EDA-CT Application(s) Assessment Summary Public Report (CT-ASPR)

- **Protocol Title:** An Open-Label Extension Study of Voxelotor Administered Orally to Participants with Sickle Cell Disease Who Have Participated in Voxelotor Clinical Trials.
- **Protocol Code Number:** GBT440-038
- **Public Registry Number:** EudraCT Number: 2019-003144-76
- **Version:** 5.0
- **Date:** 15 Jun 2023

- **Investigational Medicinal Product being Tested:**

Biological ☐ **Pharmaceutical** ■ **Innovative** ☐

Herbal Medicine ☐ **Medical Device** ☐

- **Sponsor:** Global Blood Therapeutics, Inc., a wholly owned subsidiary of Pfizer

- **Indication:** Sickle Cell Disease

- **Investigator's Brochure (IB)**

Version: Pfizer Version 1.0
Date: January 2024

- **Name of all Sites:**
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- **EDA Approval Date:**

- Amendment Approval for Investigator's Brochure: (by Pfizer) Version 1.0, dated Jan 2024, on 12 Sep 2024
- Amendment Approval for Protocol Version 5.0, dated 15 Jun 2023, on 02 Apr 2024
- Initial Approval on 30 Mar 2023

- **Brief Description of IMP:** Voxelotor 500mg tablet, 100 and 300 mg dispersible tablets, and 300, 400, 600, and 900 mg powder for oral suspension (packaged as stick packs).

- **Summary of Pre-Clinical Studies**

Voxelotor (GBT440; PF-06759497) is a small molecule inhibitor of sickle hemoglobin (HbS) polymerization which allosterically modifies hemoglobin-oxygen (Hb-O2) affinity that is being developed by the Sponsor (Global Blood Therapeutics Inc. [GBT], a wholly owned subsidiary of Pfizer, Inc.) for the treatment of sickle cell disease (SCD).

Voxelotor increases Hb-O2 affinity and stabilizes hemoglobin (Hb) in the oxyhemoglobin (OxyHb) state thereby inhibiting the underlying mechanism of disease in SCD: the polymerization of HbS in red blood cells (RBCs). By addressing this underlying mechanism of SCD, voxelotor constitutes a disease modifying therapy, improving anemia, reducing hemolysis and has the potential to reduce the end-organ damage resulting from hemolytic anemia.

Nonclinical Pharmacology, Pharmacokinetics, and Toxicology

Voxelotor has been evaluated in standard nonclinical pharmacology, pharmacokinetics (PK), and toxicology studies.

1.1. Safety Pharmacology

Safety pharmacology assessments of voxelotor did not identify any biologically relevant cardiovascular, respiratory or neurobehavioral effects. Cardiovascular safety pharmacology studies revealed minor effects: a mild increase in systolic BP at higher doses (1000 mg/kg) and a small decrease (15.3%) in hERG channel current at 10 µM. Based on these results, voxelotor appears to be a low risk to humans for adverse effects on CNS, respiratory, or cardiovascular function.

1.2. Pharmacokinetics

The PK of voxelotor was studied in mouse, rat, dog, and monkey. The PK studies in animals show that voxelotor has a low volume of distribution and systemic clearance, good oral bioavailability, and a long half-life ($t_{1/2}$). The PK properties of voxelotor in animals indicate preferential binding to Hb. The major route of elimination of voxelotor is by metabolism.

1.3. Nonclinical Toxicology

Nonclinical toxicity studies have identified the NOAEL in rats for up to 26 weeks and cynomolgus monkeys for up to 39 weeks, and dogs for up to 28 days of dosing. Toxicokinetics have been assessed in 5 species (mice, rats, rabbits, dogs, and monkeys). Effects in animals attributed to administration of

voxelotor are monitorable and have shown reversibility of effects. The majority of effects in rats, specifically hematologic changes including increased RBCs, reticulocytes, and Hct, with increased cellularity of bone marrow and extramedullary hematopoiesis in spleen were considered related to the mechanism of action (adaptive and reversible physiologic effects). In dogs and monkeys, dose-limiting GI effects were also noted. In some animals, these effects resulted in deterioration of physical condition, requiring early termination of some animals. A genotoxicity battery indicated a low risk of genotoxic effects, and embryo-fetal and fertility studies in rats and rabbits did not reveal notable effects on embryo-fetal development or fertility. Findings from the 26-week study in rats and the 39-week study in cynomolgus monkeys are consistent with those reported in shorter duration studies. Voxelotor did not show evidence of carcinogenicity in a 26-week study in hemizygous RasH2 mice or in male rats in the 104-week carcinogenicity study. Increased benign tumors in female rats at the highest dose evaluated in the 104-week carcinogenicity study in rats were not considered relevant to human risk

