regarding nonclinical studies, clinical studies, and safety is available in the Oxbryta® (Voxelotor) US prescribing information (Oxbryta® (Voxelotor)® USPI).[6]

8. RESEARCH QUESTION AND OBJECTIVES

8.1. Objectives and Endpoints

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

8.1.1. Objectives

8.1.1.1. Primary Objective

The primary objective is 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
- Health-related quality of life (HRQoL), as assessed by participants, parents/caregivers, and clinicians
- Assess the safety and tolerability of Oxbryta® (Voxelotor) Oxbryta® (Voxelotor)Outcome Measures

8.1.1.2. Effectiveness Endpoint Measures

- Change from pre-Oxbryta® (Voxelotor) treatment period in the following hematologic parameters corresponding to treatment with Oxbryta® (Voxelotor):
  - Hb
  - Hemolysis measures, including % reticulocytes, absolute reticulocytes, bilirubin (total, direct, and indirect)
  - Measures of iron overload, including ferritin, iron, total iron binding capacity (TIBC), T2-weighted magnetic resonance imaging (T2*MRI)
- Change from pre-Oxbryta® (Voxelotor) treatment period in renal function, as measured by the following:
  - Creatinine (Serum)
  - Albuminuria (urine albumin/creatinine ratio [ACR])
  - Hemoglobinuria (urine dipstick positive for blood +1 or greater and ≤2 RBC by high power field)

- Serum cystatin C
- Estimated glomerular filtration rat (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, chronic or end stage kidney disease iron overload, leg ulcers, cardiac malfunction, and pulmonary hypertension (PH)
  - Treatment initiation or modification of SCD-related medications (eg, hydroxyurea, crizanlizumab, L-glutamine, opioids [in daily morphine equivalents], iron chelating agents, erythropoiesis-stimulating agents [ESAs], nonsteroidal anti-inflammatory drugs [NSAIDs], folic acid, and penicillin)
  - Change from pre-Oxbryta® (Voxelotor) treatment period in healthcare resource utilization: rate of outpatient visits (including infusion center, acute care, or telemedicine visit), emergency department (ED) visits, hospitalizations (including total length of stay and time in intensive care unit [ICU], if applicable), acute and chronic RBC transfusions, home oxygen supplementation, and renal dialysis
- Change from pre-Oxbryta® (Voxelotor) treatment period in the following HRQoL measures:
  - Patient-Reported Outcomes Measurement Information System (PROMIS)
  - Patient Global Impression of Change (PGIC)
  - Clinical Global Impression of Change (CGIC)
  - Other measures: Acute pain intensity as measured by Numerical Pain Rating Scale (NPRS) and any objective measure of exercise tolerance

8.1.1.3. Safety Endpoint Measures

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

9. RESEARCH METHODS

9.1. Study Design

9.1.1. Study Plan

9.1.1.1. Overall Study Design

This registry is an observational study designed to evaluate the effect of Oxbryta® (Voxelotor) in individuals with SCD. This registry is intended to benefit and support interests of participants, clinicians, regulatory bodies, payers, and industry by obtaining longitudinal data on Oxbryta® (Voxelotor). Approximately 500 SCD participants who are prescribed and treated with Oxbryta® (Voxelotor) will be enrolled. The study will be conducted at approximately 45 sites in the US.

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

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

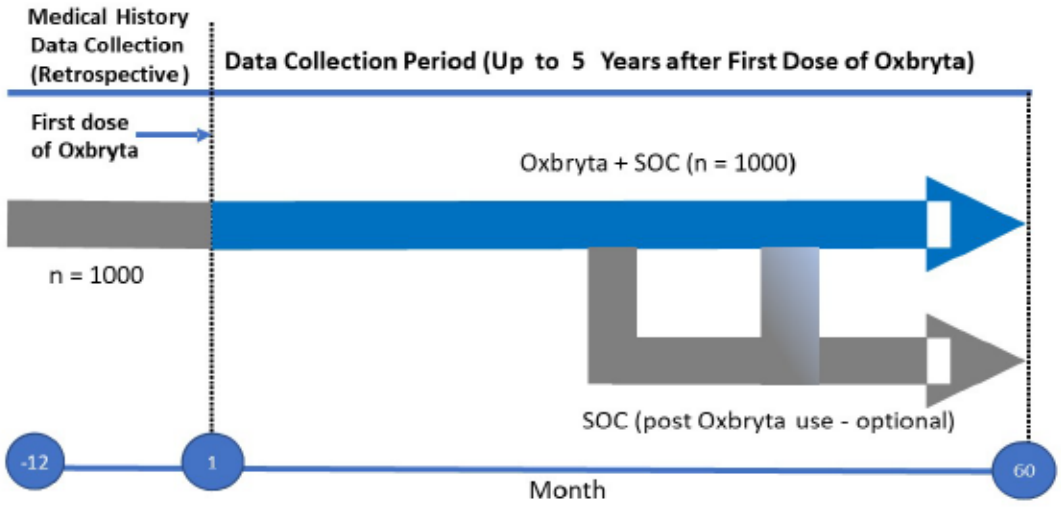
This study will collect data that are recorded in the participants' medical records and other secondary data sources such as Insurance and Pharmacy Claims. Study data will be collected at regular intervals and entered in case report forms (CRFs) via an electronic data capture (EDC) system by the study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

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

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

The overall study design is illustrated in Figure 1.

Figure 1: Study Schema



SOC, standard of care.

9.2. Setting

9.2.1. Duration of Study Participation

The approximate duration of study participation for an individual participant includes an observation period of up to 5 years after the first dose of Oxbryta® (Voxelotor) treatment.

9.2.1.1. End of Study

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

9.3. Study Population

All participants at each participating study site who have been treated with Oxbryta® (Voxelotor) will be considered for inclusion in this study.

9.3.1. Inclusion Criteria

Evidence of a personally signed and dated informed consent document indicating that the patient (or a legally acceptable representative) has been informed of all pertinent aspects of the study.

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

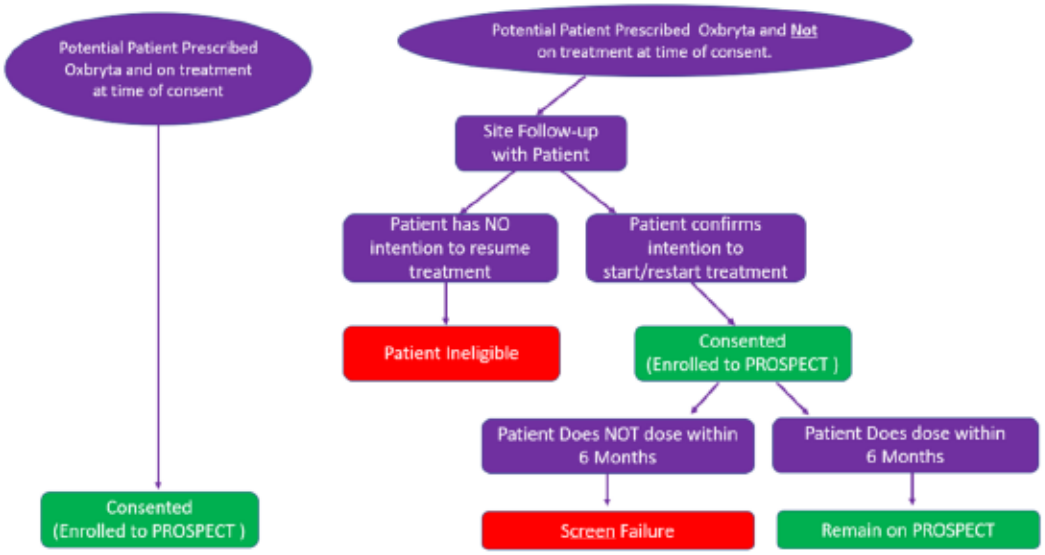
1. Willing and able to provide written informed consent (aged ≥ 18 years), parental/guardian consent and participant assent (aged ≥12 to <18 years) per local regulations, or pediatric participants (aged 4 to <12 years) with parental/guardian consent per Institutional Review Board (IRB) policy and requirements,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

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

3. Participants who are currently taking Oxbryta® (Voxelotor) or have been prescribed and will initiate treatment with Oxbryta® (Voxelotor) according to the Oxbryta® (Voxelotor) USPI

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

Figure 2. Enrollment Process Flow



9.3.2. Exclusion Criteria

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

1. Current participation in an investigational clinical trial or expanded access program, in which the participant may be receiving Oxbryta® (Voxelotor).

2. Medical, psychological, or behavioral condition that, in the opinion of the study doctor, would confound or interfere with evaluation of safety and/or effectiveness of the study drug, prevent compliance with the study protocol; preclude informed consent; or render the participant unable/unlikely to comply with the study procedures.

