PART 1: Administrative Details	
Full Study Title	An Open-Label Extension Study of Voxelotor Administered Orally to Participants with Sickle Cell Disease Who Have Participated in Voxelotor Clinical Trials.
Protocol/ Document Number	GBT440-038 (C5341023)
Date of Receipt of the Application	10th February 2023
Phase of Study	3
Study Registration Details	**PACTR202209867711506** Clinical trial approval certificate no. **KBTH- FDA/CT/2314a** **KATH- FDA/CT/2314b**
Name and Address of Applicant(s)	Ms. Adebukunola Telufusi Executive Director Xcene Research
Name and Address of Sponsor(s)	Global Blood Therapeutics, Inc., a wholly owned subsidiary of Pfizer Inc. 181 Oyster Point Blvd South San Francisco, CA 94080, United States of America
Name and Address of Principal Investigator(s)	Dr. Vivian Paintsil Sickle Cell Unit, Directorate of Child Health, Komfo Anokye Teaching Hospital Kumasi Tel: +233509860185 E-mail: vivpee@yahoo.com Dr. Catherine Segbefia Korle-Bu Teaching Hospital Dept of Child Health P. O. Box 77 Korle Bu Tel: +23308887888 E-mail: csegbefia@gmail.com
Study Sites	1. Korle-Bu Teaching Hospital (KBTH) 2. Komfo Anokye Teaching Hospital (KATH)
Study Duration	24 Months
FAPAR Number	FDA/CT/PAR/243

PART 2: Investigational Product(s)	
Name of Investigational Product(s) including Comparator(s).	Oxbryta® (voxelotor)
Justification of Investigational Product(s) including comparators	This open-label extension (OLE) is being conducted to assess the safety and the incidence of SCD-related complications associated with long-term voxelotor treatment by providing participants from Global Blood Therapeutics (GBT)-sponsored voxelotor clinical studies with continued access to voxelotor treatment after participating in their originating study and before the product is potentially available commercially. All participants enrolled in this study will receive voxelotor.

PART 3: Study Summary

Study Objectives

The objective of this OLE is to assess the safety of, and SCD-related complications with, long-term treatment with voxelotor in participants who have completed treatment in a GBT-sponsored voxelotor clinical study, based on the following parameters:

- Adverse events (AEs), clinical laboratory tests, physical examinations (PEs), and other clinical measures
- Frequency of SCD-related complications

Study Design

This is a multicenter, nonrandomized OLE is designed to assess the safety of, and SCD-related complications with, long-term treatment with voxelotor in participants with SCD. The study will be conducted globally and will be available to eligible participants from GBT-sponsored voxelotor clinical studies. Participants must have completed participation in their originating clinical study and must meet the entry criteria for this study to be eligible for enrolment. The study will be conducted at approximately 70 global clinical sites, and up to approximately 600 participants will be enrolled.

Eligibility Criteria

Inclusion criteria

1. Male or female participant with SCD who participated and received study drug in a GB-sponsored voxelotor clinical study

PART 3: Study Summary

Note: Participants who discontinued study drug due to an AE, but who remained on study, may be eligible for treatment in this study provided the AE does not pose a risk for treatment with voxelotor.

Note: Participants who discontinued Study GBT440-032 as a result of an abnormal transcranial Doppler (TCD) flow velocity assessment (> 200 cm/sec) are eligible for treatment in this study.

2. Female participant of childbearing potential is required to have a negative urine pregnancy test prior to dosing on Day 1.

Note: Female participants who become childbearing during the study must be willing to have a negative urine pregnancy test to remain in the study.

3. If sexually active, female participant of childbearing potential must use highly effective methods of contraception until 30 days after the last dose of study drug. If sexually active, male participant must use barrier methods of contraception until 30 days after the last dose of study drug.

4. Participant has provided written consent/assent (for pediatric participants, both the consent of the participant's legal representative or legal guardian and the participant's assent [where applicable] must be obtained)

Exclusion criteria

Female participant who is breastfeeding or pregnant

2A. Participant withdrew consent from a GBT-sponsored voxelotor clinical study

3A. Participant was lost to follow-up from a GBT-sponsored voxelotor clinical study

4. Participant has any medical, psychological, safety, or behavioral conditions that, in the opinion of the investigator, may confound safety interpretation, interfere with compliance, or preclude informed consent

5. Active symptomatic coronavirus disease of 2019 (COVID-19) infection

PART 3: Study Summary

6. Known hypersensitivity to voxelotor or any other components of the study drug

7. Use of St. John's wort, sensitive cytochrome P450 (CYP) 3A4 substrates with a narrow therapeutic index, or moderate or strong CYP3A4 inducers within 30 days of Day 1.

Sex of participants

Male and Female

Age boundaries

Male or female participant with SCD who participated and received study drug in a GBT sponsored voxelotor clinical study.

