CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213137Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Cross Discipline Team Leader Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

Division Director Summary Review for Regulatory Action

Date	(electronic stamp)
From	Ann T. Farrell, MD
Subject	Division Director Summary Review
NDA/BLA # and Supplement #	NDA #213137
Applicant	Global Blood Therapeutics
Date of Submission	06/26/2019
PDUFA Goal Date	2/26/2020
Proprietary Name	Oxbryta
Established or Proper Name	Voxelotor (GBT440)
Dosage Form(s)	500 mg tablet
Applicant Proposed Indication(s)/Population(s)	Indicated for the treatment of sickle cell disease in adult (b) (4) patients.
Action or Recommended Action:	*Accelerated Approval*
Approved/Recommended Indication(s)/Population(s) (if applicable)	Indicated for the treatment of sickle cell disease in adults and pediatric patients 12 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 trial(s) (1).

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Regulatory Project Manager	**Katie Chon, PharmD, RPh**
Medical Officer Review	**Patricia Oneal, MD/Rosanna Setse, MD PhD**
Statistical Review	**Lola Luo, PhD/ Yeh-Fong Chen, PhD**
Pharmacology Toxicology Review	**Pedro L. Del Valle, PhD/Brenda J. Gehrke, PhD/ Haleh Saber, PhD, MS**
OPQ Review	**Gaetan Ladoucer/Su Tran/Nina Ni/Anamitro Banerjee/Abdullah Mahmud/Sherita McLamore, PhD/Mei Ou, PhD; Banu Zolnik, PhD; Angelica Dorantes, PhD; Rabiya Haider, PharmD;James Laurensen**
Microbiology Review	**N/A**
Clinical Pharmacology Review	**Salaheldin Hamed, PhD, Jianghong Fan, PhD, Liang Li, PhD, Robert Schuck, PharmD, PhD/Christian Grimstein, PhD, Lian Ma, PhD Xinyuan Zhang, PhD, Ruby Leong, PharmD/ Brian P Booth, PhD**
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Labeling	**Virginia Kwitkowski**
Others	**Please see unireview**

OND=Office of New Drugs
OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
CDTL=Cross-Discipline Team Leader
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

Benefit-Risk

Sickle cell disease (SCD) is a serious and life-threatening inherited chronic disorder affecting approximately 100,000 Americans and millions world-wide. The disease is caused by a mutation in the beta-globin gene resulting in the polymerization of deoxygenated HbS and resultant sickling of red blood cells (RBCs). SCD is characterized clinically by hemolytic anemia and recurrent painful vasoocclusive crisis (VOC), acute chest syndrome (ACS), priapism as well as progressive multiple end-organ damage including stroke/silent cerebral infarct, chronic kidney disease, leg ulcers, pulmonary hypertension and sickle cell anemia-associated nephropathy (SCAN). Patients with SCD can have significant morbidity as well as a shortened lifespan. 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. Treatment includes symptom improvement, antibiotic prophylaxis, strategies to increase the fetal hemoglobin, and reduce the number of vasooclusive crises. For a few patients, hematopoietic stem cell transplantation can be quite effective.

Despite the availability of hydroxyurea, L-glutamine, and crizanlizumab, all of which have been demonstrated effectiveness in reducing the number of vasoocclusive pain or acute chest syndrome episodes, a significant need still exists for effective treatments. Interventions that may reduce hemolysis resulting in an increase in blood hemoglobin (Hgb) levels may confer a clinical benefit in this patient population.

Global Blood Therapeutics has developed a hemoglobin S polymerization inhibitor for daily oral use for use in patients with SCD. The pivotal study, GBT440-031, demonstrated a statistically significant improvement in the number of patients treated with 1500 mg voxelotor compared to the number of patients treated with placebo who had a one gram per deciliter of hemoglobin rise in their hemoglobin levels from baseline at Week 24 (51.2% vs 6.2%, respectively). Additionally, there was a dose dependent reduction in hemolysis markers (bilirubin and percent reticulocytes). The most common treatment emergent adverse events were headache, diarrhea, abdominal pain, nausea, rash, fatigue and pyrexia. Serious adverse reactions included headache, drug hypersensitivity and pulmonary embolism. Labeling addresses the safety concerns and includes warnings for hypersensitivity reactions and potential laboratory interference as voxelotor administration may interfere with measurement of Hb subtypes (HbA, HbS, and HbF) by high performance liquid chromatography (HPLC).

Potential theoretical risks with voxelotor include tissue hypoxia due to ineffective tissue oxygen extraction with the high Hgb occupancy from voxelotor-bound hemoglobin. 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. The long-term safety of voxelotor will be assessed with post-marketing requirements and commitments.

In summary, the overall safety profile of voxelotor appears acceptable for proposed registrational dose of 1,500 mg and current data support a favorable benefit-risk assessment for voxelotor for patients with sickle cell disease. The labeling adequately addresses known risks and the Applicant intends to confirm and verify clinical benefit with an ongoing confirmatory study.

Rationale for Accelerated Approval

Section 21 CFR 314.500 provides that the FDA may grant marketing approval on the basis of adequate and well-controlled clinical trials establishing that the product has an effect upon a surrogate endpoint that is reasonably likely to predict clinical benefit. Approval under these regulations requires that the applicant study the product further to verify and describe the clinical benefit. The regulation states that the expectation that the verification study would usually be underway at the time of the approval and that the confirmatory study be adequate and well-controlled.

As noted above, the Applicant has demonstrated the effect of voxelotor on an endpoint that is reasonably likely to predict clinical benefit in adults and pediatric patients with sickle cell disease age 12 years and older. The hemoglobin improvement was due to a reduction in hemolysis. While the increase in hemoglobin results represent substantial evidence of an effect, it is not entirely clear that an increase of a gram per deciliter or more of hemoglobin due to voxelotor results in a tangible benefit to patients. For that reason, this application is receiving accelerated approval with a post-marketing requirement to provide evidence of clinical benefit. During negotiations with the Applicant several proposals for demonstrating clinical benefit were discussed. At this time, the Applicant has chosen to demonstrate that an improvement in hemoglobin due to voxelotor is associated with a reduction in cerebral blood flow velocity as assessed by transcranial doppler (TCD) velocity.

Background for the accelerated approval

A major benefit in the treatment of sickle cell disease would be to demonstrate a decrease in the risk of strokes for patients with sickle cell disease.

An NHLBI analysis of patients with SCD identified two phenotypes: those who had complications (stroke, renal failure, pulmonary hypertension, priapism, leg ulcers, early mortality) that appeared to be associated with a “hyper-hemolytic phenotype” and those who had complications that appeared to be associated with vasooclusive events.

Patients with sickle cell disease experience significant morbidity due to the risk of strokes including silent strokes. A recent analysis suggests that 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. TCD is used to assess cerebral artery blood flow velocity and is a reliable predictor of stroke.

Several important trials have been conducted to understand hemoglobin levels and stroke or silent cerebral infarct risk in patients with sickle cell. Two clinical trials have established that routine TCD screening and chronic red cell transfusions for children with abnormal TCD as the standard of care for stroke prevention: The Stroke Prevention Trial in Sickle Cell Anemia (STOP) and Optimizing Primary Stroke Prevention in Sickle Cell Anemia (STOP 2). STOP was a randomized multicenter controlled trial comparing prophylactic blood transfusion with standard care in children aged 2 to 16 years with SCD selected for high stroke risk by TCD. The study showed a reduction in stroke with transfusion. In STOP2, discontinuing transfusions after 30 months or more resulted in a reversion to abnormal TCD values and increased stroke risk. The Silent Cerebral Infract Transfusion (SIT) trial randomized patients to chronic blood transfusion or observation and followed them with magnetic resonance imaging (MRI). The patients who received chronic transfusions had fewer recurrences of infarct or hemorrhage. The chronic transfusions that patients with SCD receive are not risk free and can lead to alloantibody formation, iron overload and risks of infections.

TCD readings are usually reported as normal, conditional, and abnormal or inadequate for assessment. Based on the trials mentioned above a chronic transfusion program is recommended for patients with high risk TCD measurements (abnormal category) to reduce stroke risk. The risk of stroke based on TCD measurement is thought to be a continuous variable and not a discrete one. Therefore, patients with conditional TCD results may still be at risk for stroke albeit less than those patients with abnormal TCD results.

The Applicant has proposed a controlled study (STUDY GBT440-032) to confirm the clinical benefit of voxelotor by evaluating the effect of voxelotor on stroke risk reduction as measured by TCD flow velocity in patients with sickle cell anemia and will include patients aged < 12 years as the confirmatory trial under subpart H.

1. Background

The following text is excerpted from the draft unireview:

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). A single point mutation in the hemoglobin β-globin chain of affected persons produces mutant hemoglobin molecules (Hemoglobin S [Hb S]). The most common form of sickle-cell disease (homozygous Hb SS) accounts for 60%-75% of sickle cell disease in the United States. Approximately 25% of patients have coinheritance of Hb

S with another β-globin chain variant such as sickle-Hb C disease and sickle β-thalassemia.

During periods of deoxygenation, Hb S polymerizes within erythrocytes resulting in intermittent vaso-occlusive events and chronic hemolytic anemia. Vaso-occlusion occurs as a result of the formation of multicellular aggregates that block blood flow in small blood vessels, resulting in tissue ischemia & reperfusion damage to downstream tissues which lead to recurrent acute pain/crises episodes. Vaso-occlusive pain episodes are the most frequent cause of recurrent morbidity in SCD and account for the majority of SCD-related hospitalizations (Platt, Thorington et al. 1991, Gill, Sleeper et al. 1995). 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.

SCD is associated with decreased life expectancy (Platt 1994, Lanzkron, Carroll et al. 2013, Elmariah, Garrett et al. 2014, Maitra, Caughey et al. 2017). Acute chest syndrome (ACS) is a serious acute complication and a leading cause of mortality in both children and adults with SCD (Vichinsky, Neumayr et al. 2000, Bakanay, Dainer et al. 2005). Other causes of death in patients with SCD include infections (Adamkiewicz, Sarnaik et al. 2003) and cerebrovascular events (Platt 2005, Verduzco and Nathan 2009).

Children have higher rates of death from infection and sequestration crises (Manci, Culberson et al. 2003). Cardiopulmonary complications represent a major mortality risk in adults (Fitzhugh, Lauder et al. 2010). Currently, the management of sickle cell crises (SCC) episodes is generally supportive and includes symptomatic treatment with intravenous fluids, analgesics, oxygen and RBC transfusion support. Hematopoietic stem cell transplantation (HSCT) and gene therapy offers potential cure; however only few patients are eligible for these treatment option. Hydroxyurea (HU) was approved in 1998 and 2017; for reducing the frequency of sickle cell crises in adult patients with SCD and reducing the frequency of painful crises and the need for blood transfusions in adult patients with sickle cell anemia with recurrent moderate to severe painful crises (generally at least 3 during the preceding 12 months) and for reducing the frequency of painful crises and the need for blood transfusions in patients age 2 and older who have sickle cell anemia with recurring moderate to severe painful crises. L-glutamine (approved in 2017) is indicated to reduce the acute complications of sickle cell disease in adult and pediatric patients 5 years of age and older.

Recently Novartis received approval for a monoclonal antibody targeting selectin to reduce the frequency of vaso-occlusive crises (VOCs) in adults and pediatric patients aged 16 years and older with sickle cell disease.

Global Blood Therapeutics has submitted an NDA for GBT440 (Voxelotor (OXBRYTA)), a new molecular entity, which is not currently marketed anywhere in the world. GBT440 binds to the N-terminal α chain of Hb, increases HbS affinity for

oxygen, delays in vitro HbS polymerization and prevents sickling of red blood cells (RBCs).

2. Product Quality

From the Office of Product Quality Summary review:

NDA 213137 was submitted as a 505(b)(1) NDA under the Federal Food, Drug and Cosmetic Act for Voxelotor Tablets, 500 mg. Voxelotor is a once daily, orally bioavailable, small-molecule, hemoglobin S polymerization inhibitor …Voxelotor is a new molecular entity (NME) that was granted Fast Track designation (October 2015); Orphan Designation (December 2015); Rare Pediatric Disease Designation (Jun 2017); and Breakthrough Therapy Designation (January 2018)… Voxelotor is a small, achiral, BCS Class 2 molecule, that is manufacturedcby (b) (4) *. The drug product is presented as 500 mg immediate-release solid oral dosage form and is formulated as a light yellow to yellow, biconvex, oval-shaped, film-coated, tablet with "GBT 500" debossed on one side.*

Voxelotor is to be administered alone or in combination with hydroxyurea. The recommended dosing regimen for Voxelotor Tablets is 1500 mg taken orally once daily with or without food and 1000 mg taken orally once daily in patients with severe hepatic impairment (Child Pugh C)…

The applicant provided sufficient information to assure the identity, strength, purity, quality, and bioavailability of the proposed drug product. The key review issues (Section IV) have been adequately resolved and were deemed to have minimal likely impact on patient efficacy or safety and do not preclude approval of this product. The labels and labeling include adequate quality information as required. All associated manufacturing, testing, packaging facilities were deemed acceptable. Based on the OPQ review team's evaluation of the information provided in the submission, Oxbryta (Voxelotor) Tablets possess the necessary attributes to ensure that the product meets the quality target product profile (b) (4)

3. Nonclinical Pharmacology/Toxicology

From the executive summary portion of the nonclinical review (unireview):

Evidence from X-ray crystallography studies show that voxelotor binds covalently and reversibly via a Schiff-base to the N-terminal valine of one hemoglobin α-chain to stabilize the oxyHb state. Voxelotor increases O2 affinity with a half maximal EC50 of approximately 21 μM in a dose-dependent manner. Because the binding of voxelotor is distant from the heme pockets, voxelotor increases O2 affinity without sterically blocking the release of O2. Approximately 90% of voxelotor partitions into RBC when added to human whole blood favored by its higher affinity (10-fold) for Hb over albumin indicating that less compound remains in the plasma compartment upon oral dosing to humans. Voxelotor bound to Hb maintains and stabilizes oxyHb under hypoxic conditions that delays the transition from oxyHb to deoxygenated Hb

(deoxyHb) and favors the delay in polymerization as well. Results of ex vivo studies provided evidence that voxelotor may delay in vivo HbS polymerization in patients with SCD and causes a corresponding dose-dependent decrease in the number of sickled RBC (SSRBC) under hypoxic conditions. Voxelotor was also shown to reduce the viscosity of SS blood and improves deformability of SSRBC under hypoxic conditions in ex-vivo studies using blood samples from patients with SCD. Blood samples of Townes sickle cell mice treated with voxelotor showed an increase in Hb-O2 affinity and anti-sickling activity with a significant reduction in the number of ex vivo SSRBC.

In secondary pharmacology screens, voxelotor had activity in micromolar ranges, producing >50% inhibition against the dopamine transporter, the GABA receptor complex, the angiotensin receptor 1, the phosphodiesterase 4A1A enzyme, and the insulin receptor. The safety pharmacology evaluation of voxelotor included a panel of in vitro and in vivo studies. No voxelotor-related effects occurred in the neurological evaluations in rats or in the in vitro assessments on the hERG potassium current. In a cardiovascular study in dogs, voxelotor produced higher (↑8%) mean systolic pressure at 1000 mg/kg at 6 hours post-dose. In an assessment of respiratory function in rats, voxelotor produced lower tidal volume (↓13%) at 1000 mg/kg and increased respiration rate (↑19%) at 320 and 1000 mg/kg; no voxelotor-related effects on respiratory function occurred at the low dose of 100 mg/kg.

The pharmacokinetics of voxelotor was characterized in multiple species, including mice, rats, dogs and monkeys. The time to maximal blood concentration (tmax) of voxelotor following oral administration was approximately 0.6 to 8 hours. Voxelotor oral bioavailability ranged from 36% to 71% and was limited by both absorption in the gut and first-pass metabolism in the liver. Terminal elimination half-life was similar between whole blood and plasma for each species tested and ranged from approximately 6 hours in mouse plasma to 94 hours in dogs. Blood:plasma concentration ratios ranged from 69 to 74, consistent with the preferential binding to Hb and partition into RBC. Voxelotor binds to plasma proteins (99%) across all animal species tested and human. In general, voxelotor displayed less than dose-proportional increases in exposure in all species with limited or no increase above 250 mg/kg in the rat, 300 mg/kg in the dog, and 300 mg/kg in the monkey. Voxelotor showed lower exposures in pregnant rats and rabbits compared to non-pregnant animals, and there were no differences in exposure between sexes. Distribution trends of radiolabeled [14C]-voxelotor in the nonpigmented rats were generally comparable to those seen in pigmented male rats with the highest peak concentrations in blood, lung, spleen, liver, bone marrow and kidney. Elimination of labeled voxelotor from tissues was nearly complete by 168 hours postdose and not detectable by 672 hours postdose.

Voxelotor was extensively metabolized by oxidation-reduction and conjugation reactions in in vitro metabolism studies using human liver microsomes and recombinant enzymes and in vivo in rat and dog (approximately 85% of the dose

administered). Rats excreted approximately 15-16% and dogs excreted < 1% of the administered dose unchanged in feces and urine, respectively. The majority of metabolites generated in humans were also present in the mouse, rat and dog. The major circulating metabolite in human plasma accounting for 16.8% of the total radioactivity was M218/1, an O-dealkylated voxelotor metabolite that is conjugated with sulfate. This conjugated metabolite does not partition into RBC and it is not expected to be pharmacologically active. Further results of voxelotor metabolism in vitro and in vivo conditions are discussed in the Clinical Pharmacology section.

