CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216157Orig1s000

SUMMARY & CLINICAL REVIEW(S)

Deputy Division Director Summary Review

Application Type	NDA
Application Number	NDA 216157
Completion Date	December 16, 2021
Division/Office	Division of Nonmalignant Hematology (DNH)/Office of Cardiology, Hematology, Endocrinology, and Nephrology (OCHEN)
Deputy Division DIrector Name	Albert Deisseroth MD, PhD
Established (Proper) Name	Voxelotor
Proprietary Name	Oxbryta
Applicant	Global Blood Therapeutics, Inc.
Regulatory Recommendation	Accelerated Approval
Recommended Indication(s)/Population(s)	For the treatment of Sickle Cell Disease in pediatric patients 4 year of age and older

Documents	Reviewers
Primary Clinical and Team Leader Review	Patricia O'Neal and Tanya Wroblewski
CDTL Summary Review	Tanya Wroblewski

Deputy Division Director Summary Review:

I concur with the review and conclusions of the Clinical Reviewer and the Team Leader expressed in the Team Leader Review for NDA 216157, saved in DARRTS on December 17, 2021.

Regulatory Recommendation of the Deputy Division Director DNH: Accelerated Approval

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/s/

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CLINICAL REVIEW

Application Type	Efficacy Supplement 006 and new dosing formulation NDA
Application Number(s)	sNDA 213137 and NDA 216167
Priority or Standard	Priority
Submit Date(s)	June 25, 2021
Received Date(s)	June 25, 2021
PDUFA Goal Date	December 25, 2021
Division/Office	Division of Non-Malignant Hematology
Reviewer's Name(s)	Patricia Oneal, MD
Cross Discipline Team Leader Reviewer's Name(s)	Tanya Wroblewski, MD
Review Completion Date	15 December 2021
Established/Proper Name	Voxelotor
(Proposed) Trade Name	OXBRYTA®
Applicant	Global Blood Therapeutics, Inc.
Dosage Form(s)	Tablets: 500 mg Tablets for oral suspension: 300 mg
Applicant Proposed Dosing Regimen(s)	<u>For sNDA 213137 S-006 and NDA 216167</u> <u>Recommended dosage:</u> •Adults and pediatric patients 12 years (b) (4) and older: 1500 mg orally once daily. •Pediatric patients 4 to less than 12 years: Dosing with OXBRYTA is based on body weight. If body weight is 40kg or greater, recommended dose is 1500mg, 20kg to less than 40kg, recommended dose is 900mg and if 10kg to less than 20kg, recommended dose is 600mg. <u>Recommended dosage for severe hepatic impairment (Child Pugh C):</u> •Adults and pediatric patients 12 years (b) (4) and older: 1000 mg orally once daily. •Pediatric patients 4 to less than 12 years: Reduce the dose of OXBRYTA based on body weight.
Applicant Proposed Indication(s)/Population(s)	<u>For sNDA 213137 S-006 and NDA 216167</u> For the treatment of sickle cell disease in adults and pediatric patients 4 years of age and older
Recommendation on Regulatory Action	<u>Accelerated Approval for sNDA 213137 S-006 and NDA 216167</u> Indicated for the treatment of sickle cell disease in adults and pediatric patients 4 years of age and older. This indication is approved under accelerated approval based on increase in hemoglobin (Hb). Continued approval for this indication may be

	contingent upon verification and description of clinical benefit in confirmatory trials.
Recommended Indication(s)/Population(s) (if applicable)	For the treatment of sickle cell disease in adults and pediatric patients 4 years of age and older

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Glossary

AC	advisory committee
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
HGB	hemoglobin
ICH	International Council for Harmonization
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application

NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
RBC	red blood cell
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SCD	sickle cell anemia
SGE	special government employee
SOC	standard of care
TCD	transcranial doppler
TEAE	treatment emergent adverse event

1. Executive Summary

1.1. Product Introduction

Voxelotor (GBT440, OXBRYTA®) is an orally administered, hemoglobin S (Hgb S) polymerization inhibitor which binds with 1:1 stoichiometry and exhibits preferential partitioning to red blood cells (RBCs). By increasing the affinity of Hb for oxygen, voxelotor demonstrates dose-dependent inhibition of HbS polymerization.

The Applicant was granted accelerated approval for voxelotor 500-mg oral dose for the treatment of sickle cell disease (SCD) in adults and patients 12 years of age and older on November 25, 2019.

Efficacy Supplement 006 to NDA 213137: The Applicant seeks an extension of the authorized sickle cell population to lower the indicated age range for voxelotor in treatment of sickle cell disease to pediatric patients 4 years of age and older.

NDA 216157: This NDA introduces a voxelotor tablet for oral suspension (300mg tablets). The tablets are intended to be dispersed in water or clear liquid vehicle before administration, giving a dispersion suitable for administration to pediatric population and adults unable to tolerate tablets. The proposed indication for the oral suspension tablets is the same as the proposal for the 500mg tablets under sNDA 213137 S006: treatment of sickle cell disease in adults and pediatric patients 4 years and older.

1.2 Conclusions on the Substantial Evidence of Effectiveness

The Applicant has provided substantial evidence of effectiveness of voxelotor to extend the indicated age range to pediatric patients 4 years and older for the following indication: the treatment of sickle cell disease (SCD) in adults and pediatric patients 4 years of age and older under accelerated approval as described in 21 CFR 314.500 (subpart H).

Evidence of effectiveness for pediatric patients with SCD 4 years to < 12 years of age is based on the results of Study GBT440-007 (Part C) (HOPE KIDS), an ongoing, Phase 2a, multicenter, four-part, open-label, single-and multiple-dose study. Part C of the trial enrolled 45 pediatric patients between 4 to less than 12 years of age with Hgb SS or Hgb $S\beta^0$thalassemia who were administered a weight-based dosing of voxelotor using a dispersible oral tablets for 24 weeks.

Efficacy was demonstrated by hemoglobin response defined as an increase of > 1g/dL at 24 weeks of 35.6% (95% CI: 21.6, 49.5) years in the treated population (took at least one dose of

voxelotor) at Week 24. No outlier subgroups were observed. Efficacy was further supported by demonstration of improvement in measures of hemolysis: mean change from baseline for hemoglobin, indirect bilirubin and reticulocyte count. The weight-based dosing for pediatric patients with SCD 4 to < 12 years of age is further supported by the Applicant's updated population pharmacokinetic (PK) analysis and achieved similar exposures of voxelotor in whole blood and plasma compared with the 1500mg dose given to adults and pediatric subjects aged ≥ 12 years.

The HOPE KIDS study included a sufficient number of pediatric patients age 4 to < 12 years of age to assess efficacy and safety. Overall, demographics, baseline characteristics are representative of a pediatric SCD population. Therefore, the study results are applicable to pediatric patients with SCD in clinical practice.

There are numerous published natural history studies in patients with SCD demonstrating that without therapeutic intervention, the chronic hemolysis does not improve, nor do vaso-occlusive crisis (VOCs), acute chest syndrome and other sickle cell disease complications. Therefore, the laboratory abnormalities and hemolysis measurement findings do not resolve spontaneously in SCD, even in setting of ongoing hydroxyurea (HU) use and the findings in the HOPE KIDS trial establishes compelling evidence of a drug effect.

Furthermore, the disease and treatment outcomes are similar between pediatric patients and adults, therefore it is reasonable to partially extrapolate efficacy and pharmacokinetic and pharmacodynamic (PK/PD) data from an adequate and well-controlled study in an adult population along with updated PK data. Therefore, the prior determination of effectiveness of voxelotor for the treatment of SCD in adults is further evidence of effectiveness applicable to pediatric patients age 4 to < 12 years of age.

The rationale for recommendation for accelerated approval is that while an increase in hemoglobin represents substantial evidence of effect, it is not entirely clear that an increase of a gram per deciliter or more of hemoglobin due to voxelotor results in tangible benefit to patients. For that reason, voxelotor received accelerated approval with the initial approval for adults and adolescents 12 years of age and older and why this extension of the indication to pediatric patients ages 4 to less than 12 years of age also will receive an accelerated approval with a post-marketing requirement to provide evidence of clinical benefit. During negotiations with the Applicant several proposals for clinical benefit were discussed and at this time, the Applicant has chosen to demonstrate that improvement in hemoglobin due to voxelotor is associated with a reduction in cerebral blood flow velocity as assessed by transcranial doppler (TCD) velocity. The Applicant has an ongoing controlled study (STUDY GBT 440-032) to confirm the clinical benefit of voxelotor by evaluating the effect of voxelotor on stroke risk reduction as measured by TCD velocity in patients with sickle cell anemia and will include patients aged < 12

years as the confirmatory trial under subpart H. Please refer to the original NDA clinical and summary reviews (November 24, 2019) for additional details and discussion.

In summary, the results of HOPE indicate that the use of weight-based dosing of voxelotor (dispersible tablets) in pediatric patients age 4 to < 12, demonstrates a treatment effect in terms of increase in hemoglobin and improvement in measurements of hemolysis.
The toxicity profile is manageable, and the most frequently reported adverse reactions (incidence > 10%) reported in pediatric patients 4 to < 12 years are pyrexia, vomiting rash, abdominal pain, diarrhea and headache. SCD-related events, such as sickle cell anemia with crisis and acute chest syndrome were anticipated based on the underlying disease of SCD. The frequencies of these events did not raise concern that voxelotor was precipitating or increasing the risk for occurrence of these SCD events. There were no new safety signals observed.

Approval based on a single adequate and well-controlled trial in 45 pediatric patients with SCD, and partial extrapolation of efficacy and PK/PD from the adult study and updated population PK and exposure-response (E-R) data is appropriate given the rarity and seriousness of SCD in pediatric patients and the unmet medical need for new therapeutics in younger pediatric patients. The Sponsor has an ongoing confirmatory trial, GBT440-032.

NDA 216167

The Applicant conducted a relative bioavailability study (Study 0113) to demonstrate that the dispersible tablet (900mg) is bioequivalent to the F1 tablet (300mg). The C_{max}, AUC_t, and AUC_{inf} were all approximately 10% lower for voxelotor when administered as a single 900mg dispersible tablet compared to 3 x 300mg tablets. The 10% lower overall exposure following administration of the voxelotor dispersible tablet is not expected to have any clinical relevance. In this NDA, Applicant is seeking approval of the 300mg dispersible tablets because only the 300mg dispersible tablets were tested in Study 007 (Part C, 4-17 yrs. old). Although Study 0113 tested the 900mg dispersible tablet strength, not the 300mg, the 300mg dispersible tablet and the 900mg dispersible tablet strengths are adequately bridged because they are compositionally proportional and have comparable dissolution profiles.

The Applicant also provided data from Study 0114 to support the bioequivalence between the F2 tablet (900mg) and the F1 tablets (300mg). The C_{max}, AUC_t and AUC_{inf} were all similar for voxelotor when administered as a single 900mg F2 tablet compared to a 3 x 300mg F1 tablet. Study 0114 was reviewed during the original NDA and was found to be acceptable.

The bridge established among the F1 tablet (300mg), the F2 tablet (300mg) the approved oral tablet (500mg) during the original NDA and results from Study 0113, the clinical pharmacology team found it is acceptable to claim that the dispersible tablet (300mg), normalized to administered dose, is bioequivalent to the approval oral tablet (500mg).

The Office of Product Quality reviewed the manufacturing and recommended approval of dispersible tablets.

1.3 Benefit-Risk Assessment

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Benefit-Risk Integrated Assessment

Sickle cell disease (SCD) is an inherited disorder caused by a mutation in the B-globin gene resulting in the polymerization of deoxygenated HbS and resultant sickling of RBCs. SCD is characterized clinically by hemolytic anemia and recurrent painful vasoocclusive crisis (VOC) and acute chest syndrome (ACS), priapism as well as progressive multiple end-organ damage including stroke/silent cerebral infarct, chronic kidney disease, leg ulcers, and pulmonary hypertension and sickle cell anemia-associated nephropathy[4-10]. Sickle cells undergo hemolysis with typical red blood life span of 17 days leading to chronic compensated anemia with general hemoglobin levels of approximately 8 to 10g/dL. Acute drops in hemoglobin occur due to aplastic crisis, which is frequently due to infections, splenic sequestrations and can occur in settings of acute painful crisis and acute chest syndrome. There is no spontaneous improvement in hemoglobin levels to normal hemoglobin levels in patients with sickle cell disease.

There are two FDA approved agents for younger pediatric patients (< 12 years of age): Droxia®/Siklos® (Hydroxyurea) is indicated to reduce the frequency of painful crises and to reduce the need for blood transfusions in patients with sickle cell anemia with recurrent moderate to severe painful crises and Endari® (L-Glutamine) is indicated to reduce the acute complications of sickle cell disease in adult and pediatric patients 5 years of age and older. Despite the availability of hydroxyurea and L-glutamine, all of which have demonstrated effectiveness in reducing the number of VOC pain or acute chest syndromes episodes, a significant need still exists for effective treatments. Interventions that may reduce hemolysis resulting in an increase in blood hemoglobin levels may confer a clinical benefit in patients with SCD.

Voxelotor is an orally administered hemoglobin S (Hgb S) polymerization inhibitor which binds with a 1:1 stoichiometry and exhibits preferential partitioning to red blood cells (RBCs). By increasing the affinity of Hb for oxygen, voxelotor demonstrates dose-dependent inhibition of HbS polymerization. Voxelotor received accelerated approval for the treatment of SCD in adults and pediatric patients 12 years of age and older based on increase in Hgb at 24 weeks in the Phase 3 Study GBT440-031 on November 25, 2019. In Study GBT440-031 (90 adolescent and adult patients) treated with 1500mg voxelotor compared to the number of patients (N=90) treated with placebo who had one gram per deciliter of hemoglobin rise in hemoglobin levels from baseline at Week 24 was 51.2% versus 6.2%, respectively ($p < 0.001$). The rationale for accelerated approval is that while an increase in hemoglobin represents substantial evidence of effect, it is not entirely clear that an increase of a gram per deciliter or more of hemoglobin due to voxelotor results in tangible benefit to patients. For that reason, voxelotor received accelerated approval with initial approval and why this extension of the indication to pediatric patients ages 4 to < 12 years of age also will receive an accelerated approval with a post-marketing requirement to provide evidence of clinical benefit. During negotiations with the Applicant several proposals for clinical benefit were discussed and the Applicant has chosen to demonstrate that improvement in hemoglobin

due to voxelotor is associated with a reduction in cerebral blood flow velocity as assessed by transcranial doppler (TCD) velocity. The Applicant has an ongoing controlled study (STUDY GBT 440-032) to confirm the clinical benefit of voxelotor by evaluating the effect of voxelotor on stroke risk reduction as measured by TCD velocity in patients with sickle cell anemia and will include patients aged ≤12 years as the confirmatory trial under subpart H. Please refer to the original NDA multidisciplinary reviews (November 25, 2019) for additional details and discussion.

NDA 213137 S-006

This supplemental application is supported by the results of Study GBT440-007 (Part C) an open-label, multicenter study in 56 patients (45 pediatric patients between 4 to less than 12 years of age and 11 patients are between 12-17 years of age) with Hgb SS or Hgb SB^0Thalassemia who were administered voxelotor 1500 mg orally daily (or weight based dosing for subjects aged 4-to less than 12 years of age) for 24 weeks. The primary efficacy population is patients age 4 to < 12 years of age and the mean age was 7 years (range 4 to 11). Overall, demographics, baseline characteristics were representative of the pediatric SCD population and the study results are appliable to pediatric patients with SCD in in clinical practice.

The efficacy outcome was hemoglobin response defined as a hemoglobin increase of > 1g/dL at 24 weeks and was 47.1% (95% CI: 30.3, 63.8) and 35.6% (95% CI:21.6, 49.5) for subjects aged 4 to less than 12 years of age in the Efficacy Evaluable (EE) and treated population at Week 24, respectively. No outlier subgroups were observed. The EE population exclude 11 subjects who were treated with the study drug in the 4 to < 12 years age group and thus reduced the analysis sample size by 24% and may not be reliable, therefore the treated population should be used in the prescribing information and to inform the efficacy outcome. Voxelotor weight based dosing in subjects with SCD ages 4 to <12 years in Study GBT440-007 also showed that improvement in clinical measures of hemolysis at Week 24 were consistent with results in subjects age ≥12 years who received voxelotor 1500mg in Study GBT440-031. There was similar improvements in hemoglobin from baseline to Week 24 in GBT440-031 with mean change of 1.0g/dL (1.21) in Study GBT440-007 and LS mean change (SE) of 1.13 g/dL (0.132 g/dL) in GBT440-031. Similar improvements in clinical measure of hemolysis of indirect bilirubin from baseline to week 24: mean percent change (SD) of -38.6% (28.2%) and LS mean percent change (SE) of -29.1% (3.5%),respectively.

In addition in GBT440-007, 6 of the 8 subjects aged 4 to 17 years with conditional TCD flow velocity at baseline reverted to normal TCD flow velocity at Week 24, with a mean change of -18.4 cm/sec in subjects with conditional TCD at baseline (n = 8). No subject converted to an abnormal TCD flow velocity (≥ 200 cm/sec) after treatment with voxelotor.

The weight-based dosing for pediatric patients with SCD 4 to < 12 years of age is further supported by the Applicant's updated population pharmacokinetic (PK) analysis and achieved similar exposures of voxelotor in whole blood and plasma compared with the 1500mg dose given to adults and pediatric subjects aged ≥ 12 years. The proposed dosing regimen achieves the target% Hb occupancy (i.e. 20-30%) at Cmin in subjects older than equal to 4 years. Overall, the analyses suggest that the exposure-response (E-R) relationship for Hgb change from baseline is comparable between pediatric patients 4 to 11 years and patients 12 years and older and further supports the Applicant's proposed body weight-based dosing regimen for voxelotor in patients aged 4 to <12 years.