9.4. Variables

Variable	Role	Data source(s)	Operational definition
Index date	Study period	Case report form	Inform consent date
Index year	Study period	Case report form	Inform consent date
Pre-Oxbryta	Study period	Case report form	Baseline: the most recent observation before receiving Oxbryta
Post-Oxbryta	Study period	Case report form	Follow up period up to 5 years
End of Treatment	Study period	Case report form	Captured from end of treatment form
End of Study	Study period	Case report form	Captured from end of study form
Age	Demographics	Case report form	Age at index year
Sex	Demographics	Case report form	Captured from the inform consent and eligibility form
Race/Ethnicity	Demographics	Case report form	Captured from the inform consent and eligibility form
SCD genotype	SCD disease history	Case report form	Captured from SCD disease history form
Hydroxyurea use	SCD disease history	Case report form	Captured from SCD disease history form
Height	Baseline characteristics	Case report form	Captured from Physical examination form
Weight	Baseline characteristics	Case report form	Captured from Physical examination form
Pre-Oxbryta SCD complications	Medical history	Case report form	Captured from Pre-Oxbryta treatment form
Concomitant Medications	Concomitant Medications	Case report form	Captured from concomitant medications form
Hemoglobin	Effectiveness endpoint measures - Hematology	Case report form	Captured from laboratory assessment-Hematology form
Reticulocyte count (%)	Effectiveness endpoint measures – Hematology	Case report form	Captured from laboratory assessment-Hematology form
Reticulocyte count	Effectiveness endpoint	Case report form	Captured from laboratory

Variable	Role	Data source(s)	Operational definition
(absolute)	measures – Hematology		assessment-Hematology form
White blood cells (WBC)	Effectiveness endpoint measures – Hematology	Case report form	Captured from laboratory assessment-Hematology form
Absolute neutrophil count (ANC)	Effectiveness endpoint measures – Hematology	Case report form	Captured from laboratory assessment-Hematology form
Mean corpuscular volume (MCV)	Effectiveness endpoint measures – Hematology	Case report form	Captured from laboratory assessment-Hematology form
Mean corpuscular hemoglobin concentration (MCHC)	Effectiveness endpoint measures – Hematology	Case report form	Captured from laboratory assessment-Hematology form
Platelets	Effectiveness endpoint measures – Hematology	Case report form	Captured from laboratory assessment-Hematology form
Aspartate Aminotransferase (AST)	Effectiveness endpoint measures – Hematology	Case report form	Captured from laboratory assessment-Hematology form
Alanine Aminotransferase (ALT)	Effectiveness endpoint measures – Hematology	Case report form	Captured from laboratory assessment-Hematology form
Lactate Dehydrogenase (LDH)	Effectiveness endpoint measures - Hematology	Case report form	Captured from laboratory assessment-Hematology form
Bilirubin (Total)	Effectiveness endpoint measures - Chemistry	Case report form	Captured from laboratory assessment-Chemistry form
Bilirubin (Direct)	Effectiveness endpoint measures - Chemistry	Case report form	Captured from laboratory assessment-Chemistry form
Bilirubin (Indirect)	Effectiveness endpoint measures - Chemistry	Case report form	Captured from laboratory assessment-Chemistry form
Creatinine	Effectiveness endpoint measures – Chemistry	Case report form	Captured from laboratory assessment-Chemistry form
Ferritin	Effectiveness endpoint measures – Chemistry	Case report form	Captured from laboratory assessment-Chemistry form
Iron	Effectiveness endpoint measures – Chemistry	Case report form	Captured from laboratory assessment-Chemistry form

Variable	Role	Data source(s)	Operational definition
Serum cystatin C	Effectiveness endpoint measures – Chemistry	Case report form	Captured from laboratory assessment-Chemistry form
Total Iron Binding Capacity (TIBC)	Effectiveness endpoint measures – Chemistry	Case report form	Captured from laboratory assessment-Chemistry form
T2*MRI	Effectiveness endpoint measures – Chemistry	Case report form	Captured from laboratory assessment-Chemistry form
Urine Albumin	Effectiveness endpoint measures – Renal function	Case report form	Captured from laboratory assessment- Renal function form
Urine Creatinine	Effectiveness endpoint measures – Renal function	Case report form	Captured from laboratory assessment- Renal function form
Albumin Creatinine Ratio (ACR)	Effectiveness endpoint measures – Renal function	Case report form	Captured from laboratory assessment- Renal function form
Hemoglobinuria	Effectiveness endpoint measures – Renal function	Case report form	Captured from laboratory assessment- Renal function form
GFR	Effectiveness endpoint measures – Renal function	Case report form	Captured from laboratory assessment- Renal function form
Transfusions	Safety endpoint measures	Case report form	Captured from transfusions form
Healthcare Resource Utilization	Effectiveness endpoint measures	Case report form	Captured from Healthcare Resource Utilization form
PROMIS	Effectiveness endpoint measures	Case report form	Captured from PROMIS form
Patient Global Impression of Change (PGI-C)	Effectiveness endpoint measures	Case report form	Captured from Patient Global Impression of Change (PGI-C) form
Clinical Global Impression of Change (CGI-C)	Effectiveness endpoint measures	Case report form	Captured from Clinical Global Impression of Change (CGI-C) form
Pain Scale	Effectiveness endpoint measures	Case report form	Captured from Pain Scale form
Sheehan Disability Scale	Effectiveness endpoint measures	Case report form	Captured from Sheehan Disability Scale form
Exercise Tolerance	Effectiveness endpoint	Case report form	Captured from Exercise

Variable	Role	Data source(s)	Operational definition
	measures		Tolerance form
Pregnancy Testing and Fertility	Safety endpoint measures	Case report form	Captured from PregnancyTesting and Fertility form
SCD Complications/Adverse Events	Safety endpoint measures	Case report form	Captured from SCD Complications/Adverse Events Question form
Pregnancy	Safety endpoint measures	Case report form	Captured from Pregnancy Notification and Outcome forms
Oxbryta Physician Administration	Exposure measures	Case report form	Captured from Oxbryta Physician Administration form
Oxbryta Participant Adherence	Exposure measures	Case report form	Captured from Oxbryta Participant Adherence form

9.5. Treatment of Participants

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

9.5.1. Description of Oxbryta® (Voxelotor)

Oxbryta® (Voxelotor) is a hemoglobin S polymerization inhibitor indicated for the treatment of SCD in adults and pediatric patients 4 years of age and older.

Refer to the Oxbryta® (Voxelotor) US prescribing information (Oxbryta® (Voxelotor)® USPI)[6] for details on the dosage, administration, formulation, packaging, storage, and handling of Oxbryta® (Voxelotor).

9.5.2. Concomitant Medications

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

Pre-specified medications for SCD-related conditions taken by the participant from 12 months before screening through the end of study participation (5 years after the first dose of Oxbryta® (Voxelotor) treatment or early discontinuation) will be recorded in the CRF.

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

Refer to the Oxbryta® (Voxelotor)® USPI[6] for details on concomitant medications and contraindications.

9.6. Data Sources

The main data source is through the electronic data capture in the study, while secondary data sources may include insurance claims, electronic medical records, hospital administrative data, and specific rare disease databases.

9.7. Study Data Collection

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

There are not any required study procedures or assessments beyond the SOC. The SOA should be used as a guide for what data to enter and not for what assessments to perform. Therefore, if an assessment listed in the schedule of activity of the protocol is considered standard of care, the sites are asked to enter the assessment result into the study database. If an assessment is not conducted as SOC, the sites can just leave the relevant data fields blank.

Since Health-Related Quality of Life Measures (PROMIS, PGIC, NPRS and CGIC) are not commonly conducted as SOC, in order to allow important quality-of-life data to be gathered in the registry, questionnaires are provided to the sites and participants, and we recommend (but not require) the sites to perform these assessments.

9.8. Study Size

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

9.9. Data Management

Study data will be collected at regular intervals and entered in case report forms (CRFs) via an electronic data capture (eEDC) system. All data management and data analysis will be performed by UBC using statistical software SAS®, SAS Institute Inc., Cary, NC, USA.

9.9.1. Case Report Forms (CRFs)/Data Collection Tools (DCTs)/Electronic Data Record

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included patient. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer. The investigator shall ensure that the CRFsare securely stored at the study site in encrypted electronic and/or paper *form and will be* [password protected or secured in a locked room] to prevent access by unauthorized third parties.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFsare true. Any corrections to entries made in the CRFs or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

The source documents are the hospital or the physician's chart. In these cases, data collected on the CRFs must match those charts.