Repeat-dose toxicology studies of up to 26-week in rats and 39-week in monkeys were conducted. In the rat study, voxelotor was administered at 0, 15, 50, or 250 mg/kg/day. Findings of increased erythroid and myeloid parameters (red blood cell mass, reticulocytes and WBC), increases in spleen and thymus organ weights, microscopic findings of hypercellularity in the bone marrow, and extramedullary hematopoiesis and changes in lymphocytes in the spleen occurred mostly at the mid-dose (MD) and high dose (HD). These findings may be associated with a physiological response to the pharmacological action of voxelotor of increased oxygen affinity of hemoglobin. Additional findings included increases in liver weight that corresponded with microscopic findings of periportal hepatocyte hypertrophy and bile duct hyperplasia, and thyroid follicular hypertrophy and pituitary basophil hypertrophy that may be associated with the induction of hepatic metabolizing enzymes. Lower glucose, cholesterol and triglycerides concentrations may be associated with effects on body weight. There were signs of inflammation in several organs at the HD including the harderian gland, kidney, lung, nonglandular stomach, prostate, rectum and thymus that were not present at recovery except for the nonglandular stomach. Urine volume increases at the MD and HD corresponded with diuresis and microscopic findings of chronic progressive nephropathy that was not present at recovery. Most findings were not present at recovery except for the hyperplasia/hyperkeratosis in the stomach and chronic active inflammation in the nonglandular stomach.

In the 39-week monkey study, voxelotor was administered at 0, 15, 30, or 60 mg/kg/day. Mortality occurred at MD and HD with adverse clinical signs, macroscopic findings in the GI tract and skin and adverse microscopic findings in lymphatic organs, GI tract and kidney. Increases in red blood cells at all doses, increases in reticulocytes at the HD, increases in hematocrit, and increases in spleen weight with corresponding increases in red pulp cellularity occurred in male monkeys. Increases in red blood cells, hemoglobin, hematocrit and reticulocytes were present in the HD at recovery. Decreased mean corpuscular volume of ≤10% occurred at all dose levels in males and females and were still present in the HD at the end of recovery. Decreases in white blood cells were present only in males at the HD but values rebounded at the end of recovery. Voxelotor produced a general decrease in all immunophenotype cell subsets that was transient and not dose-dependent. A delayed/transient suppressed

immune response across dose levels was observed. Relevant microscopic findings that suggest an inflammatory response in the heart, liver, lungs and spleen, mostly at the MD and HD, were still present at recovery.

Voxelotor was not mutagenic in a bacterial reverse mutation (Ames) assay, or clastogenic in an in vivo micronucleus test in rats. Voxelotor was not carcinogenic in the 6-month Tg.rasH2 transgenic mouse model.

Developmental and reproductive toxicology studies conducted with voxelotor included: fertility and early embryonic development (FEED) in rats, embryo fetal development (EFD) in rats and rabbits, and pre- and postnatal development (PPND) in rats. In the FEED study in rats, voxelotor was administered at doses of 0, 15, 50, or 250 mg/kg/day following the standard ICH S5(R2) design. Relevant findings in HD animals included higher testis and prostate weights, lower seminal vesicle with fluid weight and adverse findings in sperm motility and morphology, compared to control. Despite those findings, there were no functional effects on male or female fertility. No voxelotor effects occurred in EFD studies in rats at doses of 0, 15, 50, or 250 mg/kg/day and in rabbits at doses of 0, 25, 75 or 150 mg/kg/day. In the PPND study in rats, voxelotor was administered at doses of 0, 15, 50 or 250 mg/kg/day during gestation day (GD) 6 through Lactation Day 20. Voxelotor-related effects in F0 dams at the HD included lower body weight gain during gestation, lower food consumption during gestation and lactation, and increased mean postimplantation loss. Effects in offspring at the maternal HD included lower Day 4 viability index, and adverse lower body weight of pups during Lactation Day 0-21. An increased number of stillborn pups occurred at all doses but was not dose-dependent. Voxelotor-related effects in F1 offspring included lower body weights through the maturation phase to Post-Pairing Day 55 (males) and Maturation Day 7 (females). Effects on the reproductive performance in F1 males included lower fecundity and fertility indexes in MD and HD, and in F1 females, lower fertility index, lower number of corpora lutea, lower number of implantations and lower number of live fetuses also in the MD and HD.

*The adopted pharmacologic class for voxelotor is a hemoglobin S polymerization inhibitor. Because voxelotor preferentially partition into RBC, all comparisons in animal and human exposure defined in the label were based on assessments in whole blood. The AUC for human exposure in whole blood used for this purpose was 3820 µg/mL*h.*

There are no outstanding issues from a nonclinical perspective that would prevent approval of voxelotor for the treatment of sickle cell disease in adult (b) (4) *patients.*

4. Clinical Pharmacology

From the executive summary of the Clinical Pharmacology Section of the unireview:

Exposure-efficacy analyses identified a positive and a statistically significant relationship between voxelotor exposure in whole blood and hemoglobin response (change from baseline, CFB). Exposure-safety analyses identified a positive relationship between Grade ≥ 1 ALT elevation and voxelotor plasma exposure; additionally, a relationship was identified for decreased white blood cell count (WBC) and diarrhea. Collectively, exposure-response analyses supported the proposed 1500 mg dose.
The key review questions focused on dose recommendations for patients with severe hepatic impairment, exposure in HbSC genotype, and drug-drug interactions based on coadministration of CYP3A4 modulators.
In subjects with severe hepatic impairment, voxelotor whole blood and plasma AUC increased by 90% compared to subjects with normal hepatic function. A dose reduction to 1000 mg daily is recommended in patients with severe hepatic impairment.

Patients with the HbSC genotype had a 50% higher whole blood AUC and 45% higher Cmax compared to HbSS or HbSβ0 at steady-state. No dose adjustment is recommended for patients with HbSC genotype.

CYP3A4 exhibits the most significant contribution to the metabolism of voxelotor (36% to 56%). A PBPK model based on detailed in vitro metabolism and ADME studies was utilized to predict the effect of CYP3A4 modulation on the PK of voxelotor. Concomitant administration of drugs that are strong CYP3A4 inhibitors is predicted to increase voxelotor by 40% to 80%. Concomitant administration of fluconazole (a moderate CYP3A/CYP2C9 and strong CYP2C19 inhibitor) is predicted to increase voxelotor by 73% to 100%; of note, fluconazole inhibits other enzymes that play a marginal role in the metabolism of voxelotor. Concomitant administration of strong CYP3A4 inhibitors or fluconazole should be avoided. If unavoidable, a dose reduction to 1000 mg daily is recommended for patients receiving concomitant medications that are strong inhibitors of CYP3A4 or fluconazole.
Concomitant medications that are strong or moderate inducers of CYP3A4 are predicted to decrease voxelotor exposure by 50 to 73%. Concomitant administration of strong or moderate CYP3A4 inducers should be avoided. If unavoidable, the recommended dose for patients receiving concomitant strong or moderate inducers of CYP3A4 is 2500 mg daily.

Recommendations

The proposed dosing regimen of 1500 mg once daily in adult (b) (4) *patients with sickle cell disease is acceptable. From a clinical pharmacology standpoint, the NDA is approvable provided the Applicant and the FDA reach an agreement regarding the labeling language. There are no postmarketing requirements or commitments.*

5. *Clinical* Microbiology – N/A

6. Clinical/Statistical-Efficacy

GBT conducted a randomized, double-blind, placebo-controlled, multi-center trial (HOPE). The Hope trial enrolled 274 patients randomized based on hydroxyurea usage and geographic region and age to receive 1500 mg daily (n=90), 900 mg daily (n=92), or placebo (n=92). Approximately 65% of patients were on stable doses of hydroxyurea. Approximately 67% of enrolled patients were African-American with almost 22% were Arab/Middle Eastern. Most patients had the SCD genotype SS. The enrolled population reflects those with the condition. Efficacy was based on Hb response rate defined as the proportion of patients with Hb increase of greater than or equal to 1 g/dL at Week 24. Approximately 23% of all enrolled patients discontinued early from the study. The most common reason was withdrawal of consent. The response rate for voxelotor 1500 mg was 51.1% (46/90) and 900 mg was 32.6% (30/92) compared to 6.5% (6/92) in the placebo group ($p < 0.0001$). Trial results also demonstrated dose dependent improvements in bilirubin and percent reticulocytes. There was a trend for an improvement in LDH but it was not statistically significant. There was no difference in annualized vasoocclusive events across the three arms and specifically, no increase in the voxelotor treatment arms. An unusual finding concerning leg ulcers was seen in the trial. Although the incidence of leg ulcers was low, in the 1500 mg group all 4 patients with leg ulcers improved whereas no patients with leg ulcers improved in the placebo group and two patients developed them. In the 900 mg group the results were mixed with some patients having an improvement and some patients having no change, and at least one patient who developed a leg ulcer.

The HOPE trial was supported by multiple other studies including Bioequivalence and Bioavailability studies, Pharmacokinetic, and Initial Tolerability Studies, Drug-Drug Interaction Studies, Food Effect, Exercise Physiology, Controlled and Uncontrolled Clinical Studies in healthy subjects, patients with SCD and patients with idiopathic pulmonary fibrosis.

7. Safety

GBT submitted data came from 22 trials in healthy volunteers, patients with SCD, and patients with idiopathic pulmonary fibrosis. Approximately 280 patients with SCD were exposed to at least one dose of voxelotor including 29 pediatric patients. Most of the safety data came from the HOPE trial where patients had the longest exposure to treatment. The Applicant also enrolled a few patients on an expanded access program.

In the pivotal HOPE trial, the most common treatment emergent adverse events were headache, diarrhea, abdominal pain, nausea, rash, fatigue and pyrexia. Serious adverse reactions considered related to voxelotor treatment were headache, drug hypersensitivity and pulmonary embolism (reported in no more than 1 subject each).

The two major issues for labeling were 1) hypersensitivity reactions of which a grade 3 was reported in one patient who had positive rechallenges and 2) reported laboratory test interference when using chromatography to document hemoglobinopathy result. Otherwise most of the adverse events were headache, pyrexia, gastrointestinal (diarrhea, abdominal pain, nausea) rash or fatigue.

Specifically, not seen with this application were TQT prolongation and liver injury or any significant changes to other laboratory parameters (other than those reported in section 6 above).

8. Advisory Committee Meeting

This application was not referred to an Advisory Committee meeting as there were no major concerns regarding the safety or efficacy findings from the trials.

9. Pediatrics

Pediatric patients from less than 17 to 12 were eligible to enroll in the clinical trials. The HOPE trial enrolled 29 pediatric patients of which 14 received the 1500 mg daily dose. Efficacy, safety and pharmacokinetics were similar to those seen with adult patients.

The required confirmatory PMR trial under accelerated approval will study younger pediatric patients and more efficacy and safety data will be obtained.

10. Other Relevant Regulatory Issues

No outstanding regulatory issues were uncovered during the review process including:

- Application Integrity Policy (AIP)- none
- Exclusivity or patent issues of concern - none
- Office of Scientific Investigations (OSI) Audits did not uncover any issues during inspection.
- Financial Disclosure - none

- Other Good Clinical Practice (GCP) issues - none

11. Labeling

The labeling adequately reflects the data GBT submitted with respect to the discipline reviews. The HOPE trial results are in sections 6 and 14 of the labeling. Two Warnings are placed in the labeling: hypersensitivity and laboratory test interference.

12. Postmarketing

- Postmarketing Risk Evaluation and Mitigation Strategies

A REMS plan was not necessary for product approval.

- Other Postmarketing Requirements and Commitments

PMR-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
(based on primary analysis): 07/2025
Study/Trial Completion: 03/2026
Final Report Submission: 09/2026

PMR-2 (Accelerated Approval PMR)

Complete follow-up of patients (on treatment) enrolled in Study GBT440-031: A Phase 3, Double-Blind, Randomized, Placebo-Controlled, Multicenter Study of Voxelotor Administered Orally to Patients with Sickle Cell Disease (HOPE Trial).
Conduct an updated safety and efficacy analysis and submit datasets at the time of final clinical study report submission.

Study/Trial Completion: 12/2019
Final Report Submission: 09/2020

PMC

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

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/s/

ANN T FARRELL
11/25/2019 10:26:50 AM

NDA Multi-Disciplinary Review and Evaluation

Application Type	Original NDA
Application Number	NDA 213137
Priority or Standard	Priority
Submit Dates	March 29, 2019, and June 26, 2019
Received Dates	March 29, 2019, and June 26, 2019
PDUFA Goal Date	February 26, 2020
Division/Office	Division of Hematology Products and the Office of Oncologic Diseases
Review Completion Date	November 24, 2019
Established/Proper Name	Voxelotor
(Proposed) Trade Name	OXBRYTA™
Pharmacologic Class	Hemoglobin S polymerization inhibitor
Code name	GBT440
Applicant	Global Blood Therapeutics, Inc. (GBT)
Dosage form	500 mg Tablets
Applicant proposed Dosing Regimen	1,500 mg orally once daily with or without food Recommended dosage for severe hepatic impairment: 1,000 mg orally once daily in patients with severe hepatic impairment (Child Pugh C)
Applicant Proposed Indication(s)/Population(s)	The treatment of sickle cell disease (SCD) in adult (b) (4) patients.
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	417357006 Sickling disorder due to hemoglobin S
Recommendation on Regulatory Action	Accelerated Approval Indicated for the treatment of sickle cell disease in adults and pediatric patients 12 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)	Treatment of sickle cell disease in adults and pediatric patients 12 years of age and older
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	417357006

Recommended Dosing Regimen	Recommended dosage: 1,500 mg orally once daily with or without food Recommended dosage for severe hepatic impairment: 1,000 mg orally once daily in patients with severe hepatic impairment (Child Pugh C)

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OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology

DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management
DPV = Division of Pharmacovigilance
PLT = Patient Labeling Team

Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
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
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
EFD	Embryo fetal development
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
FEED	Fertility and early embryonic development
GCP	good clinical practice
GD	Gestation day
GRMP	good review management practice
Hb	Hemoglobin
HbF	Fetal hemoglobin
HbS	Sickle hemoglobin
HD	High-dose
ICH	International Conference on Harmonisation
IND	Investigational New Drug
ISE	integrated summary of effectiveness

ISS	integrated summary of safety
ITT	intent to treat
LD	Low-dose
MedDRA	Medical Dictionary for Regulatory Activities
MD	Mid-dose
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
ODA	Oxygen dissociation assay
OEC	Oxygen equilibrium curve
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
OxyHb	Oxyhemoglobin
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert (also known as Patient Information)
PPND	Pre- and postnatal development
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
SGE	special government employee
SCD	Sickle Cell Disease
SOC	standard of care
SSRBC	Sickle RBC
TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

Voxelotor (GBT440, OXBRYTA), a new molecular entity (NME), 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 proposed indication is for treatment of sickle cell disease in adults and pediatric patients 12 years of age and older.

Voxelotor is supplied as a 500-mg oral tablet formulation to be taken with or without food. The recommended dosage is 1,500-mg orally once daily. Patients with severe hepatic impairment (Child Pugh C) should take 1,000-mg orally once daily.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant has demonstrated the effect of voxelotor on an endpoint (increase in hemoglobin of > 1g/dL from baseline) that is reasonably likely to predict clinical benefit in adults and pediatric patients with sickle cell disease.

The recommendation for accelerated approval under 21 CFR 314.500 is based on the results of Study GBT440-031 (HOPE) which is a randomized, multicenter, double-blind, placebo controlled trial. In this study, 274 patients were randomized to daily oral administration of voxelotor 1,500mg (N=90), voxelotor 900mg (N=92), or placebo (N=92). Patients were included if they had 1 to 10 vasoocclusive crisis (VOC) events within 12 months prior to enrollment and baseline hemoglobin (Hb) ≥5.5 to ≤10.5 g/dL. Eligible patients on stable doses of hydroxyurea for at least 90 days were allowed to continue hydroxyurea therapy throughout the study. Randomization was stratified by patients already receiving hydroxyurea (yes, no), geographic region (North America, Europe, Other), and age (12 to ≤17 years, 18 to 65 years).

The efficacy outcome was hemoglobin response rate defined as a hemoglobin increase of > 1g/dL from baseline to week 24. The response rate for voxelotor 1,500mg was 51.1% (46/90) compared to 6.5% (6/92) in the placebo group ($p<0.001$). Additional efficacy evaluation included change in hemoglobin, percent change in indirect bilirubin and percent reticulocyte count from baseline to week 24. In the voxelotor 1,500mg group, the mean change from baseline to week 24 for hemoglobin, indirect bilirubin and percent reticulocyte count were 1.14g/dL, -29.08%, -19.93%, respectively. In the placebo group, the mean change from baseline to week 24 for hemoglobin, indirect bilirubin and percent reticulocyte count were -0.08g/dL, 3.16% and 4.54%, respectively.

Section 21 CFR 314.50 provides that the FDA may grant marketing approval on the basis of adequate and well-controlled clinical trials establishing that the product has an effect upon a clinical endpoint that is reasonably likely to predict clinical benefit. Approval under these regulations require that the applicant study the product further to verify and describe the clinical benefit. The regulation states that the expectation is that the verification study is adequate and well-controlled and would be underway at the time of the approval.

Voxelotor is a HbS polymerization inhibitor and works to increase the affinity of hemoglobin for oxygen, stabilize hemoglobin in the oxyhemoglobin state and help to prevent or impede polymerization of HbS in red blood cells. 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. The organ dysfunction that occurs in SCD progresses slowly and is related to the chronic hemolytic anemia.

The rationale for the recommendation of accelerated approval for voxelotor is founded upon the following considerations:

<u>Pathophysiology of sickle cell disease and role of chronic hemolytic anemia in development of end-organ damage and complications.</u>

- The underlying basis of sickle cell disease is well understood; it is caused by a point mutation in the B-globin gene leading to hemoglobin S formation. The polymerization of Hgb S leads to sickling of red blood cells resulting in hemolytic anemia and vasoocclusive crises.
- The pathophysiologic role of chronic hemolytic anemia in SCD with a variety of morbid clinical outcomes is also well described. Patients with SCD have an increased risk for end-organ complications to include chronic kidney disease, pulmonary hypertension, stroke and silent cerebral infarctions and early mortality. (Kato 2017) (Ford 2018).