There are numerous published natural history studies in patients with SCD demonstrating that without therapeutic intervention, the chronic hemolysis does not improve, nor do VOCs, acute chest syndrome and other sickle cell disease complications. Therefore, the laboratory abnormalities and findings do not resolve spontaneously in SCD, even in setting of concomitant hydroxyurea (HU) and the findings in the HOPE Kid trial establishes compelling evidence of a drug effect. Although a clinical benefit such as decrease in VOCs or stroke reduction has not yet been established for voxelotor, the Applicant has an ongoing trial (HOPE KIDS 2) as part of accelerated approval under Subpart H.

The safety population in the 4 to < 12 age group included 45 patients. For patients in this age group, 77.8% (35/45) of patients completed 24 weeks of treatment, and 58% (26/45) completed 48 weeks of treatment. No deaths were reported in Study GBT440-007 Part C. The most common serious adverse events (both SCD and non-SCD) greater than > 5% were hypersplenism (6.7%), pneumonia (8.9%), pyrexia (11.1%) and acute chest syndrome (28.9%). Most of these can be considered disease related although pyrexia can be considered non-SCD adverse event. The most frequently reported adverse reactions (incidence > 10%) reported in pediatric patients 4 to < 12 years are pyrexia, vomiting rash, abdominal pain, diarrhea and headache. SCD-related events, such as sickle cell anemia with crisis and acute chest syndrome were anticipated based on the underlying disease of SCD. The frequencies of these events did not raise concern that voxelotor was precipitating or increasing the risk for occurrence of these SCD events.

Potential theoretic risks with voxelotor include tissue hypoxia due to ineffective tissue oxygen extraction with the high Hgb occupancy from voxelotor-bound hemoglobin and this theoretical risk of tissue hypoxia could lead to end-organ dysfunction. Overall, no clinical safety concerns with inadequate tissue oxygenation were identified in the voxelotor program to date.

Overall, the benefit-risk profile is favorable for voxelotor in pediatric patients (4 to < 12 years) for the treatment of SCD. The HOPE Kids study was an adequate and well-controlled trial and provided sufficient data to establish weight-based dosing of voxelotor (tablets or tables oral suspension) as an effective treatment for pediatric patients with SCD as demonstrated by a treatment effect of an increase in hemoglobin.

Furthermore, the course of disease and voxelotor' s treatment effects are sufficiently similar in adults and pediatric patients and the review team concludes that partial extrapolation of efficacy and PK/PD from the adequate and well-controlled study in adults (GBT440-032) supplemented with updated population PK analysis is appropriate given the rarity and seriousness of SCD in pediatric patients and the unmet medical need for new therapeutics in pediatric patients. The HOPE KIDs study demonstrated a tolerable safety profile for voxelotor weight-based dosing using a dispersible tablet in subjects with SCD aged 4 to < 12 years of age and the safety profile was similar with the safety profile in subjects with SCD aged 12 years and older with no new safety observations. The risks of voxelotor can be adequately addressed in labeling.

NDA 216167

The Applicant conducted a relative bioavailability study (Study 0113) to demonstrate that the dispersible tablet (900mg) is bioequivalent to the F1 tablet (300mg). The C_{max}, AUC_t, and AUC_{inf} were all approximately 10% lower for voxelotor when administered as a single 900mg dispersible tablet compared to 3 x 300mg tablets. The 10% lower overall exposure following administration of the voxelotor dispersible tablet is not expected to have any clinical relevance. In this NDA, Applicant is seeking approval of the 300mg dispersible tablets because only the 300mg dispersible tablets were tested in Study 007 (Part C, 4-17 yrs. old) the pivotal study in pediatric patients with sickle cell disease. Although Study 0113 tested the 900mg dispersible tablet strength, not the 300mg, the 300mg dispersible tablet and the 900mg dispersible tablet strengths are adequately bridged because they are compositionally proportional and have comparable dissolution profiles.

The Applicant also provided data from Study 0114 to support the bioequivalence between the F2 tablet (900mg) and the F1 tablets (300mg). The C_{max}, AUC_t and AUC_{inf} were all similar for voxelotor when administered as a single 900mg F2 tablet compared to a 3 x 300mg F1 tablet. Study 0114 was reviewed during the original NDA and was found to be acceptable.

The bridge established among the F1 tablet (300mg), the F2 tablet (300mg) the approved oral tablet (500mg) during the original NDA and results from Study 0113, the clinical pharmacology team found it is acceptable to claim that the dispersible tablet (300mg), normalized to administered dose, is bioequivalent to the approval oral tablet (500mg). The voxelotor dispersible tablets provide the benefit of available as an oral solution so it can be administered to younger age groups as well as older patients who cannot tolerate tablets.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• SCD is an inherited hematological disorder characterized by sickled hemoglobin due to mutation in beta globin gene that leads to faulty hemoglobin protein, called Hemoglobin S. Hemoglobin S changes flexible red blood cells into rigid sickle cells. • SCD manifests clinically with chronic hemolytic anemia and recurrent painful vasoocclusive crisis (VOC), and progressive multiple end-organ damage. • The cumulative effect of recurrent vasoocclusive episodes and sustained hemolytic anemia result in multiple end-organ complications including diastolic heart disease, pulmonary hypertension, splenic dysfunction, hepatobiliary disease and chronic kidney disease. Further consequences that start in childhood include cognitive dysfunction and stroke, increases risk of infections and premature mortality. In absence of primary prevention, 11% of children with Hemoglobin SS SCD experience and overt stroke by age 18. • Chronic compensated hemolysis occurs in all patients with SCD with only 17 day lifespan of the red blood cell. Average hemoglobin ranges from 8-10 g/dL with no improvements to normal levels. The chronic hemolysis is exacerbated by acute hemolytic crisis due to infections, hypersplenism or other SCD complications. • The course of SCD in pediatric patients is similar to the course of disease in adult patients with same underlying pathophysiology of a single-point mutation on the β-globin subunit of hemoglobin resulting in mutant form of hemoglobin Hgb S). The clinical sequalae include VOC, acute chest syndrome, priapism, stroke and splenic sequestration. Adults experiencing the same symptoms as children but the disease	Sickle Cell Disease is a serious and life threatening condition with significant morbidity and mortality and reduced life expectancy. Hemoglobin is a laboratory measurement and represents an endpoint that can be measured earlier than irreversible morbidity or mortality and reasonably likely to predict clinical benefit in patients with SCD. The organ dysfunction that occurs in SCD progresses slowly and is related to the chronic hemolytic anemia. Hemoglobin does not improve spontaneously in patients with SCD. The hemoglobin level in patients with sickle cell disease is one measure that reflects the severity and clinical course of the disease. Patients with lower hemoglobin levels have an increased risk for end-organ complications to include chronic kidney disease, pulmonary hypertension, stroke and silent cerebral infarctions and early mortality.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	manifestations worsen as the patients age include leg ulcers, sickle retinopathy, nephropathy, pulmonary hypertension, transfusional iron overload, avascular necrosis.	Course of SCD is similar in adults and pediatric patients with onset of symptoms around 6 months of age with symptoms worsening in adult hold due to patients age and comorbidities.
Current Treatment Options	• There are two FDA-approved medications for pediatric patients with sickle cell disease and only two for patients < 12 years of age. o Siklos® (Hydroxyurea) is indicated to reduce the frequency of painful crises and to reduce the need for blood transfusions in pediatric patients, 2 years of age and older with sickle cell anemia with recurrent moderate to severe painful crises. o Endari® (L-Glutamine) is indicated to reduce the acute complications of sickle cell disease in adult and pediatric patients 5 years of age and older. Additional FDA approved medications for patients greater than 12 years with SCD include: • Voxelotor is indicated for the treatment sickle cell disease adults and 12 years and older (accelerate approval). • Crizanlizumab is approved for the reduction of vaso-occlusive crisis in patients aged 16 years and older who have sickle cell anemia. • Hematopoietic stem cell transplantation (HSCT) offers potential cure. Only a small percentage of patients are eligible for this treatment option. • Management of acute sickle cell episodes is generally only supportive.	There is still an unmet medical need existing in therapies available for pediatric patients with sickle cell disease.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	o Blood transfusions and red cell exchanges: RBC transfusion are used to treat anemia, while RBC exchange transfusions are used to prevent or treat the complications arising from the presence of Hgb S. Red cell exchange can reduce the Hgb S percentage without a significant increase in hematocrit or blood viscosity or provision of excess iron. o Pain medications (including NSAIDS and opiates) are used for acute pain relief. o Other supportive therapies include intravenous fluids, supplemental oxygen, etc.	
Benefit	sNDA 213137 • Study GBT440-007 (Part C) an open-label, multicenter study in 56 patients (45 pediatric patients between 4-<12years of age and 11 patients between 12-17 years of age) with Hgb SS or Hgb SB^0Thalassemia who were administered voxelotor 1500 mg orally daily (or weight based dosing for subjects aged 4-11 using tables for oral suspension) for 24 weeks. Voxelotor doses of 600mg, 900mg, or 1500mg once daily were administered to patients weighing 10kg to < 20kg, 20kg to < 40kg, or > 40kg, respectively and 1500mg once daily for patients 12 to < 17 years of age. • The 4 to < 12 year old age group provided the basis for this application. Patients were enrolled if baseline hemoglobin was < 10.5 g/dL and most patients were receiving background hydroxyurea therapy (80%). Median age was 7 (range 4, 11) in the 4-< 12 year old age group and their mean baseline Hb was 8.6g/dL (range 6.1, 10.5 g/dL). The efficacy outcome was hemoglobin response defined as a hemoglobin increase of > 1g/dL at 24 weeks and was 47.1% (95% CI: 30.3, 63.8) and 35.6% (95% CI:21.6, 49.5)	Voxelotor has demonstrated evidence of efficacy of 35.6% (95% CI: 21.6, 49.5) in the all treated population. This response is considered a meaningful treatment effect in terms of hemoglobin response in pediatric patients. Even the lower bound of the confidence interval of 21% is considered a meaningful treatment effect as patients with SCD will not have a spontaneous improvement in hemoglobin levels. Partial extrapolation of efficacy from adult population is acceptable given similar disease course and sufficiently similar response to therapy in adolescent and adult patients as well as updated population PK

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	for subjects aged 4 to less than 12 years in the Efficacy Evaluable (EE) and treated population at Week 24, respectively. No outlier subgroups were observed. The EE population excluded 11 subjects who were treated with the study drug in the 4 to < 12 years age group and thus reduced the analysis sample size by 24% and may not be reliable, therefore the treated population should be used in the prescribing information. • The weight-based dosing for pediatric patients with SCD 4 to < 12 years of age is supported by the data from Study GBT440-007, Part C. Based upon the Applicant's updated population PK analysis, voxelotor PK exposures in plasma and whole blood in patients aged 4 to < 12 years are similar to those in patients 12 years and older. The proposed dosing regimen achieved the targeted% Hb occupancy (i.e. 20-30%) at the C_{min} in subjects aged ≥4 years. • In the adolescent and adult study (GBT440-031/HOPE), an adequate and well-controlled trial, the hemoglobin response rate was 51.1% compared to 6.5% in the placebo group (p< 0.001). Voxelotor weight based dosing in subjects with SCD ages 4 to < 12 years showed that improvement in Hb and clinical measures of hemolysis at Week 24 in subjects aged 4 to < 12 years were consistent with results in subjects age > 12 years who received voxelotor 1500mg in Study GBT440-031: o Similar improvements for hemoglobin from baseline to Week 24 in GBT 440-007 (HOPEKIDS) to GBT440-031 (HOPE) with mean change of 1.0g/dL (1.21) and least square (LS) mean change (SE) of 1.13 g/dL (0.132 g/dL), respectively. o Similar improvements in clinical measure of hemolysis of indirect bilirubin from baseline to week 24: mean percent change (SD) of -	analysis demonstrating similar E-R in the 4-11 age group to patients 12 years and older. A bridge was established among the F1 tablet (300mg), the F2 tablet (300mg) the approved oral tablet (500mg) during the original NDA and BA study results from Study 0113. It is acceptable to claim that the dispersible tablet (300mg), normalized to administered dose, is bioequivalent to the approval oral tablet (500mg).

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	38.6% (27.2%) in HOPEKIDS and LS mean percent change (SE) of -29.1% (3.5%) in HOPE. NDA 216167 The Applicant conducted a relative bioavailability study (Study 0113) to demonstrate that the dispersible tablet (900mg) is bioequivalent to the F1 tablet (300mg). The C_{max}, AUC_t, and AUC_{inf} were all approximately 10% lower for voxelotor when administered as a single 900mg dispersible tablet compared to 3 x 300mg tablets. The 10% lower overall exposure following administration of the voxelotor dispersible tablet is not expected to have any clinical relevance. In this sNDA, Applicant is seeking approval of the 300mg dispersible tablets because only the 300mg dispersible tablets were tested in Study 007 (Part C, 4-17 yrs. old). Although Study 0113 tested the 900mg dispersible tablet strength, not the 300mg, the 300mg dispersible tablet and the 900mg dispersible tablet strengths are adequately bridged because they are compositionally proportional and have comparable dissolution profiles. The Applicant also provided data from Study 0114 to support the bioequivalence between the F2 tablet (900mg) and the F1 tablets (300mg). The C_{max}, AUC_t and AUC_{inf} were all similar for voxelotor when administered as a single 900mg F2 tablet compared to a 3 x 300mg F1 tablet. Study 0114 was reviewed during the original NDA and was found to be acceptable.	

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	• Safety population in the 4-< 12 age group included 45patients. The median age was 7 (range 4, 11). • For patients aged 4 to 11 years, 77.8% (35/45) of patients completed 24 weeks of treatment, and 58% (26/45) completed 48 weeks of treatment. • No deaths were reported in Study GBT440-007 Part C. • Most common serious adverse events (both SCD and non-SCD) greater than > 5% were hypersplenism (6.7%), pneumonia (8.9%), pyrexia (11.1%) and acute chest syndrome (28.9%). Most of these can be considered disease related although pyrexia can be considered non-SCD adverse event. • The most frequently reported adverse reactions (incidence > 10%) reported in pediatric patients 4 to < 12 years are pyrexia, vomiting rash, abdominal pain, diarrhea and headache. • SCD-related events, such as sickle cell anemia with crisis and acute chest syndrome were anticipated based on the underlying disease of SCD. The frequencies of these events did not raise concern that voxelotor was precipitating or increasing the risk for occurrence of these SCD events. • Potential theoretic risks with voxelotor include tissue hypoxia due to ineffective tissue oxygen extraction with the high Hgb occupancy from voxelotor-bound hemoglobin and this theoretical risk of tissue hypoxia could lead to end-organ dysfunction. Overall, no clinical safety concerns with inadequate tissue oxygenation were identified in the voxelotor program to date.	Voxelotor weight-based dosing in subjects with SCD aged 4 to 11 years demonstrated an acceptable safety profile with no new safety signals. The safety profile was similar with the safety profile in subjects with SCD aged 12 years and older with no new safety observations. The product label adequately addresses the risk of using voxelotor in this pediatric patient population. Warnings and Precautions include hypersensitivity reactions and laboratory test interference. The long term safety of voxelotor will be assessed with ongoing post-marketing requirements and commitments.

1.4 Patient Experience Data

Patient experience data was not assessed in this application. However, a Taste and Palatability Questionnaire was administered to the caregiver/legal guardian and/or children (≥ 6 years old) at Week 2 and Week 12 who received the dispersible tablets. This questionnaire was also administered to the caregiver/legal guardian and/or children (all ages) at the formulation transition visit which occurred within 30 days the powder for oral suspension was available.

Patient Experience Data Relevant to this Application (check all that apply)

☐	The patient experience data that was submitted as part of the application include:			Section where discussed, if applicable
	☐	Clinical outcome assessment (COA) data, such as		[e.g., Sec 6.1 Study endpoints]
		☐	Patient reported outcome (PRO)	
		☐	Observer reported outcome (ObsRO)	
		☐	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		[e.g., Sec 2.1 Analysis of Condition]
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify)		
☐	Patient experience data that were not submitted in the application, but were considered in this review:			
		☐	Input informed from participation in meetings with patient stakeholders	
		☐	Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Current Treatment Options]
		☐	Observational survey studies designed to capture patient experience data	
		☐	Other: (Please specify)	
☒	Patient experience data was not submitted as part of this application.			

2. Therapeutic Context

2.1. Analysis of Condition

Sickle-cell disease (SCD) is a life-threatening, hereditary, chronic hemolytic anemia that affects nearly 100,000 individuals in the United States (Yawn, Buchanan et al. 2014). The most common form of sickle-cell disease (homozygous Hb SS) accounts for 60%-75% of sickle cell disease in the United States.

During periods of deoxygenation, Hgb S polymerizes within erythrocytes resulting in intermittent vasoocclusive events and chronic hemolytic anemia. The cumulative effect of recurrent vasoocclusive episodes and sustained hemolytic anemia result in multiple end-organ complications including diastolic heart disease, pulmonary hypertension, splenic dysfunction, hepatobiliary disease and chronic kidney disease. Both the chronic anemia and hemolysis contribute markedly to the complications of sickle cell. In the brain, anemia leads to a decrease in arterial oxygen saturation, and places patients at risk for cerebral vascular events. Whereas in other organs like the kidney, hemolysis leads to the presentation of free hemoglobin to the kidneys, that in itself can cause acute kidney injury that can progress to chronic kidney disease. Hemolysis and free hemoglobin also lead to inflammation and the chronic inflammatory milieu compounding the acute and chronic sickle cell complications.