9.9.2. Record Retention

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent/assent documents, copies of all CRFs[/DCTs], safety reporting forms, source documents, detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, and telephone call reports). The records should be retained by the investigator according to local regulations or as specified in the clinical study agreement (CSA), whichever is longer. The investigator must ensure that the records continue to be stored securely for so long as they are retained.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer.

Study records must be kept for a minimum of 15 years after completion or discontinuation of the study, unless UBC and Pfizer have expressly agreed to a different period of retention via a separate written agreement. Record must be retained for longer than 15 years or as required by applicable local regulations.

The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

9.10. Data Analysis

There is not a separate statistical analysis plan (SAP) for this protocol. The detailed data analysis of endpoint measures are described in the Section 9.11.3 and Section 9.11.4.

9.11. Statistics

9.11.1. Analysis Population

Effectiveness and safety analyses will primarily be based on the treated population, defined as all participants receiving at least one dose of Oxbryta® (Voxelotor).

9.11.2. Sample Size

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

9.11.3. Effectiveness Endpoint Measures Analyses

Baseline Demographic Characteristics:

Baseline demographic characteristics will be summarized descriptively.

Endpoints:

- Change from pre-Oxbryta® (Voxelotor) treatment period in Hb, hemolysis measures, measures of iron overload, and renal function over time will be summarized descriptively.
- Annualized rate of significant SCD-related clinical events, for example VOC, ACS, priapism, stroke, TIA, chronic or end stage kidney disease, iron overload, leg ulcers, cardiac malfunction, and PH will be calculated. The association between change in Hbhemolysis marker and rates of SCD-related clinical events will be evaluated.
- Rates of outpatient visits (including infusion center, acute care, or telemedicine visit), ED visits, hospitalizations, acute and chronic RBC transfusions, home oxygen supplementation, and renal dialysis will be summarized with a similar approach as incidences of SCD-related clinical events. The total cost associated with clinical interventions will be summarized descriptively.

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

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

Subgroup analysis:

Similar comparisons may be performed between the subgroup of participants who discontinue Oxbryta® (Voxelotor) treatment but remain in the study and those participants who remain on Oxbryta® (Voxelotor).

Other subgroup or sensitivity analyses may be performed.

9.11.4. Safety Analysis

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

9.12. Quality Control

9.12.1. Data Quality Assurance

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

- Guidance on completion of CRFs will be provided in the CRF completion guideline.

- The study doctor must permit as needed study-related monitoring, audits, IRB review, and regulatory agency inspections and provide direct access to source data documents.

- Monitoring details will be provided in the monitoring plan.

- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the study doctor for 2 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

9.12.2. Source Documents

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

9.12.3. Essential Documentation Requirements

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

9.13. Strengths and Limitations of the Research Methods

A post marketing product registry enables robust and systematic data collection on product use in the real-world setting. It can also provide details on measures such as care pattern, long-term efficacy and safety which require long-term follow up and large number of patients.

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 standard of care vary among study sites, and susceptibility to multiple sources of bias for comparing outcomes.

9.14. Other Aspects

9.14.1. Financial Disclosure

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

9.14.2. Study and Site Start and Closure

9.14.2.1. First Act of Recruitment

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

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

9.14.2.2. Site Closure

Study sites will be closed upon study completion. A study site is considered closed when the Sponsor/CRO has confirmed that all participant data entered into EDC is confirmed final and signed by the Principal Investigator (PI); all required documents and study supplies have been destroyed and a study-site closure visit has been performed.

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

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

- Failure of the study doctor to comply with the protocol, the requirements of the IRB or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the study doctor
- Enrollment goal met earlier than expected

The study doctor shall inform the participant and the Institutional Review Boards (IRBs), of any site closure.

9.14.2.3. Study Termination

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

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

- Discontinuation of further Oxbryta® (Voxelotor) development

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

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

10. PROTECTION OF HUMAN PARTICIPANTS

10.1. Patient Information

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of patient personal data. Such measures will include omitting patient names or other directly identifiable data in any reports, publications, or other disclosures, except where required by applicable laws.

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

To protect the rights and freedoms of natural persons with regard to the processing of personal data, when study data are compiled for transfer to Pfizer and other authorized parties, patient names will be removed and will be replaced by a single, specific, numerical code, based on a numbering system defined by Pfizer. All other identifiable data transferred to Pfizer or other authorized parties will be identified by this single, patient-specific code. The investigator site will maintain a confidential list of patients who participated in the study, linking each patient's numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patients' personal data consistent with the clinical study agreement and applicable privacy laws.

To protect the rights and freedoms of natural persons with regard to the processing of personal data, when study data are compiled for transfer to Pfizer and other authorized parties, any patient names will be removed and will be replaced by a single, specific, numerical code. All other identifiable data transferred to Pfizer or other authorized parties will be identified by this single, patient-specific code. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patients' personal data consistent with the CRO SOP and applicable privacy laws.

10.2. Patient Consent

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

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

As applicable, the consent will include language for the use of de-identification and tokenization technology that will allow for the acquisition and linkage of the participant to their healthcare data that exists in pharmacy and medical administrative claims databases.

Guidelines for the informed consent/assent process are outlined in Section 10.7.2.

10.3. Patient Withdrawal

10.3.1. Participant ID Number

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

10.3.2. Eligibility Assessment

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

10.3.3. Medical History, Demographic Data, and Insurance Information

Medical history will be recorded for up to 12 months prior to the first dose of Oxbryta® (Voxelotor) (retrospective data). Medical history will include all available SCD genotype results and significant medical history, including hematological parameters.

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

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

10.3.4. SCD Genotype

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

10.3.5. Physical Examination

Height and weight will be collected at the screening visit for all participants of age 18 and above, and at screening and all follow up visits for participants up to age 18. Pulse oximetry [%SpO2] will be collected for all participants at screening and all follow up visits per SOC.

10.3.6. Effectiveness Data

10.3.6.1. Clinical Outcomes

10.3.6.1.1. Laboratory Assessments

The following data will be recorded on the CRF:

For pre-Oxbryta® (Voxelotor) Treatment Visits, only the most recent results from regularly scheduled outpatient visit will be entered.

For post-Oxbryta® (Voxelotor) Treatment Regularly Scheduled Outpatient Visits, all available results during the data collection period will be entered.

For post-Oxbryta® (Voxelotor) Acute Visits (Emergency Department, Hospitalization, Acute Pain/Infusion Center), only the results on the day of presentation (or first available results during the visit) and day of discharge will be entered, if available.

The following data from the most recent results will be recorded in the CRF:

- Hb (including % HbF at baseline and all follow up visits), white blood cells (WBC), absolute neutrophil count (ANC), mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC), Platelets, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and lactate dehyrogenase (LDH).
- Hemolysis measures, including % reticulocytes, absolute reticulocytes, bilirubin (total, direct, and indirect)
- Measures of iron overload (ferritin, iron, TIBC, T2*MRI)
- Creatinine (Serum)
- Albuminuria (urine albumin/creatinine ratio [ACR])
- Hemoglobinuria (urine dipstick positive for blood +1 or greater and $\leq$ 2 RBC by high power field)
- Serum cystatin C
- eGFR calculated using CKD-EPI equation

10.3.6.1.2. SCD Complications

For the pre Oxbryta® (Voxelotor) treatment SCD complications, all events that occurred within 12 months prior to starting Oxbryta® (Voxelotor) treatment will be recorded in the CRF.

For the post- Oxbryta® (Voxelotor) treatment SCD complications, all events occurring since the last collection timepoint will be recorded in the CRF.

10.3.6.1.3. Vaso-Occlusive Crises (VOCs) and Acute Chest Syndrome (ACS)

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

A VOC is defined as an acute episode of pain that:

- Has no medically determined cause other than a vaso-occlusive event, and
- Results in a visit to a medical facility (hospitalization, emergency department, urgent care center, outpatient clinic, or infusion center),or results in a remote contact with a healthcare provider; and
- Requires parenteral narcotic agents, parenteral nonsteroidal anti-inflammatory drugs (NSAIDs), or an increase in treatment with oral narcotics.

Data related to any events of ACS will be collected.

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

10.3.6.1.4. Priapism

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

10.3.6.1.5. Stroke and Transient Ischemic Attack

Data related to any events of stroke (Ischemic, Hemorrhagic, and Silent), and Transient ischemic attack (TIA), for example, as identified via MRI or TCD (TAMMV measures in ICA, MCA, ACA), will be collected.

10.3.6.1.6. Leg Ulcers

Data on leg ulcer(s) assessments will be collected, including information on existing and new ulcers.

10.3.6.1.7. Cardiac Malfunction and Pulmonary Hypertension

Cardiac malfunction, for example, as assessed by cardiac ECHO or cardiac catheterization will be collected.