<u>Chronic hemolysis and anemia and low hemoglobin: risk for cerebrovascular events in patients with SCD.</u>

- The hemoglobin level in patients with sickle cell disease is one measure that reflects the severity and clinical course of the disease. Low hemoglobin levels and hemolysis are critical pathogenic factors in development of cerebrovascular complications such as stroke (Kato 2017) (Ford 2018).
- Patients with SCD and lower hemoglobin levels are predisposed to stroke as the cerebral blood flow increases and vasculature dilates to meet the increased cerebral metabolic demand for oxygen. As the anemia becomes more severe, the imbalance between oxygen demand and oxygen delivery becomes greater thus resulting in cerebral ischemia or stroke (DeBaun, 2012).

- The prevention of cerebrovascular events in sickle cell disease remains an area of high unmet medical need. In pediatric SCD, the development of central nervous system events such as stroke and silent cerebral infarcts produces significant neurocognitive deficits.
- Prophylactic transfusions help to prevent stroke in children with sickle cell anemia who have abnormalities on transcranial Doppler ultrasonographic examination. The Stroke Prevention Trial in Sickle Cell Anemia (STOP 1) trial showed that pediatric patients at high risk for stroke can be identified using transcranial doppler ultrasonography (TCD) and the incidence of stroke can be reduced in those children by scheduled blood transfusions. These chronic transfusions are not without risks and predispose these patients to risks of iron overload, alloantibody formation and infections.
- The Optimizing Primary Stroke Prevention in Sickle Cell Anemia (STOP2) showed that discontinuining transfusions after 30 months resulted in reversion back to abnormal TCD values and increased stroke risk. The Silent Cerebral Infarct Transfusion (SIT) trial randomized patients to chronic blood transfusions or observation and followed them with magnetic resonance imaging (MRI). The patients who received chronic transfusions had fewer recurrences of infarcts or hemorrhahages.
- Interventions such as chronic transfusions that increase hemoglobin levels have demonstrated a decrease or decline in abnormal TCD flow velocity (Stroke Prevention in Sickle Cell Anemia [STOP II] trial) (Kwiatkowski, 2011).
- TCD readings are reported as normal, conditional, and abnormal or inadequate for assessment. Based on the trials discussed above, patients with high risk TCD measurements are initiated on chronic transfusions programs. However, the risk of stroke based on TCD measurement is thought to be a continuous variable, thus patients with conditional TCD results still carry a risk for stroke.
- A change in hemoglobin by 1g/dL is similar magnitude to the effect of 1-unit blood transfusion. (Carson 2012)

The Applicant conducted an unpublished retrospective analysis of subject-level data collected as part of the STOPII and SIT Analysis report. Based on analysis of the STOPII data, a 1g/dL higher baseline Hb was associated with a lower baseline TCD flow velocity. Taking all the above considerations, it is probable that an increase in hemoglobin would likely predict a decrease in stroke risk as measured by TCD.

The Applicant is conducting a randomized, multi-center, controlled study (STUDY GBT440-032) to confirm the clinical benefit of voxelotor by evaluating the effect of voxelotor on increasing hemoglobin and decreasing hemolysis on stroke risk reduction as measured by TCD flow velocity in patients with sickle cell anemia.

The study population includes patients age 2 to < 15 years with baseline conditional TCD flow velocity (170cm/s to < 200cm/s) and the primary endpoint is the change from baseline at 24 weeks in averaged maximum of the mean velocity (TAMMV) arterial cerebral blood flow as

measured by TCD. Patients are scheduled to undergo TCD at week 8, 16 and 24 with 2 sonograms performed at each visit. The secondary endpoints include the incidence of conversion to abnormal TCD over 24, 48 and 96 weeks, change in hemoglobin from baseline at week 24, 48, 96, incidence of reversion to normal TCD over 24, 48 and 96 weeks and change in TCD flow velocity from baseline at week 48 and Week 96.

The recommendation for accelerated approval for voxelotor allows for earlier approval of a drug that treats a serious condition and fills an unmet medical need. Data from Study GBT440-031 (HOPE) demonstrated an improvement in hemoglobin response rate (> 1g/dL) and this clinical endpoint is reasonably likely to predict clinical benefit. Hemoglobin can be measured earlier than irreversible morbidity or mortality in patients with SCD. The confirmation of the clinical benefit is proposed to be established in an adequate and well-controlled study to show the effects of voxelotor on stroke risk reduction as measured by TCD flow velocity in patients with SCD age 2 to < 15 years of age. In conclusion, voxelotor is approved under the accelerated approval regulations as described in 21 CFR 314.500 (subpart H).

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and 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 (SCAN). Current available therapy for sickle cell disease includes hydroxyurea (Droxia; Bristol Myers Squibb), L-Glutamine (Endari; Emmaus Medical, Inc) and crizanlizumab-tmca (Adakveo, Novartis).

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.

Study GBT440-031 (HOPE) is a randomized, multicenter, double-blind, placebo controlled trial. In this study, 274 patients were randomized to daily oral administration of voxelotor 1500mg (N=90), voxelotor 900mg (N=92), or placebo (N=92). Patients were included if they had from 1 to 10 vasoocclusive crisis (VOC) events within 12 months prior to enrollment and baseline hemoglobin (Hb) ≥5.5 to ≤10.5 g/dL. Eligible patients on stable doses of hydroxyurea for at least 90 days were allowed to continue hydroxyurea therapy throughout the study. Randomization was stratified by patients already receiving hydroxyurea (yes, no), geographic region (North America, Europe, Other), and age (12 to ≤17 years, 18 to 65 years). In patients who received voxelotor 1500mg, the median age was 24 years (range 12,59) with 65% female and 66% Black or African American and 23% Arab/Middle Eastern and 65% receiving hydroxyurea at baseline.

The efficacy outcome was hemoglobin response rate defined as a hemoglobin increase of > 1g/dL from baseline to week 24. The response rate for voxelotor 1500mg was 51.1% (46/90) compared to 6.5% (6/92) in the placebo group ($p<0.001$). Additional efficacy evaluation included change in hemoglobin, percent change in indirect bilirubin and percent reticulocyte count from baseline to week 24. In the voxelotor 1,500mg group, the mean change from baseline to week 24 for hemoglobin, indirect bilirubin and percent reticulocyte count were 1.14g/dL, -29.08%, -19.93%, respectively. In the placebo group, the mean change from baseline to week 24 for hemoglobin, indirect bilirubin and percent

reticulocyte count were -0.08g/dL, -3.16% and 4.54%, respectively.

In general, voxelotor was well tolerated. Safety data for voxelotor is derived primarily from the pivotal Phase 3 Study (GBT440-031 (HOPE), and supported by data from the open-label Phase 2a study, GBT440-007 (Part B). In both studies, patients were treated with at either 900mg , 1,500mg or placebo daily for at least 24 weeks. The majority of patients in both trials experienced at least one treatment emergent adverse event (TEAE) (GBT440-031: 94.3% in the voxelotor 1,500-mg, 93.5% in the voxelotor 900-mg and 89.0% in the placebo arm) and similar in the GBT440-007 study. In the HOPE trial, the most common adverse reactions (> 10%) were headache, abdominal pain, diarrhea, nausea, fatigue, rash and pyrexia. A total of 6 deaths were reported, none of which were assessed by the investigator as related to voxelotor. Serious adverse events (SAEs) were balanced across treatment groups: 19.3% in the voxelotor 1,500-mg, 17.4% in the voxelotor 900-mg and 16.5% in the placebo arm. Study drug related SAEs occurred in 3% of patients receiving voxelotor 1,500mg and included headache, drug hypersensitivity and pulmonary embolism.

Permanent discontinuation due to adverse reactions occurred in 5% of patients who received voxelotor 1,500mg. Dosage modifications (dose reduction or dosing interruption) due to an adverse reaction occurred in 41% of patients who received voxelotor 1,500mg. Most frequent adverse reactions requiring dosage interruption occurring in more than one patient who received voxelotor 1,500 mg included diarrhea, headache, rash, and vomiting. Safety considerations that are adequately addressed in the prescribing information include hypersensitivity reactions and potential laboratory interference as voxelotor administration may interfere with measurement of Hb subtypes (HbA, HbS, and HbF) by high performance liquid chromatography(HPLC). The long-term safety of voxelotor in adults and pediatric patients will be important and will be addressed in post-marketing requirements and commitments.

In summary, the overall safety profile of voxelotor appears acceptable for proposed registrational dose of 1,500mg current data support a favorable benefit-risk assessment for voxelotor for patients with sickle cell disease. The USPI adequately addresses known risks and the Applicant intends to confirm and verify clinical benefit with ongoing confirmatory study.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• SCD is an inherited hematological disorder characterized clinically by hemolytic anemia leading to recurrent painful vasoocclusive crisis (VOC), anemia as well as 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 • 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.	Sickle Cell Disease is a serious and life-threatening condition with significant morbidity and mortality and reduced life expectancy.
Current Treatment Options	There are three FDA-approved medications for patients with sickle cell disease. 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. o 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. o Adakveo® (Crizanlizumab-tmca) is indicated to reduce the frequency of vasoocclusive crisis in patients age 16 years and older with sickle cell disease.	A significant unmet medical need exists for therapies for the treatment of SCD.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	Hematopoietic stem cell transplantation (HSCT) offers potential cure; however, only a small percentage of patients are eligible for this treatment option. Management of acute sickle cell episodes is generally only supportive. 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 HbS. Red cell exchange can reduce the HbS 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. Other supportive therapies include: intravenous fluids, supplemental oxygen, etc.	
Benefit	• The response rate (increase of hemoglobin by > 1g/dL from baseline to week 24) for voxelotor 1500mg was 51.1% (46/90) compared to 6.5% (6/92) in the placebo group (p<0.001). • Additional efficacy evaluation included change in hemoglobin, percent change in indirect bilirubin and percent reticulocyte count from baseline to week 24. In the voxelotor 1,500mg group, the mean change from baseline to week 24 for hemoglobin, indirect bilirubin and percent reticulocyte count were 1.14g/dL, -29.08%, -19.93%, respectively. In the placebo group, the mean change from baseline to week 24 for hemoglobin, indirect bilirubin and percent reticulocyte count were -0.08g/dL, -3.16% and 4.54%, respectively.	Voxelotor treatment demonstrated an effective increase in hemoglobin levels and hemolysis markers among patients with SCD at the registrational dosage of 1,500mg compared to placebo. The Applicant is conducting a randomized phase 3 trial to verify and confirm clinical benefit.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	• Safety results pooled from GBT440-031 and GBT440-007 (Part B) showed that the majority of patients in both trials experienced at least one TEAE (GBT440-031: 94.3% in the voxelotor 1500-mg, 93.5% in the voxelotor 900-mg and 89.0% in the placebo arm) and similar in the GBT440-007 study. • The most commonly reported TEAEs in the voxelotor 1500mg group were headache (26%), diarrhea (21%), abdominal pain (20%), nausea (17.0%), fatigue (14%), rash (14%) and pyrexia (12%); and these were generally Grade 1 to 2 in severity. • The incidence of non-sickle cell disease related serious adverse events were similar between treatment groups with 19.3% of patients with any event in the voxelotor group and 16.5% in the placebo group. • Serious drug related SAEs occurred in 3% of patietns receiving voxelotor in the 1500mg group and included drug hypersensitivity, headache and pulmonary embolism. • Permanent discontinuation due to an adverse reaction (Grades 1-4) occurred in 5% (4/88) of patients who received voxelotor 1500 mg. • Dosage modifications (dose reduction or dosing interruption) due to an adverse reaction occurred in 41% [36/88] of patients who received voxelotor with the most frequent adverse reactions requiring dosage interruption of diarrhea, headache, rash, and vomiting. • A total of 6 deaths were reported, none of which were assessed by the investigator as related to voxelotor. • Serious hypersensitivity reactions have occurred after administration of voxelotor and include generalized rash, urticaria, mild shortness of breath and facial swelling.	In patients with SCD, the safety profile of voxelotor is acceptable. The product label adequately addresses the risk of using this product in patients with SCD. Long-term safety profile of voxelotor remains important consideration. Long-term safety of the drug will be addressed with post marketing requirements and commitments.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Voxelotor may interfere with the measurement of Hb subtypes (HbA, HbS and HbF) by high performance liquid chromatography and if precise measurements required, chromatography should be performed when patient not receiving drug. • Additional potential theoretical risks include tissue hypoxia due to ineffective tissue oxygen extraction with the high Hb occupancy from voxelotor-bound hemoglobin. 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 include cardiovascular parameters and hematological measures to assess for compensatory erythropoiesis.	

1.4. Patient Experience Data

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

x	**The patient experience data that were submitted as part of the application include:**			Section of review where discussed, if applicable
	□	Clinical outcome assessment (COA) data, such as		See Section 8- clinical efficacy
		X	Patient reported outcome (PRO)	
		□	Observer reported outcome (ObsRO)	
		x	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		
	□	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		
	□	Observational survey studies designed to capture patient experience data		
	□	Other: (Please specify):		
□	**Patient experience data was not submitted as part of this application.**			

The Sickle Cell Disease Severity measure (SCDSM) total symptom score and EuroQOL 5-dimension 5-level(EQ-5D-5L) index value and visual analog scale scores were measured in this trial. There were no differences in patient-reported outcomes in the voxelotor groups compared with the placebo groups.

Reviewer Comment: The patient reported outcomes were exploratory endpoints and no formal conclusions can be drawn from these results.

X see signature page

Tanya Wroblewski, MD
Cross Discipline Team Leader

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). A single point mutation in the hemoglobin β-globin chain of affected persons produces mutant hemoglobin molecules (Hemoglobin S [Hb S]). The most common form of sickle-cell disease (homozygous Hb SS) accounts for 60%-75% of sickle cell disease in the United States. Approximately 25% of patients have coinheritance of Hb S with another β-globin chain variant such as sickle-Hb C disease and sickle β-thalassemia.

During periods of deoxygenation, Hb S polymerizes within erythrocytes resulting in intermittent vasoocclusive events and chronic hemolytic anemia. Vasoocclusion occurs as a result of the formation of multicellular aggregates that block blood flow in small blood vessels, resulting in tissue ischemia & reperfusion damage to downstream tissues which lead to recurrent acute pain/crises episodes. Vaso-occlusive pain episodes are the most frequent cause of recurrent morbidity in SCD and account for the majority of SCD-related hospitalizations (Platt, Thorington et al. 1991, Gill, Sleeper et al. 1995). 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.

SCD is associated with decreased life expectancy (Platt 1994, Lanzkron, Carroll et al. 2013, Elmariah, Garrett et al. 2014, Maitra, Caughey et al. 2017). Acute chest syndrome (ACS) is a serious acute complication and a leading cause of mortality in both children and adults with SCD (Vichinsky, Neumayr et al. 2000, Bakanay, Dainer et al. 2005). Other causes of death in patients with SCD include infections (Adamkiewicz, Sarnaik et al. 2003) and cerebrovascular events (Platt 2005, Verduzco and Nathan 2009).

Children have higher rates of death from infection and sequestration crises (Manci, Culberson

et al. 2003). Cardiopulmonary complications represent a major mortality risk in adults (Fitzhugh, Lauder et al. 2010). Currently, the management of sickle cell crises (SCC) episodes is generally supportive and includes symptomatic treatment with intravenous fluids, analgesics, oxygen and RBC transfusion support. Hematopoietic stem cell transplantation (HSCT) and gene therapy offers potential cure; however only few patients are eligible for these treatment option. Hydroxyurea (HU) was approved in 1998 and 2017; for reducing the frequency of sickle cell crises in adult patients with SCD and reducing the frequency of painful crises and the need for blood transfusions in adult patients with sickle cell anemia with recurrent moderate to severe painful crises (generally at least 3 during the preceding 12 months) and for reducing the frequency of painful crises and the need for blood transfusions in patients age 2 and older who have sickle cell anemia with recurring moderate to severe painful crises . L-glutamine (approved in 2017) is indicated to reduce the acute complications of sickle cell disease in adult and pediatric patients 5 years of age and older.

A requisite step in the molecular pathogenesis of SCD is the polymerization of deoxygenated hemoglobin S (deoxy-HbS). Polymerization of deoxy-HbS leads to the formation of dense, mechanically fragile and poorly deformable sickled RBCs. Red blood cell deformability has a major influence on blood rheology and hemodynamics in SCD. Under deoxygenated conditions, extensive HbS polymerization, resulting in sickling and irreversible membrane damage of SS RBCs leads to aggravated hyperviscosity that affects in vivo microcirculatory flow dynamics contributing to vasoocclusion and impaired oxygen delivery to tissues. GBT440, a small molecule which binds to the N-terminal α chain of Hb, increases HbS affinity for oxygen, delays in vitro HbS polymerization and prevents sickling of RBCs. In a murine model of SCD, GBT440 extends the half-life of RBCs, reduces reticulocyte counts and prevents ex vivo RBC sickling. SCD patients' RBCs were transiently (<1 min) exposed to hypoxic conditions in tissues, and with the HbS modification with GBT440 at or below 30% was shown to be sufficient to achieve reduced ex vivo sickling while achieving Hb occupancies >11%. Furthermore, there was evidence of reduction in hemolysis and a reduction in reticulocyte counts which translated to an increase in hemoglobin levels (Vichinsky 2018, Oksenberg D 2016, Metcalf 2016).

2.2. Analysis of Current Treatment Options

The clinical complications of SCD result from a cascade of events that starts with the polymerization of HbS. Thus, the goal of disease-modifying therapies is to decrease Hgb S concentration, either by increasing HbF levels (HU) or increasing HbA levels (transfusion). 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.