The clinical sequalae include VOC, acute chest syndrome, priapism, stroke and splenic sequestration are seen among children with SCD. As patients progress to adulthood, the complications present in childhood may worsen due to aging process and due to chronicity of ongoing damage to organs as well as development of comorbidities which include leg ulcers, sickle retinopathy, nephropathy, pulmonary hypertension, transfusional iron overload, avascular necrosis. Overall, the types of disease presentations (VOC, acute chest syndrome, pulmonary hypertension, stroke) still occur in both pediatric and adult patients with SCD.

As people with sickle cell disease get older, the impact of the anemia on daily functioning becomes more evident. As patients with SCD become older, often their anemia will worsen. This reflects early kidney disease and decreased production of erythropoietin, and potentially some decreased responsiveness of the bone marrow. Due to the chronic transfusions that patients have received, and number of transfusions increase as patients age, complications such as iron overload and alloimmunization can emerge in adolescence and adulthood; although they can also occur in earlier childhood. The hemoglobin level in patients with SCD is one measure that reflects the severity and clinical course of the disease. Patients with lower hemoglobin levels tend to have an increased risk for end-organ complications such as chronic

kidney disease, pulmonary hypertension, stroke and silent cerebral infarctions and early mortality.

GBT440, a small molecule which binds to the N-terminal α chain of Hgb, increases HbS affinity for oxygen, delays in vitro Hgb S polymerization and prevents sickling of red blood cells (RBCs). In a murine model of SCD, GBT440 was shown to extends the half-life of RBCs, reduces reticulocyte counts and prevents ex vivo RBC sickling. In SCD patients' RBCs were transiently (<1 min) exposed to hypoxic conditions in tissues, Hgb S modification with GBT440 at or below 30% was shown to be sufficient to achieve reduced ex vivo sickling while achieving Hgb occupancies >11%. It remains unclear if the quantitative increase in total hemoglobin levels by > 1 g/dL and evidence of reduction in hemolysis and reticulocyte counts would translate into a clinically meaningful impact on acute and chronic organ dysfunction implicated in this disease.

2.2. Analysis of Current Treatment Options

The goal of disease-modifying therapies is to target Hgb S polymerization, vasoocclusion and inflammation. Curative options, such as hematopoietic stem cell transplantation (HSCT) and gene therapy, strive to eliminate the production of HbS. Supportive therapies, such as antibiotic prophylaxis, have increased survival of children by preventing death from overwhelming infection, but have not increased overall life expectancy for people living with SCD. With the increasingly widespread use of disease-modifying and curative therapies, the life expectancy will increase and approach that of the average American in the near future.

Hydroxyurea has been used in the treatment of SCD for over 20 years to include the treatment of pediatric patients with SCD. Available therapies for pediatric patients age > 4 include hydroxyurea and L-Glutamine. The following table provides overview of available therapy for all patients with SCD.

Table 1: Summary of Treatment Armamentarium Relevant to Sickle Cell Disease

Product (s) Name	Relevant Indication	Year of Approval	Route and Frequency of Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments (e.g., subpopulation not addressed
FDA Approved Treatments [Combine by Pharmacologic Class, if relevant]						

APPEARS THIS WAY ON ORIGINAL

Hydroxyurea	For reducing the frequency of SCD crises in adult patients with SCD and reducing the frequency of painful crises and the need for blood transfusions	1998/ 2017/ 2021	15-30 mg/kg/day as a single daily dose	MSH Study: Resulted in a 44% reduction of VOCs and fewer episodes of ACS and fewer RBCs transfusions, higher hemoglobin and HbF levels, lower reticulocyte, neutrophil, and platelet counts	Myelosuppression, animal studies have demonstrated it to be a mutagen and teratogen, hyperpigmentation darkening of nail beds, hair thinning, nausea, headache, and small increases in creatinine because is cleared by the kidneys	HU-induced hemolytic anemia
L-Glutamine	Reduce the acute complications of sickle cell disease in adult and pediatric patients 5 years of age and older	July 2017	< 30 kg: 5 g Orally twice daily, 30- 65 kg: 10 g Orally twice daily, >65 kg: 15 g Orally twice daily	GLUSCC09-01 Study: # of VOCs were reduced by 25% in the L-glutamine group compared to placebo	Gastrointestinal side effects (constipation, abdominal pain, nausea)	N/A

Crizanlizumab-tmca	To reduce the frequency of vasoocclusive crises in adults and pediatric patients aged 16 years and older with sickle cell disease.	October 2019	Administer 5 mg/kg by intravenous (IV) infusion over a period of 30 minutes on Week 0, Week 2, and every 4 weeks thereafter (10 mg/mL)	SUSTAIN Study lower median annual rate of VOC leading to a healthcare visit compared to placebo (1.63 vs 2.98, respectively) (Hodges-Lehmann, median absolute difference of -1.01 VOC per year compared with placebo, 95%CI [-2.00, 0.00]), which was statistically significant (p=0.010). Nausea, arthralgia, back	Nausea, arthralgia, back pain and pyrexia.	Infusion-related reactions
Voxelotor *(Accelerated approval)*	Treatment of sickle cell disease in adults and pediatric patients 12 years of age and older.	November 2019	1,500 mg orally once daily with or without food; 1,000 mg orally once daily in patients with severe hepatic impairment	HOPE Study: The response rate (Hb increase of >1 g/dL from baseline to Week 24) was 51.1% (46/90) compared to 6.5% (6/92) in the placebo group ($p < 0.001$).	Headache, diarrhea, abdominal pain, nausea, fatigue, rash and pyrexia	N/A
Other Treatments – [Combine by Pharmacologic Class, if relevant]						
Gene Therapy	-	-	Offers possible	-	-	

Hematopoietic stem cell transplantation (HSCT)	-	-	Offers possible cure in patients eligible for this treatment.	-	-	Blood 2011
RBC Transfusions and RBC Exchange Transfusions	-	-	Treatment of anemia and reduction in Hb S %.	-	-	-
Penicillin	Reduce the rate of invasive pneumococcal disease in children less than 5 years of age		Children <3 years: Oral: 125 mg twice daily Children ≥3 years: Oral: 250 mg twice daily until age 5	PROPS Study (1986): 84% reduction in incidence of infection compared with placebo (13 of 110 patients vs. 2 of 105; P = 0.0025), with no deaths from pneumococcal septicemia	-	-
Folic Acid	Increase erythrocyte production in individuals with SCD at risk of folate deficiency		Any patient with SCD	No differences in hematologic indices or clinical complications compared to placebo	-	-

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Voxelotor was granted accelerated approval for the treatment of sickle cell disease in adults and pediatric patients 12 years of age and older on November 25, 2019.

3.2. Summary of Presubmission/Submission Regulatory Activity

Table 2: Regulatory History of Voxelotor

Date	Event Type	Purpose
October 7, 2015	Fast Track Designation Granted	-
December 29, 2015	Orphan Designation Granted (Designation #15-4997)	-
June 5, 2017	Rare Pediatric Disease Designation (RPD-(b) (4))	-
January 3, 2018	Breakthrough Therapy Designation	-
November 25, 2019	Accelerated Approval	Treatment of sickle cell disease in adults and pediatric patients ≥ 12 years of age
May 26, 2020	Type B Meeting	Discuss lowering the age limit for Voxelotor Share preliminary results of GBT440-007 (Part C)
March 30, 2021	Type B Meeting	Discuss results of ongoing GBT440-007 (Part C) Provide information on new dispersible tablet for pediatric patients Provide supplemental data from the completed Phase 3 GBT440-031 (pivotal study)

3.3. Foreign Regulatory Actions and Marketing History

The Applicant has submitted a marketing application for pediatric use of voxelotor in the European Union (EU) for similar proposed indication, which is pending final decision at the time of this review.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical

Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

St. Jude Children's Research Hospital and Children's Health Care of Atlanta were identified as sites for inspection by the Office of Scientific Investigations (OSI) on the basis of the single open-label study, GBT440-007, in support of NDA 213137.

Based on the results of the above inspection, there were no significant deficiencies identified during the inspection.

Table 3: OSI Inspections

Site Information	Inspection Dates	Number of Subjects	Findings
Sponsor Site # 01-015 Name: Jeremie Estepp, MD Address: St. Jude Children's Research Hospital 262 Danny Thomas Place; Mail Stop 802 Memphis, TN 38105 Email: jeremie.estepp@stjude.org Phone: (b) (6)	-	6 enrolled; 9 screened	No significant deficiencies
Sponsor Site# 01-018 Name: Robert Clark Brown, MD, PhD Address: Children's Health Care of Atlanta 5455 Meridian Mark Road NE 4th Floor MOB Atlanta, GA 30342 Email: clark.brown@choa.org Phone: (b) (6) Phone: (b) (6)		16 enrolled; 21 screened	No significant deficiencies

Please refer to the review by in DARRTS dated September 1, 2021 by Anthony Orencia, M.D., Ph.D.

4.2. Product Quality

sNDA 213137

This supplement is an efficacy supplement with proposal to lower the indicated age range for voxelotor from > 12 years of age to greater than 4 years of age with updated adverse reactions, drug-drug interactions and long-term safety and durability of response in adolescent and adult population.

The Applicant did not submit Environment Analysis in support of the original efficacy supplement and in response to an IR requesting for EA, the applicant submitted an amendment on July 6, 2021 with a request for categorical exclusion pursuant to 21 CFR 25.31 (b) for r the subject voxelotor NDA for the treatment of sickle cell disease. The Applicant stated that , "the estimated concentration of voxelotor at the point of entry into the aquatic environment (EIC), Expected Introductory Concentration) will be well below 1 part per billion. The Office of Product Quality agreed with the Applicant's request for categorical exclusion from EA is considered adequate from the product quality perspective and the request for categorical exclusion from EA may be granted. Please see the review by Pallaiah Thammana, Ph.D and Ramesh Raghavachari, Ph.D. for review.

NDA 216167

The Quality review was conducted by primary reviewers: Zhengfu Wang, Dhanaklakshmi Kasi, Binjie Liang, Jing Li, Grafton Adams and Dhanalakshmi Kasi. From the CMC/quality perspective, NDA 216157 is recommended for approval. As part of this action, an expiration period of (b) (4) months is granted for the 300mg product stored at (b) (4) 20 to (b) (4) degrees Celsius (68°F to (b) (4) °F).

The drug product, voxelotor tables, for oral use, 300mg is a new dosage form. The drug product formulation is an immediate release solid organ dosage from with a high drug content. The tablets are intended to be dispersed in water or clear liquid vehicle before administration, giving a dispersion suitable for administration to pediatric population. NDA 213137 is referenced for all CMC information related to the drug substance voxelotor and found adequate to support NDA 216157. The drug product manufacturing process involves (b) (4). Drug substance and drug product manufacturing, testing, and packaging facilities are adequate as per the facility review. The proposed dissolution acceptance criterion (NLT (b) (4) % (Q) in 15 minutes is deemed acceptable.

4.3. Clinical Microbiology

There was no product quality microbiology review required for this efficacy supplement.

4.4. Nonclinical Pharmacology/Toxicology

NDA 213137 S-006 and NDA 216167

The Applicant had two special protocol assessments for carcinogenicity studies under IND 121691 one each in mice and rats and submitted the final carcinogenicity study report in mice with the original NDA application. The Applicant submitted the final study report for a 104-week carcinogenicity study in Hsd: Sprague Dawley®SD® rats late in the review cycle (September 24, 2019) of the original NDA submission (SDN 27) and is being reviewed under Supplement 6. No other nonclinical studies under NDA 213137 or NDA 216157.

Review of the carcinogenicity in rats and the statistical analysis for trend and pairwise comparison is completed, however, results and interpretation should be first discussed by the ECAC. Once ECAC final conclusion is issued to the Applicant, the full carcinogenicity study in rats will be submitted to DARTTS. Labeling language in Section 13.1 was tentatively approved as proposed by the Applicant and will be revised bases on EAC conclusion. A supplement request letter asking the Applicant to insert specific language is an option to incorporate ECAC conclusion reflecting findings in the carcinogenicity study in rats.

Refer to the Nonclinical Pharmacology review by Pedro DelValle, Ph.D. in DARRTS dated October 29, 2019 of the original application for additional details.

4.5. Clinical Pharmacology

NDA 213137 S006

The clinical pharmacology review teams finds the efficacy supplement approvable.

The Applicant included the following clinical pharmacology related information in the United States Prescribing Information (USPI):

- A new, age-appropriate dispersible tablet dosage form (also referred to as tablet for oral suspension) for pediatric patients aged 4 to 11 years with SCD, including weight-based dosage and administration instructions.
- An update of the voxelotor pharmacokinetic parameter estimates based on the updated PK evaluation including data through 72 weeks from Study GBT440-031 in adult and pediatric patients aged 12 to 17 years with SCD.
- An update of the potential DDIs with coadministration of voxelotor with cytochrome P450 (CYP) 3A4 inhibitors and inducers and with sensitive CYP3A4 substrates.

The weight-based dosing for pediatric patients with SCD 4-11 years of age is supported by the data from Study GBT440-007, Part C. Based upon the Applicant's updated population PK

analysis, voxelotor PK exposures in plasma and whole blood in patients aged 4-11 years are similar to those in patients 12 years and older. The Applicant's E-R analysis for efficacy suggests a linear relationship (P<0.001) between Hgb change from baseline and time-matched whole blood voxelotor concentrations. The clinical pharmacology reviewer's independent analysis of the slope of the E-R relationship indicated that the difference in slope was minor (4 to < 6 years: 0.00707(95% CI: 0.0068-0.01337) versus overall: 0.00738 (95% CI: 0.00687-0.00789) and may be due to limited sample size (n=9) in this age group. Overall, the analyses suggest that the E-R relationship for Hgb change from baseline is comparable between pediatric patients 4 to 11 years and patients 12 years and older and further supports the Applicant's proposed body weight-based dosing regimen for voxelotor in patients aged 4 to 11 years.

The Applicant's E-R analyses for safety were performed for both SCD-related AEs and non-SCD related AEs. Similar to the previous analysis in the original NDA submission, there was no significant E-R relationship for the evaluated safety measures, except decreased WBC. The clinical pharmacologist reviewer's multivariate analysis showed age was not a significant covariate, demonstrating comparable E-R for Grade > 1 decreased WBC between patients 4-11 years and patients > 12 years. Overall, the ER relationships for safety measures were comparable between patients 4-11 years and patients > 12 years.

The Applicants population PK analyses are acceptable to support the proposed labeling changes in Section 12.3 of the USPI.

In this submission, the Applicant conducted a clinical DDI study (Study 018) with itraconazole in healthy subjects and about 10% increase in in voxelotor exposure was observed with itraconazole. The PBPK model was updated based on the clinical DDI data and then used to predict the effect of CYP3A4 modulators on the PK of voxelotor in healthy subjects and patients with SCD. The model predicted ketoconazole (400mg QD), a strong CYP3A4 inhibitor. to increase the voxelotor AUC by approximately 10% at steady state, therefore no dose adjustment is recommended when voxelotor is co-administered with a CYPE3A4 inhibitor. The model also evaluated rifampin and efavirenz and the recommended voxelotor doses are 2500mg with a strong CYP3A4 inducer and 2000mg with a moderate YCP3A4 inducer, respectively, if unavoidable.

The Applicants PNPK analysis is inadequate to evaluate the effect of fluconazole (moderate CYP3A4, CYP2C9 and strong CYP2C19 inhibitor and fluvoxamine (moderate CYPE3A4, strong CYP2C19 inhibitor and weak CYP2C9 inhibitor)on the PK of voxelotor.

The Applicant's proposed body weigh-based dosing regimen for voxelotor in patients aged 4 to 11 years are supported by comparable PK, E-R for both efficacy and safety in patients aged 12 years and above.

NDA 216167

The Applicant conducted a relative bioavailability study (Study 0113) to demonstrate that the dispersible tablet (900mg) is bioequivalent to the F1 tablet (300mg). The C_{max}, $AUC_{t,}$ and AUC_{inf} were all approximately 10% lower for voxelotor when administered as a single 900mg dispersible tablet compared to 3 x 300mg tablets. The 10% lower overall exposure following administration of the voxelotor dispersible tablet is not expected to have any clinical relevance. In this NDA, Applicant is seeking approval of the 300mg dispersible tablets because only the 300mg dispersible tablets were tested in Study 007 (Part C, 4-17 yrs. old) the pivotal study in pediatric patients with sickle cell disease. Although Study 0113 tested the 900mg dispersible tablet strength, not the 300mg, the 300mg dispersible tablet and the 900mg dispersible tablet strengths are adequately bridged because they are compositionally proportional and have comparable dissolution profiles.

The Applicant also provided data from Study 0114 to support the bioequivalence between the F2 tablet (900mg) and the F1 tablets (300mg). The C_{max}, AUC_t and AUC_{inf} were all similar for voxelotor when administered as a single 900mg F2 tablet compared to a 3 x 300mg F1 tablet. Study 0114 was reviewed during the original NDA and was found to be acceptable.

The bridge established among the F1 tablet (300mg), the F2 tablet (300mg) the approved oral tablet (500mg) during the original NDA and BA study results from Study 0113, the clinical pharmacology team found it is acceptable to claim that the dispersible tablet (300mg), normalized to administered dose, is bioequivalent to the approval oral tablet (500mg).

It was concluded that the dispersible tablet (300 mg), normalized to administered dose, is bioequivalent to the approved oral tablet (500 mg). Based on the Applicant's updated population PK analysis, voxelotor PK exposures in plasma and whole blood in patients aged 4-11 years are similar to those in patients 12 years and older. No dose adjustment was recommended when voxelotor is co-administered with a CYP3A4 inhibitor. The recommended voxelotor doses are 2500 mg with a strong CYP3A4 inducer and 2000 mg with a moderate CYP3A4 inducer, respectively, if unavoidable.