- **Assessment of Nonclinical Data:**

The nonclinical pharmacology package is considered adequate and supports the proposed mechanism of action of voxelotor as a sickle haemoglobin polymerization inhibitor. The submitted primary and safety pharmacology studies demonstrated pharmacological activity consistent with the intended therapeutic effect and did not identify biologically relevant adverse effects on the cardiovascular, respiratory, or central nervous systems. The observed minor cardiovascular findings, including limited hERG inhibition and transient blood pressure changes at high exposures, do not appear to indicate a clinically significant safety concern.

The pharmacokinetic programme is considered adequate and provides sufficient characterization of the absorption, distribution, metabolism, and elimination of voxelotor. The demonstrated preferential binding to haemoglobin is consistent with the proposed mechanism of action and the intended therapeutic use.

The toxicology package is generally in accordance with the recommendations of ICH M3(R2), comprising repeat-dose toxicity studies of appropriate duration in relevant animal species, supported by toxicokinetic evaluations, reproductive and developmental toxicity studies, genotoxicity testing, and carcinogenicity studies. The identified toxicological findings were generally reversible or monitorable and were largely attributable either to the pharmacological activity of the compound or to dose-limiting gastrointestinal toxicity observed at high exposures in non-rodent species.

Reproductive toxicity studies did not identify adverse effects on fertility or embryo-fetal development, and the overall genotoxicity assessment was negative. Carcinogenicity studies did not identify a

carcinogenic risk considered relevant to humans, despite the occurrence of benign tumors in female rats at the highest tested dose.

Overall, the submitted nonclinical data provide an adequate characterization of the pharmacological and toxicological profile of voxelotor and are considered sufficient to support its continued clinical development for the proposed indication.

- **Summary of Previous Clinical Studies:**

Clinical Pharmacology

In vitro and in vivo studies indicate that voxelotor is extensively metabolized through Phase I (oxidation and reduction), Phase II (glucuronidation), and combinations of Phase I and II metabolism. Oxidation of voxelotor is mediated primarily by cytochrome P450 3A4 (CYP3A4), while CYP2C9, CYP2C19, and CYP2B6 also contribute. Glucuronidation of voxelotor is mediated through two uridine 5′-diphospho-glucuronosyltransferase (UGT) isoenzymes, UGT1A1 and UGT1A9.

Voxelotor and metabolites are primarily excreted in feces (62.6%) and urine (35.4%) following an oral administration. Approximately one-third of the administered dose was excreted as unchanged drug in the feces, presumably from the unabsorbed drug. In urine, unchanged voxelotor accounted for 0.08% of the administered dose.

Assessment of drug-drug interactions (DDIs) based on in vitro studies, clinical pharmacology studies, and physiologically based pharmacokinetic (PBPK) modeling and simulation showed that voxelotor is a moderate reversible and time-dependent inhibitor of CYP3A4 but does not inhibit CYP1A2, 2C8, 2C9, 2C19, or 2D6.

Results suggest that voxelotor bioavailability is not reduced in acid-reduced conditions using the proton pump inhibitor (PPI), omeprazole.

CYP450 induction was assessed for CYP1A2, CYP2B6, and CYP3A4 using human cryopreserved hepatocytes (Study PRC-14-017-R). No induction for CYP1A2 and CYP3A4 was observed. Voxelotor at ≥10 µM may cause increases CYP2B6 expression and may be acting through the constitutive androstane receptor.

Co-administration of voxelotor with a strong CYP3A4 inhibitor (itraconazole) did not have a clinically relevant effect on voxelotor PK exposures.

Simulations using the PBPK model predict that strong CYP3A4 inducers such as rifampicin could decrease voxelotor steady-state exposure by approximately 40% (GBT-CP-012), which is likely to diminish efficacy.

Voxelotor inhibited organic anion transporter 3 (OAT3), organic anion transporter protein 1B1 (OATP1B1), organic cation transporter 2 (OCT2), and multidrug and toxin extrusion 1 and 2K (MATE1 and MATE2K) in vitro (Study PRC-15-012-R). However, based on the target therapeutic maximum blood or plasma concentration of voxelotor and unbound concentration, the potential for in vivo DDIs based on inhibition of OATP1B1, OCT2, or OAT3 by voxelotor were considered low. Voxelotor was not a substrate of P-glycoprotein (P-gp), Breast Cancer Resistance Protein (BCRP), OATP1A2, OATP1B1, organic anion transporter protein 1B3 (OATP1B3), or bile salt export pump (BSEP) transporters.