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]						
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 in adult patients with sickle cell anemia with recurrent moderate to severe painful crises (generally at least 3 during the preceding 12 months)/For reducing the frequency of painful crises and the need for blood	1998/2017	15-20 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 BABYHUG Study: Rates of VOCs, ACS, and unscheduled erythrocyte transfusions decreased who received	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	N/A

	transfusions in patients age 2 and older who have sickle cell anemia with recurring moderate to severe painful crises			HU		
L-Glutamine	Reduce the acute complications of sickle cell disease in adult and pediatric patients 5 years of age and older	2017	< 30 kg: 5 g twice daily, 30- 65 kg: 10 g twice daily, >65 kg: 15 g 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)	
Crizanlizumab-tmca	To reduce the frequency of vasoocclusive crises in adults and pediatric patients aged 16 years and older with sickle cell disease.	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 pain and pyrexia.	N/A
Other Treatments – [Combine by Pharmacologic Class, if relevant]						
Penicillin	Reduce the rate of invasive pneumococcal disease in children less than 5 years of age	N/A	Children <3 years: Oral: 125 mg twice daily Children ≥3 years: Oral: 250 mg twice	PROPS Study (1986): 84% reduction in incidence of infection compared with placebo	N/A	N/A

			daily until age 5	(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	N/A	Any patient with SCD	No differences in hematologic indices or clinical complications compared to placebo	N/A	N/A

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Voxelotor is a new molecular entity and is not currently marketed in the United States.

3.2. Summary of Presubmission/Submission Regulatory Activity

Table 2 Summary of Key Presubmission/Submission Regulatory Activity

Date	Description
October 14, 2014	IND 121691 submitted with Phase 1 randomized, placebo-controlled, double-blind single and multiple ascending dosing study
October 7, 2015	Fast Track Designation Granted
December 29, 2015	Orpah Drug Designation granted
July 26, 2016	EOP 2 meeting to discuss phase3 trial design
June 5, 2017	Rare Pediatric Disease Designation
January 3, 2018	Breakthrough Therapy Designation Granted
November 13, 2018	Type A meeting to Discuss surrogate endpoint of increase in hemoglobin
Feb 26, 2019	Pre-NDA Meeting, agreement on rolling submission timeline
May 9, 2019	Type A meeting to discuss confirmatory trial design
May 29, 2019	Type B meeting to discuss the data available to perform analysis of the SIT and STOP II data to support hypothesis for confirmatory trial.

1.3 Foreign Regulatory Actions and Marketing History

Voxelotor is not currently marketed in any foreign countries.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

An OSI audit was requested. Site inspections included review of: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, correspondence, and informed consent documents. CRFs were compared with source data to assess that the primary study endpoint was verifiable at the study site. Study GBT440-031, was conducted internationally with the highest enrollment at sites in Nairobi, Kenya with 36 subjects enrolled. The largest US site was at Brigham and Women's Hospital in Boston, MA with 10 subjects enrolled. There are 2 other US sites with high enrollment which were included in this audit (New York: 8 subjects and California: 7 subjects).

Table 3 OSI Site Inspections

Site	Principal Investigator	Site Number/Enrollment	Inspection Dates	Findings
Brigham and Women's Hospital; Hematology Division 75 Francis Street Boston, MA 02115	Maureen Achebe	Site# 01025/10	August 14-23, 2019	VAI (Voluntary Action Indicated): Clinical site appeared to be in compliance with Good Clinical Practice. A Form FDA 483 (Inspectional Observations) was not issued at the end of the inspection.
New York Presbyterian Hospital 161 Fort Washington Avenue New York, NY 10032	David Diuguid	Site# 01010/8	July 29-August 2, 2019	VAI (Voluntary Action Indicated): • Inadequate or inaccurate case histories for Subjects (b) (6)). • Not all concomitant medications were recorded in the electronic case report forms (eCRFs). • Subject (b) (6) eported headaches during Week 36 follow-up visit on (b) (6) which was not reported as either a pre-existing condition or as an adverse event in the

Site	Principal Investigator	Site Number/Enrollment	Inspection Dates	Findings
				eCRF. *Site has completed review of all patients' concomitant medications, and research staff has entered these medications and the adverse event of headache into the subjects' e-CRFs on August 20, 2019. The study site planned the following corrective actions: (1) a clinic research manager will conduct monthly quality assurance reviews for data entry and verification, and (2) two study coordinators will monitor the study electronic data capture system to verify accurate and complete entry.*
UCSF Benioff Children's Hospital 747 52nd Street Oakland, CA 94609	Anne Marsh	Site# 01014/7	August 26-30, 2019	VAI (Voluntary Action Indicated): Clinical site appeared to be in compliance with Good Clinical Practice. A Form FDA 483 (Inspectional Observations) was not issued at the end of the inspection
Global Blood Therapeutics, Inc. (GBT) 171 Oyster Point Blvd., Suite 300 South San Francisco, CA 94080	Applicant	Applicant	August 1-12, 2019	VAI (Voluntary Action Indicated): • Inaccurate and complete records. • Six lot numbers of the investigational product was not attached • Lack of adequate records covering quantity of products received from four study sites (Sites 01062, 01039, 05002, and 01045). *The firm (1) clarified that investigational drug product lot numbers incorporate a booklet label*

Site	Principal Investigator	Site Number/Enrollment	Inspection Dates	Findings
				affixed to the top of the blister card (primary package) with lot number, expiry date, kit number, subject ID and investigator name, including a booklet label page with the cautionary investigational drug label page, per 21CFR312.6(a); and (2) stated that investigational sites supervised by sponsor list kit numbers, and whether or not the return kit is unused or used. However, the firm will create tracking forms to be completed when returning drug products to reflect the quantity of dosage form units, in addition to the quantity of containers returned.

Refer to the OSI review by Min Lu M.D. Ph.D. and Anthony Orencia M.D. in DARRTs for more details.

4.2. Product Quality

No significant issues. Refer to the Integrated Quality Assessment by the CMC review team.

4.3. Clinical Microbiology

Not applicable. Refer to Integrated Quality Assessment.

4.4. Devices and Companion Diagnostic Issues

There were no devices or companion diagnostic issues with this application.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Sickle cell disease (SCD) is an inherited disease caused by a point mutation in the hemoglobin (Hb) β-globin gene leading to formation of sickle hemoglobin (HbS) that polymerizes under the low oxygen tension of the microvasculature. Voxelotor (also referred to as GBT440) is an orally administered drug designed to bind the sickle hemoglobin (HbS) to increase its oxygen (O_2) affinity resulting in the stabilization of the oxyhemoglobin (oxyHb) state and inhibition of polymerization. Similar to fetal hemoglobin (HbF), oxyHb is an inhibitor of HbS polymerization. The goal for an effective treatment of patients with SCD is to increase the proportion of oxyHb in RBC and maintain approximately 30% of Hb in the nonpolymerizing state in all RBC.

Evidence from X-ray crystallography studies show that voxelotor binds covalently and reversibly via a Schiff-base to the N-terminal valine of one hemoglobin α-chain to stabilize the oxyHb state. Voxelotor increases O_2 affinity with a half maximal EC50 of approximately 21 µM in a dose-dependent manner. Because the binding of voxelotor is distant from the heme pockets, voxelotor increases O_2 affinity without sterically blocking the release of O_2. Approximately 90% of voxelotor partitions into RBC when added to human whole blood favored by its higher affinity (10-fold) for Hb over albumin indicating that less compound remains in the plasma compartment upon oral dosing to humans. Voxelotor bound to Hb maintains and stabilizes oxyHb under hypoxic conditions that delays the transition from oxyHb to deoxygenated Hb (deoxyHb) and favors the delay in polymerization as well. Results of ex vivo studies suggest that voxelotor may delay in vivo HbS polymerization in patients with SCD and decrease the number of sickled RBC (SSRBC) under hypoxic conditions. Voxelotor was also shown to reduce the viscosity of SS blood and improve deformability of SSRBC under hypoxic conditions in ex-vivo studies using blood samples from patients with SCD. Blood samples of Townes sickle cell mice treated with voxelotor showed an increase in Hb-O_2 affinity and anti-sickling activity with a significant reduction in the number of ex vivo SSRBC.

In secondary pharmacology screens, voxelotor had activity in micromolar ranges, producing >50% inhibition against the dopamine transporter, the GABA receptor complex, the angiotensin receptor 1, the phosphodiesterase 4A1A enzyme, and the insulin receptor. The safety pharmacology evaluation of voxelotor included a panel of in vitro and in vivo studies. No voxelotor-related effects occurred in the neurological evaluations in rats or in the in vitro assessments on the hERG potassium current. In a cardiovascular study in dogs, voxelotor produced higher (↑8%) mean systolic pressure at 1000 mg/kg at 6 hours post-dose. In an assessment of respiratory function in rats, voxelotor produced lower tidal volume (↓13%) at 1000 mg/kg and increased respiration rate (↑19%) at 320 and 1000 mg/kg; no voxelotor-related effects on respiratory function occurred at the low dose of 100 mg/kg.

The pharmacokinetics of voxelotor was characterized in multiple species, including mice, rats, dogs and monkeys. The time to maximal blood concentration (tmax) of voxelotor following oral administration was approximately 0.6 to 8 hours. Voxelotor oral bioavailability ranged from 36% to 71% and was limited by both absorption in the gut and first-pass metabolism in the liver. Terminal elimination half-life was similar between whole blood and plasma for each species tested and ranged from approximately 6 hours in mouse plasma to 94 hours in dogs. Blood:plasma concentration ratios ranged from 69 to 74, consistent with the preferential binding to Hb and partition into RBC. Voxelotor binds to plasma proteins (99%) across all animal species tested and human. In general, voxelotor displayed less than dose-proportional increases in exposure in all species with limited or no increase above 250 mg/kg in the rat, 300 mg/kg in the dog, and 300 mg/kg in the monkey. Voxelotor showed lower exposures in pregnant rats and rabbits compared to non-pregnant animals, and there were no differences in exposure between sexes. Distribution trends of radiolabeled [^{14}C]-voxelotor in the nonpigmented rats were generally comparable to those seen in pigmented male rats with the highest peak concentrations in blood, lung, spleen, liver, bone marrow and kidney. Elimination of labeled voxelotor from tissues was nearly complete by 168 hours postdose and not detectable by 672 hours postdose.

Voxelotor was extensively metabolized by oxidation-reduction and conjugation reactions in in vitro metabolism studies using human liver microsomes and recombinant enzymes and in vivo in rat and dog (approximately 85% of the dose administered). Rats excreted approximately 15-16% and dogs excreted < 1% of the administered dose unchanged in feces and urine, respectively. The majority of metabolites generated in humans were also present in the mouse, rat and dog. The major circulating metabolite in human plasma accounting for 16.8% of the total radioactivity was M218/1, an O-dealkylated voxelotor metabolite that is conjugated with sulfate. This conjugated metabolite does not partition into RBC and it is not expected to be pharmacologically active. Further results of voxelotor metabolism in vitro and in vivo conditions are discussed in the Clinical Pharmacology section.

Repeat-dose toxicology studies of up to 26-week in rats and 39-week in monkeys were conducted. In the rat study, voxelotor was administered at 0, 15, 50, or 250 mg/kg/day. Findings of increased erythroid and myeloid parameters (red blood cell mass, reticulocytes and WBC), increases in spleen and thymus organ weights, microscopic findings of hypercellularity in the bone marrow, and extramedullary hematopoiesis and changes in lymphocytes in the spleen occurred mostly at the mid-dose (MD) and high dose (HD). These findings may be associated with a physiological response to the pharmacological action of voxelotor of increased oxygen affinity of hemoglobin. Additional findings included increases in liver weight that corresponded with microscopic findings of periportal hepatocyte hypertrophy and bile duct hyperplasia, and thyroid follicular hypertrophy and pituitary basophil hypertrophy that may be associated with the induction of hepatic metabolizing enzymes. Lower glucose, cholesterol and triglycerides concentrations may be associated with effects on body weight. There were signs of inflammation in several organs at the HD including the harderian gland, kidney, lung,

nonglandular stomach, prostate, rectum and thymus that were not present at recovery except for the nonglandular stomach. Urine volume increases at the MD and HD corresponded with diuresis and microscopic findings of chronic progressive nephropathy that was not present at recovery. Most findings were not present at recovery except for the hyperplasia/hyperkeratosis in the stomach and chronic active inflammation in the nonglandular stomach.

In the 39-week monkey study, voxelotor was administered at 0, 15, 30, or 60 mg/kg/day. Mortality occurred at MD and HD with adverse clinical signs, macroscopic findings in the GI tract and skin and adverse microscopic findings in lymphatic organs, GI tract and kidney. Increases in red blood cells at all doses, increases in reticulocytes at the HD, increases in hematocrit, and increases in spleen weight with corresponding increases in red pulp cellularity occurred in male monkeys. Increases in red blood cells, hemoglobin, hematocrit and reticulocytes were present in the HD at recovery. Decreased mean corpuscular volume of ≤10% occurred at all dose levels in males and females and were still present in the HD at the end of recovery. Decreases in white blood cells were present only in males at the HD but values rebounded at the end of recovery. Voxelotor produced a general decrease in all immunophenotype cell subsets that was transient and not dose-dependent. A delayed/transient suppressed immune response across dose levels was observed. Relevant microscopic findings that suggest an inflammatory response in the heart, liver, lungs and spleen, mostly at the MD and HD, were still present at recovery.

Voxelotor was not mutagenic in a bacterial reverse mutation (Ames) assay, or clastogenic in an in vivo micronucleus test in rats. Voxelotor was not carcinogenic in the 6-month Tg.rasH2 transgenic mouse model.

Developmental and reproductive toxicology studies conducted with voxelotor included: fertility and early embryonic development (FEED) in rats, embryo fetal development (EFD) in rats and rabbits, and pre- and postnatal development (PPND) in rats. In the FEED study in rats, voxelotor was administered at doses of 0, 15, 50, or 250 mg/kg/day following the standard ICH S5(R2) design. Relevant findings in HD animals included higher testis and prostate weights, lower seminal vesicle with fluid weight and adverse findings in sperm motility and morphology, compared to control. Despite those findings, there were no functional effects on male or female fertility. No voxelotor effects occurred in EFD studies in rats at doses of 0, 15, 50, or 250 mg/kg/day and in rabbits at doses of 0, 25, 75 or 150 mg/kg/day. In the PPND study in rats, voxelotor was administered at doses of 0, 15, 50 or 250 mg/kg/day during gestation day (GD) 6 through Lactation Day 20. Voxelotor-related effects in F0 dams at the HD included lower body weight gain during gestation, lower food consumption during gestation and lactation, and increased mean postimplantation loss. Effects in offspring at the maternal HD included lower Day 4 viability index, and adverse lower body weight of pups during Lactation Day 0-21. An increased number of stillborn pups occurred at all doses but was not dose-dependent. Voxelotor-related effects in F1 offspring included lower body weights through the maturation phase to Post-Pairing Day 55 (males) and Maturation Day 7 (females). Effects on the

reproductive performance in F1 males included lower fecundity and fertility indexes in MD and HD, and in F1 females, lower fertility index, lower number of corpora lutea, lower number of implantations and lower number of live fetuses also in the MD and HD.

The adopted pharmacologic class for voxelotor is a hemoglobin S polymerization inhibitor. Because voxelotor preferentially partition into RBC, all comparisons in animal and human exposure defined in the label were based on assessments in whole blood. The AUC for human exposure in whole blood used for this purpose was 3820 µg/mL*h.

There are no outstanding issues from a nonclinical perspective that would prevent approval of voxelotor for the treatment of sickle cell disease in adult (b) (4) patients.

5.2. Referenced NDAs, BLAs, DMFs

None

5.3. Pharmacology

Primary pharmacology

A. In Vitro Studies

A single point mutation in the gene of beta-globin (Glu6Val) leads to the formation of HbS and introduces a surface exposed hydrophobic patch that leads to decreased solubility and susceptibility to polymerization. Polymerization of deoxygenated hemoglobin is a required step in the molecular pathogenesis of SCD. Hb naturally transitions from the R-conformation (oxygenated state - oxyHb) to the T-conformation (deoxygenated state - deoxyHb) when placed in a low oxygen environment.

Voxelotor is an aldehyde that binds covalently and reversibly via a Schiff-base to the N-terminal valine of one hemoglobin α-chain to stabilize the oxyHb state as confirmed using X-ray crystallography at 2.1 angstrom max resolution (Study: PRC-18-048). Voxelotor binds with 1:1 stoichiometry, with one molecule binding to an available N-terminal valine residue at a time. The binding site of voxelotor is distant from the heme pockets and therefore does not directly prevent release of O_2 from HbS. Thus, voxelotor increases O_2 affinity without sterically blocking the release of O_2.

Voxelotor displayed a 10-fold greater affinity for Hb over albumin as evaluated using oxygen dissociation assay (ODA) (Study: PRC-14-032-R). When voxelotor was added to whole blood, approximately 90% of voxelotor partitions into RBCs and primarily associates with Hb and not cell membranes (Study: PRC-14-035-R). The preferential binding of voxelotor to Hb indicates a potential for selective partitioning of voxelotor into RBC with less compound remaining in the plasma compartment upon oral dosing to humans.

Studies conducted using whole blood from healthy volunteers, patients with sickle cell disease, and from different animal species analyzed with a hemox analyzer indicate that the voxelotor increase in Hb-O2 affinity is directly proportional to the whole blood Hb concentration (Study: PRC-14-027-R). Voxelotor increases O_2 affinity in a dose-dependent manner with a half maximal EC_{50} of 21.4 ± 0.4 µM. Voxelotor-bound Hb maintains and stabilizes the oxygenated Hb (oxyHb) state during two hours of passive deoxygenation under hypoxic conditions as measured using the ODA, e.g. voxelotor delays the transition from oxyHb to deoxyHb (Study: PRC-14-033-R).

The ability of H^+ ions and 2,3-diphosphoglycerate (DPG) to reduce Hb-O2 affinity are among key physiologic mechanisms that drive O_2 offloading to metabolically active tissues in vivo. Voxelotor-bound Hb can deliver more oxygen at pH 6.8 than at pH 7.4 while still maintaining a subpopulation of oxyHb (Study: PRC-14-029-R). Thus, O_2 release from voxelotor-bound Hb increases with acidity and/or increasing 2,3-DPG concentration, suggesting that voxelotor may not limit the key physiologic mechanisms for O_2 release in vivo (Study: PRC-18-046). A qualified in vitro polymerization assay was used to show that voxelotor dose-dependently delays in vitro HbS polymerization (Study: PRC-14-040-R). Voxelotor delayed polymerization of deoxyHb (50 µM) with a change in delayed time of 4.6, 8.8, and 13.2 min at 25, 50 and 100 µM, respectively, providing evidence that voxelotor may delay in vivo HbS polymerization in patients with SCD that causes a corresponding dose-dependent decrease in the number of SSRBC under hypoxic conditions.