Refer to the Clinical Pharmacology review by Lin Zhou, Ph.D. and Sudharshan Hariharan, Ph.D. and Ye Yuanm Ph.D. as well as Pharacometics team with Jianghong Fan, Ph.D. (PBPK) and Liang Li, Ph.D. and Xinyuan Zhangm Ph.D. in DARRTS dated December 01, 2021.

4.6. Devices and Companion Diagnostic Issues

There were no companion device or diagnostic included in the application.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Study GBT440-007 is an ongoing, Phase 2a, multicenter, open-label, single- and multiple-dose study. Part C of the study was designed to assess the efficacy and safety of voxelotor in a cohort of 56 pediatric patients with SCD from 13 study sites in the US, Lebanon and the UK aged 4 years to 17 years of age. The efficacy data is primarily from the cohort of 45 patients aged 4-11 years. The efficacy data for the 11 patients aged 12 to 17 years is not included in the clinical efficacy analysis due to the small sample size. The majority of the patients were African American (41/45; 91%); the four remaining patients were Middle Eastern and Caucasian (2 each; 4.4%).

Table 4: Listing of Clinical Trials Relevant to NDA 213137

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population
		Controlled Studies to Support Efficacy and Safety					
GBT440-007 (HOPE KIDS) Part C	NCT02850406	Part C: Ongoing, open-label, Phase 2a, multicenter, single- and multiple dose study efficacy and safety of voxelotor in pediatric patients with SCD age 4-17 years of age.	4-11 years: Voxelotor weight-based dosing 12-17 years: Voxelotor 1500 mg orally daily	Primary endpoint: (Hb response (> 1 g/dL at Week 24) Secondary endpoint: Change from baseline in Hb and clinical measures of hemolysis at Week 24	24 weeks up to 48 weeks	4-11 years: 45 patients 12 to 17 years: 11 patients	Hgb SS/Hgb SB^0Thalassemia
		Studies to Support Safety					
GBT440-007 (HOPE KIDS) Part C	NCT02850406	Part C: Ongoing, open-label, Phase 2a, multicenter, single- and multiple dose study efficacy and safety of voxelotor in pediatric patients with SCD age 4-17 years of age.	4-11 years: Voxelotor weight-based dosing 12-17 years: Voxelotor 1500 mg orally daily	Primary endpoint: (Hb response (> 1 g/dL at Week 24) Secondary endpoint: Change from baseline in Hb and	24 weeks up to 48 weeks	4-11 years: 45 patients 12 to 17 years: 11 patients	Hgb SS/Hgb SB^0Thalassemia

				clinical measures of hemolysis at Week 24			
		Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)					
GBT440-031 (HOPE)	NCT03573882	Phase III, Double- blind randomized, placebo-controlled, long-term, efficacy, PK and safety of voxelotor in patients ≥ 12 years and older with SCD	Voxelotor tablet 900 mg 1500 mg placebo; QD; Oral	Primary endpoint: (Hb response (> 1 g/dL at Week 24) Secondary endpoint: Change from baseline in Hb and clinical measures of hemolysis at Week 24	72 weeks (completed)	N = 271; total treated N = 91; placebo N = 92; voxelotor 900 mg N = 88; voxelotor 1500 mg N = 46; 12 to 17 years N = 17; placebo N = 15; voxelotor 900 mg N = 14; voxelotor 1500 mg	Hgb SS/Hgb SB0Thalassemia
GBT440-0113	-	Open-label, single-dose, randomized crossover in healthy subjects	Treatment A: Voxelotor 900 mg dispersible tablet administered in a fasted state (test)	To determine the relative bioavailability of a 900 mg dispersible	2 doses were separated by a 28-day washout period	20 subjects randomized; 19 subjects completed	Healthy Subjects

			Treatment B: Voxelotor 900 mg (3 × 300 mg F1 tablets) administered in a fasted state (reference)	tablet formulation of voxelotor administered as a single dose versus 3 × 300 mg F1 tablets (900 mg total) in healthy subjects under fasted conditions			

5.2. Review Strategy

The clinical review was primarily based on the efficacy and safety data of Study GBT440-007 (Part C) , with support from the previous findings of efficacy and safety the pivotal Phase 3 trial, GBT440-031, which supported approval of voxelotor in adolescent and adult patients with SCD. The electronic submission, with the CSRs were reviewed and analyzed. The key review materials and activities are listed below:

- The electronic submission of the NDA
- Relevant published literature
- Relevant prior regulatory history
- Relevant applicant submissions in response to the review team's information requests
- Sponsor presentations to the FDA and
- Major efficacy and safety analyses were reproduced or audited.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. Study GBT440-007 (GBT440-007/Part C)

6.1.1. Study Design

Overview and Objective

Study GBT440-007 is an ongoing, Phase 2a, multicenter, four-part, open-label, single-and multiple-dose study designed to evaluate pharmacokinetic (PK), safety, tolerability, and efficacy of voxelotor in pediatric patients with SCD. Part C of the study was designed to assess the safety tolerability, PK and efficacy of multiple doses of voxelotor administered for up to 48 weeks in pediatric subjects with SCD. Treatment in Part C is ongoing at time of submission and the data included has a cutoff date of 30 September 2020.

Primary Efficacy Objective:
To evaluate effect of voxelotor on clinical measures of anemia and hemolysis
To evaluate the effect of voxelotor on cerebral hemodynamics as measured by TCD flow velocity.

Trial Design

This portion of the multicenter, open-label study (Part C) was designed to assess the efficacy, safety, tolerability, and PK of voxelotor administered in pediatric patients with SCD aged 4-17 years. Subjects aged 4 to 17 years were enrolled in Part C. Subjects aged 12 to 17 received voxelotor at 1500mg QD and subjects aged 4-11 received weight based dosing (See Table 5). Baseline data on the individuals' history of SCD, manifestations of SCD complications, history of malignancy, SCD treatment history as well as laboratory data were collected from each patients.

Patients were evaluated at inclusion, then at Week 2, 4 then every 4 weeks up to Week 48.

Key Inclusion Criteria for enrollment are:

- Male or female patients (aged 4-17 years)
- Hgb SS or Hgb S/B^0Thalassemia
- Have a hemoglobin level ≤ 10.5 g/dL
- If on hydroxyurea, stable dose for ≥ 3 months before signing informed consent
- Obtained an informed consent to participate in the cohort
- Patients 12 to 17 years of age have a TCD velocity ≥ 140 cm/sec by nonimaging TCD or ≥125 cm/sec by TCD, measured anytime during screening.

The starting dosage of voxelotor for patients aged 4-11 was weight-based oral dispersible tablets (see Table 5); otherwise, the dosing was 1500 mg orally daily for up to 48 weeks.

Table 5: Weight-Based Dosing for Pediatric Patients (4-11 years)

Weight Range	Dosing of Voxelotor
5 to < 10 kg	400 mg
10 to < 20 kg	600 mg
20 to < 40 kg	900 mg
≥ 40 kg	1500 mg

Source: Table 3 of Applicant's CSR

The planned Part C of GBT440-007 also includes up to 50 patients (age 4-17 years) where ≥ 30 subjects must have a TCD flow velocity ≥ 140 and < 200 cm/sec by nonimaging upon screening and ≥ 20 subjects must be between 4 and 11 years of age.

Study Endpoints

The primary efficacy endpoint of GBT440-007 was the Hgb response (increase in hemoglobin of > 1 g/dL from baseline) compared to Week 24 which is consistent with the primary endpoint in the pivotal GBT440-031 trial.

The secondary endpoints for the study include the change from baseline to Week 24 in Hgb, the percent change from baseline in hemolysis markers (indirect bilirubin, LDH and reticulocyte

percentage) to Week 24 and change from baseline to Week 24 in cerebral blood flow as measured by the time-averaged mean of the maximum (TAMM) TCD flow velocity.

The assessment of evaluating the effect of voxelotor on pediatric patients' cerebral blood hemodynamics as measured by TCD velocity is ongoing.

Statistical Analysis Plan

Sample Size Calculation: Total of 56 subjects were enrolled in GBT440-007 as of 30 September 2020, including 45 subjects age 4-11 years of age and 11 subjects who were 12-17 years of age.

Hematology parameters (hemoglobin, reticulocyte count, indirect bilirubin, and LDH) and cerebral blood flow as measured by TAMM TCD flow velocity were summarized at Week 24 for observed values and changes (absolute and percent) from baseline using appropriate descriptive statistics. If indirect bilirubin was missing and direct and total bilirubin are collected, indirect bilirubin can be calculated as:

Indirect Bilirubin = Total Bilirubin – Direct Bilirubin.

The Efficacy Evaluable (EE) population in this study is defined as all enrolled patients who have received at least one dose of the study drug. Enrolled Population is all subjects who were enrolled and the treated population is all subjects who were enrolled and received at least one dose of the study drug.

Protocol Amendments

The original protocol (dated 05 February 2016) was amended 6 times. The most important modifications/amendments to the study protocol (Part C) are listed below:

- June 14, 2018: Addition of Part C including objectives, endpoints, subjects, schedule of assessments and analysis methods to assess the efficacy, safety, PK and effect on TCD flow velocity in pediatric patients with SCD aged 4-17 years of age. The addition of the dispersible tablet formulation of voxelotor for administration to the pediatric patients (4-11 years of age).

6.1.2. Study Results

Compliance with Good Clinical Practices

The Applicant provided attestation that this study was conducted in accordance with U.S. regulations governing the protection of human subjects, Institutional Review Boards, and the obligations of clinical investigators in accordance with good clinical practice (GCP).

Financial Disclosure

The applicant submitted financial disclosure information for investigators. There were no principal investigators or sub-investigators from Study GBT440-007 who reported financial interest or arrangements as described in 21 CFR 54.4(a)(3).

Patient Disposition

A total of 56 subjects (45 subjects aged 4 to 11 years and 11 subjects aged 12-17 years) were enrolled.

Table 6: Patient Disposition of GBT440-007

Patient Disposition	4 to < 12 Years Age Group (n = 45)	Percentage	12-17 Years Age Group (n = 11)	Percentage	Total (n = 56)	Percentage
Screening Status						
Screen Failure	21	46.7%	6	54.5%	27	49.0%
Subjects Never Dosed	2	4.4%	0	0.0%	2	3.7%
Subjects Received Treatment	45	100.0%	11	100.0%	56	100.0%
Reasons for Discontinuation						
Adverse Event	4	8.9%	2	18.2%	6	10.9%
Discretion of Investigator	1	2.2%	2	18.2%	3	5.4%
Withdrawal of Consent	5	11.1%	3	27.3%	8	14.5%
Other	1	2.2%	0	0.0%	1	1.8%
End of Treatment Status						
Completed	26	57.8%	1	9.1%	28	49.2%
Discontinued	11	24.4%	7	63.6%	18	32.6%
Ongoing	8	17.8%	3	27.3%	11	20.0%
End of Study Status						
Completed	6	13.3%	1	9.1%	7	12.7%
Discontinued	31	68.9%	7	63.6%	39	69.1%
Ongoing	8	17.8%	3	27.3%	11	20.0%
Completed 24 Weeks of Treatment						
Yes	35	77.8%	6	54.5%	42	74.6%
No	10	22.2%	5	45.5%	15	27.2%

Source: FDA reviewer analysis

Reviewer's Comments: The reasons for discontinuation was highest among the younger age group (i.e. adverse events and withdrawal of consent). Anecdotal reasons could be the heightened awareness of adverse events in the pediatric group versus the adolescent group or the palatability of the oral dispersion tablets. In addition, the number of adolescents who discontinued treatment was higher for a variety of reasons including adverse reactions, investigator discretion and withdrawal of consent. It is concerning that a larger number of adolescents discontinued treatment.

Protocol Violations/Deviations

There were three critical protocol deviations which occurred during the treatment period. One of which occurred during the informed consent process. One patient received the investigational product twice in one day. One patient was admitted twice to hospital due to vasoocclusive crises and these serious adverse events were not reported within 24 hours of the occurring event.

Reviewer's Comments: The additional dose of voxelotor taken by the patient did not result in a notable increase in the patient's hemoglobin level as documented in an unscheduled laboratory visit after the occurrence of the event. The adverse event of a vasoocclusive crisis is one of the expected SCD complications to occur among these patients. The reporting of SCD-related adverse events within 24 hours of the occurring event are crucial due to the variability of the severity, duration and other inciting triggers to other SCD-related adverse events that can occur during a vasoocclusive crises.

Table of Demographic Characteristics

In the GBT440-007 Part C study, over 50% of pediatric patients were female. The majority of patients were of African ancestry. As expected, 95% of the patients were of Hgb SS genotype. Over 50% of the pediatric patients had a baseline weight of 20 to less than 30 kg. Among the pediatric group, over 80% of patients were currently using hydroxyurea. The baseline hemoglobin F levels were nearly 18%.

In the adolescent group, there was a male preponderance (7/11; 64%) and all were African-American and were homozygous for Hgb S. Only 63.6% of adolescents were currently using hydroxyurea at the time of study treatment. In this population, Hgb F levels reached above 10%. The mean baseline hemoglobin levels was 8.5 g/dL among both age groups.

Table 7: Baseline Demographics of GBT440-007

Demographics Information	4 to <12 Years Age Group (n = 45)	Percentage	12-17 Years Age Group (n = 11)	Percentage	Total (n = 56)	Percentage
Age						
Mean	7.3 ± 2.1	-	13.1 ± 1.0	-	8.5 ± 3.0	-
Median	7.0	-	13.0	-	8	-
Min, Max	4,11	-	12,15	-	4,15	-
Sex						
Female	23	51.1%	4	36.4%	27	48.2%
Male	22	48.9%	7	63.6%	29	51.8%
Race						
Black or African American	41	91.1%	11	100.0%	52	92.9%
Middle Eastern or North African	2	4.4%	0	0.0%	2	3.6%
White	2	4.4%	0	0.0%	2	3.6%
Ethnicity						
Hispanic or Latino	2	4.4%	0	0.0%	2	3.6%
Not Hispanic or Latino	43	95.6%	11	100.0%	54	96.4%
Genotype						
Hgb SS	43	95.6%	11	100.0%	54	96.4%
Hgb SB^0 Thalassemia	2	4.4%	0	0.0%	2	3.6%
Baseline Weight (kg)						
≥ 40 kg	2	4.4%	7	63.6%	9	16.1%
10 to < 20 kg	8	17.8%	0	0.0%	8	14.3%
20 to < 30 kg	24	53.3%	1	9.1%	25	44.6%
30 to < 40 kg	11	24.4%	3	27.3%	14	25.0%
Current Use of Hydroxyurea						
Yes	38	84.4%	7	63.6%	45	80.4%
No	7	15.6%	4	36.4%	11	19.6%
Baseline Hgb F (%)						
Mean ± SD	43	17.7 ± 7.9	11	11.0 ± 8.7	54	16.4 ± 8.4
Baseline Reticulocyte Count (%)						
Mean ± SD	43	10.4 ± 4.4	9	8.8 ± 4.7	52	10.1 ± 4.5
Baseline Hgb (g/dL)						
Mean ± SD	45	8.6 ± 1.0	11	8.1 ± .78	56	8.5 ± .98

Source: FDA reviewer analysis

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

The majority of patients in both age groups had zero vasoocclusive crises in the previous 12 months (Peds: 21/45; 47%; Adolescents: 5/11; 46%), one vasoocclusive crises in the previous 12 months requiring hospitalizations (Peds: 8/45; 18%; Adolescents: 1/11; 9%) and zero transfusions in the previous 12 months (Peds: 34/45; 76%; Adolescents: 8/11; 75%).

Table 8: Other Baseline Characteristics of GBT440-007 Study

Demographics Information	4 to < 12 Years Age Group (n = 45)	Percentage	12-17 Years Age Group (n = 11)	Percentage	Total (n = 56)	Percentage
Number of VOCs in previous 12 months						
0	21	46.7%	5	45.5%	26	46.4%
1	12	26.7%	2	18.2%	14	25.0%
2	1	2.2%	1	9.1%	2	3.6%
3	5	11.1%	1	9.1%	6	10.7%
4	3	6.7%	1	9.1%	4	7.1%
7	1	2.2%	0	0.0%	1	1.8%
8	2	4.4%	0	0.0%	2	3.6%
Number of VOCs in previous 12 months requiring hospitalization						
1	8	17.8%	1	9.1%	9	16.1%
2	4	8.9%	0	0.0%	4	7.1%
3	1	2.2%	0	0.0%	1	1.8%
4	1	2.2%	1	9.1%	2	3.6%
8	1	2.2%	0	0.0%	1	1.8%
Number of transfusions in previous 12 months						
0	34	75.6%	8	72.7%	42	75.0%
1	6	13.3%	2	18.2%	8	14.3%
2	3	6.7%	0	0.0%	3	5.4%
3	1	2.2%	0	0.0%	1	1.8%
7	1	2.2%	0	0.0%	1	1.8%
12	0	0.0%	1	9.1%	1	1.8%
SCD Complications						
Acute Chest Syndrome	22	48.9%	2	18.2%	24	42.9%
Acute Painful Crises	18	40.0%	4	36.4%	22	39.3%
Cholecystectomy	4	8.9%	1	9.1%	5	8.9%

Demographics Information	4 to < 12 Years Age Group (n = 45)	Percentage	12-17 Years Age Group (n = 11)	Percentage	Total (n = 56)	Percentage
Hematuria	1	2.2%	0	0.0%	1	1.8%
Priapism	3	6.7%	1	9.1%	4	7.1%
Icteric Sclera	7	15.6%	0	0.0%	7	12.5%
Splenic Sequestration	13	28.9%	1	9.1%	14	25.0%
Splenectomy	2	4.4%	0	0.0%	2	3.6%
Asthma	1	2.2%	0	0.0%	1	1.8%
Normal TCD (< 170 cm/sec)	0	0.0%	2	18.2%	2	3.6%
Conditional TCD (170-200 cm/sec)	1	2.2%	6	54.5%	7	12.5%
Abnormal TCD (> 200 cm/sec)	0	0.0%	0	0.0%	0	0.0%
Hepatic Sequestration	0	0.0%	2	18.2%	2	3.6%
Kidney Dysfunction	0	0.0%	1	9.1%	1	1.8%
Aplastic Crisis due to parvovirus	0	0.0%	1	9.1%	1	1.8%
Detailed Reasons for Continuation/Discontinuation						
Rollover to GBT440-038 OLE	21	46.7%	0	0.0%	21	37.5%
Taste of Drug	0	0.0%	1	9.1%	1	1.8%
Intolerance to Study Drug	1	2.2%	0	0.0%	1	1.8%
No Direct Benefit	1	2.2%	0	0.0%	1	1.8%
Poor Palatability of Study Drug	1	2.2%	0	0.0%	1	1.8%
Parent's Decision	2	4.4%	0	0.0%	2	3.6%
COVID-19 pandemic	0	0.0%	2	18.2%	2	3.6%
Maternal concern regarding cardiac findings	1	2.2%	0	0.0%	1	1.8%

Source: FDA reviewer analysis

Reviewer's Comments: The histories of acute chest syndrome and painful crises are not unexpected in both age groups. There was a notable higher number of pediatric patients with a history of splenic sequestration (13/45; 29%). The largest percentage of patients in both groups were confirmed having conditional TCD velocities (170-200 cm/sec). None had abnormal TCD velocities documented at the time of study treatment. The majority of pediatric patients (21/45; 47%) who remained on study did agree to be continue treatment on the open-label extension study, GBT440-038 OLE.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Since voxelotor is a moderate inhibitor of cytochrome P450 CYP3A4, moderate or strong inducers of CYP3A4 were prohibited and coadministration of strong CYP3A4 inhibitors were avoided.