Voxelotor may be given with or without food. Whole blood exposure of voxelotor increased by approximately 45% when administered with a high-fat meal. Given the observed interpatient PK variability, the differences in exposures of voxelotor under fasted and high-fat conditions are not expected to be clinically relevant; therefore, voxelotor may be given with or without food. Likewise, relative bioavailability assessments demonstrated that a standardized moderate-fat breakfast has no effect on exposure of voxelotor.

Efficacy

1. Study GBT440-031 (C5341043)

The primary evidence for efficacy of voxelotor is from data in the Phase 3 study (HOPE, GBT440-031 [C5341043]), which demonstrated a robust and clinically significant increase in Hb and concomitant reduction in clinical markers of hemolysis.

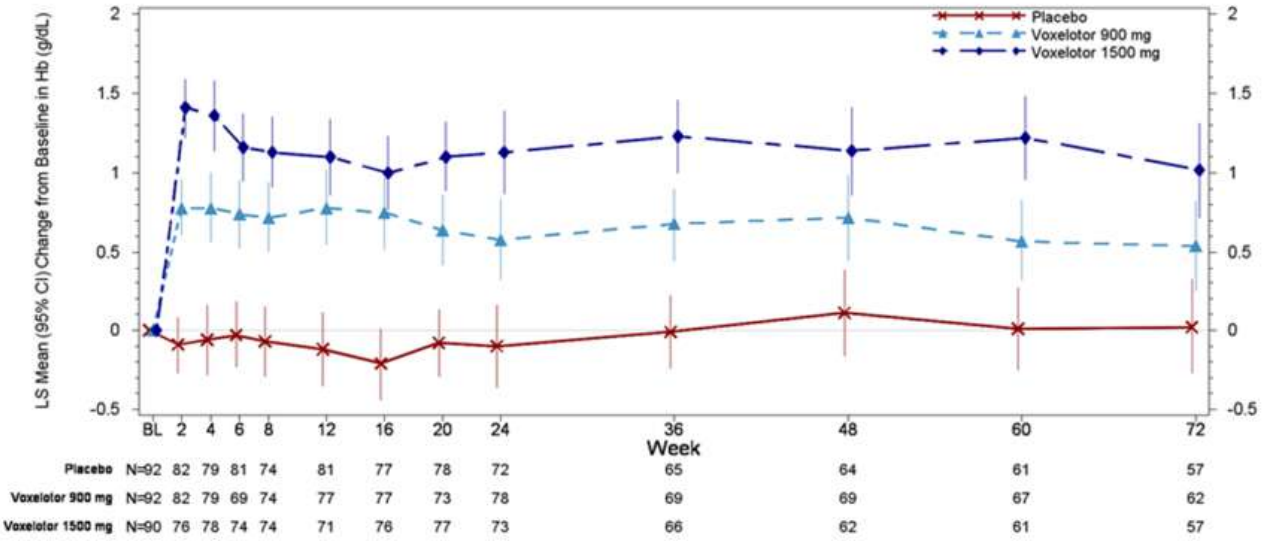
1.1. Effects on Hemoglobin

Efficacy was based on Hb response defined as a Hb increase of > 1g/dL from baseline to Week 24. The response rate was 51.1% (46/90) for voxelotor 1500 mg and 32.6% (30/91) for voxelotor 900 mg compared to 6.5% (6/92) in the placebo group ($p < 0.001$, each dose group vs placebo).

The Hb response was achieved in participants with or without concurrent HU use.

On average, a dose-dependent increase from baseline in Hb level was readily observable for the voxelotor groups beginning at Week 2 and continuing through Week 72. In the placebo group, little to no change from baseline was observed in the average Hb level over time. At Week 24, the LS mean change from baseline in Hb was 1.13 g/dL for the voxelotor 1500 mg group, compared with 0.58 g/dL for the voxelotor 900 mg group and -0.10 g/dL for the placebo group; the difference between the voxelotor group and placebo at Week 24 was statistically significant ($p < 0.001$).