The hyperviscosity of blood that results from HbS polymerization, sickling and irreversible membrane damage is a major contributor to the pathophysiology of sickle cell disease. Using a Wells- Brookfield cone/plate viscometer, voxelotor was shown to dose-dependently reduce the viscosity of SS blood by reducing polymer load under both normoxic and hypoxic conditions (Study: PRC-14-044-R). Voxelotor at 1.6 mM in the presence of hematocrit at 30% reduced the blood viscosity (measured as Centipoise, cP) of 11 different patients with SCD from 6.1 cP to 4.3 cP, a value similar to that obtained for SS blood under normoxic conditions (3.9 cP). Similar results were obtained when the assay was conducted under hypoxic conditions.

Voxelotor improved in vitro deformability of SSRBC under hypoxic conditions as evaluated in three independent deformability assays (Study: PRC-14-031-R). Voxelotor enabled efficient migration of SSRBCs through a packed sephacryl column, reduced the pressure required to pass SSRBCs through a polycarbonate filter and lowered the tension required to aspirate SSRBCs into a micropipette under hypoxic conditions. Similar test was conducted using SSRBC under hypoxic conditions in the absence of voxelotor; results were greater in magnitude in the opposite direction.

B. In Vivo Studies

Voxelotor was administered as a single dose of 100 mg/kg to HbSS second generation Townes sickle cell mice and tested for changes in Hb-O_2 affinity and anti-sickling activity at 4 hours postdose using a combination of hemoximetry and morphometric measurements (Study: PRC-

14-025-R). Voxelotor-treated mice showed a reduction in the number of SSRBC (26 ± 4% compared to 59 ± 7% in control mice) following ex vivo exposure to low pO_2 (10 mm Hg). An increase in Hb-O_2 affinity was reflected by the left-shifted oxygen equilibrium curves (OECs) and changes in p20 and p50. A single dose of voxelotor achieved an average blood concentration of 158 + 31 µM (Mean + SEM) and a calculated hemoglobin (Hb) occupancy of 12% that was enough to significantly ($P<0.05$) reduce the number of ex vivo SSRBC present at pO_2 of 10 mm Hg.

Secondary pharmacology

In a pharmacological profiling study (Study: PRC-15-021-R), voxelotor (15 µM) showed no activity against a broad panel of receptors, enzymes, and ion channels (binding assays and enzyme in vitro inhibition). No inhibition was detected in hERG binding in this panel. Inhibition(> 50%) was detected for the dopamine transporter (95.1%), GABA receptor complex (83.9%), angiotensin receptor 1 (52.6%), phosphodiesterase 4A1A (50.0%), and insulin receptor (77.6%).

Safety pharmacology

The ability of voxelotor to inhibit the hERG potassium channel was evaluated at near-physiological temperature in stably transfected HEK293 cells that express the hERG gene (Study: PRC-14-058-R). Voxelotor inhibited hERG current by (Mean ± SEM) 4.7% ± 1.2% at 1 µM (n = 4) and 15.3% ± 1.3% at 10 µM (n = 4) versus 1.6% ± 0.6% (n = 3) in control. hERG inhibition at 10 µM was statistically significant ($p < 0.05$) when compared to vehicle control values. The IC_{50} for the inhibitory effect of voxelotor on hERG potassium current was not calculated but is greater than 10 µM. The IC_{50} for inhibition of hERG potassium channel currents, corrected for protein binding, is approximately 70-fold the maximum plasma concentration of voxelotor in patients receiving 1500 mg once daily.

Cardiovascular evaluations were conducted in conscious telemetered male beagle dogs (Study: PRC-14-054-R). Surgically-telemetered male dogs (iliac-based vascular access port) were administered a single dose of vehicle control (0.5% [w/w] Methocel E50 in reverse osmosis water containing 0.01% [w/w] polysorbate 80 and 10 mM phosphate buffer [pH 7 ± 0.2]), or 100, 300, or 1000 mg/kg (2000, 6000, or 20000 mg/m^2) voxelotor at a dose volume of 5 mL/kg by oral gavage in a parallel study design. The top dose of 1000 mg/kg was chosen because voxelotor is well tolerated and the human dose was expected to be less than 1 g/day. Voxelotor-related clinical observations consisted of abnormal feces and vomitus at the HD but no effects on body weight were observed. Voxelotor had no effect on any of the ECG parameters, including PR interval, QRS duration, QT interval, and QTc interval or qualitative ECG abnormalities. Voxelotor-related changes included higher (↑8%) mean systolic pressure in HD dogs at 6 hours post-dose. No changes in diastolic and mean arterial pressures, heart rate, or pulse pressure occurred.

Assessment of respiratory function was conducted in Hsd:Sprague Dawley rats using head-out plethysmography and analysis of tidal volume, respiration rate, and minute volume (Study: PRC-14-053-R). Rats were administered a single dose of vehicle control (0.5% [w/w] Methocel E50 in reverse osmosis water containing 0.01% [w/w] polysorbate 80 and 10 mM phosphate buffer [pH 7 ± 0.2]), or 100, 320, or 1000 mg/kg (600, 1920, or 6000 mg/m^2) voxelotor at a dose volume of 10 mL/kg by oral gavage. No voxelotor-related clinical observations occurred. Voxelotor-related changes included lower tidal volume by 0.24 mL (↓13%) at the HD and increased respiration rate by as much as 14 breaths/minute (↑19%) at the MD and HD. No voxelotor-related effects on respiratory function occurred at the low dose.

Evaluations for potential neurological effects were conducted in Hsd:Sprague Dawley rats based on observations collected approximately 7, 24, and 96 hours postdose using a modified Irwin test. The battery of neurological assessments including group home cage, hand-held, open-field, and elicited response observations (Study: PRC-14-052-R). Rats were administered a single dose of vehicle control (0.5% [w/w] Methocel E50 in reverse osmosis water containing 0.01% [w/w] polysorbate 80 and 10 mM phosphate buffer [pH 7 ± 0.2]), or 100, 320, or 1000 mg/kg (600, 1920, or 6000 mg/m^2) voxelotor at a dose volume of 10 mL/kg by oral gavage. No voxelotor-related clinical observations or neurological effects occurred in the study.

5.4. ADME/PK

Absorption

Summary of single-dose oral PK studies. Repeat-dose evaluations are under TK
(Studies # PRC-14-003-R, PRC-14-004-R, PRC-14-007-R, PRC-14-012-R)

- Volume of distribution at steady state (Vss) in whole blood was small and equivalent to blood volume (0.041 to 0.171 L/kg), but much larger in plasma (1.44 to 8.45 L/kg), indicating that RBC are a reservoir of voxelotor and act as a peripheral compartment.
- Systemic clearance (CLs) was low in both blood (0.016– 0.113 mL/min/kg) and plasma (0.943–3.16 mL/min/kg).
- Terminal elimination half-life (t1/2) was similar between whole blood and plasma for each species and ranged from 6.4 hours in mouse plasma to 93.5 hours in dog plasma. This suggests that the drug does not have off-target high affinity binding to other proteins in plasma.
- Voxelotor was well absorbed and absolute oral bioavailability measured in whole blood ranged from 36% to 71% in mouse, rat, dog and monkeys.
- Blood:plasma concentration ratios in mouse, rat, dog, and monkey ranged from 69.0 to 74.4. At an estimated hematocrit of 45%, this ratio corresponded to an RBC:plasma ratio of approximately 150. These data are consistent with voxelotor having a high affinity and specificity for Hb within the target compartment (RBC).

Table 4: Mean (%CV) Pharmacokinetic Parameters of Voxelotor Hydrochloride Following a Single Dose in Mouse, Rat, Dog and Monkey

Species	Matrix	Intravenous			Oral					
		Dose (mg/kg)	T ½ (hr)	$AUC_{(0-\infty)}$ (µg/mL*h)	Dose (mg/kg)	T ½ (hr)	C_{max} (µg/mL)	$AUC_{(0-\infty)}$ (µg/mL*h)	F (%)	Blood: Plasma Ratio
Mouse C57BL/6J	Blood	71	11.7	10409	30	4	81.9	3122	71	70
	Plasma		6.4	372		4	1.72	34.2	22	
SD Rat	Blood	1.6	19.1	874.2	7.2	19.2	71.2	2353	59.8	69
	Plasma		21.8	14.8		19.8	2.4	39.6	59.3	
Beagle Dog	Blood	1	66.0	559	2.5	8	5.6	607	36.6	74
	Plasma		93.5	13.4		0.6	1.0	8.3	36.0	
Cynomolgus monkey	Blood	1	28.8	1073	4.25	39.3	25.2	1604	36.1	71
	Plasma		28.8	17.7		28.1	8.6	25.1	33.2	

Factors determining oral bioavailability of voxelotor (Study PRC-14-021-R)

A portal vein study was conducted in 4 Sprague Dawley rats. An oral dose of 7.2 mg/kg voxelotor was administered to the rats and blood samples were collected from the portal and femoral veins to determine the fraction escaping the gut and liver. The fractions of voxelotor that escaped the gut and liver were 0.64 and 0.74, respectively. Results suggest that oral bioavailability of voxelotor was limited by both absorption in the gut and first-pass metabolism in the liver.

Distribution

Tissue distribution (Study PRC-14-024-R)

Quantitative whole-body autoradiography (QWBA) following an oral administration of 10 mg/kg (150 µCi/kg) ^{14}C-voxelotor was conducted in male Sprague Dawley rat at 0.5, 4, 8, 24, and 72 hours postdose and in partially-pigmented Long Evans rats at 0.5, 4, 8, 24, 48, 72, 168, 336, and 672 hours postdose.

In pigmented rats, voxelotor–derived radioactivity was widely distributed in tissues and organs, but it was not selectively associated with melanin-containing tissues. Most tissues had peak radioactivity concentrations at 8 hours postdose; tissues with the highest peak concentrations were blood, lung, red pulp of spleen, spleen, liver, bone marrow, and kidney medulla. Low peak concentrations were found in central nervous system tissues protected by the blood-brain barrier (cerebellum, cerebrum, medulla, and spinal cord). Elimination of drug-derived radioactivity from the tissues was nearly complete by 168 hours postdose, and not detectable by 672 hours postdose. Distribution trends in the nonpigmented rats were generally comparable to those seen in pigmented male rats. Most tissues had peak radioactivity concentrations at 4 hours postdose, and the tissues showing the highest peak concentrations were blood, lung, red pulp of spleen, liver, brown fat, and urinary bladder.

Protein binding (Studies PRC-14-014-R, PRC-19-001)

Voxelotor preferentially binds to Hb and selectively partitions into RBC with less compound remaining in the plasma compartment when tested in the presence of both Hb and plasma protein (e.g., whole blood). Protein binding studies with voxelotor were performed in vitro using plasma (in the absence of Hb) from human, monkey, dog, rat, and mouse at 5 and 50 µM using an ultracentrifugation method. The percent of voxelotor bound to plasma from human, monkey, dog, rat, and mouse was similar ranging from 99.6% to 99.8%. Recovery of voxelotor ranged from 90% to 109% indicative of a lack of nonspecific binding.

Metabolism (see also the Clinical Pharmacology Section)
In vitro metabolism using microsomes and hepatocytes (Study PRC-14-015-R) The in vitro metabolite profile of voxelotor was obtained following incubation with Sprague-Dawley rat, beagle dog, cynomolgus monkey, and human liver microsomes and hepatocytes. Voxelotor was moderately metabolized by oxidation-reduction and conjugation reactions (approximately 25% to 40% of the initial incubation) in rat, dog, monkey, and human hepatocytes at 1 µM and 10 µM. Metabolites GBT572, GBT1659, GBT1756, and GBT1757 were found at similar abundance in rat, beagle dog, cynomolgus monkey, and human liver microsomal preparations. Inhibition of Drug Transporters by Voxelotor (Studies PRC-15-011-R, PRC-17-011, PRC-18-039, PRC-17-012) Results show that for most transporter enzymes, the inhibitory activity is below the threshold of clinical relevance.
Excretion
Excretion of Radiolabeled Voxelotor in Rats (Study PRC-14-024-R) Excretion of voxelotor was determined after a single (2 mg/kg; 150 µCi/kg) IV dose of [^{14}C]-voxelotor to 4 male bile duct cannulated (BDC) rats. Levels measured in the bile, feces, and urine accounted for mean values of 84.2%, 1.80%, and 7.5% of the administered dose, respectively. Approximately 1% of the dose was found in expired air. There were 24 minor metabolites each representing < 0.67% of the radioactive dose. Metabolism was the main route of elimination of voxelotor (approximately 93% of the administered dose) following an IV administration. Approximately 6.6% of the dose was excreted into bile and <1% was excreted into urine as unchanged voxelotor. Most of metabolites were excreted into bile (approximately 77% of the dose) and a minor amount into urine (approximately 7.5% of the dose).
TK data from general toxicology studies
26-Week Oral Gavage Toxicity and Toxicokinetic Study with Voxelotor in Rats with a 4-Week Recovery Phase / PRC-16-008 The exposure in whole blood at the dose of 250 mg/kg/day (AUC=20200 µg/mL*h) in Sprague Dawley rats is approximately 5.8 times the clinical exposure in whole blood (3820 µg/mL*h) at the recommended human dose of 1500 mg/day.

Table 5: Summary of Voxelotor Toxicokinetic Parameters in Sprague-Dawley Rat Whole Blood on Week 26

(Excerpted from Submission)

Interval	Dose Group	Dose Level (mg/kg/day)	Sex	C_{max} (ng/mL)	DN C_{max} [(ng/mL)/(mg/kg/day)]	T_{max} (hr)	AUC_{0-24} (ng·hr/mL)	DN AUC_{0-24} [(ng·hr/mL)/(mg/kg/day)]	B:P AUC_{0-24}	AR C_{max}	AR AUC_{0-24}
Week 26	2	15	M	327000	21800	8.00	6570000	438000	50.4	3.36	3.59
			F	278000	18500	8.00	5200000	346000	45.5	3.60	3.48
			MF	302000	20100	8.00	5880000	392000	48.1	3.47	3.54
	3	50	M	712000	14200	8.00	14000000	281000	37.8	1.86	2.30
			F	570000	11400	1.00	11000000	219000	33.2	2.19	2.24
			MF	621000	12400	8.00	12500000	250000	35.6	1.96	2.27
	4	250	M	1160000	4630	4.00	22000000	88000	19.7	1.85	1.91
			F	926000	3710	8.00	18100000	72300	20.5	1.54	1.72
			MF	1040000	4150	4.00	20200000	80700	20.1	1.69	1.83

Note: Half-life could not be calculated in blood for any group.

Half-life in plasma at the HD was estimated at 11.8 hours; DN= dose-normalized values; B:P= blood-to-plasma ratio; AR= accumulation ratio.

39-Week Daily Gavage Toxicity and Toxicokinetic Study with Voxelotor in Cynomolgus Monkeys with a 4-Week Recovery Phase / PRC-16-007

The exposure in whole blood at the dose of 60 mg/kg/day (AUC=8030 µg/mL*h) in Cynomolgus monkey is approximately 2.1 times the clinical exposure in whole blood (3820 µg/mL*h) at the recommended human dose of 1500 mg/day.

Table 6: Summary of Voxelotor Toxicokinetic Parameters in Cynomolgus Monkeys Whole Blood on Week 39

Dose (mg/kg/day)	C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-t} (µg/mL*h)	B:P
15	195000	7.3	4140	28.1
30	239000	6.0	5100	20.1
60	375000	6.0	8030	20.4

Male and female mean values are presented;
B:P= blood-to-plasma ratio

TK data from reproductive toxicology studies

An Oral Embryo-Fetal Development Study of GBT440 in Rats / PRC-16-001-R

Exposure in rats' whole blood at 250 mg/kg/day (10500 µg/mL*h) is approximately 2.8 times the clinical exposure in whole blood based on AUC (3820 µg/mL*h) at the recommended human daily dose of 1500 mg.

Table 7: Summary of Voxelotor Toxicokinetic Parameters in Female Sprague-Dawley Rat Whole Blood on GD 7 and 17

(Excerpted from Submission)

Dose (mg/kg)	Study Day	Tmax (hr)	C_{max} (ng/mL)	AUC (0-t) (hr•ng/mL)	Ratio AUC (0-t)[a]	RAUC[b]
15	DG 7	8	83700	1500000	41.6	NA
	DG 17	4	133000	2060000	34.6	1.37
50	DG 7	4	277000	4840000	35.7	NA
	DG 17	4	330000	5600000	31.8	1.16
250	DG 7	4	578000	11200000	17.5	NA
	DG 17	8	719000	10500000	18.4	0.935

NA = Not Applicable.
[a] Whole blood/Plasma ratio.
[b] RAUC = DG 17 $AUC_{(0-t)}$/ DG 7 $AUC_{(0-t)}$.

An Oral Embryo-Fetal Development Study of Voxelotor in Rabbits / PRC-16-002-R

Exposure in rabbits' whole blood at 150 mg/kg/day (1060 µg/mL*h) is approximately 0.3 times the clinical exposure in whole blood based on AUC (3820 µg/mL*h) at the recommended human daily dose of 1500 mg.