Concurrent treatment with HU was allowed if the dose and regimen had been stable for at least 3 months prior to signing the informed consent. The concomitant medications that were reported in more than 50% of patients are presented below in Table 9.

Table 9: Concomitant Medications Reported in ≈50% of Patients in GBT440-007 Study

Concomitant Medications	4 to < 12 Age Group (n = 45) (%)	12-17 Age Group (n = 11) (%)	Total (n = 56) (%)
Hydroxyurea	39 (87%)	7 (64%)	46 (82%)
Ibuprofen	36 (80%)	9 (82%)	45 (80%)
Folic Acid	27 (60%)	10 (91%)	37 (66%)
Paracetamol	25 (56%)	6 (55%)	31 (55%)
Opium Alkaloids	18 (40%)	6 (55%)	24 (43%)

Source: FDA reviewer analysis

Reviewer's Comments: As expected the use of hydroxyurea in both age groups was significant in both age groups at nearly 82%. The most common analgesic used among both age groups was ibuprofen at 80%. The use of opioids were reported higher among the adolescents at 55%.

Efficacy Results – Primary Endpoint

The efficacy of voxelotor is based on the achievement of a greater than 1 g/dL increase in hemoglobin from baseline to Week 24. Here, the applicant used data from the efficacy evaluable (EE) population. In the EE population, sixteen (47.1%) patients achieved a > 1 g/dL increase in hemoglobin at Week 24. By Week 48, only 9 (36%) patients were able to achieve a > 1 g/dL increase compared to baseline.

Table 10: Primary Endpoint Analysis of GBT440-007 based on the Efficacy Evaluable (EE) Population

Hemoglobin Response*	4 to < 12 Year Age Group n = 45 (%)	12-17 Year Age Group n = 11 (%)
Week 12		
N	37	6
Hgb Responder	14 (37.8)	1 (16.7)
95% CI	(22.2, 53.5)	(0, 46.5)

Week 24		
N	34	6
Hgb Responder	16 (47.1)	2 (33.3)
95% CI	(30.3, 63.8)	(0, 71.1)
Week 48		
N	25	1
Hgb Responder	9 (36.0)	0
95% CI	(17.2, 54.8)	-

**Hgb Response: > 1 g/dL increase in hemoglobin from baseline to Week 24*
Source: FDA reviewer analysis

Reviewer's comment: Using the efficacy evaluable population, It appears that voxelotor has a treatment effect on increasing the hemoglobin level among the pediatric population at Week 24. Of note, the number of Hgb responders in the Phase 3 pivotal trial , GBT-440-031 was 51.2% (46/90 patients; 95% CI: 40.6, 61.8). It is unclear why the number of hemoglobin responders are lower in the pediatric study given that nearly 87% of patients in the 4-11 year age group were on hydroxyurea at baseline. A possible reason for difference is the higher percentage of pediatric patients on HU at baseline compared to adults and that the response in adults may have larger treatment effect since they are not having the treatment effect of HU at baseline. Nonetheless, a response rate of 47% in the EE population is a significant treatment effect and likely will predict for a clinical benefit in ongoing confirmatory trial. The sample size among the adolescent population is too small to comment on the efficacy of voxelotor.

Sensitivity Analysis

In a single arm trial, the treated population, which includes all enrolled subjects who took at least one dose of study drugs, is of interest and all subjects in this population should be accounted for in the analysis. Therefore, the statistical and clinical teams re-estimated the Hb response with the treated population. The subjects who did not have a valid Hb value at week 24 were considered non-responders. Since all enrolled subjects took the study drug, the treated population is the same as the enrolled population.

Using the enrolled population (treated population) who are patients who took at least one dose of study drug, sixteen (35.6%)(95% CI: 4.3, 77.7) patients achieved a > 1 g/dL increase in hemoglobin at Week 24. By Week 48, only 9 (20%) patients were able to achieve a > 1 g/dL increase compared to baseline.

Table 11: Primary Endpoint Analysis of GBT440-007 based on the Enrolled Population

Hemoglobin Response*	4 to <12 Year Age Group n = 45 (%)	12-17 Year Age Group n = 11 (%)
Week 12		
N	37	6
Hgb Responder	14 (31.1)	1 (9.1)
95% CI	(17.6, 44.6)	(0, 26.1)
Week 24		
N	34	6
Hgb Responder	16 (35.6)	2 (18.2)
95% CI	(21.6, 49.5)	(0, 41.0)
Week 48		
N	25	1
Hgb Responder	9 (20)	0
95% CI	(8.3, 31.7)	-

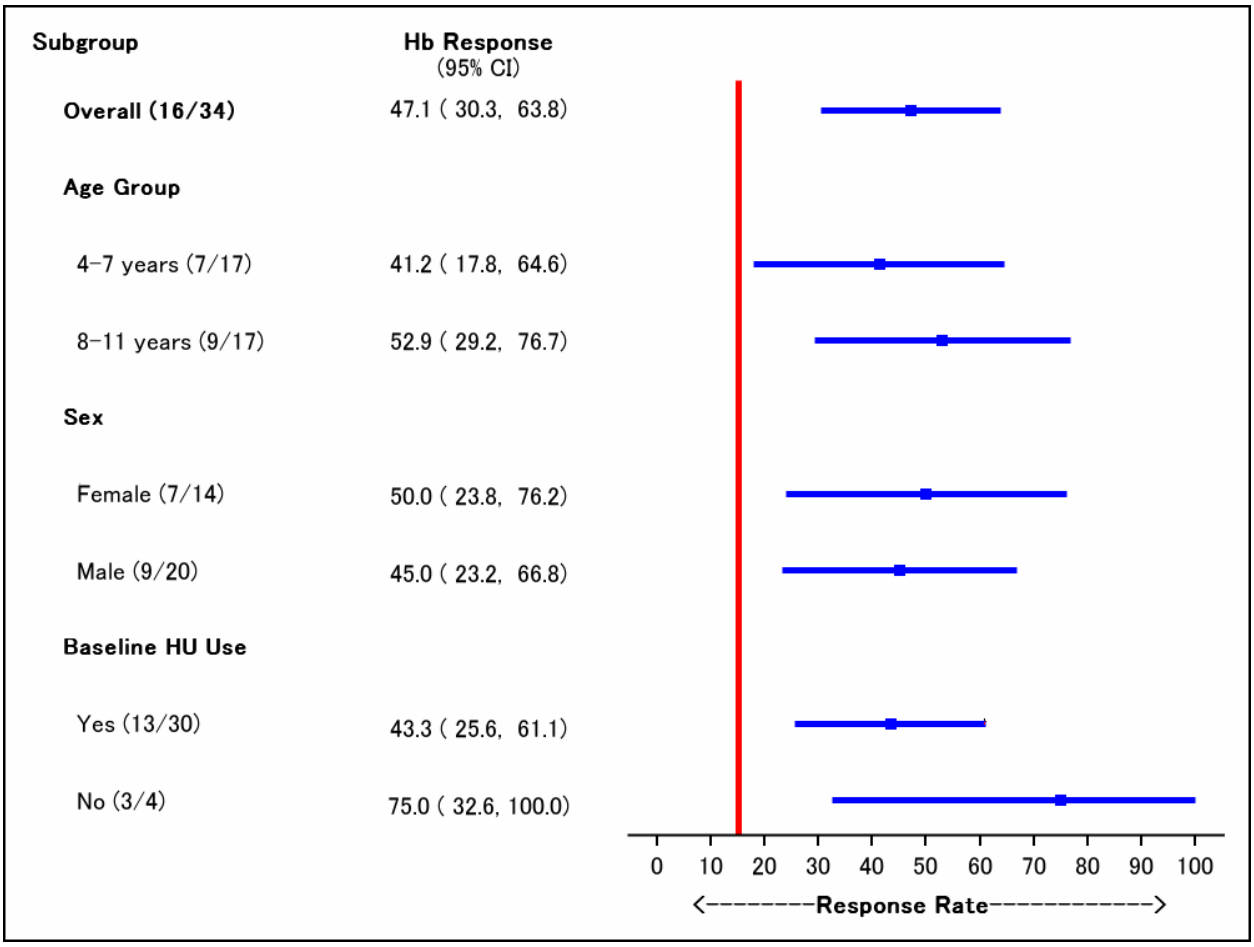
**Hgb Response: > 1 g/dL increase in hemoglobin from baseline to Week 24; Source: FDA reviewer analysis*

Reviewer's Comments: The results from the treated population should be used in the labeling (b) (4) *. The EE population excluded 11 subjects (age 4-11) who were treated with study drug and reduced the analysis sample size by 24%. The estimated Hb response from the EE may not be as reliable. Therefore, the treated population was used for basis for the efficacy evaluation.*

The lower bound of the 95% CI of 21.6% still represents a meaningful treatment effect due to voxelotor in the 4-11 year age group. Of note, the number of Hgb responders in the Phase 3 pivotal trial , GBT-440-031 was 51.2% (46/90 patients; 95% CI: 40.6, 61.8) and accounted for the intention to treat population. In addition, the response of achieving > 1 g/dL increase in hemoglobin at Week 24 was highest among patients who were on hydroxyurea at baseline.

Subgroup Analyses

Please refer to the statistical review by Lola Luo, PhD. No outlier subgroups were observed. The following figure was taken from the statistical review by Lola Luo, PhD.



Source: Statistical Review dated November 22, 2021 Lola Luo, PhD

Efficacy Results – Secondary and other relevant endpoints

Change from Baseline in Hemoglobin

Evaluation of the change from baseline for hemoglobin for voxelotor was evaluated up to Week 48 and there is demonstratable increase in hemoglobin level among the pediatric patients by Week 24 and slightly decreases by Week 48. These changes would not occur by chance alone with this disease as baseline hemoglobin levels are 8-10g/dL.

The following table (Table 12) demonstrate the changes. Please note that the change in hemoglobin levels in the adolescent age group is uninterpretable due to the small sample size.

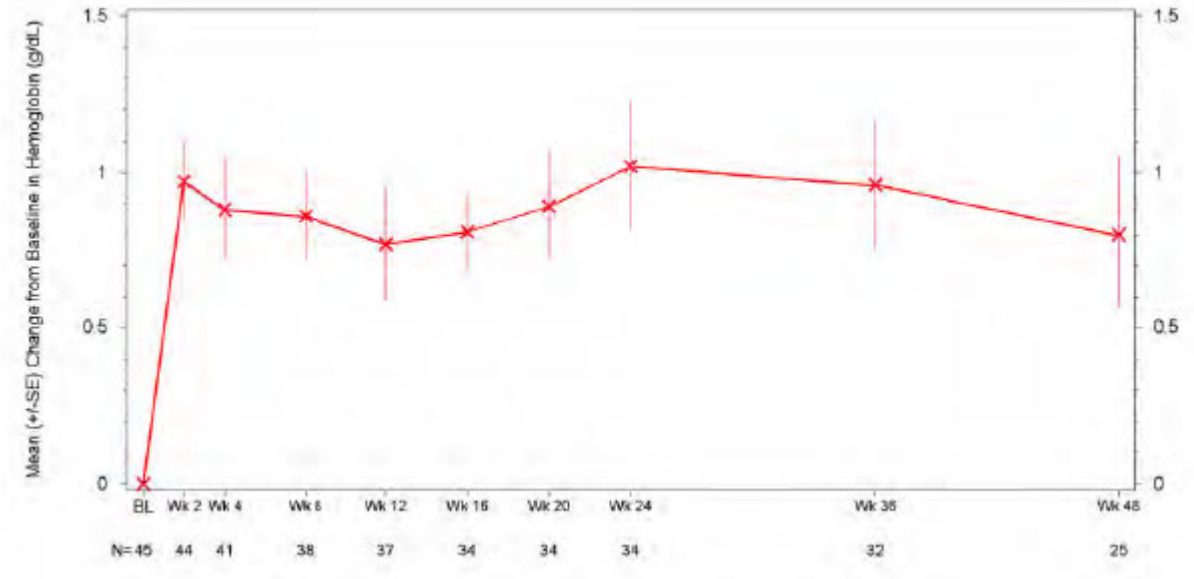
Table 12: Change from Baseline for Hemoglobin Levels in the GBT440-007 Study

Change from Baseline	4 to <12 Year Age Group n = 45	12-17 Year Age Group n = 11
Baseline Hgb (g/dL)		
n	45	11
Mean ± SD	8.6 ± 1.0	8.1 ± .78
Week 12		
n	37	6
Mean ± SD	9.5 ± 1.4	8.2 ± .44
Mean Change from Baseline to Week 12	.76 ± 1.2	.64 ± .37
Mean Percent Change from Baseline to Week 12	9.3 ± 13.9	8.2 ± 5.1
Week 24		
n	34	6
Mean ± SD	9.7 ± 1.5	8.3 ± 1.1
Mean Change from Baseline to Week 24	1.0 ± 1.2	.75 ± 1.1
Mean Percent Change from Baseline to Week 24	12.1 ± 14.4	10.1 ± 15.1
Week 48		
n	25	1
Mean ± SD	9.6 ± 1.4	8.1
Mean Change from Baseline to Week 48	.80 ± 1.2	-0.2
Mean Percent Change from Baseline to Week 48	9.6 ± 14.3	8.1 ±-2.4

Source: FDA reviewer analysis

The Applicant presented a graphical demonstration (Figure 1 of the change in baseline in hemoglobin levels among the efficacy evaluable (EE) pediatric patients. The rise in hemoglobin is seen as early as Week 2, peaking at Week 24 and plateauing near Week 48.

Figure 1: Change in Baseline in Hemoglobin to Week 48 in the Pediatric (EE) Population



The secondary endpoints of GBT440-007 focuses on the percent change from baseline to Week 24 of hemolysis markers, in particular, indirect bilirubin, percent reticulocyte count and lactate dehydrogenase as well as a change from baseline in TCD flow velocity.

Table 13: Change from Baseline of Hemolysis Markers in the Pediatric Population

Change from Baseline	4 to <12 Year Age Group n = 45
Indirect Bilirubin (mg/dL)	
n	38
Baseline Mean ± SD	2.06 ± .97
n	32
Mean ± SD at Week 24	1.07 ± .46
Mean Change from Baseline to Week 24	-.84 ± .68
Mean Percent Change from Baseline to Week 24	-38.6 ± 27.2
n	22
Mean ± SD at Week 48	1.45 ± 1.1
Mean Change from Baseline to Week 48	-.50 ± 1.07
Mean Percent Change from Baseline to Week 48	-23.3 ± 41.1
Reticulocyte Count (%)	
n	43
Baseline Mean ± SD	10.4 ± 4.5
n	31
Mean ± SD at Week 24	8.7 ± 4.5

Change from Baseline	4 to <12 Year Age Group n = 45
Mean Change from Baseline to Week 24	-1.2 ± 4.9
Mean Percent Change from Baseline to Week 24	-3.3 ± 45.9
n	24
Mean ± SD at Week 48	9.1 ± 5.1
Mean Change from Baseline to Week 48	-1.1 ± 4.6
Mean Percent Change from Baseline to Week 48	-3.4 ± 49.4
Lactate Dehydrogenase (U/L)	
n	45
Baseline Mean ± SD	671 ± 425.6
n	32
Mean ± SD at Week 24	550 ± 242.2
Mean Change from Baseline to Week 24	-27.7 ± 117
Mean Percent Change from Baseline to Week 24	-2.5 ± 21.5
n	24
Mean ± SD at Week 48	585.0 ± 302.7
Mean Change from Baseline to Week 48	-2.2 ± 142.7
Mean Percent Change from Baseline to Week 48	.74 ± 27.1

Source: FDA reviewer analysis

There was a notable decrease in the known hemolysis markers associated with the extravascular hemolysis associated with sickle cell disease. At Week 24, the mean ± SD percent change from baseline was -38.6% ± 27.2%; n = 32 for indirect bilirubin, -3.3% ± 45.9%; n = 31 for percent reticulocyte count, and -2.6% ± 21.5%; n = 32 for lactate dehydrogenase (LDH). The decrease in the known hemolysis markers continued to trend downward toward normalization and plateau near Week 48.