Figure 1: Least Squares Mean Change from Baseline in Hemoglobin Over Time up to Week 72 (Study GBT440-031 [C5341043] ITT Population)



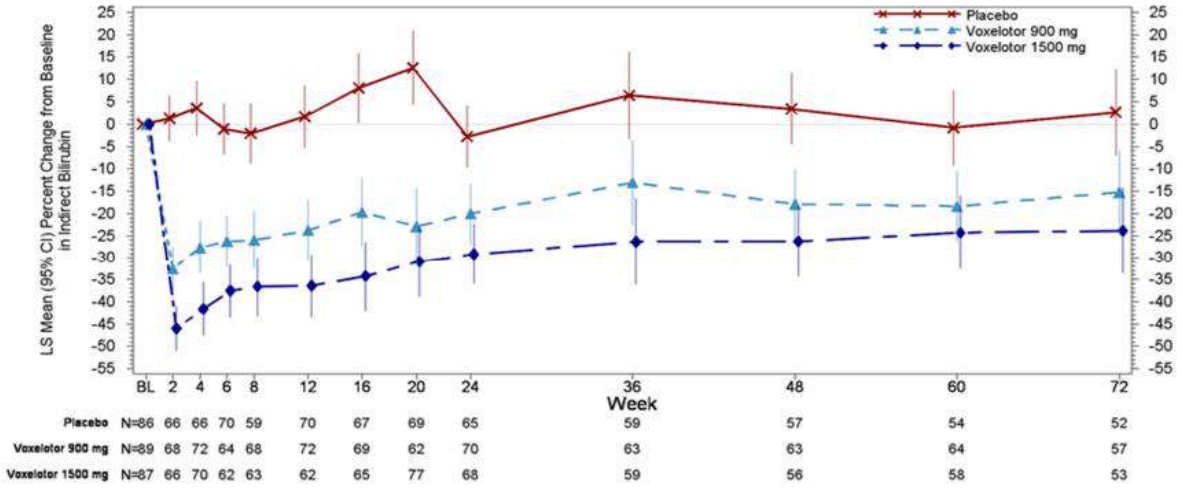
The Hb response showed a consistent treatment benefit for voxelotor 1500 mg vs. placebo across all subgroups examined, including age, VOC history, and HU use.

1.2. Clinical Measures of Hemolysis

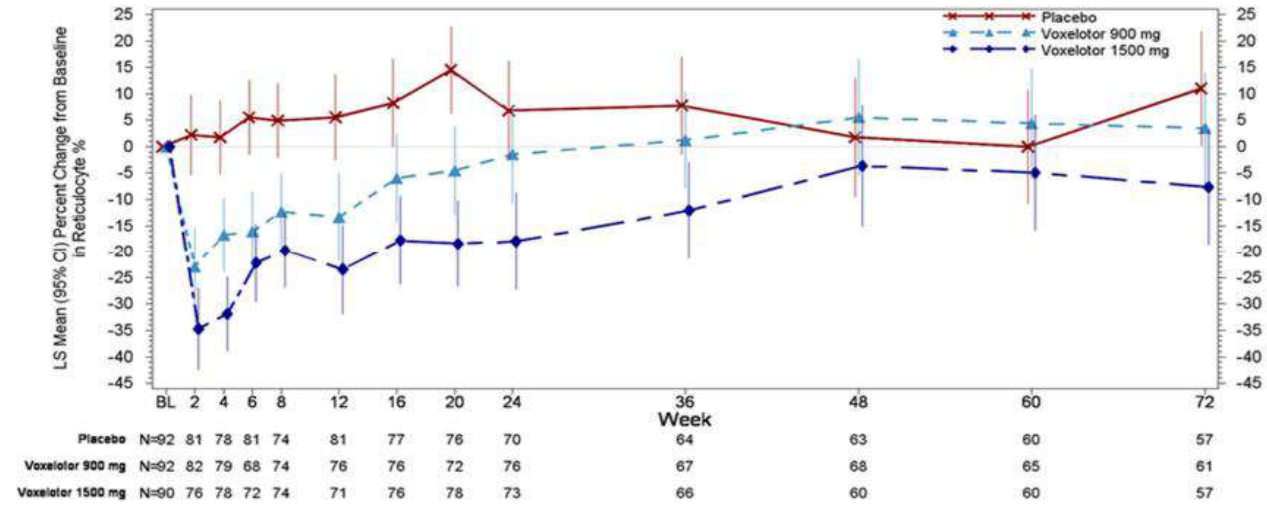
Consistent with the increase from baseline in Hb, dose-dependent decreases in clinical measures of hemolysis (indirect bilirubin, reticulocyte percentage, absolute reticulocytes, and lactate dehydrogenase [LDH]) were observed with voxelotor treatment. Improvements in hemolysis measures and Hb occurred within 2 weeks of treatment initiation. Following this initial reduction in hemolysis measures, mean decreases from baseline in indirect bilirubin and reticulocyte percentage demonstrated a durable treatment effect over 72 weeks.