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

10.3.6.1.8. Other SCD Complication

Data on other SCD complications will be collected. This may include sickle cell anemia, splenomegaly/splenectomy, dactylitis, cholelithiasis/cholecystectomy, aplastic crisis, chronic or end stage kidney disease (as defined by GFR <60), iron overload (as diagnosed by T2* MRI or R2* MRI), pneumonia, retinopathy, avascular necrosis, deep vein thrombosis, and chronic/acute pain.

10.3.6.1.9. RBC Transfusion

The history of RBC transfusions will be collected.

10.3.6.1.10. SCD-Related Medication Use

Administration of SCD-related medications, such as hydroxyurea, crizanlizumab, L-glutamine, opioids (in daily morphine equivalents), iron chelating agents, ESAs, NSAIDs, folic acid, and penicillin, will be collected.

10.3.6.2. Healthcare Resource Utilization

Data on any outpatient visits (including infusion center, acute care, or telemedicine visit), ED visits, hospitalizations (including total length of stay and time in ICU, if applicable), acute and chronic RBC transfusions, home oxygen supplementation, and renal dialysis will be collected.

10.3.6.3. Health-Related Quality of Life (HRQoL)

Data on HRQoL measures will be collected and completed by the participant electronically. During an event that limits or prevents on-site SOC visits, the HRQoL can be completed remotely if permitted/approved by the IRBs. The questionnaires are provided in Appendix 2.

10.3.6.3.1. Patient Reported Outcome Measurement Information System (PROMIS)

The National Institute of Health self-reported (or caregiver-reported) PROMIS measures of function, symptoms, behaviors, and feelings, will be collected.

If not performed as part of the participant's usual care, standardized PROMIS forms Pediatric-37 v2.0-Profile; Parent Proxy v2.0 Profile-37 and 49 v2.1 Profile will be provided.

10.3.6.3.2. Patient Global Impression of Change (PGIC)

Data from the self-reported Patient Global Impression of Change (PGIC) will be collected. The PGIC is a single question that reflects a participant's or caregiver's belief about the effectiveness of treatment with Oxbryta® (Voxelotor). PGIC is a 7-point scale depicting a participant's rating of overall improvement. Participants/caregivers rate their change as "very much improved," "much improved," "minimally improved," "no change," "minimally worse," "much worse," or "very much worse".

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

10.3.6.3.3. Numerical Pain Rating Scale (NPRS)

Data from the NPRS will be collected, if it was used to assess acute pain intensity for VOCs and the result was recorded as part of the participant's SOC. Participants will be asked verbally to choose a whole number from 0 to 10 that best describes the severity of pain during the last SCD related vaso-occlusive crisis/pain attack/pain crisis, with 0 being "no pain" and 10 being "the worst pain imaginable."

10.3.6.3.4. Clinical Global Impression of Change (CGIC)

Data from the CGIC will be collected. The CGIC is a brief, stand-alone assessment of the clinician's view of the participant's global functioning prior to and after initiating Oxbryta® (Voxelotor). The CGI provides an overall clinician-determined summary measure that takes into account all available information, including a knowledge of the participant's history, psychosocial circumstances, symptoms, behavior, and the impact of the symptoms on the participant's ability to function. CGIC will be collected, if it does not influence the participant's usual care.

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

10.3.6.3.5. Exercise Tolerance

Any objective measures or reports of exercise tolerance will be collected, if they were recorded as part of the participant's SOC.

10.4. Patient Withdrawal

10.4.1. Discontinuation of Oxbryta® (Voxelotor) and Participant Discontinuation

10.4.1.1. Withdrawal of Consent

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

10.4.1.2. Early Discontinuation of Oxbryta® (Voxelotor)

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

Participants who are discontinued or withdraw from Oxbryta® (Voxelotor) treatment will continue to be followed for up to 5 years after the first dose of Oxbryta® (Voxelotor) treatment unless they withdraw consent for study participation.

10.4.1.3. Lost to Follow Up

- A participant will be considered lost to follow-up if he or she repeatedly fails to return for their routine visits per SOC for ≥1 year and is unable to be contacted by the study site.
    - A participant who is deemed lost to follow-up and later unexpectedly returns to the site for SOC treatment may be re-consented prior to any new data collection.
    - Any data that was missed during the lost to follow-up period will not be collected.

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

There must be prospective approval of the study protocol, protocol amendments, and other relevant documents (eg, informed consent forms if applicable) from the relevant IRBs/IECs. All correspondence with the IRB/IEC must be retained. Copies of IRB/IEC approvals must be forwarded to Pfizer.

10.6. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in CT24-WI-GL02-RF04.

10.7. Regulatory, Ethical, and Study Oversight Considerations

10.7.1. Regulatory and Ethical Considerations

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

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable ICH Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations

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

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

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

The study doctor will be responsible for the following:

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

10.7.2. Informed Consent and Assent Process

- The study doctor or his/her representative will explain the nature of the study to the participant (or their legally authorized representative) and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants (or their legally authorized representative) will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability, and Accountability Act (HIPAA) requirements, where applicable, and the IRB or study center.
- Participants under 18 years of age (and their parent or legally authorized representative) will review the ICF and sign an Assent Form, according to local IRB guidelines. Participants who initially sign the assent form and subsequently legally become an adult while actively participating in the study (before the end of study) should be re-consented using the adult ICF soon after their status changes.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- During an event that limits or prevents on-site SOC visits, the site can obtain consent/assent of a participant remotely, if permitted/approved by the IRBs.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.

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

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

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

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

10.7.3. Data Protection

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

- The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.

- The participant must be informed that his/her medical records and secondary data sources may be examined by study auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB members, and by inspectors from regulatory authorities.

- Linked Pharmacy & Medical Claims Data:

    - By signing the ICF, participants are agreeing to have health records made available as part of the collection of medical and pharmacy claims in order to evaluate concomitant medication and clinical outcomes. This data would be obtained from pharmacy & medical claims databases that have been de-identified and tokenized to match the participant in the study. This de-identified data would be mapped into the project database. Logic checks to confirm accurate linkage would be performed by the clinical monitoring and data management teams.

- All data should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification. All integrated data would be presented to the site in a 21 CFR Part 11 compliant system for review and clarification of accuracy and quality.

- The investigator/designee is responsible for assuring that all data (whether entered into the eCRF or abstracted from the electronic health records (EHR) is complete, accurate, and that entry and updates are performed in a timely manner. The Investigator must certify that the data entered are complete and accurate.

- After final database lock, the investigator will receive copies of all participant data for archiving at the investigational site.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

In this study, data will be collected by the following two methods 1) Human review of Unstructured Data, and 2) Survey of patients to assess HRQoL. AEs and SAEs reporting requirement for both methods are described below.

11.1. Human Review of Unstructured Data

This study protocol requires human review of patient-level unstructured data; unstructured data refer to verbatim medical data, including text-based descriptions and visual depictions of medical information, such as medical records, images of physician notes, neurological scans, x-rays, or narrative fields in a database. The reviewer is obligated to report adverse events (AEs) with explicit attribution to any Pfizer drug that appear in the reviewed information (defined per the patient population and study period specified in the protocol). Explicit attribution is not inferred by a temporal relationship between drug administration and an AE but must be based on a definite statement of causality by a healthcare provider linking drug administration to the AE.

The requirements for reporting safety events on NIS AE Report Form for Protocols with Stipulated Active Collection of AEs to Pfizer Safety are as follows:

- All serious and non-serious AEs with explicit attribution to **any Pfizer drug** that appear in the reviewed information must be reported, within 24 hours of awareness, to Pfizer Safety using the NIS AEM Report Form.
- Scenarios involving drug exposure, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, lack of efficacy, and occupational exposure associated with the use of a Pfizer product must be reported, within 24 hours of awareness, to Pfizer Safety using the NIS AEM Report Form.
- If an embryo or fetus has been exposed to the study drug, as soon as exposure during pregnancy (EDP) has been diagnosed, send the EDP supplemental form with the NIS AEM Report Form with the appropriate fields completed.
- For these AEs with an explicit attribution or scenarios involving exposure to a Pfizer product, the safety information identified in the unstructured data reviewed is captured in the Event Narrative section of the report form, and constitutes all clinical information known regarding these AEs. No follow-up on related AEs will be conducted.

All the demographic fields on the NIS AEM Report Form may not necessarily be completed, as the form designates, since not all elements will be available due to privacy concerns with the use of secondary data sources. While not all demographic fields will be completed, at the very least, at least one patient identifier (eg, gender, age as captured in the narrative field of

the form) will be reported on the NIS AEM Report Form, thus allowing the report to be considered a valid one in accordance with pharmacovigilance legislation. All identifiers will be limited to generalities, such as the statement "A 35-year-old female..." or "An elderly male..." Other identifiers will have been removed.