Reviewer's Comments: The decrease in the known hemolysis markers is consistent with the Hgb response resulting in an increase in hemoglobin levels due to voxelotor. Longer term data (≈ 52 weeks) is warranted to demonstrate if voxelotor can achieve a complete normalization of hemolysis with longer use of the drug and its concurrent use with hydroxyurea.

Stroke is a common and potentially devastating manifestation of sickle cell disease (SCD) that can affect children. The primary method of stroke risk assessment in children is transcranial Doppler (TCD) velocity, a noninvasive ultrasound-based procedure that can be used to measure the mean blood flow velocity in the large intracranial vessels. Among the 45 patients enrolled in the 4-11 year age group, 33 had normal TCD flow velocity at baseline (< 170 cm/sec) and 12 had conditional TCD flow velocity (≥ 170 to < 200 cm/sec). Among the 11 patients in the 12-17 year age group, 7 had normal TCD flow velocity at baseline and 4 had conditional TCD flow

velocity. None of the patients in either group converted to an abnormal TCD velocity (≥ 200 cm/sec) while on study treatment.

At the time of data cutoff, only five patients in the 4-11 year age group had TCD flow velocity data which showed a mean change from baseline to Week 24 of -12.4 ± 8.6 cm/sec. Among all patients with conditional TCD flow velocity, the mean change from baseline to Week 24 was -18.4 ± 11.8 cm/sec. Among all patients, six of the patients (3 from the 4-11 age group and 3 from the 12-17 age group) did revert to normal TCD velocity at Week 24.

Table 14 highlights the change from baseline to Week 24 in TCD flow velocity in both groups.

Table 14: TCD Flow Velocity Change from Baseline to Week 24

TCD Flow Velocity at baseline (cm/sec)	4 to < 12 Year Age Group (n = 45)		12-17 Year Age Group (n = 45)		Total (n = 56)	
	Normal TCD	Conditional TCD	Normal TCD	Conditional TCD	Normal TCD	Conditional TCD
Baseline						
N	33	12	7	4	40	16
Mean ± SD	135.1 ± 18.0	177.3 ± 5.0	157.0 ± 8.3	175.2 ± 4.0	139 ± 18.7	176.8 ± 4.7
Min, Max	80, 163	170, 189	148.9, 169.5	170, 179.7	80,169.5	170,189
Week 24						
N	28	5	3	3	31	8
Mean ± SD	132.2 ± 20.1	166.6 ± 8.4	159.0 ± 21.6	148.6 ± 10.5	134.8 ± 21.4	159.9 ± 12.6
Min, Max	87, 173	157, 176	141, 183	138, 159	87,183	138,176
Change from Baseline to Week 24						
N	28	5	3	3	31	8
Mean ± SD	-1.3 ± 16.4	-12.4 ± 8.6	0.0 ± 18.3	-28.3 ± 10.3	-1.2 ± 16.3	-18.4 ± 11.8
Min, Max	-39.6, 26	-24, 0	-12, 21	-37, -17	-39.6,26	-37,0

Source: FDA reviewer analysis

Reviewer's Comments: There is a trend toward improvement in the TCD velocity; however, the small sample size does not allow for any definitive conclusions. The results demonstrated in this study are encouraging and the Sponsor's ongoing confirmatory trial is evaluating change in TCD velocity.

Dose/Dose Response

Voxelotor weight-based dosing in pediatric patients aged 4 to 11 years was compared to patients aged ≥ 12 years treated with voxelotor 1500 mg in Study GBT440-031. The results showed improvements in Hgb from baseline to Week 24 in patients aged 4 to 11 years in Study GBT440-007 Part C (mean change: 1.0 g/dL ± 1.21 g/dL compared to patients aged 12 years and older in the voxelotor 1500 mg treatment group in Study GBT440-031 (mean change: 1.13 g/dL ± 0.132 g/dL.

The dosing with voxelotor resulted in reductions in clinical measures of hemolysis beginning as early as Week 2 in subjects aged 4 to 11 years, consistent with improvements observed with voxelotor 1500 mg in subjects aged ≥ 12 years.

Durability of Response

The durability of response achieved with voxelotor was reviewed and demonstrated on the basis of assessing the > 1 g/dL increase of hemoglobin at Week 24 and maintaining a reduction in clinical measures of hemolysis at Week 24.

Persistence of Effect

The comparable improvements or maintenance of the > 1 g/dL increase of hemoglobin and reduction in the clinical measures of hemolysis after Week 24 appear to be consistent with the similar findings noted in the Phase 3 pivotal trial, GBT440-031.

Additional Analyses Conducted on the Individual Trial

The concurrent use of hydroxyurea was further analyzed. This analysis was done to determine if the concurrent use of hydroxyurea had an impact on the number of Hgb responders in each age group. Due to the small sample size in both groups, it is difficult to determine if the impact of voxelotor is benefited by the concurrent use of hydroxyurea.

Table 15: Baseline and Week 24 Hemoglobin and Hgb F Levels among the Hydroxyurea Users in relation to Hgb Response (4-11 Year Age Group and 12-17 Year Age Group)

	Baseline Hgb (g/dL)	Baseline Hgb F (%)	Week 24 Hgb (g/dL)	Hgb Responders
Age 4 to < 12 (Total: 38)				

	Baseline Hgb (g/dL)	Baseline Hgb F (%)	Week 24 Hgb (g/dL)	Hgb Responders
Mean ± SD	8.6 ± 1.0	17.3 ± 8.3	9.4 ± 1.5	Yes*: 14
				No: 21
Age 12-17 (Total: 7)				
Mean ± SD	8.2 ± .81	11.9 ± 8.7	8.7 ± .79	Yes: 2
				No: 5

**2 patients were identified as Hgb Responders at Week 4; Source: FDA reviewer analysis*

6.2. Study GBT440-031

Study GBT440-031: Efficacy Results Through Week 72 in subjects Aged ≥12 years

Study GB440-31 provided the data in the original NDA (NDA 213137) and included study data based on week 24 of the hemoglobin response. The study is now completed, reflecting 72 weeks of study treatment. The improvements in hemoglobin and decreases in clinical measures of hemolysis aged 12 years and older observed at Week 24 were sustained through 72 weeks of voxelotor treatment demonstrating durability of response. The Sponsor proposed to update the USPI with updated 72 weeks of durability data for Study GBT440-031.

Table 16 presents the LS change in hemoglobin and hemolysis parameters from baseline at week 24 and week 72. For further details on the study design and study results that formed the basis for the original NDA review, please refer to the multidisciplinary review dated November 25, 2019 in DARRTS.

Table 16: Study GBT440-031: LS Mean (SE) Change in Hemoglobin and LS Mean Percent Change in Clinical Measures of Hemolysis from Baseline to Week 24 and Week 72 (ITT Population)

	24 weeks			72 weeks		
	Voxelotor 1500mg N=90	Placebo N=92	P-value	Voxelotor 1500mg N=90	Placebo N=92	P-value
Hemoglobin (g/dL)	1.13 (0.130)	-0.10 (0.13)	< 0.001	1.02 (0.150	0.02 (0.15)	< 0.001
Indirect bilirubin (%)	-29.1 (3.5)	-2.8 (3.5)	< 0.001	-23.9 (4.9)	2.7 (4.9)	<0.001

Reticulocyte percentage (%)	-18.0 (4.7)	6.8 (4.7)	< 0.001	-7.6 (5.5)	11.0 (5.5)	0.017

Source: Clinical Overview (Table 7) CSR GBT440-031 (Week 72)

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

7.1.1. Primary Endpoints

In Study GBT440-031, 51.1% (46/90) of patients in the 1500mg dose group achieve a Hgb response at Week 24 compared to 6.5% (6/92) in the placebo group. In Study GBT440-007, the estimated Hgb response for the treated subjects was 35.6% (95% CI: 21.6, 49.5) in the 4-11 years age group.

7.1.2. Secondary and Other Endpoints

Similar reductions in hemolysis parameters were observed in Study GBT440-031. The differences between the voxelotor 1500mg and placebo groups at week 24 were notable for indirect bilirubin (-25.9%, p<0.001) and percent reticulocytes (-24.5%, p <0.001). In Study GBT440-007, the mean indirect bilirubin observed a decrease of 38.6% from baseline for the 4-11 years age group and a decrease of 3.3% in the reticulocyte count from the baseline for the 4-11 years age group at Week 24.

7.1.3. Subpopulations

No analyses for other special populations were performed.

7.2. Integrated Assessment of Effectiveness

To support this supplemental application, the applicant submitted one study: GBT440-007 (HOPE KIDS), a phase II study to demonstrate effectiveness of voxelotor in pediatric patients age 4 years and older. The proportion of Hgb response for subjects aged 4 to < 12 years was 35.6% (95% CI:21.6, 49.5) in treated population at week 24. No outlier subgroups were observed. The secondary endpoints of change in hemoglobin from baseline and hemolysis markers demonstrate a reduction in hemolysis consistent with mechanism of action of this drug. The findings of this study are similar to the Phase 3 pivotal study in adults and patients ≥ 12 years of age with SCD.

Verification of clinical benefit of the increase in hemoglobin is required and is currently being evaluated in ongoing confirmatory trial (GBT440-032) among pediatric patients with known conditional TCD flow velocity a significant risk reduction in strokes. For many patients, risk reduction requires indefinite chronic transfusion therapy.

Please also refer to the statistical review by Lola Luo, PhD for this supplemental application dated November 22, 2021.

8. Review of Safety

8.1. Safety Review Approach

The GBT440-007 (Part C) study serves as the primary source of safety data. The safety population of the 4 to < 12 year age group (n = 45) who received voxelotor weight-based dosing for up to 48 weeks. The 12-17 year age group (n = 11) safety data serves as supportive safety data for the proposed indication in pediatric patients with SCD. Study GBT440-007 Part C data cutoff date was September 30, 2020. The 120-day safety update has a cutoff date of April 2, 2021. The long-term safety of voxelotor is supported by the GBT440-031 pivotal study which was up to 72 weeks of voxelotor treatment.

Primary Safety Analysis

The primary safety analyses included all treated population (patients who received at least one dose of study drug) for the GBT440-007 study and includes adverse events collected up to 28 days after discontinuation of the study drug. The applicant proposed reviewing adverse events on the basis of two separate categories: non-SCD-related treatment emergent adverse events (TEAEs) and SCD-related TEAEs. SCD-related events by preferred terms (PTs) include acute chest syndrome, pneumonia, sickle cell anemia with crisis, osteonecrosis, and priapism. The Division agrees with evaluating non-SCD related TE and SCD TEs given the unique clinical features and sequelae of SCD.

Other potential safety signals were assessed by searching treatment-emergent adverse event (TEAES) using all levels of MedDRA terms, standardized MedDRA query (SMQ) and FDA MedDRA Query (FMQ). Other safety assessments of laboratory evaluations, vital signs and ECGs were also performed.

The safety analysis included a review of the following:

- Data quality
- Baseline characteristics and concomitant medications
- Incidence and severity of AEs

- Incidence of TEAEs, SAEs and adverse drug reactions (ADRs) such as drug-related rashes
- Non-SCD-related treatment emergent adverse events (TEAEs) and SCD-related TEAEs
- Incidence of discontinuation, dose interruptions and dose delays
- Laboratory tests, vital signs and electrocardiogram results
- Analysis of deaths.
- Summary of clinical safety
- Patient narratives and case report forms

8.2. Review of the Safety Database

8.2.1. Overall Exposure

The median exposure to voxelotor was 43.3 weeks among the 4-11 year age group and 26.6 weeks for the 12-17 year age group.

For patients aged 4 to 11 years, 77.8% (35/45) of patients completed 24 weeks of treatment, and 58% (26/45) completed 48 weeks of treatment. For patients 12 to 17 years of age, 55% (6/11) of patients completed 24 weeks of treatment, and 9.1% (1/11) completed 48 weeks of treatment.

Table 17: Extent of Exposure and Disposition of Patients in GBT440-007

Safety Database for the Voxelotor Individuals exposed to any treatment in this development program for the indication under review N=56			
	4-11 Year Age Group n= 45	12-17 Year Age Group n= 11	Total n= 56
Exposure (weeks)			
Median	43.3	26.6	40.2
Min, Max	1.3,60	.30,42.4	.30,60
Number of Patients who completed 24 weeks of treatment			
N (%)	35 (77.8)	6 (55)	41 (73)
Number of Patients who completed 48 weeks of treatment, n (%)			
Yes	26 (58)	1 (9.1)	27 (48)
No	11 (24)	7 (64)	18 (32)
Ongoing	8 (18)	3 (27)	11 (20)
Number of dose reductions, n (%)			
One dose reduction	1 (2.2)	0	1 (1.8)

Safety Database for the Voxelotor Individuals exposed to any treatment in this development program for the indication under review N=56			
	4-11 Year Age Group n= 45	12-17 Year Age Group n= 11	Total n= 56
Two dose reductions	0	1 (9)	1 (1.8)

Source: FDA reviewer analysis

Reviewer's Comments: Among the dose reductions of voxelotor, one patient in the 4-11 year age group dosing was reduced due to a Grade 2 rash. It was in the 12-17 year age group where one patient's dosing was reduced due to thrombocytopenia w/o sequalae which resolved (additional information is presented in Section 8.4.2 in Serious Adverse Events). The Sponsor did note that among the 26 patients aged 4 to 11 years who completed study treatment in Part C, 21 chose to continue receiving voxelotor in open-label extension Study GBT440-038 (see Table 8). Twenty-four percent of patients in the 4-11 group did not completed 48 weeks and 64% did not continue in the 12-17 year old age group. Among the 4-11 years age group, the primary reason for discontinuation of treatment was due to withdrawal of consent. Among the 12-17 years age group, adverse event, discretion of investigator and withdrawal of consent were reasons for discontinuation. Two patients among the 12-17 year age group discontinued due to the investigator's discretion due to the COVID-19 pandemic (see Table 8).

8.2.2. Relevant characteristics of the safety population:

The median age in the GBT440-007 Part C study was 7.0 years in the 4-11 year age group and 8.0 years in the 12-17 year age group. Over 50% of patients in the 4-11 year group had a baseline weight between 20 to < 30 kg. In the 12-17 year group, over 60% were ≥ 40 kg.

Table 17: Demographics and Other Baseline Characteristics for Safety Population of GBT440-007

Demographics Information	4-11 Years Age Group (n = 45)	Percentage	12-17 Years Age Group (n = 11)	Percentage	Total (n = 56)	Percentage
Age						
Mean	7.3 ± 2.1	-	13.1 ± 1.0	-	8.5 ± 3.0	-
Median	7.0	-	13.0	-	8	-
Min, Max	4,11	-	12,15	-	4,15	-
Sex						
Female	23	51.1%	4	36.4%	27	48.2%
Male	22	48.9%	7	63.6%	29	51.8%
Race						

Demographics Information	4-11 Years Age Group (n = 45)	Percentage	12-17 Years Age Group (n = 11)	Percentage	Total (n = 56)	Percentage
Black or African American	41	91.1%	11	100.0%	52	92.9%
Middle Eastern or North African	2	4.4%	0	0.0%	2	3.6%
White	2	4.4%	0	0.0%	2	3.6%
Genotype						
Hgb SS	43	95.6%	11	100.0%	54	96.4%
Hgb SB0 Thalassemia	2	4.4%	0	0.0%	2	3.6%
Baseline Weight (kg)						
≥ 40 kg	2	4.4%	7	63.6%	9	16.1%
10 to < 20 kg	8	17.8%	0	0.0%	8	14.3%
20 to < 30 kg	24	53.3%	1	9.1%	25	44.6%
30 to < 40 kg	11	24.4%	3	27.3%	14	25.0%
Current Use of Hydroxyurea						
Yes	38	84.4%	7	63.6%	45	80.4%
No	7	15.6%	4	36.4%	11	19.6%
Baseline Hgb (g/dL)						
Mean ± SD	45	8.6 ± 1.0	11	8.1 ± .78	56	8.5 ± .98

Demographics Information	4-11 Years Age Group (n = 45)	Percentage	12-17 Years Age Group (n = 11)	Percentage	Total (n = 56)	Percentage
Number of VOCs in previous 12 months						
0	21	46.7%	5	45.5%	26	46.4%
1	12	26.7%	2	18.2%	14	25.0%
2	1	2.2%	1	9.1%	2	3.6%
3	5	11.1%	1	9.1%	6	10.7%
4	3	6.7%	1	9.1%	4	7.1%
7	1	2.2%	0	0.0%	1	1.8%
8	2	4.4%	0	0.0%	2	3.6%
Number of VOCs in previous 12 months requiring hospitalization						
1	8	17.8%	1	9.1%	9	16.1%
2	4	8.9%	0	0.0%	4	7.1%
3	1	2.2%	0	0.0%	1	1.8%
4	1	2.2%	1	9.1%	2	3.6%
8	1	2.2%	0	0.0%	1	1.8%
Number of transfusions in previous 12 months						
0	34	75.6%	8	72.7%	42	75.0%

1	6	13.3%	2	18.2%	8	14.3%
2	3	6.7%	0	0.0%	3	5.4%
3	1	2.2%	0	0.0%	1	1.8%
7	1	2.2%	0	0.0%	1	1.8%
12	0	0.0%	1	9.1%	1	1.8%

Source: FDA reviewer analysis

Reviewer's Comment: Demographics and disease characteristics of the safety population are representative of patients with SCD in the US and adequately representative of the target population of patients with SCD likely to be treated in clinical practice.