Figure 2: Least Squares Mean Percentage Change from Baseline in Indirect Bilirubin and Reticulocyte Percentage Over Time up to Week 72 (Study GBT440-031 [C5341043], ITT Population)

A Indirect Bilirubin



B Reticulocyte Percentage



2. Effect of voxelotor on patient-reported quality of life in adolescents and adults with SCD

GBT440-039 (C5341024); ActIVe study; NCT04400487] was a phase 4, multicenter, open-label study to evaluate patient-reported quality of life (QOL) and safety in adolescents and adults. Patients aged 12-55 years with SCD received voxelotor 1500 mg/day for up to 24 weeks across 10 US sites. Outcomes were evaluated using the Patient Global Impression of Change (PGI-C), the National Institutes of Health Patient-Reported Outcome Measurement Information System-43 (PROMIS-43) for adults (aged >17 years), PROMIS-37 for adolescents (aged ≤17 years), a 10-point Numeric Rating Scale (NRS) for pain intensity, and the Clinical Global Impression of Change (CGI-C). A total of 25 subjects with SCD were treated with at least one dose of study drug during the 24-week Treatment Period, consisting of a voxelotor daily dose of 1500 mg. Twenty-three subjects completed study treatment; primary reasons for early discontinuation of study treatment were withdrawal of consent and noncompliance.

Twenty-five patients were enrolled: median (range) age was 20.0 (12-51) years, 64.0% were female, and 92.0% were Black or African American. At week 24, hemoglobin increased in 78% of patients (14/18); the mean (SD) increase was 0.53 (0.839) g/dL. Clinicians reported improvement in health status among 84.6% (11/13) of patients at week 24: 7.7% (1/13) were 'very much improved', 46.2% (6/13) were 'much improved' and 30.8% (4/13) were minimally improved; 2 patients had no change. At week 24, 92.9% (13/14) of patients self-reported improved health status: 21.4% (3/14) were 'very much improved', 42.9% (6/14) were 'much improved', and 28.6% (4/14) were minimally improved; 1 patient reported minimally worse health status. In adults, a meaningful change from baseline (defined as a ≥5-point group-level change) for fatigue [mean (SD) of -7.9 (5.12)] and pain interference [mean (SD) of -6.5 (5.29)] was found at week 24, with near-meaningful improvements for anxiety, sleep disturbance, and ability to participate in daily activities. Whilst some PROMIS domains improved among adolescents, none reached a meaningful level.

3. Study GBT440-007 (C5341020)

3.1. Voxelotor in Adolescents (12 to < 18 Years) With SCD (Part B)

For both doses of voxelotor (1500 mg and 900 mg), improvements in Hb were observed as early as Week 2 and were maintained through Week 24. The median (quartile [Q] 1, Q3) changes from Baseline to Week 24 in Hb were 0.5 (-0.7, 1.0) g/dL for the voxelotor 1500-mg group and 0.7 (0.0, 1.2) g/dL for the voxelotor 900-mg group.

An ad hoc analysis of the change from Baseline to the average of Week 20 and Week 24 values was performed to provide a more stable estimate of the change from Baseline in Hb. This analysis showed a median change of 0.7 g/dL for both treatment groups. At Week 24, Hb response (> 1 g/dL Hb increase from Baseline) rates were 25.0% (3/12 participants) in the voxelotor 1500-mg group and 36.4% (8/22 participants) in the voxelotor 900-mg group.

An ad hoc analysis of the Week 20/24 average data showed Hb response rates of 41.7% (5/12 participants) in the voxelotor 1500-mg group and 13.6% (3/22 participants) in the voxelotor 900-mg group.

Consistent with the changes in Hb, concurrent improvements in hemolysis were observed at Week 24 for the voxelotor 1500- and 900-mg groups.

3.2. Voxelotor in Pediatric Participants (Aged 4 to < 18 years With SCD (Study GBT440-007 [C5341020] Part C)

The primary endpoint for Part C of study GBT440-007 was the effect of voxelotor on cerebral hemodynamics by analyzing the changes in TCD flow velocity at 24 and 48 weeks. Overall, no subjects converted to abnormal TCD flow velocity (≥ 200 cm/sec) over the course of the study.