Table 8: Summary of Voxelotor Toxicokinetic Parameters in Female New Zealand White Rabbit Whole Blood on GD 7 and 19

(Excerpted from Submission)

Dose (mg/kg/day)	Study Day	Tmax (hr)	C_{max} (ng/mL)	AUC (0-t) (hr•ng/mL)	T1/2 (hr)
25	DG 7	3.33	4690	74300	8.98
	DG 19	5.33	17700	251000	9.61
75	DG 7	6.00	19100	206000	NR
	DG 19	5.33	43900	632000	NR
150	DG 7	6.67	26300	434000	NR
	DG 19	5.33	63400	1060000	NR

NR = Not reportable

GBT440 Oral Gavage Study for Effects on Pre- and Post-Natal Development, Including Maternal Function, in Rats / PRC-17-005

Toxicokinetic analysis was not performed; therefore, the exposure in whole blood estimated in the EFD in Sprague Dawley rats was used to estimate exposure ratios. Voxelotor effects in the offspring were observed at the maternal dose of 250 mg/kg/day with an exposure in whole blood (AUC=20200 µg/mL*h) of approximately 2.8 times the exposure in whole blood (AUC=3820 µg/mL*h) at the recommended human dose of 1500 mg/day.

Voxelotor concentration in rats was evaluated and reported in plasma and not in whole blood. The study report mentions that voxelotor concentrations in pups plasma increased with the increase in dose; however, there is not data in the study report to support this statement. Voxelotor concentrations in rat plasma and milk increased with increasing dosing concentrations.

Table 9: Summary of Voxelotor Concentration in Rat Plasma and Milk

Voxelotor (mg/kg/day)	Plasma	Milk
	Mean ng/mL (STD)	Mean ng/mL (STD)
15	661 (599.1)	722 (58.5)
50	1167 (745.2)	2837 (483.4)
250	1638 (501.6)	8025 (799.0)

Samples collected on Lactation Day 14 at 4 hours post-dose from 3 TK rats in the LD and MD and 2 TK rats from the HD; STD= standard deviation

5.5. Toxicology

5.5.1. General Toxicology

Study title / number: 26-Week Oral Gavage Toxicity and Toxicokinetic Study with Voxelotor in Rats with a 4-Week Recovery Phase / PRC-16-008

- Increased erythroid and myeloid parameters (red blood cell mass, reticulocytes and WBC), increases in spleen and thymus organ weights, microscopic findings of hypercellularity in the bone marrow, and extramedullary hematopoiesis and changes in lymphocytes in the spleen mostly at the MD and HD may be associated with a physiological response to the pharmacological action of voxelotor of increased oxygen affinity of hemoglobin.
- Increases in liver weight, microscopic findings of periportal hepatocyte hypertrophy and bile duct hyperplasia, thyroid follicular hypertrophy and pituitary basophil hypertrophy may be associated with the induction of hepatic metabolizing enzymes by voxelotor.
- There were signs of inflammation in several organs at the HD including the harderian gland, kidney, lung, nonglandular stomach, prostate, rectum and thymus that were not present at recovery except for the nonglandular stomach.
- The exposure (AUC) in whole blood at the highest dose of 250 mg/kg/day is approximately 5.8 times the clinical exposure in whole blood at the recommended human dose of 1500 mg/day.

Conducting laboratory and location: (b) (4) (b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing:	0, 15, 50, or 250 mg/kg/day Dose levels based on the results of a 13-week toxicology study in rats
Route of administration:	Oral

Formulation/Vehicle:	0.5% (w/w) Methocel E50 in reverse osmosis water containing 0.01% (w/w) polysorbate 80 and 10 mM phosphate buffer (pH 7 ± 0.2)
Species/Strain:	Hsd:Sprague Dawley rats
Number/Sex/Group:	20/sex control and HD; 15/sex LD and MD groups. 5/sex control and HD assigned for 4-week recovery
Age:	6 to 7 weeks old
Satellite groups/ unique design:	TK: 3/sex control; 9/sex voxelotor groups.
Deviation from study protocol affecting interpretation of results:	Yes. Protocol deviations neither affected the overall interpretation of study findings nor compromised the integrity of the study

Observations and Results: changes from control

Parameters	Major findings
Mortality	One MD male found dead on Day 91 considered accidental One MD male found dead on Day 193; no macroscopic observations were found and the cause of death undetermined
Clinical Signs	No voxelotor-related observations
Body Weight gain	Voxelotor-related lower body weight gain but not adverse Males Dosing Phase: MD and HD significantly ↑ or ↓ body weight gain, but these were preceded or followed by trends in the opposite direction. Recovery Phase: ↓14% overall body weight gain Females Dosing Phase: trend for ↓ body weight with a significant ↓12% overall body weight gain Recovery Phase: ↓20% overall body weight gains No differences in food consumption
Ophthalmoscopy	No voxelotor-related observations
Hematology	

Voxelotor-related effects: ↑ in red blood cell mass and reticulocytes mostly at the MD and HD. These changes may be associated with the physiological response to voxelotor increased oxygen affinity of hemoglobin and corresponded microscopically with marrow hypercellularity and increased extramedullary hematopoiesis in the spleen; other changes included ↑ in corpuscular volume, corpuscular hemoglobin, corpuscular hemoglobin concentration, lymphocytes, neutrophils, monocytes, basophils and large unstained cells mostly at the HD. Notable decreases were observed in platelets and eosinophils at the MD and HD. Values similar to control at the end of recovery.

Table 10: Summary of Voxelotor Effects on Hematological Parameters in Rats

Parameter	Voxelotor (mg/kg/day)					
	Males			Females		
	15	50	250	15	50	250
RBC	↑5.6*	↑10.0*	↑11.5*	↑3.1	↑6.8*	↑12.8*
HGB	↓3.0	↑9.1*	↑25.5*	↑2.5	↑6.9*	↑22.0*
HCT	↑3.9	↑8.7*	↑22.7*	↑2.6	↑5.5*	↑18.5*

MCV	--	--	↑10.3*	--	--	↑4.9*
MCH	↓7.7	--	↑12.4*	--	--	↑8.3*
MCHC	↓6.6	--	↑2.0	--	--	↑3.2*
Reticulocytes	↑8.5*	↑24.7*	↑233	--	↑5.1	↑104*
Platelets	↓6.8	↓18.9*	↓47.3*	--	↓16.3*	↓31.7*
WBC	↑4.3	↑4.5	↑61.2*	↓23.8*	↓16.7	↑53.3*
Lymphocyte	↑6.8	↑11.4	↑90.7*	↓25.7*	↓17.6	↑51.0*
Neutrophil	--	--	↑6.6	--	--	↑83.6*
Monocyte	--	--	↑44.4*	↓38.5*	↓30.1	↑30.7*
Eosinophils	↓10.0	↓30.0	↓40.0*	↓20.0	↓20.0	↓30.0
Basophils	--	↑33.3*	↑300*	--	--	↑150*
LUC	--	--	↑80*	--	--	↑100*

* p≤0.05; -- no difference; ↑↓= % increase/decrease compared to control group

Coagulation

Minor changes occurred mostly at the HD that lacked microscopic correlates. Values were similar to control at the end of recovery.

Table 11: Summary of Voxelotor Effects on Coagulation Parameters in Rats

Parameter	Voxelotor (mg/kg/day)					
	Males			Females		
	15	50	250	15	50	250
Prothrombin time	--	--	↑4.6*	--	--	--
APTT	--	--	↑7.5*	↑5.2	↑5.2	↑10.8*
Fibrinogen	↓1.9	↓3.1	↓8.1*	↓7.3	↓3.7	↓5.5

* p≤0.05; -- no difference; ↑↓= % increase/decrease compared to control group

Clinical Chemistry

Voxelotor-related effects: ↑ in AST, ALT, LDH and ALP that corresponded with ↑ in liver weight parameters and microscopically with periportal hepatocyte hypertrophy and bile duct hyperplasia. Higher albumin concentration and A:G ratio in females at all dose levels may be associated with hemoconcentration and diuresis, see urinalysis. Lower glucose, cholesterol and triglycerides concentrations may be associated with effects on body weight. Values were similar to control at the end of recovery.

Table 12: Summary of Voxelotor Effects on Clinical Pathology Parameters in Rats

Parameter	Voxelotor (mg/kg/day)					
	Males			Females		
	15	50	250	15	50	250
AST	--	--	↑22.0*	↑1.9	--	↑7.8
ALT	↑6.5	↑23.9*	↑111*	--	↑23.7*	↑60.5*
LDH	↑6.6	↑11.1	↑31.5	↑5.9	--	↑58.8
ALP	↑8.2	↑11.5	↑16.4	↑4.5	↑20.1	↑18.2
Glucose	↑17.5*	--	↓28.8*	--	↓5.5	↓16.5*
Urea nitrogen	--	↓12.5*	↓12.5*	↓10.5	↓15.8*	↓31.6*
Albumin	--	--	--	↑4.3*	↑4.3*	↑4.3*
Globulin	--	--	↓9.7*	--	--	--
A:G	--	--	↑15.4*	↑11.1*	↑5.6	↑11.1*
Cholesterol	↑3.9	↑8.5	↓15.5*	--	↑4.7	↑18.1*
Triglycerides	↓13.3	↓21.7	↓41.7*	--	↓8.3	↓22.2*
Calcium	--	--	↓3.6*	--	--	--
Phosphorus	↑5.2	↑5.2	↑25.9*	↓11.3	↓13.2*	↑20.8*
Potassium	↑5.5	--	↑5.5	--	--	↑9.8*

* p≤0.05; -- no difference; ↑↓= % increase/decrease compared to control group

Erythropoietin	No voxelotor-related effects
Urinalysis	Voxelotor-related increases in urine volume were observed in males and females at the MD (54.8%, 24.5%) and HD (143%, 96.8%), respectively. Urine volume increases corresponded with diuresis and was associated with microscopic findings of chronic progressive nephropathy.
Gross Pathology	Voxelotor-related raised areas were present in the mucosa of the nonglandular stomach in four HD that corresponded microscopically with hyperplasia/hyperkeratosis. Not present at recovery.

Organ Weights

↑/↓ in organ weight with microscopic correlates
Liver: periportal hepatocyte hypertrophy, bile duct hyperplasia and induction of hepatic metabolic enzymes.
Spleen: increased germinal center lymphocytes and increased extramedullary hematopoiesis in relation to the pharmacological action of voxelotor.
Thyroid/parathyroid: thyroid follicular cell hypertrophy, secondary to increase in hepatic metabolism.
Kidney: increased incidence of chronic progressive nephropathy and increased urine volume.

Table 13: Summary of Voxelotor Effects on Organ Weight Ratio[1] in Rats

Organ	Voxelotor (mg/kg/day)					
	Males			Females		
	15	50	250	15	50	250
Heart	↑3.1	↑7.9*	↑24.9*	--	↑9.7*	↑33.5*
Kidney	--	--	↑11.5*	--	--	↑16.8*
Liver	--	↑12.1*	↑43.1*	↑4.1	↑8.9*	↑48.0*
Lung	--	--	↑10.6*	--	--	↑14.0*
Mandibular Salivary Gland	↓9.0*	↓8.1*	↓7.9*	--	↓3.5	↓7.7*
Spleen	↓12.8*	--	↑61.9	--	↑6.9	↑34.1*
Thymus	↑10.5	↑18.7	↑19.6	↑11.8	↑12.3	↑24.3*
Thyroid/Parathyroid	↓18.3	--	↑26.7*	--	↑6.4	↑26.9*
	Recovery					
Adrenal			--			↑17.5*
Heart			↑10.1			↑18.8*
Kidney			↑8.9*			↑12.8*
Liver			↑13.1*			↑9.6*
Lung			↑10.0			↑5.2
Mandibular Salivary Gland			--			↑10.1
Prostate			↓13.3			
Seminal vesicle			↓9.5			
Spleen			↑51.0*			↑16.3*
Testis			↑10.6			
Thymus			↑14.4*			
Thyroid/Parathyroid			↑43.1*			↑23.5

1 organ-to-body weight ratio; -- no difference; * p≤0.05; ↑↓= % increase/decrease compared to control group

↑/↓ in organ weight with no microscopic correlates
Heart, lung, mandibular salivary gland, and thymus
Recovery: ↑/↓ in organ weight with microscopic correlates
Liver: periportal hepatocyte hypertrophy and bile duct hyperplasia.
Recovery: ↑/↓ in organ weight with no microscopic correlates
Adrenal, heart, kidney, lung, mandibular salivary gland, prostate, seminal vesicle, spleen, testis, thymus and thyroid/parathyroid.

Histopathology Adequate battery: Yes
Most microscopic findings were considered non-adverse because of:

- Minimal to slight severity in most of the findings;
- Adaptative responses to xenobiotics (liver hepatocellular hypertrophy and secondary effects on the thyroid) or to the pharmacological action of voxelotor (bone marrow and/or spleen increased extramedullary hematopoiesis) were resolved or almost resolved at the end of recovery and they were not considered adverse.

- Common spontaneous finding in Sprague Dawley rats (degenerative cardiomyopathy, perivascular mineralization in the sciatic nerve in aged rats);
- Absence of findings at recovery euthanasia

Microscopic findings were present at recovery in the HD although with less severity compared to terminal euthanasia.

- Hyperplasia/hyperkeratosis in the stomach and chronic active inflammation in the nonglandular stomach
- minimal epithelium hyperplasia in the thymus

Table 14: Incidence and Severity of Voxelotor-Related Hematopoietic and Lymphoid Tissue Microscopic Findings in Rats - Terminal Euthanasia

(Excerpted from Submission)

	GBT440							
Sex	Males				Females			
Dose Level (mg/kg/day)	0	15	50	250	0	15	50	250
Number Examined[a]	15	15	13	15	15	15	15	15
Marrow, Femur								
Hypercellular								
Minimal	0	0	0	0	0	0	0	7
Slight	0	0	0	3	0	0	0	8
Moderate	0	0	0	12	0	0	0	0
Marrow, Sternum								
Number Examined	15	15	13	15	14	15	15	15
Hypercellular								
Minimal	0	0	0	15	0	0	0	15
Spleen								
Hematopoiesis, extramedullary, increased								
Minimal	0	0	2	7	0	0	0	3
Slight	0	0	0	8	0	0	0	0
Lymphocytes, increased, germinal centers								
Minimal	0	4	7	9	0	2	6	3
Slight	0	0	2	5	0	0	1	10
Lymphocytes, decreased, marginal zone								
Minimal	0	0	0	5	0	0	2	4
Slight	0	0	0	10	0	0	1	8

a Number examined per tissue unless otherwise noted.

Table 15: Incidence and Severity of Voxelotor-Related Liver, Thyroid and Pituitary Microscopic Findings in Rats - Terminal Euthanasia

(Excerpted from Submission)

	GBT440							
Sex	Males				Females			
Dose Level (mg/kg/day)	0	15	50	250	0	15	50	250
Number Examined	15	15	13	15	15	15	15	15
Liver								
Hypertrophy, hepatocyte, periportal								
Minimal	0	0	0	1	0	0	0	5
Slight	0	0	0	2	0	0	0	7
Moderate	0	0	0	12	0	0	0	2
Hyperplasia, bile duct								
Minimal	0	0	0	7	0	0	0	4
Thyroid								
Hypertrophy, follicular cell								
Minimal	0	0	0	5	0	0	0	13
Pituitary								
Hypertrophy, basophil cell								
Minimal	0	0	0	10	0	0	0	0
Slight	0	0	0	5	0	0	0	0

Table 16: Incidence and Severity of Selected Voxelotor-Related Microscopic Findings in Rats - Terminal Euthanasia

(Excerpted from Submission)

	GBT440							
Sex	Males				Females			
Dose Level (mg/kg/day)	0	15	50	250	0	15	50	250
Number Examined	15	15	13	15	15	15	15	15
Heart								
Cardiomyopathy, degenerative								
Minimal	4	8	6	3	2	0	0	0
Slight	0	0	0	3	0	0	0	0
Moderate	0	0	0	2	0	0	0	0
Kidney								
Nephropathy, chronic progressive								
Minimal	11	11	9	12	7	8	6	13
Slight	3	3	2	3	1	0	1	1
Moderate	0	0	1	0	0	0	0	0
Stomach, Nonglandular								
Hyperplasia/hyperkeratosis								
Minimal	0	0	0	8	0	0	0	4
Slight	0	0	0	4	0	0	0	1
Nerve, Sciatic								
Mineralization, perivascular								
Minimal	1	2	3	12	0	0	1	4
Slight	0	0	0	1	0	0	0	0

Hyperplasia/hyperkeratosis in the nonglandular stomach was observed macroscopically as raised areas in some males and attributed to local contact irritation and not a systemic effect.

Table 17: Incidence and Severity of Selected Voxelotor-Related Microscopic Findings in Rats - Recovery Euthanasia

(Excerpted from Submission)

	GBT440			
Sex	Males		Females	
Dose Level (mg/kg/day)	0	250	0	250
Number Examined	5	5	5	5
Heart				
Cardiomyopathy, degenerative				
Minimal	1	4	0	0
Liver				
Hypertrophy, hepatocyte, periportal				
Minimal	0	4	0	1
Slight	0	1	0	0
Hyperplasia, bile duct				
Minimal	0	4	0	2
Stomach				
Hyperplasia/hyperkeratosis				
Minimal	0	1	0	0
Nerve, Sciatic				
Mineralization, perivascular				
Minimal	0	2	0	0
Slight	0	3	0	0

Additional findings at the recovery euthanasia included:
- minimal hyperplasia/hyperkeratosis and chronic active inflammation in the nonglandular stomach of one HD male
- minimal epithelium hyperplasia in the thymus in one HD male and three HD females

Study title / number: 39-Week Daily Gavage Toxicity and Toxicokinetic Study with Voxelotor in Cynomolgus Monkeys with a 4-Week Recovery Phase / PRC-16-007

- Mortality at MD and HD with adverse clinical signs, macroscopic findings in the GI tract and skin and adverse microscopic findings in lymphatic organs, GI tract and kidney.
- Increases in red blood cells at all doses, increases in reticulocytes at the HD, minor increases in hematocrit, and increases in spleen weight with corresponding increases in red pulp cellularity occurred in male monkeys. Decreased mean corpuscular volume of ≤10% occurred at all dose levels in males and females and were still present at the end of recovery in the HD. Decreases in white blood cells were present only in males at the HD but values rebounded at the end of recovery. A general decrease in all immunophenotype cell subsets was transient and not dose-dependent. A delayed/transient suppressed immune response across dose levels was observed.
- Minor increases in metabolizing enzymes and triglycerides, and decreases in cholesterol were not present at recovery. Relevant microscopic findings that suggest an inflammatory response in the heart, liver, lungs and spleen, mostly at the MD and HD, were still present at recovery.