8.2.3. Adequacy of the safety database:

The size of the safety database is acceptable given the disease and long-standing challenges in enrolling pediatric patients in SCD trials. The characteristics of patients in the GBT440-007 study are generally similar to indicated US population.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

8.3.2. Categorization of Adverse Events

Adverse events were analyzed using the Medical Dictionary for Regulatory Activities (MedDRA) version 18.1 and reported down to the investigator's verbatim term. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTAE, version 4.0) in the GBT440-007 study and graded per numerical (Grade 1-4) categorization in the trial. The applicant used standard procedures to collect and analyze AE data. AEs (both serious and non-serious non-SCD related and SCD related) were recorded as all subject visits from the first dose through the last subject's last visit. TEAE is defined as an event which b begins after start of treatment or which worsens during course of study until the last dose + 28 days.

8.3.3. Routine Clinical Tests

Safety assessments included physical examinations, vital signs (including blood pressure, pulse rate, body temperature, respiratory rate), 12-lead electrocardiograms (ECGs, collected in triplicate) clinical laboratory tests, concomitant medication usage, and adverse event (AE) monitoring (see Figure 2 below).
For Part C, TCD measurements were obtained to determine a preliminary treatment effect. Abnormal TCD values would indicate a safety concern and would be followed up as appropriate for standard clinical care.

Figure 2: Schedule of Assessments (GBT440-007 Part C)

APPENDIX 5. PART C SCHEDULE OF ASSESSMENTS

Procedure	Screening (Up to 35 Days Before Dosing)	Day 1[a]	Treatment Period: Week 2 (Day 14) (± 2 days)	Week 4 (Day 28) (± 3 days)	Week 8 (Day 56) (± 3 days)	Week 12 (Day 84) (± 3 days)	Week 16 (Day 112) & Week 20 (Day 140) (± 5 days)	Week 24 (Day 168) (± 5 days)	Week 36 (Day 252) (± 5 days)	Week 48 (Day 336) (± 5 days)	Follow-Up: EOS (last dose + 4 Weeks) (± 2 days)	Formulation Transition Visit[b]	Early Termination/ Withdrawal
Assent (if appropriate) & Informed Consent	X												
Review Inclusion/ Exclusion Criteria	X	X											
Medication & Medical History	X	X											
Height[c]	X												
Body Weight	X	X		X	X	X	X	X	X	X	X	X	X
Vital Signs	X	X	X	X	X	X	X	X	X	X	X		X
ECG[d]	X			X		X		X		X	X		X
Physical Examination	X	X		X	X	X	X	X	X	X	X	X	X
Serum Pregnancy Test[e]	X												
Urine Pregnancy Test[e]		X	X	X	X	X	X	X	X	X	X		X
Hemoglobin Electrophoresis	X												
Hematology, Serum Chemistry, Liver Function, Urinalysis[f]	X[g]	X	X	X	X	X	X	X	X	X	X		X
Serum Erythropoietin		X								X	X		
PK Sampling (plasma & whole blood)[h]		X		X	X	X	X	X	X	X		X	X
Voxelotor Drug Dosing in Clinic[i]		X		X	X	X	X	X	X	X		X	X
Transcranial Doppler (without sedation)	X							X		X			X
Exploratory Assessments (at select centers)[j]		X				X		X		X			X
Postdose Taste and Palatability Questionnaire [k]			X			X						X	

Procedure	Screening (Up to 35 Days Before Dosing)	Day 1[a]	Treatment Period: Week 2 (Day 14) (± 2 days)	Week 4 (Day 28) (± 3 days)	Week 8 (Day 56) (± 3 days)	Week 12 (Day 84) (± 3 days)	Week 16 (Day 112) & Week 20 (Day 140) (± 5 days)	Week 24 (Day 168) (± 5 days)	Week 36 (Day 252) (± 5 days)	Week 48 (Day 336) (± 5 days)	Follow-Up: EOS (last dose + 4 Weeks) (± 2 days)	Formulation Transition Visit[b]	Early Termination/ Withdrawal
Dispensing of Study Drug for Home Use		X		X	X	X	X	X	X			X	
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X

8.4. Safety Results

8.4.1. Deaths

There were no deaths reported in Part C as of the data cutoff date and the 120-day safety update.

8.4.2. Serious Adverse Events

The serious adverse events (SAEs) reported among patients in the 4 to < 12 year age group comprised mainly of complications related to sickle cell disease in this age population (i.e.

anemia, sickle cell anemia/crisis, pyrexia, infections, priapism and acute chest syndrome). It is important to document that hypersplenism was reported among 3/45 (6.7%) patients. Among those three patients, the hypersplenism was managed conservatively (i.e. IV fluids and antibiotics for concurrent infection) in two patients and with PRBCs transfusions (due to low hemoglobin levels) in one patient. One of these patients had voxelotor permanently discontinued due to osteonecrosis. Osteonecrosis is also a commonly accepted event that occurs in patients with SCD. Pyrexia can also occur in patients with SCD but also may be related to treatment with voxelotor and is included in common adverse reactions.

Table 18: Serious Adverse Events in GBT440-007 Study (4 to <12 Year Age Group)

System Organ Class	Preferred Term	Number	Percentage
Blood and lymphatic system disorders	Anemia	2	4.4%
	Hypersplenism	3	6.7%
	Sickle Cell Anemia w/ Crisis	41	91.1%
General disorders and administration site conditions	Pyrexia	5	11.1%
	Dehydration	1	2.2%
Infections and infestations	Influenza	1	2.2%
	Pneumonia	4	8.9%
	Pneumonia Necrotizing	1	2.2%
	Salmonellosis	1	2.2%
	Viral Infection	1	2.2%
Reproductive system and breast disorders	Priapism	1	2.2%
Respiratory, thoracic and mediastinal disorders	Acute Chest Syndrome	13	28.9%
	Pleural Effusion	1	2.2%

Source: FDA reviewer analysis

Reviewer's Comments: *Splenic sequestration crisis is a potentially life-threatening complication of SCD characterized by an acute drop in hemoglobin level, typically 2 g/dL below baseline. However, this is a new reported adverse event that was not seen in the pivotal trial. It is most likely documented here since the occurrence of hypersplenism is seen primarily among pediatric patients with SCD regardless if they are receiving treatment for their SCD.*

Among the 12-17 year age group, one patient developed thrombocytopenia while on study treatment. Initially, at baseline, the platelet count was within normal limits at 476 K/µL. By Week 8, the platelet count dropped to 86 K/µL. Over the course of treatment, the platelet count fluctuated to its lowest at 69 K/µL (Day 202) and 952 K/µL (Day 217). The study drug was reduced to 1200 mg (Day 203). The investigator discontinued treatment due to the thrombocytopenia w/o sequalae on Day 237. The last reported platelet count was 312 K/µL on Day 343. It is not clear why the patient developed thrombocytopenia while receiving voxelotor. Based on mechanism and safety data from Study GBT440-031, thrombocytopenia was not reported.

Another patient was reported to have a Grade 2 electrocardiogram T wave inversion (Day 30) which persisted up to Day 39. An echocardiogram was performed on Day 58 revealing no structural abnormalities; the ECG revealed a Brugada pattern. By Day 86, the ECG revealed a Grade 2 atrioventricular block (1st degree). Cardiology ruled out Brugada syndrome and advised a 24-hour ECG recording. The 24-hour ECG tape (Day 137) revealed periods of first degree heart block w/o symptoms. The patient was discontinued from voxelotor (Day 263) due to COVID-19 pandemic/restrictions. The patient remained to display periods of first degree heart block 45 days after discontinuing study treatment. Otherwise, the serious adverse events were associated to known SCD complications such as sickle anemia with crisis and pyrexia.

Table 19: Serious Adverse Events in GBT440-007 (12-17 Age Group)

System Organ Class	Preferred Term	Number	Percentage
Blood and lymphatic system disorders	Platelet Disorder	1	9.1%
	Sickle Cell Anemia w/ Crisis	9	81.8%
Cardiac disorders	Atrioventricular Block First Degree	1	9.1%
General disorders and administration site conditions	Pyrexia	1	9.1%
Infections and infestations	Tonsillitis	1	9.1%
Investigations	Electrocardiogram T Wave Inversion	1	9.1%

Reviewer's Comments: It is unclear if the T wave inversion and Grade 2 AV block (1st degree) were associated with the use of voxelotor. The Sponsor submitted a QTc study previously with their pivotal GBT440-031 study and determined that voxelotor did not have any clinically relevant effects on cardiac conduction. Otherwise, the SAEs reported in this age group are

known adverse events associated with the complications of SCD, except for the thrombocytopenia. The etiology for the thrombocytopenia is unclear since patient had a normal platelet count at baseline. Review of concomitant medications that could cause thrombocytopenia could not explain the decline to subtherapeutic levels during therapy as well as the return to normal levels after dose reduction of voxelotor.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

For subjects aged 4 to < 12 years, 77.8% (35/45) of patients had completed 24 weeks of treatment, and 58% (26/45) had completed 48 weeks of treatment. The most common reasons for early discontinuation of treatment were withdrawal of consent (11.1%; 5/45) and adverse events (8.9%; 4/45).

For subjects 12 to 17 years of age, 55% (6/11) of patients had completed 24 weeks of treatment, and 9.1% (1/11) had completed 48 weeks of treatment. The most common reasons for early discontinuation of treatment were withdrawal of consent (27.3%; 3/11), adverse events (18.2%; 2/11), and Investigator discretion due to the SARS-CoV-2 (COVID-19) pandemic (18.2%; 2/11).

Table 20: Reasons for Discontinuation of Treatment

Reasons for discontinuation of treatment , n (%)			
	4 to < 12 Year Age Group n = 45 (%)	12-17 Age Group n = 11 (%)	Total n = 56 (%)
Adverse Event	4 (8.9)	2 (18.2)	6 (10.7)
Withdrawal of consent	5 (11.1)	3 (27.3)	8 (14.3)
Discretion of Investigator	1 (2.2)	2 (18.2)	3 (5.4)
Other	1 (2.2)	0	1 (1.8)
Rollover to GBT440-038 OLE	21 (46.7)	0	21 (38)

Among the patients (4-11 year age group), the reasons for discontinuing voxelotor due to adverse events included the following:

- Subject (b) (6): Due to Grade 3 adverse event of osteonecrosis and anemia. This patient did have voxelotor treatment interrupted due to Grade 3 hypersplenism.
- Subject (b) (6): Due to Grade 1 adverse event of decrease appetite.
- Subject (b) (6): Due to Grade 2 non-cardiac chest pain
- Subject (b) (6): Due to Grade 2 pyrexia, Grade 1 and 2 allergic reaction (pedal and facial) and Grade 3 sickle cell anemia with crisis.

Reviewer's Comments: Among the reasons for discontinuing voxelotor due to adverse events, two patients in the pediatric group discontinued treatment due to intolerance to the study drug and poor palatability of the study drug. None of the patients in the 12-17 age group elected to continue in the extension study. The reasons are unknown.

8.4.4. Significant Adverse Events

The significant adverse events were identified by the severity categories (Grade 1-3) and NCI-CTACAE scales and definitions for both age groups. The list is condensed to highlight all of the reported Grade 3 significant adverse events identified in both age groups.

Table 21: Significant Adverse Events among Patients in 4 to < 12 Year Age Group (N =45)

System Organ Class	Preferred Term	Grade 1	Percentage	Grade 2	Percentage	Grade 3	Percentage	All Grades	Percentage
Blood and lymphatic system disorders	Anemia	1	2.2%	1	2.2%	2	4.4%	4	8.9%
	Hypersplenism	0	0.0%	0	0.0%	3	6.7%	3	6.7%
	Sickle Cell Anemia Crisis	0	0.0%	30	66.7%	29	64.4%	59	131.1%
Gastrointestinal disorders	Dental Caries	0	0.0%	0	0.0%	1	2.2%	1	2.2%
General disorders and administration site conditions	Pyrexia	18	40.0%	11	24.4%	2	4.4%	31	68.9%
Infections and infestations	Febrile Infection	0	0.0%	0	0.0%	1	2.2%	1	2.2%
	Pharyngitis Streptococcal	0	0.0%	0	0.0%	1	2.2%	1	2.2%
	Pneumonia	0	0.0%	0	0.0%	4	8.9%	4	8.9%
	Pneumonia Necrotizing	0	0.0%	0	0.0%	1	2.2%	1	2.2%
	Salmonellosis	0	0.0%	0	0.0%	1	2.2%	1	2.2%
	Sepsis	0	0.0%	0	0.0%	1	2.2%	1	2.2%
	Tooth Abscess	0	0.0%	0	0.0%	1	2.2%	1	2.2%
Investigations	Blood Bilirubin Increased	0	0.0%	0	0.0%	1	2.2%	1	2.2%
	Transaminases Increased	0	0.0%	1	2.2%	1	2.2%	2	4.4%
Metabolism and nutrition disorders	Dehydration	1	2.2%	0	0.0%	1	2.2%	2	4.4%
Musculoskeletal and connective tissue disorders	Osteonecrosis	0	0.0%	0	0.0%	1	2.2%	1	2.2%
Nervous system disorders	Depressed Level Of Consciousness	0	0.0%	0	0.0%	1	2.2%	1	2.2%
Reproductive system and breast disorders	Priapism	0	0.0%	0	0.0%	1	2.2%	1	2.2%
Respiratory, thoracic and	Acute Chest Syndrome	0	0.0%	0	0.0%	13	28.9%	13	28.9%

System Organ Class	Preferred Term	Grade 1	Percentage	Grade 2	Percentage	Grade 3	Percentage	All Grades	Percentage
mediastinal disorders									
	Pleural Effusion	0	0.0%	0	0.0%	1	2.2%	1	2.2%

Table 22: Significant Adverse Events among Patients in the 12-17 Age Group (N =11)

System Organ Class	Preferred Term	Grade 1	Percentage	Grade 2	Percentage	Grade 3	Percentage	All Grades	Percentage
Blood and lymphatic system disorders	Sickle Cell Anemia W/ Crisis	0	0.0%	6	54.5%	8	72.7%	14	127.3%
General disorders and administration site conditions	Pyrexia	3	27.3%	0	0.0%	1	9.1%	4	36.4%

Reviewer's Comments: In addition to the commonly associated adverse events typically seen as SCD complications, Grade 3 elevation of bilirubin and transaminases were reported in one patient (Subject (b) (6)) in the 4-11 year age group which did not meet Hy's Law criteria.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

Among the 4-11 year age group in GBT440-007, the most common adverse events anemia, diarrhea, nausea, abdominal pain, fever, headache and rash. These findings are similar to the most common non-SCD TEAES with an incidence > 10% in the adolescent and adult trial, GBT440-031, were headache, diarrhea, abdominal pain, nausea, fatigue, rash and pyrexia. Anemia (by FDA MedDRA query) analysis was also identified among 4-11 year old group (defined as symptomatic or worsening anemia). Anemia may be more common the younger age group than adults as more children were on HU which can cause anemia. .

Table 23: Non-SCD Treatment Emergent Adverse Events (>10%) among 4-11 Year Age Group in GBT440-007

SOC and Preferred Term	4 to < 12 Year Age Group (n = 45)	Percentage
Total	311	
Blood and Lymphatic System Disorders		
Leukopenia (Neutropenia and/or Lymphopenia)	1	2.2%
Neutropenia, Granulocytopenia	1	2.2%

SOC and Preferred Term	4 to < 12 Year Age Group (n = 45)	Percentage
Thrombocytopenia	4	8.9%
Bleeding	3	6.7%
Anemia FDA N	20	44.4%
Cardiac Disorders		
Low LVEF, Low Cardiac Output, Cardiomyopathy, LV Dysfunction	1	2.2%
Edema, Non-Pulm, Fluid Retention, Overload	1	2.2%
Arrhythmia	2	4.4%
Tachycardia	2	4.4%
Eye Disorders		
Eye, Other	3	6.7%
Gastrointestinal Disorders		
Hepatitis	1	2.2%
GOT, GPT, GGTP, LFTs	4	8.9%
Hyperbilirubinemia, Alk Phos, Jaundice	1	2.2%
Constipation	2	4.4%
Diarrhea, Colitis, Enteritis, Proctitis, Gastroenteritis, C-Diff	8	17.8%
Dyspepsia, N, V, Indigestion, Epigastric Pain, Gastritis, Duodenitis	16	35.6%
Nausea, Vomiting	16	35.6%
Abdominal Pain, Distension, Bloating, Spasm, IBS, Megacolon	11	24.4%
General Disorders and Administration Site Conditions		
Fever, Rigors	17	37.8%
Asthenia, Fatigue, Malaise, Weakness, Narcolepsy	2	4.4%
Anorexia, Decreased Appetite	1	2.2%
Peripheral Edema FDA N	1	2.2%
Immune System Disorders		
Allergic RXN, Hypersensitivity	1	2.2%
Angioedema, Angioneurotic Edema, Laryngeal Edema	1	2.2%

SOC and Preferred Term	4 to < 12 Year Age Group (n = 45)	Percentage
Infections and Infestations		
Infection, All	25	55.6%
Infection, Bacterial	2	4.4%
Infection, Viral	14	31.1%
Infection, Fungal	1	2.2%
Sepsis	1	2.2%
Abscess, Boil, Furuncle	1	2.2%
Influenza	5	11.1%
URI, Cold, Rhinitis, Upper Resp Tract Infection, Flu-Like Illness	10	22.2%
Pneumonia	4	8.9%
UTI	1	2.2%
Injury, Poisoning and Procedural Complications		
Fracture	1	2.2%
Gait Disturbance, Difficulty Walking,	1	2.2%
Fall, Dizziness, Balance Disorder	1	2.2%
Metabolism and Nutrition Disorders		
Dehydration, Volume Depletion	2	4.4%
Musculoskeletal and Connective Tissue Disorders		
Arthralgia, Arthritis, Arthrosis	2	4.4%
Back pain FDA N	3	6.7%
Nervous System Disorders		
Somnolence, Fatigue, Sedation	1	2.2%
Insomnia, Sleep Disturbance, Abnormal Dreams	1	2.2%
Confusion, Delirium, Altered Mental Status, Disorientation, Coma	1	2.2%
Headache FDA N	8	17.8%
Renal And Urinary Disorders		
Nephrosis, Proteinuria, Nephropathy	2	4.4%
Dysuria	1	2.2%
Respiratory, Thoracic and Mediastinal Disorders		

SOC and Preferred Term	4 to < 12 Year Age Group (n = 45)	Percentage
Chest Pain (Non-Cardiac Or Unknown)	2	4.4%
Apnea, Respiratory Failure, Cyanosis, Hypoxemia, Desaturation, Lung Injury	1	2.2%
Cough	2	4.4%
Nasopharyngitis FDA N	2	4.4%
Epistaxis	3	6.7%
Skin and Subcutaneous Tissue Disorders		
Pruritis	2	4.4%
Rash, Eruption, Dermatitis	9	20.0%

Due to the smaller sample size among the 12-17 year age group, the percentage of treatment emergent adverse events (>10%) were representatively higher and broader across system organ class (SOC) disorders: Blood and lymphatic disorders, gastrointestinal disorders, general disorders and administration site conditions, infections, musculoskeletal and respiratory disorders.