Additionally, the onset/start dates and stop dates for "Illness," "Study Drug," and "Drug Name" may be documented in month/year (mmm/yyyy) format rather than identifying the actual date of occurrence within the month /year of occurrence in the day/month/year (DD/MMM/YYYY) format."

11.2. Patients Survey Assessing HRQoL

This study does not involve data collection on individual patients by their treating healthcare professionals and the questionnaires used in this study do not intend to identify product safety information. However, the questionnaire will be completed by participants online and via paper-based questionnaire, and a participant could volunteer product safety information in free text fields, in blank margins, to study personnels, etc. Any safety information for an individual patient that is volunteered by a study participant (e.g., the patient him/herself, health care professional, lay person) during this research must be reported as described below:

The following safety events must be reported on the NIS AE Report from for Protocols without stipulated active collection: serious and non-serious adverse events (AEs) when associated with the use of the Pfizer product, and scenarios involving exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, lack of efficacy and occupational exposure **(all reportable, regardless of whether associated with an AE)**, when associated with the use of a Pfizer product.

In the event that a study participant volunteers product safety information, study site staff must complete the NIS AE Report from for Protocols without stipulated active collection of AEs and submit to Pfizer within 24 hours of becoming aware of the safety event. Included in the completion of the NIS AEM Report Form is the study participant's contact information; complete contact information should be obtained so that, once the NIS AEM Report Form is sent to Pfizer, the NIS AEM Report Form can be assessed and processed according to Pfizer's standard operating procedures, including requests for follow-up to the study participant.

11.3. Pfizer Training Requirements:

All research staff members must complete the following Pfizer training requirements:

- *"Your Reporting Responsibilities (YRR) with Supplemental Topics."*

These trainings must be completed by research staff members prior to the start of data collection. All trainings include a "Confirmation of Training Statement" (for signature by the trainee) as a record of completion of the training, which must be kept in a retrievable format. Copies of all signed training statements must be provided to Pfizer.

Re-training must be completed on an annual basis using the most current Your Reporting Responsibilities (YRR) with Supplemental Topics training materials. Where Pfizer issues an updated safety training program, including during the course of a calendar year, vendor shall ensure all vendor personnel complete the updated safety training within sixty (60) calendar days of issuance by Pfizer.

11.4. Regulatory Agency, Institutional Review Board, and Site Reporting

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

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

In the event of any prohibition or restriction imposed (eg, clinical hold) by an applicable competent authority in any area of the world, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

12.1. Dissemination of Study Data

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

12.2. Publication Policy

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

13. REFERENCES

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6. Oxbryta® (Voxelotor)® (voxelotor) Tablets United States Prescribing Information. Available at: https://hcp.Oxbryta® (Voxelotor).com/pdf/prescribing-information.pdf. Accessed 20 December 2021.

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14. LIST OF TABLES

None.

15. LIST OF FIGURES

ANNEX 1. LIST OF STANDALONE DOCUMENTS

None.

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Not required.

ANNEX 3. ADDITIONAL INFORMATION

Not applicable.

Appendix 1. Schedule of Activities

Data Collection/Procedure	Pre-Oxbryta® (Voxelotor) treatment period	Study Data Collection Period											
Month Intervals	**–12 to 1**	**3**	**6**	**9**	**12**	**18**	**24**	**30**	**36**	**42**	**48**	**54**	**60**
Informed Consent/Assent[a]	X												
Review of eligibility[b]	X												
Medical history and SCD genotype[c]	X												
Physical examination (including height and weight) and vital signs[d]	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical outcomes and interventions[e]	X	X	X	X	X	X	X	X	X	X	X	X	X
Health resource utilization[f]	X	X	X	X	X	X	X	X	X	X	X	X	X
HRQoL assessments (PROMIS, NPRS, and exercise tolerance)[g]	X	X	X	X	X	X	X	X	X	X	X	X	X
CGIC and PGIC		X	X	X	X	X	X	X	X	X	X	X	X
SCD medications[h]	X	X	X	X	X	X	X	X	X	X	X	X	X
Safety data[i]	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum pregnancy test[j]	X												
Urine pregnancy test [k]		X	X	X	X	X	X	X	X	X	X	X	X

CGIC=Clinical Global Impression of Change; HRQoL=Health-related quality of life; PGIC=Patient Global Impression of Change; PROMIS=Patient-Reported Outcomes Measurement Information System; NPRS=Numerical Pain Rating Scale.

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

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

b. Inclusion and exclusion criteria should be reviewed at the pre-Oxbryta® (Voxelotor) treatment period to ensure participant eligibility is met.

c. Record available significant medical history for up to 12 months prior to the first dose of Oxbryta® (Voxelotor) (retrospective data) in the CRF. Record demographics (sex, race, ethnicity, and age), and SCD characteristics (including hematological parameters), using the most recent data before enrollment. Record all available SCD genotype results. Perform SCD genotype (at pre-Oxbryta® (Voxelotor) treatment period) only for a medical diagnosis of SCD, if diagnosis is not documented in medical chart.

d. Physical examination (including height and weight) will be collected at the screening visit for all participants 18 and above, and at screening and all follow up visits for participants up to age 18. Pulse oximetry [%SpO2] will be collected for all participants at screening and all follow up visits per standard of care.

e. Record available clinical outcomes data including laboratory assessments, for example: VOCs, ACS, priapism, stroke, TIAs, leg ulcers, cardiac malfunction, pulmonary hypertension, RBC transfusions, and SCD-related medication use (see Section 10.3.6.1 for details).

f. Health resource utilization includes any outpatient visits (including infusion center, acute care, or telemedicine visit), ED visits, hospitalizations (including length of stay, if applicable), acute and chronic RBC transfusions, home oxygen supplementation, and renal dialysis occurring during the period between data collection timepoints.

g. HRQoL assessments will include PROMIS, PGIC, NPRS, CGIC, and exercise tolerance. Record data from the most recent assessment before each collection timepoint. If not performed as part of the participant's usual care, the questionnaires will be provided for the participant, parent/caregiver, or clinician to complete. See Section 10.3.6.3 for details. The questionnaires are provided in Appendix 2.

h. Record medications for SCD-related conditions (eg, hydroxyurea, crizanlizumab, L-glutamine, opioids, in daily morphine equivalents, iron chelating agents, ESAs, NSAIDs, folic acid, and penicillin) taken by the participant from 12 months before screening through the end of study participation (5 years after the first dose of Oxbryta® (Voxelotor) treatment or early discontinuation).

i. Record all serious adverse events, adverse events of interest, Oxbryta® (Voxelotor)-related AEs, other safety events, pregnancy test results, and reports of fertility issues occurring during the period since the last collection timepoint. See Section 11 for definitions and for details on recoding and reporting AEs and safety events.

j. Females of child-bearing potential will have a serum pregnancy test at Screening.

k. Urine pregnancy tests will be performed at scheduled visits for females of child-bearing potential. If a urine pregnancy test is positive, the result must be confirmed with a serum pregnancy test. See Section 11.