- The exposure (AUC) in whole blood at the highest dose of 60 mg/kg/day is approximately 2.1 times the clinical exposure in whole blood at the recommended human dose of 1500 mg/day.

Conducting laboratory and location: (b) (4) (b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing:	0, 15, 30, or 60 mg/kg/day Dose levels based on the results of a 13-week toxicology study in monkeys
Route of administration:	Oral
Formulation/Vehicle:	0.5% (w/w) Methocel E50 in reverse osmosis water containing 0.01% (w/w) polysorbate 80 and 10 mM phosphate buffer (pH 7 ± 0.2)
Species/Strain:	Cynomolgus monkeys (Macaca fascicularis)
Number/Sex/Group:	6/sex control and HD; 4/sex LD and MD groups; 2/sex control and HD assigned for 4-week recovery
Age:	58 to 84 months old
Satellite groups/ unique design:	None / ECG, peripheral blood immunophenotyping and immunization with keyhole limpet hemocyanin (KLH) evaluations
Deviation from study protocol affecting interpretation of results:	Yes. Protocol deviations neither affected the overall interpretation of study findings nor compromised the integrity of the study

Observations and Results: changes from control

Parameters	Major findings
Mortality	Two MD males and one MD female and two HD males and two HD females. Remarkable clinical signs and clinical pathology changes resulted in dosing holiday and included: - Body weight loss, decreased food consumption, excessive salivation, vomiting, abnormal feces (diarrhea and/or watery stools); - Hunched posture, hypoactive, body tremors, squinted eyes, alopecia and discolored haircoat; - ↓ serum total protein and/or albumin often with concomitant↓ in serum calcium and ↑ APTT, and ↓ red blood cell parameters.
Clinical Signs	Surviving animals: ↑ incidence of fecal abnormalities (non-formed or liquid) in HD females

Body Weight gain	Voxelotor-related and adverse lower body weight gains Males Dosing phase: HD ↓50% overall body weight gain Recovery: similar to control Females Dosing phase: LD and MD ↓25%, HD ↓75% overall body weight gain Recovery: similar to control
Ophthalmoscopy	No voxelotor-related findings
ECG	No voxelotor-related changes in PR interval, QRS duration, QT interval, corrected QT (QTc) interval, RR interval, heart rate, rhythm abnormalities or qualitative ECG parameters
Hematology	

Dose-related ↑ in RBC although not statistically significant and ↑ reticulocytes in males; mean corpuscular volume from Day 89 to Day 229 of the dosing phase was statistically significantly lower in males at the MD and HD. The trend for ↓ MCV was noted on the final day of dosing across dose levels as well as ↓ in WBC, lymphocytes and neutrophils in HD males . At the end of recovery, ↑red blood cell mass and reticulocytes, ↓MCV, and lymphocytes were still present. Other parameters rebounded.

Table 18: Summary of Voxelotor Effects on Hematological Parameters in Monkeys on Day 271

Parameter	Voxelotor (mg/kg/day)					
	Males			Females		
	15	30	60	15	30	60
RBC	↑12.7	↑13.3	↑15.8*	--	--	--
HGB	--	--	--	--	--	--
HCT	↑7.7	↑3.6	↑2.9	--	--	--
MCV	↓4.7	↓8.3	↓11.1	↓4.4	↓6.8	↓4.4
Reticulocytes	--	--	↑34.0	--	--	--
WBC	--	--	↓31.9	--	--	↑22.5
Lymphocyte	--	--	↓15.1	--	--	--
Neutrophil	--	--	↓48.2	--	↑56.7	↑60.2
	Recovery					
RBC			↑18.9			--
HGB			↑9.4			--
HCT			↑5.7			↓8.6
MCV			↓11.0			↓2.5
Reticulocytes			↑25.5			↓59.5
WBC			↑22.4			↑15.4
Lymphocyte			↓20.1			↓9.7
Neutrophil			↑72.0			↑34.6

-- no difference; * p≤0.05; ↑↓= % increase/decrease compared to control group

Coagulation	No voxelotor-related findings
Clinical Chemistry	

Voxelotor-related findings included increases in metabolizing enzymes, decreases in cholesterol, increases in phosphorus at the LD and fluctuation of triglyceride values. AST (↑33.3) and ALT (↑61.5) remained elevated at the end of recovery.

Table 19: Summary of Voxelotor Effects on Clinical Pathology Parameters in Monkeys on Day 271

Parameter	Voxelotor (mg/kg/day)					
	Males			Females		
	15	30	60	15	30	60
AST	↑18.2	↑15.2	↑24.2	--	--	--
ALT	↑7.3	↑48.8	↑22	↑5.1	↑10.3	↑20.5
ALP	↑14.1	↑10.9	↑24.2	↑3.9	↑20.5	↑35.9
Cholesterol	--	--	↓23.8	↓13.6	↓32.4	↓26.7
Triglycerides	↓23.1	↑28.2	↑41.0	↓16.7	↑11.1	↓11.1
Phosphorus	↑40.9*	--	↑18.2	↑12.5	--	↑25

-- no difference; * p≤0.05; ↑↓= % increase/decrease compared to control group

Erythropoietin	No voxelotor-related effects
Urinalysis	No voxelotor-related effects
Gross Pathology	Early decedents Raised areas in the duodenal mucosa in one HD female, abnormal contents (gelatinous/clear) in the ileum, cecum, and colon and red discoloration of the colon mucosa in one HD female with microscopic correlates of erosion, edema, neutrophil infiltrates, atrophy and hemorrhages. Thickening and discoloration of eyelids in one HD male corresponded with edema and inflammatory cell infiltrates. Terminal and Recovery euthanasia No voxelotor-related findings
Organ Weights	

Table 20: Summary of Voxelotor Effects on Spleen Weight Ratio in Monkeys at Terminal Euthanasia

(Excerpted from Submission)

	GBT440							
Sex	Males				Females			
Dose Level (mg/kg/day)	0	15	30	60	0	15	30	60
Spleen								
Absolute Weight (g)	4.894	197	194	241	3.213	110	134	139
Body Weight Ratio (%)	0.0618	198*	179	289*	0.0896	112	144	155
Brain Weight Ratio (%)	7.3930	168	167	216	4.9306	104	139	146

Note: Values for absolute weight and ratio of organ weights (relative to body or brain) for dosed groups expressed as percentage control mean value.
* = Statistically significant.

No voxelotor-related findings at recovery

Histopathology Adequate battery: Yes	Early decedents • Bone marrow with severe decreased cellularity in one MD male and moderate-severe increase cellularity in two HD males. • Decreased lymphocytes in lymphatic organs (spleen, thymus, lymph nodes and GALT/Peyer's Patch) ranged from moderate to severe in most of early decedents.

	• Microscopic findings in the GI tract were described above in gross pathology. • Additional findings included the skin with multiple erosions/ulcers in one MD female, and glomerulopathy in the kidney. <u>Terminal Euthanasia</u> • Brain with minimal mononuclear cell infiltrate in one HD female • Heart with slight mixed cell infiltrate in one HD female, and minimal to slight mononuclear infiltrate in one LD, MD and HD male, respectively. • Liver with minimal to slight sinusoidal leukocytosis in one MD and one HD male. • Lung with slight fibrosis in one MD male. • Biceps muscle with minimal mononuclear cell infiltrate in two males at each dose levels and one female at each dose level. • Spleen with moderately increased red pulp cellularity in one LD male, marked congestion in one HD male, slight increased lymphocytes in one LD, MD and HD male, respectively, and slight increased pigment in one LD and one HD male. • Minimal mononuclear cell infiltrates were present in individual animals without dose correlation that may be suggestive of inflammatory responses. Some of these findings were also present in recovery animals. <u>Recovery Euthanasia</u> • Brain with minimal mononuclear cell infiltrate in one HD male • Heart with minimal mixed cell and mononuclear cell infiltrate in one HD male and minimal mixed cell infiltrate in two HD female. • Epididymis with minimal mononuclear cell infiltrate in one HD male • Kidney with minimal in one HD male and slight mononuclear cell infiltrate in one HD male. • Lung with slight fibrosis, bronchio-alveolar hyperplasia and macrophages infiltrate in one HD male. • Biceps muscle with minimal mononuclear cell infiltrate in one HD male and one HD female • Parathyroid with minimal mononuclear cell infiltrate in one HD male • Prostate with minimal mononuclear cell infiltrate in two HD males • Spleen with minimal decreased lymphocytes in one HD female. • Thyroid with minimal mononuclear cell infiltrate in one HD male • Tongue with minimal mononuclear cell infiltrate in two HD males

Peripheral Blood Immunophenotyping

Voxelotor-related effects on immunophenotype cell subsets were, in general, minimal and greater in magnitude at the LD and MD. Statistically significant lower values for LYMP and ATLY in LD males and higher values for ACD8 in MD males were noted. These changes, although statistically significant, were transient, not dose-dependent, and inconsistent between sexes. The direction of change in values was, in general, similar for males and females on Days 229 and 271. Values for some cell subsets were still higher/lower compared to control at the end of recovery.

Table 21: Summary of Voxelotor Effects on Peripheral Blood Cell Subsets in Monkeys on Day 229

Parameter	Voxelotor (mg/kg/day)					
	Males			Females		
	15	30	60	15	30	60
Total lymphocyte count (LYMP)	↓39.0*	↑12.7	↓15.1	↓29.7	↓24.9	↓19.5
Absolute total T lymphocyte count (ATLY)	↓45.9*	--	↓14.5	↓29.1	↓22.8	↓18.4
Absolute CD4 T lymphocyte count (ACD4)	↓40.3	↓11.4	↓11.4	↓28.7	↓24.5	↓11.7
Absolute CD8 T lymphocyte count (ACD8)	↓21.4	↑226*	↓9.9	↓21.0	↓14.0	↓26.0
Absolute B lymphocyte count (ABLY)	↓21.7	↑68.0	↓12.4	↓53.9	↓29.1	↓10.3
Absolute natural killer lymphocyte count (ANKL)	↓24.4	--	↓24.4	--	↓50.0	↓60.0

-- no difference; * p≤0.05; ↑↓= % increase/decrease compared to control group

Recovery HD males/females:
LYMP: ↓20.1 / ↓9.7 ; ATLY: ↓37.7 /↓14.9; ACD4: ↓24.8 / ↓5.7; ACD8: ↓46.7 / ↓26.8; ABLY: ↑31.4 /↑15.8; ANKL: ↑25.0 / ↓54.6.

Anti-Keyhole Limpet Hemocyanin (KLH) Antibody Analyses

An intact humoral immune response including maturation from anti-KLH IgM to anti-KLH IgG antibody response occurred in all groups. Voxelotor-related suppression of immune response included a delayed occurrence of mean peak IgM and IgG, and lower percent of IgG and IgM titers on Day 28 post-immunization.
A second immunization (challenge) was not conducted and thus, no comparison of primary and secondary antibody response kinetics was possible, and the adversity of effects not fully evaluated.

Table 22: Summary of Voxelotor Effects on Immune Response

Parameter	Voxelotor (mg/kg/day)					
	Males			Females		
	15	30	60	15	30	60
Mean peak IgM response Control Day 7	14	14	7	14	14	7
Mean peak IgG response Control Day 14	21	21	21	21	21	14
% Mean IgG cut-point titers 28 days post-KLH challenge	↓60	↓42	↓83	↓45	↓65	↓76
% Mean IgM cut-point titers 28 days post-KLH challenge	↑12	↓41	↓79	↓66	↓66	↓75

↑↓= % increase/decrease compared to control group

General toxicology; additional studies

Study title / number: 13-Week Oral Gavage Toxicity and Toxicokinetic Study with Voxelotor in Rats with a 4-Week Recovery / PRC-15-019-R

Voxelotor was administered to Hsd:Sprague Dawley rats at doses of 0, 15, 100 or 700 mg/kg/day. The HD was associated with decreased mean body weight and food consumption in male rats and dose levels were reduced to 0, 15, 50 or 250 mg/kg/day. Target organs of toxicity included liver, spleen, bone marrow, thyroid and pituitary glands, heart, kidney, nonglandular stomach, and sciatic nerve. Voxelotor induced CYP1A activity (~4 to 64-fold) and CYP2B activity (~3 to 9-fold) in HD male and female, induced CYP3A activity (~3-fold) in HD females, and induced UDPGT activity (~2 to 3-fold) in HD males and females. Higher ALA activity corresponded with periportal hepatocyte hypertrophy in ≥MD. Voxelotor-related clinical pathology changes were consistent with the general stimulation of erythroid and myeloid cell lineages (including immune effector cells) with microscopic correlates of bone marrow hypercellularity and splenic extramedullary hematopoiesis and included increased red cell mass (red blood cell count, hemoglobin concentration, and hematocrit) in ≥MD; increased absolute reticulocyte count, mean corpuscular volume, and mean corpuscular hemoglobin, white blood cell count (primarily influenced by higher absolute neutrophil and lymphocyte counts) in HD; and lower absolute platelet count in ≥MD. Voxelotor effects in cell subtypes included ↑ absolute values of total lymphocytes, T-cells (helper and cytotoxic subsets), and B cells, with larger increases observed in B cells relative to other increased lymphocyte subsets and concurrently decreased natural killer (NK) cells at the HD. The T-cell dependent antibody response to keyhole limpet hemocyanin (KLH) challenge was reduced (non-adverse magnitude) in HD. Higher urine volume and minimally lower urine specific gravity in HD suggested diuresis and corresponded with an increased incidence and severity of chronic progressive nephropathy in HD. Increased mean liver, mean spleen and mean kidney weight parameters corresponded with periportal hepatocyte hypertrophy (enzyme induction), increased extramedullary hematopoiesis and an increased incidence and severity of chronic progressive nephropathy in HD, respectively. Increased heart weight had no microscopic correlates and additional microscopic findings at HD included hyperplasia/ hyperkeratosis and erosion in the nonglandular stomach and perivascular mineralization in the sciatic nerve. Voxelotor-related findings were mild at MD and significantly different at HD compared to control; findings were absent or almost resolved during the 4-week recovery period.

Study title / number: 13-Week Daily Oral Gavage Toxicity and Toxicokinetic Study with Voxelotor in Cynomolgus Monkeys with an 8-Week Recovery / PRC-15-020-R

Voxelotor was initially orally administered to cynomolgus monkeys twice daily at doses of 0, 15, 65 or 300 mg/kg/day. Adverse clinical observations of liquid feces and low food consumption during the first week of dosing prompted a washout out period for 7 days and administration of voxelotor resume at the dose levels of 30, 100 or 300 mg/kg/day once daily. Voxelotor at the

HD produced mortality of 4 monkeys/sex with clinical signs of excessive salivation, swelling in different regions of the body, fecal abnormalities, decreased body weight, low overall food consumption, hunched posture, hypoactivity, ataxia and thin appearance near early euthanasia on Day 30. The remaining 2 monkeys/sex were assigned for 8-week recovery. One MD male was euthanized in moribund condition on Day 90. Early decedents presented increased RBC mass, and indices of an inflammatory response including increased WBC and absolute neutrophil counts, fibrinogen concentrations, decreased total protein concentration attributed to decreased albumin concentration, and decreased albumin:globulin ratios. Macroscopic observations were limited to the skin/subcutis that generally corresponded with the skin/subcutis clinical observations and microscopic correlates of diffuse subcutaneous edema. Microscopic findings included mucosal erosion/ulceration and/or mucosal epithelial cell degeneration/necrosis involving one or more segments of the GI tract, widespread inflammatory cell infiltrates (generally perivascular), degeneration/necrosis of the renal tubules and transitional cells of the urinary bladder. Voxelotor-related effects on QT and corrected QT (QTc) interval prolongation included 42 msec (12%) and 37 msec (11%) longer in HD monkeys, respectively. This prolongation was not present at recovery. Surviving monkeys presented increased red blood cell mass (red blood cell concentration, Hb concentration, and hematocrit) and increased absolute reticulocyte count that may correspond with the expected pharmacology of voxelotor; these effects corresponded with the microscopic findings of hypercellular bone marrow and increased splenic red pulp cellularity. Voxelotor-related effects included an inflammatory response present also at LD that corresponded with microscopic findings mentioned above for early decedents. HD monkeys also presented decreased electrolyte concentrations (sodium, chloride, and phosphorus), decreased cholesterol, glucose, and urea nitrogen and increased triglyceride concentrations. Increased spleen weight corresponded with increased red pulp cellularity and decreased thymus weight corresponded with decreased cortical lymphocytes. Microscopic findings in LD, MD and recovery HD monkeys showed decreased incidences and severities compared with findings mentioned for early decedents.

5.5.2. Genetic Toxicology

In Vitro Reverse Mutation Assay in Bacterial Cells (Ames)

Study title / number: Bacterial Reverse Mutation Assay of Voxelotor / PRC-14-060-R

Key Study Findings:

- There was no increase the number of revertant colonies in the range-finding or the confirmatory assay.
- Voxelotor was negative in the Ames assay.

GLP compliance: Yes, with noted exceptions:

- The stability of the test article and the stability of the dose formulations used in the study were not determined;

- The study conclusion was based on the test article as supplied. The identity, strength, purity and composition of the test article used in the study as well as the analysis of dose formulations were not GLP-compliant.

Test system: S. typhimurium tester strains TA98, TA100, TA1535, and TA1537 and E. coli strain WP2uvrA were incubated with and without metabolic activation.
Study is valid: Yes

In Vivo Clastogenicity Assay in Rodent (Micronucleus Assay)

Study title / number: In Vivo Micronucleus and Comet Assay in Rats / PRC-14-059-R

Key Study Findings:

- No statistically significant increase in percent tail DNA in liver and stomach or in the incidence of micronucleated polychromatic erythrocytes in voxelotor-dosed rats as compared to the vehicle control group.
- Voxelotor was considered negative in the rat mammalian micronucleus assay and comet assay at doses up to and including 2000 mg/kg.