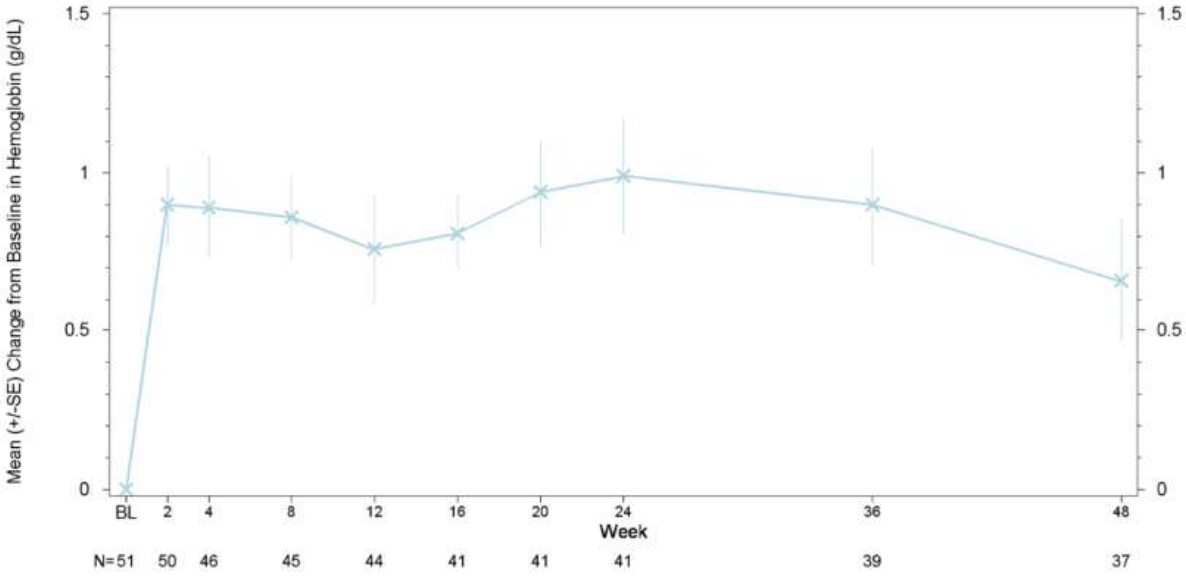
In the 4-11 years age group, at Week 48, 1 of the 27 subjects with normal TCD flow velocity (<170 cm/sec) at baseline converted to conditional (≥ 170 to < 200 cm/sec), and 3 of the 6 subjects with conditional TCD flow velocity at baseline converted to normal.

Treatment with voxelotor was also shown to improve anemia and reduce clinical measures of hemolysis in subjects aged 4 to 11 years with SCD. Efficacy was consistent with that observed in adults and pediatric subjects aged 12 years and older from Study GBT440-031 (C5341043) and Study GBT440-007 (C5341020) Part B.

- Hemoglobin response (defined as a > 1 g/dL increase in Hb from baseline) was achieved by 50% of subjects as early as Week 2 (25/50) and was maintained through Week 48 in 32.4% of subjects (25/37) (95% CI: 12.8, 37.5)
- Hemoglobin response in the Treated Population was achieved by approximately 50% of subjects as early as Week 2 (49.0% [25/51]) and was maintained through Week 24 and Week 48 in 33.3% (18/51) and 23.5% (12/51) of the subjects
- The mean increase in Hb from baseline to Week 24 and Week 48 were 1.0 (1.16 g/dL, n=41) and 0.7 g/dL (1.15 g/dL, n=37), respectively.

- Concurrent improvements in clinical measures of hemolysis were observed as early as Week 2 and mostly continued through Week 48 (mean percent change from baseline of 26.6% and -1.8% for indirect bilirubin and LDH, respectively).
- Interpretation of results for the 12- to 17-year-old group in Part C is limited by small sample size.

Figure 3: Change From Baseline Over Time in Hemoglobin for Subjects Aged 4 to 11 Years (Efficacy Evaluable Population)



Abbreviations: BL, baseline; SE, standard error; Wk, week.
Note: Subjects aged 4 to 11 years received voxelotor weight-based dosing. Baseline was defined as the average of all values prior to the first dose. Results are presented in conventional units (g/dL).