Appendix 2. Health-Related Quality of Life Measures

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

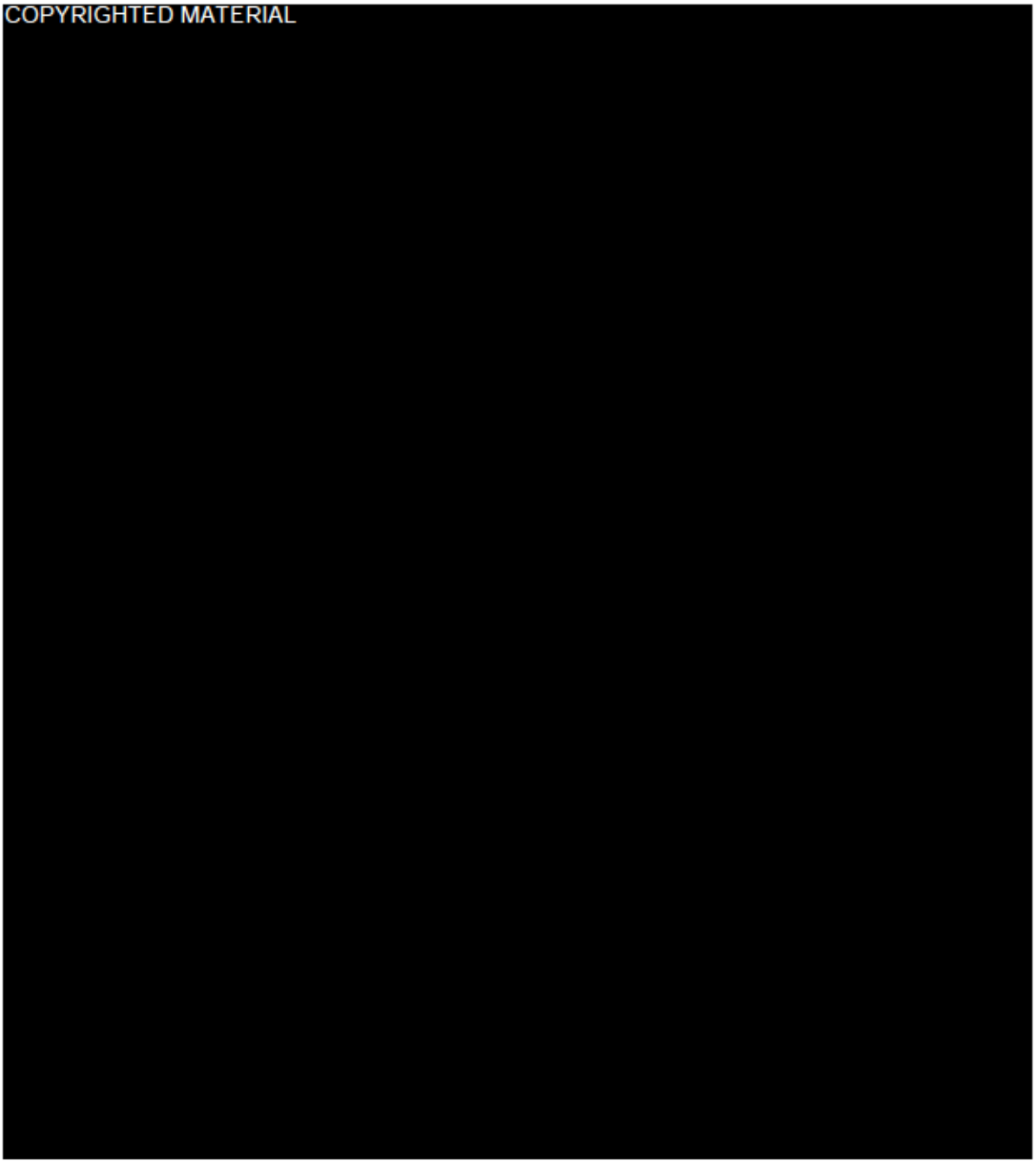
Patient-Reported Outcomes Measurement Information System (PROMIS) – Pediatric

Patient-Reported Outcomes Measurement Information System (PROMIS) – Parent Proxy

Patient Global Impression of Change (PGIC)

Clinical Global Impression of Change (CGIC)

PROMIS–43 Profile v2.1



19 September 2017
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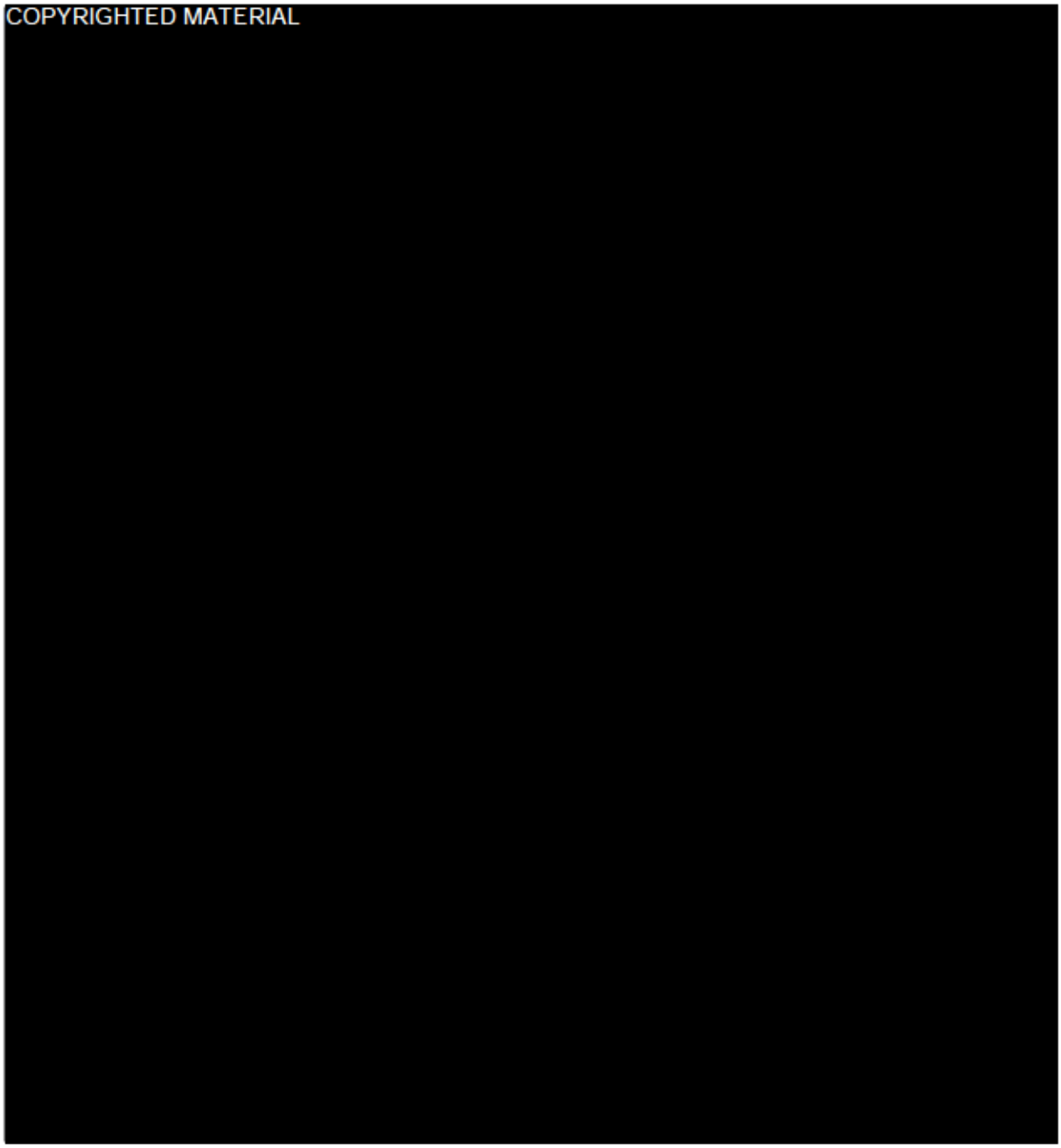
PROMIS–43 Profile v2.1



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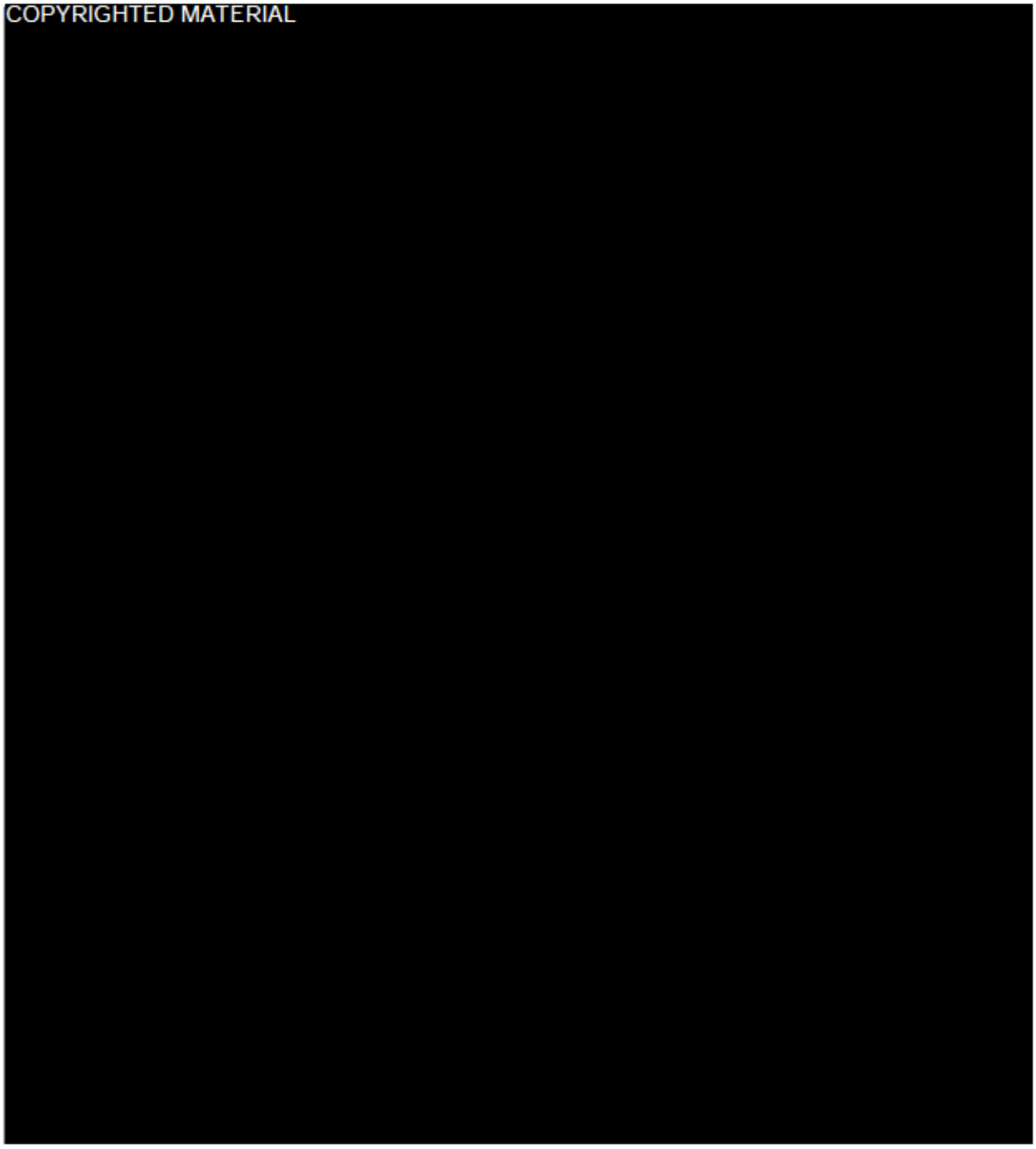
PROMIS–43 Profile v2.1