Table 24: Non-SCD Treatment Emergent Adverse Events (> 10%) in 12-17 Year Age Group of GBT440-007

System Organ Class and Preferred Terms	12-17 Year Age Group (n = 11)	Percentage
Sum	53	
Blood and lymphatic system disorders		
Anemia FDA N	6	54.5%
Cardiac disorders		
AV block	1	9.1%
Eye disorders		
Visual Disturbance	1	9.1%
Gastrointestinal disorders		
Diarrhea, colitis, enteritis, proctitis, gastroenteritis, C-diff	1	9.1%
Dyspepsia, N, V, indigestion, epigastric pain, gastritis, duodenitis	1	9.1%
Nausea, vomiting	1	9.1%
Abdominal Pain, distension, bloating, spasm, IBS, megacolon	2	18.2%
General disorders and administration site conditions		

System Organ Class and Preferred Terms	12-17 Year Age Group (n = 11)	Percentage
Fever, Rigors	4	36.4%
Edema, non-pulmonary, fluid retention, overload	1	9.1%
Injury, poisoning and procedural complications		
Fracture	1	9.1%
Infections and infestations		
Infection, All	5	45.5%
URI, cold, rhinitis, upper resp tract infection, flu-like illness	3	27.3%
Musculoskeletal and connective tissue disorders		
Arthralgia, arthritis, arthrosis	1	9.1%
Back pain FDA N	2	18.2%
Respiratory, thoracic and mediastinal disorders		
Bronchitis, bronchiolitis, tracheitis, alveolitis, bronchiectasis	2	18.2%
Chest Pain (non-cardiac or unknown)	2	18.2%
Cough	2	18.2%
Nasopharyngitis FDA N	1	9.1%

Reviewer's Comments: The smaller sample size among the 12-17 year age group makes it difficult to determine if these adverse events were random or due to voxelotor treatment.

Table 25: Treatment Emergent SCD-Related Adverse Events in GBT440-007 (4 to < 12 Year Age Group)

System Organ Class	Preferred Term	Number	Percentage
Blood and lymphatic system disorders	Sickle Cell Anemia with Crisis	59	131.1%
Infections and infestations	Pneumonia	4	8.9%
	Pneumonia Necrotizing	1	2.2%
Musculoskeletal and connective tissue disorders	Osteonecrosis	1	2.2%
Reproductive system and breast disorders	Priapism	1	2.2%
Respiratory, thoracic and mediastinal disorders	Acute Chest Syndrome	13	28.9%

Table 26: Treatment Emergent SCD-Related Adverse Events in GBT-007 (12-17 Year Age Group)

System Organ Class	Preferred Term	Number	Percentage
Blood and lymphatic system disorders	Sickle Cell Anemia with Crisis	14	127.3%

Reviewers' Comments: The known SCD complication, sickle cell anemia with crisis, was most notable in both treatment populations. Pneumonia, osteonecrosis, priapism as well as acute chest syndrome are common pediatric SCD complications.

8.4.6. Laboratory Findings

The abnormal laboratory findings in GBT440-007 were primarily associated with the underlying disease (such as anemia and thrombocytopenia). There were no reports of drug-induced liver injury. However, there was one patient (Subject (b) (6)) who displayed ALT ≥ 3 x ULN and total bilirubin level ≥ 2 x ULN during treatment which was similar to values collected at baseline. It was determined that this event was not a drug-induced liver injury.

8.4.7. Vital Signs

No clinically meaningful trends were observed in vital signs (systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate, weight, and temperature) in Study GBT440-007 Part C.

8.4.8. Electrocardiograms (ECGs)

No clinically meaningful trends were observed in ECG parameters (heart rate, PR interval, QRS interval, QT interval, QT corrected for heart rate by Fridericia's formula [QTcF] interval, and RR interval) in Study GBT440-007 Part C.

8.4.9. QT

QTc clinical trials were completed with the pivotal GBT440-031 clinical trial. It was determined that voxelotor did not have any clinically relevant effects on cardiac conduction.

8.5. Analysis of Submission-Specific Safety Issues

8.5.1. Recommend Voxelotor Dosage for Concomitant Use with Strong CYP3A4 Inducers

Dosing adjustments with concomitant (b) (4) strong or moderate CYP3A4 inducers with the use of voxelotor are provided in Section 2: Dosage and

Administration and Section 7: Drug Interactions in the voxelotor US Prescribing Information (USPI).

8.5.2. Effect of Voxelotor on Tissue Oxygen Availability

Voxelotor' s mechanism of action is presumed to specifically target the underlying mechanism of sickle cell disease by increasing the affinity of Hb for oxygen and stabilizing Hb in the oxyhemoglobin state and thereby inhibiting polymerization of HbS in RBCs. By maintaining approximately 30% of Hb in the nonpolymerizing state, voxelotor increases hemoglobin levels and decreases hemolysis, consistent with an inhibition of polymerization.

Peer-reviewed literature[5] has expressed concern about whether the 30% modification by GBT440 would be protective for HbS polymerization under in vivo conditions since the 70% of Hb tetramers left unmodified by GBT440 still have normal ability to form polymers and the presence of the GBT440-modified tetramers would still contribute to cytoplasmic macromolecular crowding that magnifies the polymer formation by deoxy-Hgb S. Also, in sickle cell patients with marginal cerebrovascular blood, the effect of the reduced functional oxygen content caused by voxelotor could enhance the cerebrovascular risk.

The Applicant is currently conducting Study GBT440-032, "A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of Voxelotor (GBT440) in Pediatric Participants with Sickle Cell Disease (HOPE Kids 2)" to evaluate the effect of voxelotor on stroke reduction, as measured by transcranial doppler (TCD) flow velocity in subjects 2 to < 15 years of age with SCD who have conditional TCD flow velocity at baseline in accordance with the conditions for accelerated approval for NDA 213137. The primary endpoint of Study GBT440-032 is change from baseline at 24 weeks in time averaged maximum of mean velocity (TAMMV) arterial cerebral blood flow as measured by TCD.

The preliminary data in GBT440-007 provided data on five patients in the 4-11 year age group had TCD flow velocity data which showed a mean change from baseline to Week 24 of -12.4 ± 8.6 cm/sec. Among all patients, six of the patients (3 from the 4-11 age group and 3 from the 12-17 age group) did revert to normal TCD velocity at Week 24. None of the patients reverted to an abnormal TCD velocity.

Whether the mean reduction or normalization of TCD flow velocity while increasing hemoglobin levels will have an impact on this population will also require supportive and validated neurocognitive testing or other clinically meaningful benefit to support this surrogate endpoint. Future results from both GBT440-007 (Part C) and GBT440-032 studies should provide us more informative information.

8.6. Additional Safety Explorations

8.6.1. Human Carcinogenicity or Tumor Development

See Pharm Tox reviewer discussion in Section 5 and non-clinical review from original approval dated October 29, 2019.

8.6.2. Human Reproduction and Pregnancy

There were no clinical studies on the effect of voxelotor on pediatric growth conducted.

8.6.3. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

There were no reported cases of toxicity due to overdose with voxelotor reported during the clinical development program. Based on the mechanism of action, there is no pharmacological evidence to suggest abuse or dependence potential for this drug.

8.7. Safety in the Postmarket Setting

8.7.1. Safety Concerns Identified Through Postmarket Experience

Since voxelotor was approved on 25 November 2019, there have been (b) (4) patients exposed in the postmarketing setting as of 31 December 2020. The current United States Prescribing Information (USPI; revised 11/2019) in Section 6: Adverse Reactions contains the following Medical Dictionary for Regulatory Activities (MedDRA) PTs listed as adverse reactions for Oxbryta: headache, diarrhea, abdominal pain, nausea, fatigue, rash, pyrexia, and drug hypersensitivity (as a contraindication). The majority of adverse events reported in totality have been non-serious at 77% and 23% serious among the 9687 adverse events identified. In the 0 to 12 years age group, the majority of adverse events reported by preferred term were non-serious at 80% which included abdominal pain upper, diarrhea, nausea and product dose omission. Among the 20% serious adverse events, sickle cell anemia of crisis was reported. In the 13 to 17 years age group, the majority of adverse events reported by preferred term were non-serious at 75%. The remaining 25% were reported as serious. The adverse events reported in the age group were similar to the AE findings in the 0 to 12 years age group. There have been 65 events with a reported fatal outcome. A review of the events did not identify any new safety signal. The lack of significant information regarding the fatal outcome prevents one to make a meaningful causality assessment.

There have been reports of patients experiencing anaphylactic reaction/anaphylactic shock after starting treatment with Oxbryta and developing angioedema. There is no additional information provided to make a meaningful causality assessment. The label highlights in Section 5 Warnings and Precautions the rarity of serious hypersensitivity reactions which have occurred in < 1% of patients treated and management of such reactions.

8.7.2. Expectations on Safety in the Postmarket Setting

There are no safety concerns in the postmarket setting to be discussed in this application.

8.7.3. Additional Safety Issues From Other Disciplines

Overall, the patient populations evaluated in the GBT440-007 study are reasonably representative of patients with SCD who are expected to take voxelotor in the postmarketing setting. Although the clinical trial safety database is small due to the rare disease and pediatric population, the safety profile observed in the clinical development program may be generalized to the target population.

8.8. Integrated Assessment of Safety

The primary safety data provided by the Applicant in support of this application for voxelotor was derived from a single phase 2 open-label study in pediatric and adolescent patients with SCD with the safety profile in adolescents and adults supported by data from their randomized, Phase 3 study, GBT440-031. The demographics of the subjects enrolled in these studies were consistent with those for the general SCD population.

Across all clinical studies included in this NDA, voxelotor demonstrated an acceptable safety and tolerability profile. There were no deaths were reported in this Phase 2a study (GBT440-007). SAES and TEAEs were appropriately classified as SCD related and non-SCD related based on the expected disease presentation in the target population. SCD-related TEAEs were defined as sickle cell anemia with crisis, ACS, pneumonia, osteonecrosis, and priapism.

<u>TEAEs leading to study drug discontinuation</u>
Aside from withdrawal of consent being the leading reason for early discontinuation of treatment among the 4 to < 12 year age group, adverse events were implicated as the seconded most reason for early discontinuation. Those reasons included Grade 3 osteonecrosis and anemia, decrease appetite, Grade 2 non-cardiac chest pain and Grade 2 pyrexia and Grade 1 and 2 allergic reaction.

<u>Non-SCD-Related Safety Profile</u>
In this study, the most common non-SCD treatment emergent adverse events among the 4 to < 12 age group included diarrhea, dyspepsia, nausea/vomiting, abdominal pain, fever, headache and rash. The majority of adverse events were of mild to moderate severity; however, among the severe (Grade 3) serious adverse events sickle cell anemia w/ crisis, pyrexia and acute chest syndrome.

<u>SCD-Related Safety Profile</u>

Among the SCD-related treatment emergent adverse events included the known SCD complications like sickle cell anemia w/ crisis and acute chest syndrome.

The TEAEs leading to study drug discontinuation, non-SCD related TEAEs and SCD-related TEAEs among the 12-17 year age group were similar to the population treated in the pivotal GBT440-031 trial.

The clinical study included in this NDA, voxelotor demonstrated an acceptable safety and tolerability profile that supports the proposed indication to include patients from age ≥ 4 and older for the treatment of sickle cell disease.

9. Advisory Committee Meeting and Other External Consultations

This application was not presented at an Advisory Committee or any other external consultants because the application did not raise efficacy or safety issues for the recommended indication.

10. Pediatrics

Global Blood Therapeutics (GBT) was granted Orphan Drug Designation on 29 December 2015 (#15-4997) for GBT440 for the treatment of sickle cell disease (SCD) and is therefore exempt from requirements under the Pediatric Research Equity Act (PREA) (FDCA 505B).

11. Labeling Recommendations

11.1. Prescription Drug Labeling

The table below summarizes the revisions that FDA made to the submitted labeling.

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	Proposed Labeling	Approved Labeling
Indication and Usage	OXBRYTA is a hemoglobin S polymerization inhibitor indicated for the treatment of sickle cell disease in adults and pediatric patients 4 years	OXBRYTA is a hemoglobin S polymerization inhibitor indicated for the treatment of sickle cell disease in adults and pediatric patients 4 years

	of age and older.	of age and older.
Dosage and Administration	Recommended dosage: •Adults and pediatric patients 12 years (b) (4) and older: 1,500 mg orally once daily. •Pediatric patients 4 to < 12 years: Dosing with OXBRYTA is based on body weight. See Table 1 for complete dosing recommendations	Recommended dosage: •Adults and pediatric patients 12 years (b) (4) and older: 1,500 mg orally once daily. •Pediatric patients 4 to less than 12 years: Dosing with OXBRYTA is based on body weight. Dosing recommendations provided in Table 1 in the USPI.
Warnings and Precautions	•Hypersensitivity Reactions: Observe for signs and symptoms and manage promptly. •Laboratory Test Interference: Perform quantification of hemoglobin species when patient is not receiving OXBRYTA.	Hypersensitivity and laboratory test interference included minor edits to language.
Adverse Reactions	Adverse reactions were on the basis of the pivotal study, GBT440-031.	Updated Section 5 and 6 to include adverse reactions for pediatric patients 4 to < 12 year. Most common adverse reactions (incidence ≥>10% with a difference of >3% compared to placebo) are headache, diarrhea, abdominal pain, nausea, rash, and pyrexia. Fatigue was removed. Updated Section 7 (Drug Interactions) to reflect updated effect of other drugs on voxelotor.
Clinical Trials Experience	The efficacy evaluation was based on GBT440-031 study.	Revised section 6.1 and 14 to include the results from GBT440-007.
Clinical Studies	Efficacy results were based	The efficacy of OXBRYTA is

	on GBT440-031 study.	based on GBT440-031 and GBT440-007. Included GBT440-007 in section 14.2 and presented the all treated population based on hemoglobin response of 36% (16/45) (b) (4)

12. Risk Evaluation and Mitigation Strategies (REMS)

The clinical review team and the Division of Risk Management (DRISK) agree that a REMS is not necessary for the safe use of voxelotor. There are no additional risk management strategies needed beyond the recommended labeling.

13. Postmarketing Requirements and Commitments

The following postmarketing requirements/commitments are ongoing:

PMR-1 3746-1 (Accelerated Approval PMR)
Complete Study GBT440-032: the ongoing Phase 3, randomized, double-blind, placebo-controlled trial in pediatric patients (age 2 years to < 15 years) with Sickle Cell Disease (HOPE KIDS 2). Expected enrollment of approximately 224 patients (age 2 years to < 15 years) with at least 15 patients from age 2 years to < 4 years of age. Include patients with baseline hemoglobin of less than 6 g/dL. The primary endpoint is change from baseline at 24 weeks in time averaged maximum of mean velocity (TAMMV) arterial cerebral blood flow as measured by transcranial doppler (TCD). The secondary endpoint is change from baseline in TCD flow velocity at Week 48 and Week 96.

Interim Report Submission: 07/2025
Study/Trial Completion: 03/2026
Final Report Submission: 09/2026

PMC 3746-3
Complete at least 5 years of follow-up for all patients (on treatment) enrolled in Study GBT440-

034: An Open-Label Extension Study of voxelotor Administered Orally to Patients with Sickle Cell Disease who have Participated in GBT440 Clinical trials. Include updated safety and efficacy analysis in yearly reports and submit datasets at the time of final clinical study report submission.

Interim Report Submission (Year 1): 06/2021
Interim Report Submission (Year 2): 06/2022
Interim Report Submission (Year 3): 06/2023
Interim Report Submission (Year 4): 06/2024
Final Report Submission (Year 5): 06/2025

14. Appendices

14.1. References

1. Kato GJ, Steinberg MH, Gladwin MT. Intravascular hemolysis and the pathophysiology of sickle cell disease. J. Clin Invest. 2017;127(3):750-60.

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14.2. Financial Disclosure

The financial disclosure for conducting the clinical trial is listed below.

Covered Clinical Study (Name and/or Number): GBT440-007 (HOPE KIDS)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 126		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455):		

0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

APPEARS THIS WAY ON ORIGINAL

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

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PATRICIA A ONEAL
12/16/2021 10:23:17 AM

TANYA M WROBLEWSKI
12/16/2021 11:39:00 AM

ALBERT B DEISSEROTH
12/16/2021 03:04:17 PM