4. Summary of Treatment Response Data and Conclusions

Treatment with voxelotor resulted in a rapid, robust, and sustained improvement in anemia and clinical measures of hemolysis in adult and pediatric (4 to < 18 years old) participants with SCD.

Data from Study GBT440-031 (C5341043) demonstrated a clinically meaningful and statistically significant ($p < 0.001$) improvement in Hb (> 1 g/dL increase) from baseline compared with placebo at week 24. In the voxelotor 1500 mg group, 51.1% (46/90) of the participants achieved a Hb response at Week 24 compared with 6.5% (6/92) of the participants receiving placebo. The increase in Hb levels (on average) was readily observable after 2 weeks of voxelotor administration and was sustained through 72 weeks.

Concurrent with a mean increase in Hb, voxelotor also decreased clinical measures of hemolysis in GBT440-031 (C5341043). This decrease was observed beginning at Week 2 and was generally maintained through 24 weeks in the voxelotor 1500 mg group. The difference between the voxelotor 1500 mg and placebo groups was sustained through Week 72 for indirect bilirubin and percentage reticulocytes.

Improvements in Hb were observed in participants with or without concurrent HU, regardless of the severity of baseline anaemia, sex, or baseline history of VOC (1 episode or ≥ 2 episodes) in GBT440-031 (C5341043).

Overall, weight-based dosing of voxelotor in participants aged 4 to 11 years in
Study GBT440-007 (C5341020) Part C resulted in improvements in Hb and clinical measures of hemolysis that were consistent with the results in participants aged ≥ 12 years who received voxelotor 1500 mg in Study GBT440-031 (C5341043). Improvements in Hb and concordant reductions in clinical measures of hemolysis begun as early as Week 2 and were sustained through Week 48. No subjects converted to an abnormal TCD during the study.

Safety:

Based on the clinical studies safety data evaluated to date, voxelotor has an acceptable safety profile and has been well tolerated in adult and pediatric participants (aged 4 to <18 years) with SCD.

The most common adverse reactions in participants with SCD ≥12 years old were diarrhea, abdominal pain, nausea, headache and rash. Other clinically relevant and less frequent adverse reactions included drug hypersensitivity (<1%).

There were no reported events of anaphylaxis or anaphylactoid reactions. The majority of Treatment Emergent Adverse Event (TEAEs) were Grade 1 to Grade 2 severity, clinically manageable, reversible or resolved. The TEAE profile of voxelotor for pediatric participants with SCD aged ≥4 to 11 years at a dose of 1500 mg or equivalent weight-based dosing is acceptable with no new safety observations and is consistent with the data for adults and adolescent participants.

Overall, the safety profile was similar between adults and pediatric participants aged ≥4 years and between participants who were or were not receiving hydroxyurea (HU) concomitantly.

In the pivotal Study GBT440-031 (C5341043), over the 72-week treatment period, there was a trend towards a lower overall incidence of vaso-occlusive crisis (VOC) with numerically fewer VOC events in the voxelotor groups compared to the placebo group, although the differences did not reach statistical significance. No increase in the incidence of VOC was observed following discontinuation of voxelotor (up to 28 days after the last dose of study drug).
No clinical safety concerns consistent with inadequate tissue oxygenation were identified in the voxelotor clinical development program, including in SCD study participants.

In the pivotal Study GBT440-031 (C5341043), over the 72-week treatment period, there was a trend towards a lower overall incidence of vaso-occlusive crisis (VOC) with numerically fewer VOC events in the voxelotor groups compared to the placebo group, although the differences did not reach statistical significance. No increase in the incidence of VOC was observed following discontinuation of voxelotor (up to 28 days after the last dose of study drug).
No clinical safety concerns consistent with inadequate tissue oxygenation were identified in the voxelotor clinical development program, including in SCD study participants.