Date of Commencement (Expected or Actual)

Study initially was expected to commence on 11th January 2024 but has been reprojected to commence in June 2024

Status of Study

Has not commenced

PART 4: Scientific Discussion

Summary of Review Comments

Quality

The quality of the Investigational product Voxelotor has been assessed by the FDA. The applicant submitted the following documents which were reviewed and found satisfactory to fulfill the quality requirement of the trial:

1. Investigational Medicinal Product Dossier for Voxelotor
2. United States Prescribing Information (USPI)-Oxbryta® (Voxelotor)
3. GMP certificates

Safety

Voxelotor has been evaluated in standard nonclinical pharmacology, pharmacokinetics (PK), and toxicology studies (Single Dose Toxicity, Repeat-Dose Toxicity, Genotoxicity, Carcinogenicity, Reproductive and Developmental Toxicity)

From the Summary of Known and Potential Risks and Benefits of Voxelotor,

PART 4: Scientific Discussion

Based on the safety data from the Phase 3 study in adult and pediatric participants with SCD (Study GBT440-031), non-SCD–related treatment-emergent adverse events (TEAEs) were predominantly of low-grade severity and transient. Adverse drug reactions (ADRs) included diarrhea, abdominal pain, nausea, rash, and drug hypersensitivity.

Safety Endpoints

• Treatment-emergent adverse events (TEAEs) and serious adverse events

Safety Analyses

All participants who receive at least 1 dose of study drug in this study will be included in the safety population. Adverse Events AEs will be classified using the Medical Dictionary for Regulatory Activities (MedDRA). The incidence of TEAEs will be tabulated by System Organ Class, Preferred Term, severity, and relationship to study drug (as assessed by the Investigator).

The following documents were reviewed and found satisfactory to fulfill the safety requirement of the trial:

1. Investigator's Brochure version 9.0 dated 17th December 2021
2. Investigational Medicinal Product Dossier for Voxelotor
3. Protocol Version 4.0 (Amendment 3) dated 10th August 2022

Efficacy

Clinical data to date have shown that treatment with voxelotor results in a dose-dependent increase in Hb within 2 weeks that is maintained through 24 weeks, with an associated decrease in clinical measures of hemolysis (including indirect bilirubin, reticulocytes, and lactate dehydrogenase [LDH]) that correlates with drug exposure (Brown, 2018; Vichinsky, 2019)

The following documents were reviewed and found satisfactory to fulfill the efficacy requirement of the trial:

1. Investigator's Brochure version 9.0 dated 17th December 2021
2. Protocol Version 4.0 (Amendment 3) dated 10th August 2022

Overall comments

After initial review, the application was deferred with queries to be addressed by the applicant. Following the satisfactory response to all queries on the submission, the study was approved and issued a clinical trial certificate.

The applicant is committed to ensuring that the study is conducted in compliance with Good Clinical Practice (GCP) and applicable regulatory requirements.

PART 4: Scientific Discussion

All participants will consent to the protocol prior to participation in any study-related activity.

Based on the assessment of medical and ethical principles, the anticipated benefits to the participant justify the foreseeable risks and inconveniences related to the conduct study.

PART 5: Application Review Process

The application was reviewed under the routine approval pathway with decision taken in 37 working days

PART 6: Status after Review

The study was approved on 18th December 2023

REFERENCES

- Protocol Version 4.0 (Amendment 3) dated 10th August 2022
- Investigator Brochure Edition Version 9.0 dated 17th December 2021
- GBT440-038 English Participant Information Sheet and Assent Form (12-17yrs) version 1.0 dated 24th August 2022
- GBT440-038 Twi Participant Information Sheet and Assent Form (12-17yrs) version 5.0 dated 18th August 2022
- GBT440-038 Child (Ages 6-11) Assent to Participate in a Research Study (English and Twi) version 1.0 dated 24th August 2022
- GBT440-038 Participant Information Sheet and Consent Form (Adult Parent) version 1.0 dated 24th August 2022
- GBT440-038 Pregnant Partner: Information Sheet and Informed Consent Form version 1.0 dated 24th August 2022
- GBT440-038 Partner Pregnancy ICF (Twi) version 1.0 dated 24th August 2022
- GBT440-038 Transcranial Doppler (TCD) Assessment Consent Form (English and Twi) version 1.0 dated 24th August 2022
- GBT440-038 Transcranial Doppler (TCD) Assessment Assent Form-Assent of a Minor (6- <15 years old) (English and Twi) to be in an Investigational Study version 1.0 dated 24th August 2022
- Investigational Medicinal Product Dossier for Voxelotor
- GBT440-031 (HOPE Study)
- United States Prescribing Information (USPI)-Oxbryta® (Voxelotor)
- GMP certificates
- FDA's Clinical Trial Assessment form version for Clinical Trial Application version 1.0 dated 2nd September 2019
- Guidelines for Authorization of Clinical Trials of Medicines, Food Supplements, Vaccines and Medical Devices in Ghana
- Guidelines for Good Clinical Practice in Ghana