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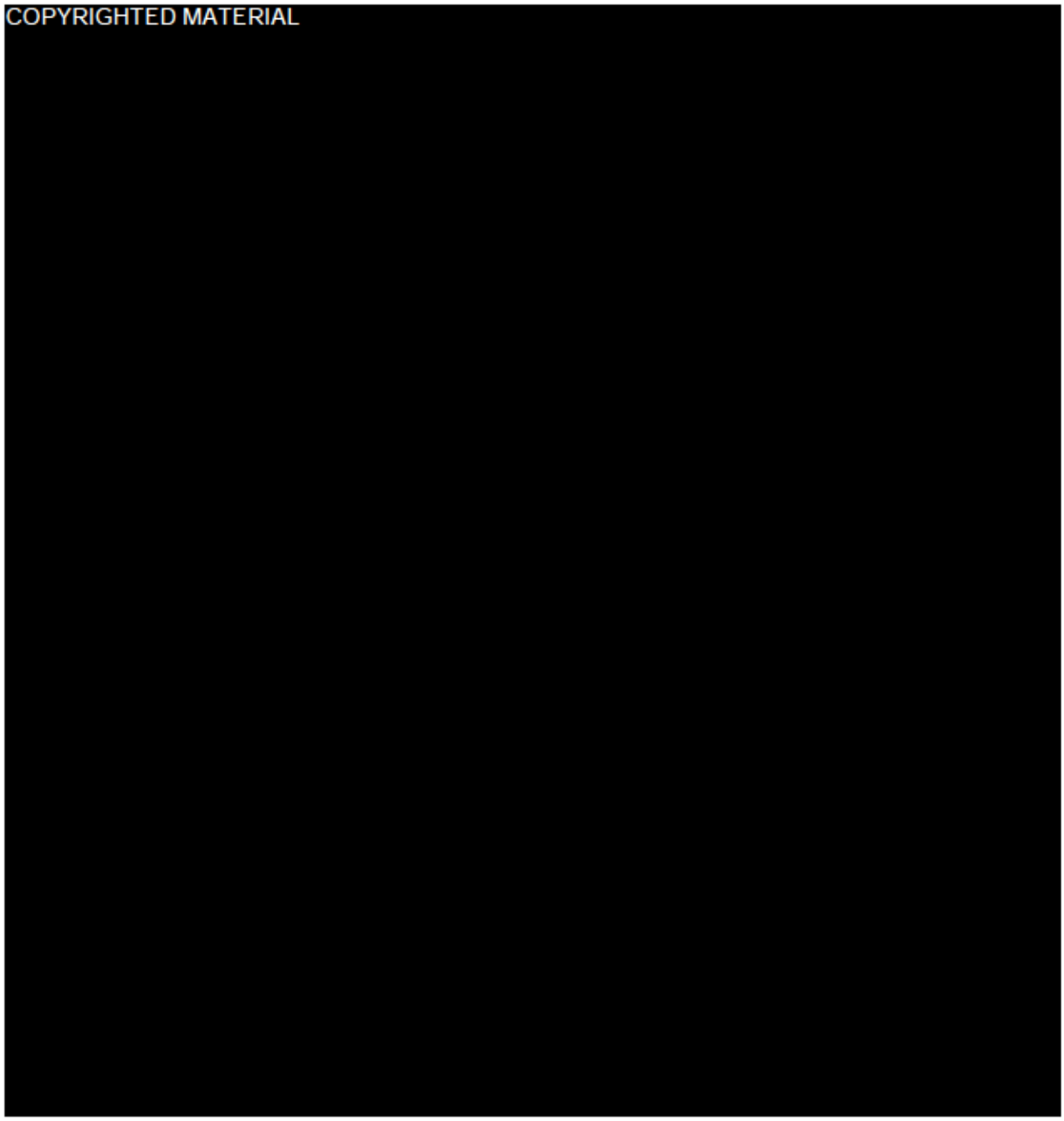
PROMIS® Pediatric Profile v2.0 – Profile-37