Assessment of Clinical Data:
The submitted clinical data comprise clinical pharmacology, efficacy, and safety information derived from an adequate clinical development programme, including a randomized, placebo-controlled Phase 3 pivotal study, supportive pediatric studies, and additional clinical pharmacology and safety studies. Overall, the clinical programme provides sufficient characterization of the pharmacokinetic profile, pharmacodynamic effects, efficacy, and safety of voxelotor in patients with sickle cell disease.
The clinical pharmacology programme adequately characterized the absorption, metabolism, elimination, food effect, and drug-drug interaction potential of voxelotor. The identified interaction with strong CYP3A4 inducers is considered clinically relevant and should be appropriately reflected in the prescribing information.
The efficacy data demonstrate a consistent and clinically meaningful improvement in haemoglobin concentration together with sustained reductions in laboratory markers of haemolysis. These findings were observed across adult and pediatric populations and were generally consistent irrespective of concomitant

hydroxyurea use. The improvement in haemoglobin response was supported by statistically significant results in the pivotal placebo-controlled Phase 3 study. However, although a numerical reduction in vaso-occlusive crises was observed, this endpoint was not statistically significant, and therefore the evidence primarily supports improvement in anaemia and haemolysis rather than reduction of vaso-occlusive events.
The safety database indicates that voxelotor is generally well tolerated in both adult and pediatric patients. Most adverse events were mild to moderate in severity and consistent with the known safety profile of the product. No clinically relevant safety signals related to impaired tissue oxygen delivery or unexpected toxicities were identified during clinical development, and the safety profile was generally consistent across age groups.
Overall, the submitted clinical data are considered adequate to support the proposed therapeutic use of voxelotor in patients with sickle cell disease. The benefit–risk profile is considered favourable with respect to improvement of anaemia and haemolysis, while the available evidence does not demonstrate a statistically significant effect on the prevention of vaso-occlusive crises.

- **Protocol:** An Open-Label Extension Study of Voxelotor Administered Orally to Participants with Sickle Cell Disease Who Have Participated in Voxelotor Clinical Trial.
- **Phase:** III
- **Objective(s):**

  The objective of this OLE study 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, clinical laboratory tests, physical examinations (PEs), and other clinical measures
  - Frequency of SCD-related complications

Endpoints

1.Safety

- TEAEs and SAEs

2. Sickle Cell Disease–Related Complications

- Frequency of SCD-related complications

- **Rationale:**

  This open-label extension (OLE) study 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.'

- **Design:**

This multicenter, nonrandomized OLE study 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 enrollment. All participants will receive voxelotor QD, administered orally as tablets, dispersible tablets, or a powder for oral suspension dosage form (packaged as stick packs). Participants aged ≥ 12 years will receive a voxelotor dose of 1500 mg QD. Participants aged < 12 years will receive a voxelotor dose based on their body weight, to provide exposure corresponding to the adult dose of 1500 mg QD. Participants receiving a voxelotor dose of 1500 mg QD, regardless of age or weight, will receive tablets.

- **Abbreviations:**

AE	Adverse Event
BCRP	Breast Cancer Resistance Protein
BP	Blood Pressure
BSEP	Bile Salt Export Pump
CA	Central Administration
CGI-C	Clinical Global Impression of Change
CI	Confidence Interval
CNS	Central Nervous System
CRC	Clinical Research Center
CT	Clinical Trial
CYP	Cytochrome P450
DDI	Drug–Drug Interaction
EDA	Egyptian Drug Authority
GA	General Administration
GBT	Global Blood Therapeutics
GCP	Good Clinical Practice
GI	Gastrointestinal
Hb	Hemoglobin
Hb-O_2	Hemoglobin–Oxygen
HbS	Sickle Hemoglobin

hERG	Human Ether-à-go-go-Related Gene
HU	Hydroxyurea
IB	Investigator's Brochure
ICH	International Council of Harmonization
IMP	Investigational Medicinal Product
LDH	Lactate Dehydrogenase
MATE	Multidrug and Toxin Extrusion
NOAEL	No Observed Adverse Effect Level
NRS	Numeric Rating Scale
OAT	Organic Anion Transporter
OATP	Organic Anion Transporting Polypeptide
OCT	Organic Cation Transporter
OLE	Open Label Extension
OxyHb	Oxyhemoglobin
PBPK	Physiology Based Pharmacokinetics
PD	Pharmacodynamics
P-gp	P-glycoprotein
PGI-C	Patient Global Impression of Change
PI	Principal Investigator
PK	Pharmacokinetics
PK/PD	Pharmacokinetic / Pharmacodynamic
PPI	Proton Pump Inhibitor
PROMIS	Patient-Reported Outcomes Measurement Information System
Q	Quartile
QD	Once Daily
QOL	Quality of Life
RBC	Red Blood Cell
SAE	Serious Adverse Event
SCD	Sickle Cell Disease
SD	Standard Deviation
TCD	Transcranial Doppler
TEAE	Treatment-Emergent Adverse Event
UGT	Uridine Diphosphate Glucuronosyltransferase
VOC	Vaso-Occlusive Crisis