Pediatric Profile– 37



7 July 2020

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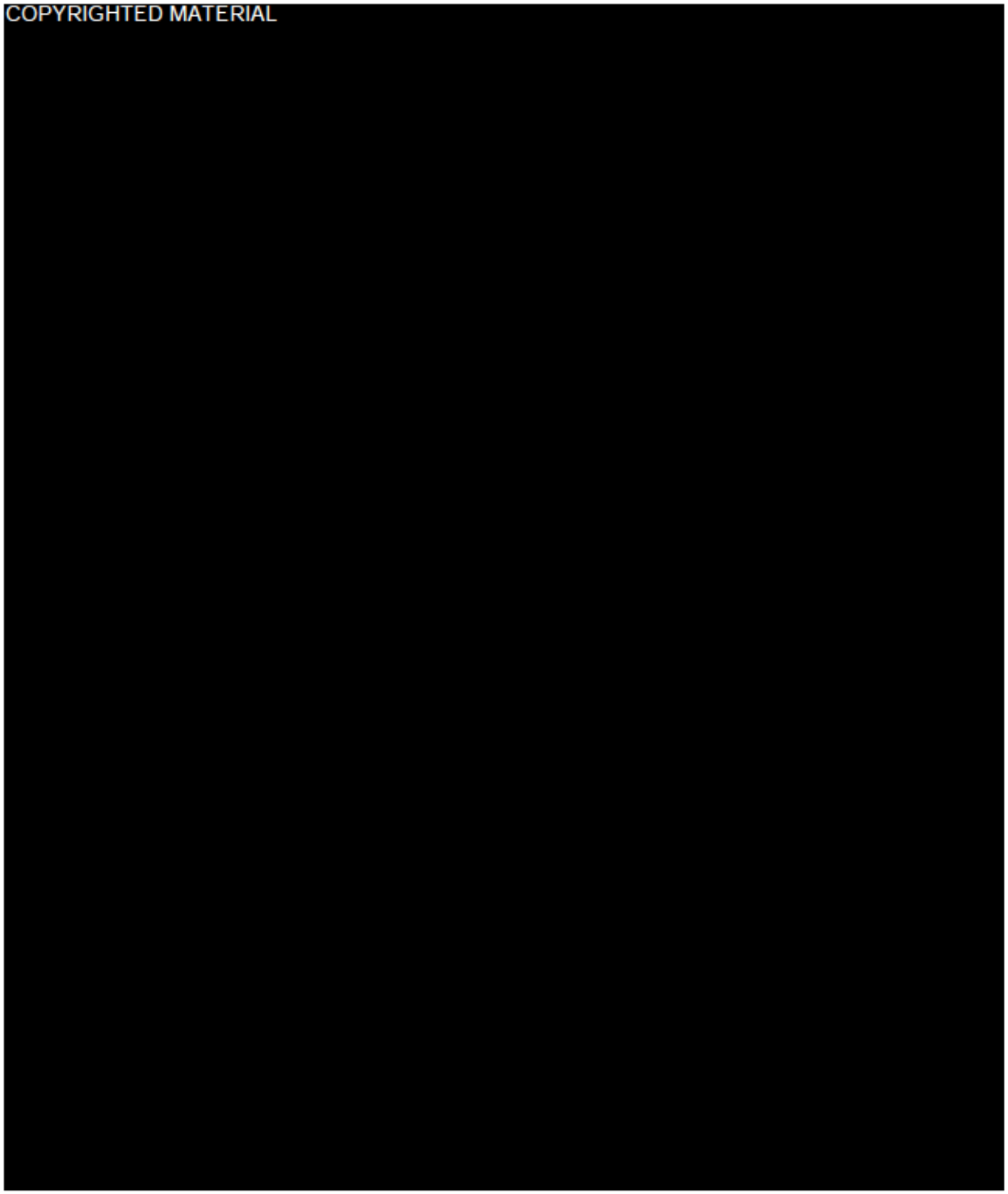
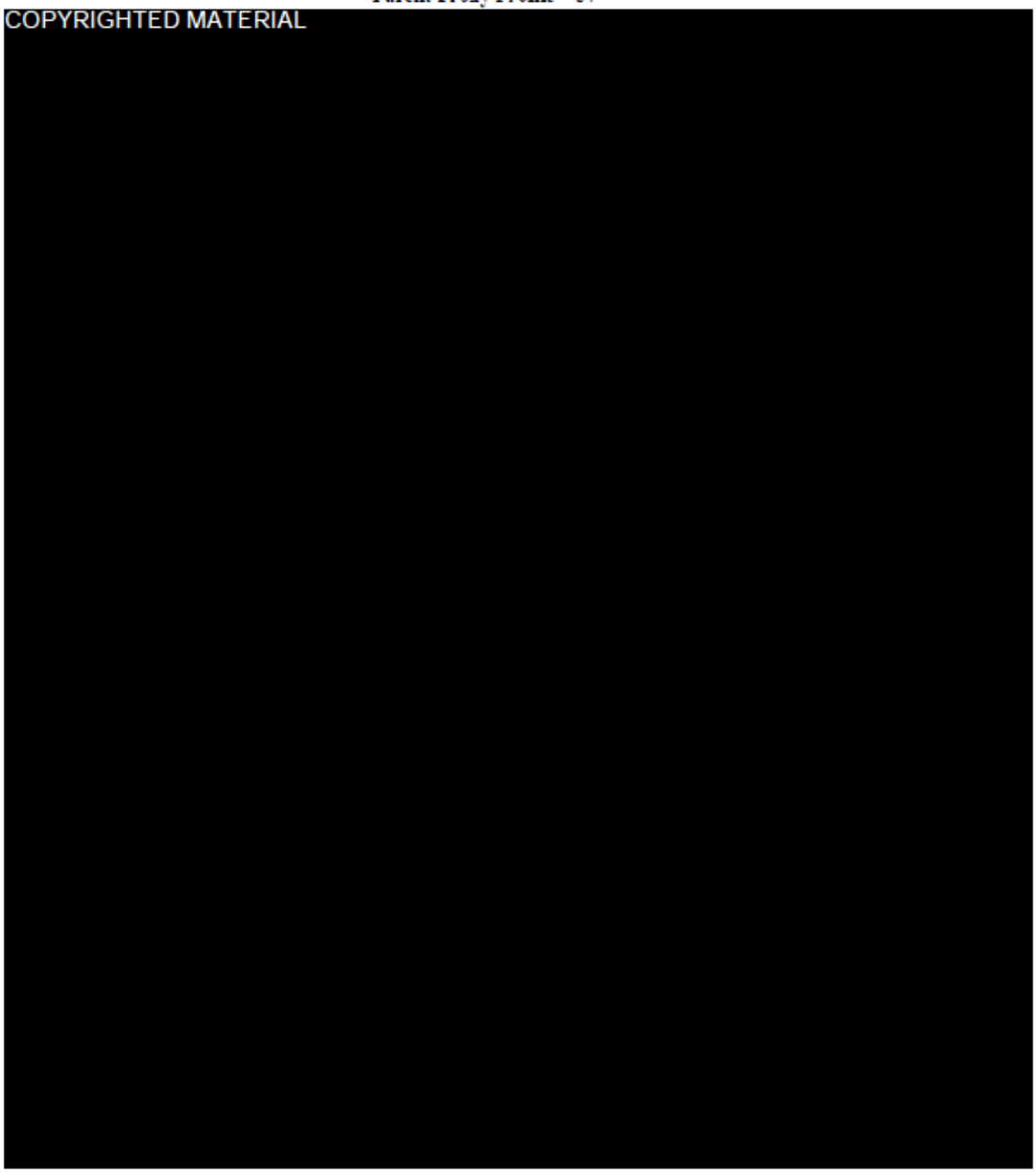


7 July 2020

PROMIS® Pediatric Profile v2.0 – Profile-37

Parent Proxy Profile – 37



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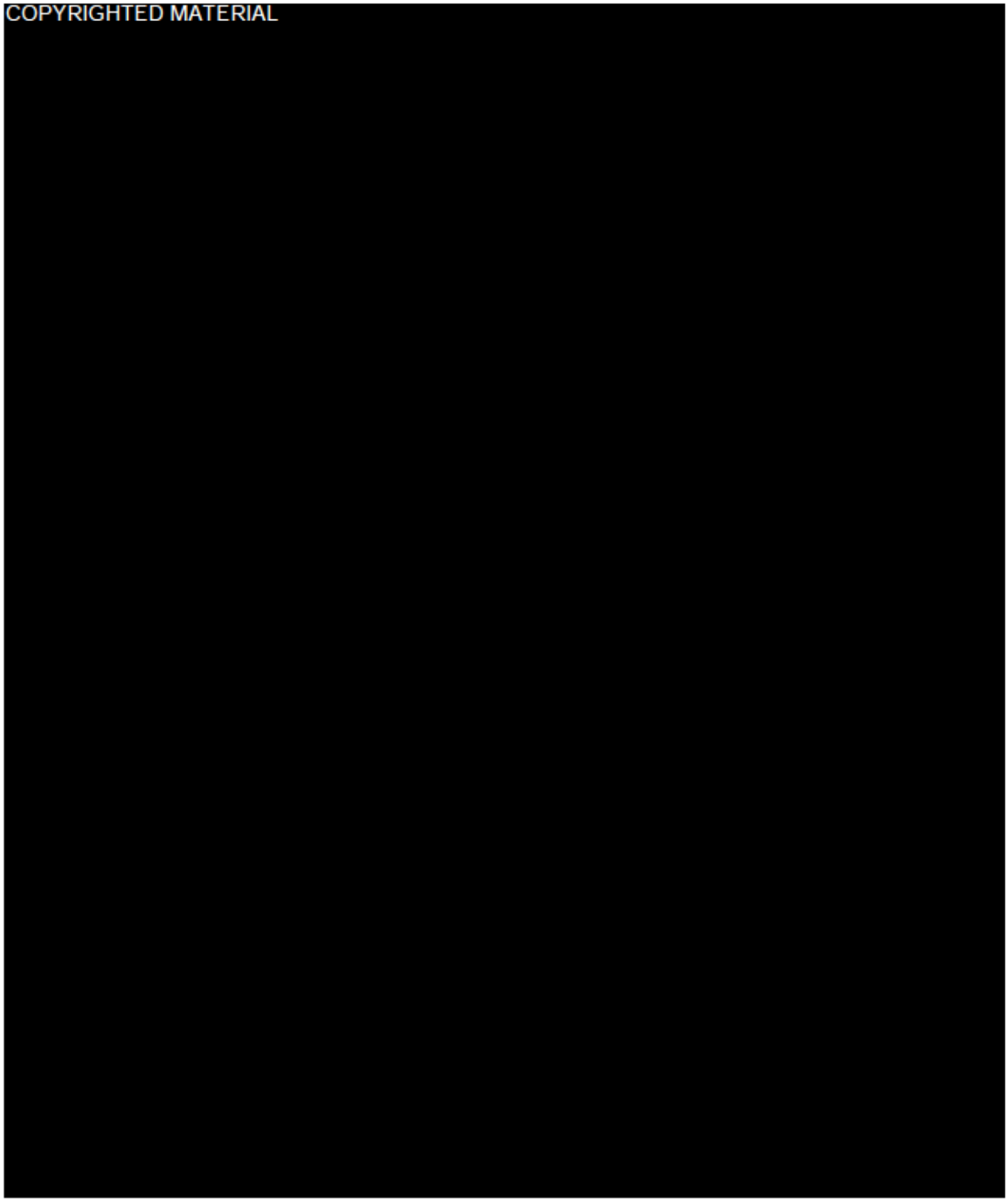

21 February 2020
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PROMIS® Parent Proxy Profile v2.0 – Profile-37

Patient Global Impression of Change (PGIC)

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

Clinical Global Impression of Change (CGIC)

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

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