GLP compliance: Yes, with noted exceptions:

- The stability of the test article used in the study was not determined;
- The study conclusion was based on the test article as supplied.

Test system: Voxelotor oral doses of 0, 500, 1000, or 2000 mg/kg/day was administered to Hsd:Sprague Dawley male rats (n=5/sex/group; 8/sex/group HD). No mortality occurred in the study.
Study is valid: Yes

5.5.3. Carcinogenicity

Study title / number: 26-Week Oral Gavage Carcinogenicity Study of Voxelotor in 001178-T (Hemizygous) RasH2 Mice / PRC-17-006

Daily oral gavage administration of voxelotor to male and female 001178-T (hemizygous) CByB6F1-Tg(HRAS)2Jic mice for at least 26 weeks at doses of 50, 150, or 500 mg/kg/day (150, 450, and 1500 mg/m^2/day) resulted in no effect on survival and no voxelotor-related neoplastic or hyperplastic effects.

- Dose-dependent lower body weight gain occurred in males at all doses and in females at ≥150 mg/kg/day.
- Dose-related increases in red blood cell mass and red blood indices were observed at all dose levels consistent with the pharmacologically mediated increased oxygen affinity of hemoglobin that corresponded microscopically with increased extramedullary hematopoiesis in the spleen.

Tumor analysis showed no GBT440-related neoplastic findings.

5.5.4. Reproductive and Developmental Toxicology

Fertility and Early Embryonic Development

Study title / number: An Oral Fertility and Early Embryonic Development to Implantation of Voxelotor in Rats / PRC-16-003-R

Key Study Findings

- HD males presented clinical signs of sparse hair coat and excessive salivation, reduced body weight gain at the initiation of dose administration, increased reproductive organ weights and adverse findings in sperm motility and morphology. HD females presented reduced body weights during the precohabitation and at the initiation of the gestation period.
- Although sperm motility was decreased and changes in sperm morphology occurred at 250 mg/kg/day (approximately 5 times the exposure in whole blood at the recommended human dose of 1500 mg/day), there were no functional effects on male or female fertility. The whole-blood TK data from the 4-week toxicology study in non-pregnant rats (Study PRC-14-051-R) were used for the animal-to-human exposure comparison
- No voxelotor-related effects occurred on estrous cycling or effects on mating and fertility in the males or females, or early embryonic survival in the fetuses.

Conducting laboratory and location	(b) (4)
GLP compliance:	Yes

Methods

Dose and frequency of dosing:	0, 15, 50 or 250 mg/kg/day Dose levels were selected based on the results of a one-month toxicity study in rats and an embryo-fetal range-finding study in the rat. Males: 28 days before cohabitation, during cohabitation and continuing through the day before euthanasia (62 doses) Females: 14 days before cohabitation, during cohabitation and continuing until day 7 of presumed gestation (DG 7)
Route of administration:	Oral
Formulation/Vehicle:	0.5% (w/w) Methocel E50 in reverse osmosis water containing 0.01% (w/w) polysorbate 80 and 10 mM phosphate buffer (pH 7 ± 0.2)
Species/Strain:	Sprague Dawley rats

Number/Sex/Group:	22/sex/group
Satellite groups:	None
Study design:	Standard ICH S5(R2)
Deviation from study protocol affecting interpretation of results:	No

Observations and Results

Parameters	**Major findings**
Mortality	One HD male found dead on dosing day 48
Clinical Signs	Males: HD statistically significant ↑of males with sparse hair coat on the head or limb(s) and ↑ total number of males observed with sparse hair coat [262 observations/12 males**], and ↑ number of males with excess salivation [16/7**] compared to control males.
Body Weight gain	Males: HD Days 1-8 ↓21.3%*; Days 1-65 ↓7.0% Females Precohabitation: HD: Days 1-8 ↓37.4%; Days 8-15 ↓9.5%; Days 1-15 ↓24.4% Gestation: HD: GD 0-5 ↓20.1%*; GD 0-13 ↓4.5%
Necropsy findings	**Table 23: Voxelotor-related Necropsy and Sperm Findings in Rats**
Estrous Cycle/Mating/Fertility Index	No effects
Ovarian and Uterine Examinations and Litter Observations	No effects

Observation	Males HD	Females HD
Macroscopic	↑ incidence large spleen 7/20* indicative of increased hematopoiesis Kidney: 2/20 extreme dilation 1/20 large	None
Organ weight ratios	↑10%** left testis; ↑8.8%* right testis; ↑12.6%* prostate; ↓9.5%* seminal vesicle w/ fluid LD: ↑13.4%* prostate; ↓10%* seminal vesicle w/ fluid	ND
Sperm Motility	↓12.1%* percent motility	NA
Sperm Morphology	↓12.6%** normal; ↑186%** abnormal; ↑108%** detached head; ↑286%** no head; ↑957%** broken flagellum	NA

* p≤0.05; ** p≤0.01 compared to Control values;
↑↓= % increase/decrease compared to control group

LD: low dose; MD: mid dose; HD: high dose; ND: not determined; NA: not applicable

Embryo-Fetal Development

Study title / number: An Oral Embryo-Fetal Development Study of Voxelotor in Rats / PRC-16-001-R

Key Study Findings

- Maternal toxicity was limited to reduced body weight gain and food consumption during the dosing phase GD 7-18 at 250 mg/kg/day.
- No voxelotor-related adverse embryofetal effects were noted.
- The exposure (AUC) at the dose of 250 mg/kg/day is approximately 2.8 times the exposure in whole blood at the recommended human dose of 1500 mg/day.

Conducting laboratory and location:	(b) (4)
GLP compliance:	Yes

Methods

Dose and frequency of dosing:	0, 15, 50 or 250 mg/kg/day Dose levels based on the results of a one-month toxicity study in rats and an embryo-fetal range-finding study in rat. Once daily GD 7-17
Route of administration:	Oral
Formulation/Vehicle:	0.5% (w/w) Methocel E50 in reverse osmosis water containing 0.01% (w/w) polysorbate 80 and 10 mM phosphate buffer (pH 7 ± 0.2)
Species/Strain:	Sprague Dawley rats
Number/Sex/Group:	20 mated females/group
Satellite groups:	TK: 3 mated females in control; 6 pre-mated females/group
Study design:	Standard ICH S5(R2). Laparohysterectomy on GD 21.
Deviation from study protocol affecting interpretation of results:	No

Observations and Results

Parameters	**Major findings**
Mortality	None
Clinical Signs	None
Body Weight gain	HD: GD 7-10 ↓99.4%**; GD 7-18 ↓14.6%*; GD 7-21 ↓4%
Food Consumption	HD: GD 7-10 ↓31.6%
Necropsy findings Cesarean Section Data	None None. Gravid uterine weights were not reported.
Necropsy findings	Similar mean fetal body weights among groups

Fetus	No fetal gross external, soft tissue or skeletal alterations (malformations or variations) Fetal ossification sites: No effects

LD: low dose; MD: mid dose; HD: high dose; * p≤0.05; ** p≤0.01 compared to Control values; ↑↓= % increase/decrease compared to control group

Study title / number: An Oral Embryo-Fetal Development Study of Voxelotor in Rabbits / PRC-16-002-R

Key Study Findings

- Maternal toxicity was limited to reduced body weight gain and food consumption during the dosing phase GD 7-20 at ≥75 mg/kg/day.
- No voxelotor-related adverse embryofetal effects were noted.
- The exposure (AUC) at the dose of 150 mg/kg/day is approximately 0.3 times the exposure in whole blood at the recommended human dose of 1500 mg/day.

Conducting laboratory and location:	(b) (4)
GLP compliance:	Yes

Methods

Dose and frequency of dosing:	0, 25, 75 or 150 mg/kg/day Dose levels based on the results of an embryo-fetal range-finding study and a toxicokinetic study in rabbits. Once daily GD 7-19
Route of administration:	Oral
Formulation/Vehicle:	0.5% (w/w) Methocel E50 in reverse osmosis water containing 0.01% (w/w) polysorbate 80 and 10 mM phosphate buffer (pH 7 ± 0.2)
Species/Strain:	New Zealand White rabbits
Number/Sex/Group:	20 mated females/group
Satellite groups:	TK: 2 mated females in control; 3 pre-mated females/group
Study design:	Standard ICH S5(R2). Laparohysterectomy on GD 29.
Deviation from study protocol affecting interpretation of results:	No

Observations and Results

Parameters	Major findings
Mortality	None
Clinical Signs	None

Body Weight gain	Dosing Phase (GD 7-20): LD ↓9.8%; MD ↓25.2%*; HD ↓28.3%*. Study Period (GD 7-29): MD ↓8.9%; HD ↓10.9%.
Food Consumption	Dosing Phase (GD 7-20): MD ↓9.2%; HD ↓9.6%. Statistically significant reductions during several intervals
Necropsy findings Cesarean Section Data	

* p≤0.05; ** p≤0.01 compared to Control values; ↑↓= % increase/decrease compared to control group

A statistically significant lower percent of live male fetuses occurred at the HD; however, the number of live fetuses was similar among the groups. Gravid uterine weights were not reported.

Table 24: Voxelotor-related Effects on Laparohysterectomy Evaluations in the Rabbit

Dose (mg/kg/day)	**0**	**25**	**75**	**150**
Number of females tested	20	20	20	20
Number of females pregnant	19	20	19	20
Number of surviving pregnant females	19	20	19	19
Dams with any resorptions N (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Mean corpora lutea	9.9	9.4	10.2	9.2
Mean no. of implantations	9.7	9.1	10.2	9.2
Mean pre-implantation loss	2.51	2.96	1.77	3.15
Mean percent post-implantation loss	2.37	1.46	2.57	1.99
Mean early / late resorptions	0.2 / 0.1	0.1 / 0.1	0.1 / 0.2	0.1 / 0.2
Total number of live fetuses	179	179	188	171
Mean Percent live fetuses	9.4	9.0	9.9	9.0
Mean Percent live male fetuses	53.5	49.6	48.6	40.0*
Fetal weight (Mean g ± SD) Combined Males + Females	41.6 (4.46)	42.7 (5.56)	42.3 (4.10)	42.9 (4.45)
Summary of Gravid Uterine Weight and Adjusted Body Weight/Body Weight Change Values				
Mean gravid uterine weight (g)				
Mean final body weight (g)				
Mean adjusted final body weight (g)				
Mean adjusted weight change from Day 0				

Percent Pre-implantation loss = [(# corpora lutea - # implantations) / # corpora lutea] x 100
Percent Post-implantation loss = [(# implantations - # live fetuses) / # implantations] x 100
* Significantly different from control (p<0.05)
** Significantly different from control (p<0.01)

Necropsy findings Fetus	Similar mean fetal body weights among groups No fetal gross external, soft tissue or skeletal alterations (malformations or variations) Fetal ossification sites: no effects

LD: low dose; MD: mid dose; HD: high dose; * p≤0.05; ** p≤0.01 compared to Control values

Prenatal and Postnatal Development

Study title / number: GBT440 Oral Gavage Study for Effects on Pre- and Post-Natal Development, Including Maternal Function, in Rats / PRC-17-005

Key Study Findings

- Voxelotor-related effects in F0 dams occurred at HD including lower body weight gain during gestation, lower food consumption during gestation and lactation, and increased mean postimplantation loss. Effects in offspring at the HD included lower Day 4 viability index and adverse lower body weight of pups during Lactation Day 0-21. An increased number of stillborn pups occurred at all doses but was not dose-dependent.
- Voxelotor-related effects in F1 offspring included lower body weights through the maturation phase to Post-Pairing Day 55 (males) and Maturation Day 7 (females). Effects on the reproductive performance in F1 males included lower fecundity and fertility indexes in MD and HD, and in F1 females, lower fertility index, lower number of corpora lutea, lower number of implantations and lower number of live fetuses also in the MD and HD.
- Toxicokinetic analysis was not performed; therefore, the exposure in whole blood from the EFD study in rats (Study PRC-16-001-R) was used to estimate animal-to-human exposure ratios. Voxelotor effects in the offspring were observed at the maternal dose of 250 mg/kg/day with an exposure in whole blood (AUC=20200 µg/mL*h) of approximately 2.8 times the exposure in while blood at the recommended human dose of 1500 mg/day.

Conducting laboratory and location:	(b) (4)
GLP compliance:	Yes

Methods

Dose and frequency of dosing:	0, 15, 50 or 250 mg/kg/day F0 dams: GD 6 – LD 20 Dose levels based on the results of the dose-range finding study in pregnant rats (PRC-018-R), the embryo-fetal toxicity study in rats (PRC-16-001-R), and the 28-day and 13-week toxicity studies in rats (PRC-14-051-R, PRC-15-019-R, respectively).
Route of administration:	Oral
Formulation/Vehicle:	0.5% (w/w) Methocel E50 in reverse osmosis water containing 0.01% (w/w) polysorbate 80 and 10 mM phosphate buffer (pH 7 ± 0.2)
Species/Strain:	Sprague-Dawley (SD) rat
Number/Sex/Group:	F0 dams, 24 mated females/group

	21-23 undosed naïve females for second breeding
Satellite groups:	F0 dams: 3/group for TK
Study design:	Standard ICH S5(R2).
Deviation from study protocol affecting interpretation of results:	No

Observations and Results

Generation	Major Findings
F0 Dams	Mortality: 2 dams attributed to gavage error; one LD dam removed from the study on Lactation Day 0 due to total litter death; macroscopic observations included dark red, tan, semi-firm, granular stomach contents. One HD dam was found dead on Lactation Day 0; dam had three remaining pups in utero, but no other remarkable findings observed. Clinical observations Gestation: None Lactation: voxelotor-related but not adverse red discoloration after dosing HD dams on Lactation Day 3. Observation was resolved before afternoon room check. Body weight gain Gestation: HD: GD 6-20: ↓17.1%* Lactation: No effects Food consumption Gestation: HD: GD 6-10 up to ↓22.4%* Lactation: HD: Lactation Day 7-21 up to ↓13.0%* Milk drug concentrations Voxelotor concentrations in milk increased with increasing dosing concentrations. Natural Delivery Data and Litter Data Summary – F0 Generation Voxelotor-related findings included an increased number of stillborn pups at all doses. The calculated increased mean postimplantation loss was not considered voxelotor-related as the mean number of implantations and the mean number of live fetuses were similar among all groups and within the historical data range.

Table 25: Voxelotor-related Effects on F0 Generation and Pup Survival

Dose (mg/kg/day)	0	15	50	250
Number of females tested	24	24	24	24
Number of females pregnant / delivering	23 / 24	24 / 24	24 / 24	23 / 24
Duration of Gestation (mean days)	22.9	22.9	23.0	23.3
Females with Liveborn pups	23	24	24	23
Females with Stillborn pups	2	7	7	5
Number of Pups delivered (mean)	276 (12.0)	280 (11.7)	294 (12.3)	268 (11.7)
Pups Liveborn (mean)	274 (11.9)	269 (11.2)	286 (11.9)	253 (11.0)
Pups Stillborn (mean)	2 (0.09)	11 (0.46)	8 (0.33)	15 (0.65)
Implantation sites (mean)	287 (12.5)	295 (12.3)	311 (13.0)	304 (12.7)
Mean Postimplantation loss	0.57	1.08	1.04	1.61 (13.5)

	(mean percent)	(4.5)	(8.3)	(8.0)	

Percent Post-implantation loss = [(# implantations - # live fetuses) / # implantations] x 100

Necropsy of Voxelotor-dosed dams
No voxelotor-related macroscopic observations

F1 Generation

Voxelotor-related finding in F1 included lower viability index on Lactation Day 4 at the HD. Although the Lactation Day 4 viability index was also statistically significant at the LD and MD, the mean values fall within the historical range.

Table 26: Voxelotor-related Effects on F1 Pup Survival

Dose (mg/kg/day)	0	15	50	250
Mean Livebirth index	99	96	97	95
Day 4 Mean Viability index	100	94**	97***	89***
Culled Day 4	90	77	85	58
Dead pup	0	5	8	15
Missing	0	3	3	13
Cannibalized	0	8	0	1
Number pups surviving at 21 days	176	176	191	162
Entire Litter Dead pup, pup moribund/killed/sacrifice, other (Days 0-4)	0	1	0	1

** p≤0.01; *** p≤0.001

Pup observations

- No clinical observations
- Voxelotor-related, significant and adverse lower body weight compared to controls from Lactation Day 0 through Lactation Day 21 in pups whose dams were exposed to HD.
- Landmark data: dose independent and transient delay in the days to pass hair growth for all pups whose dams were exposed to voxelotor.
- Necropsy of culled pups: no voxelotor-related macroscopic observations

F1 Offspring Maturation
Mortality: Two F1 male (MD dams) were found dead on Lactation Day 27 and Pairing Day 14, respectively; no macroscopic observations noted at necropsy.
Clinical observations: no voxelotor-related observations
Body weights: The lower body weights observed during lactation for pups whose dams were exposed to HD continued through the maturation phase to Post-Pairing Day 55 (males) and Maturation Day 7 (females). No effect on body weight gains or food consumption.
Neurobehavioral data
Locomotor activity and Acoustic startle: No voxelotor-related effect on F1
Morris Water maze: F1 females (HD dams) had decreased swing speed (↓11%) in the probe and spatial Day 3 and 4 trials. Changes did not correspond to decreases in locomotor activity.
Reproductive performance and indices
Estrous cycle: No voxelotor-related effects on mean estrous cycles or the number of estrous cycles

Table 27: Voxelotor-related Effects on F1 Males Reproductive Performance

(Excerpted from Submission)

Treatment Group	Control	15 mg/kg	50 mg/kg	250 mg/kg
Total males	22	23	24	21
Unscheduled Deaths Prior to Cohabitation	0	0	1	0
Males Cohabitated	22	23	23	21
Unscheduled Deaths During Cohabitation	0	0	1	0
Males mating with at least 1 female	19	20	18	16
Males impregnating at least 1 female	19	19	17	15
Mating Index (%)	86	87	78	76
Fecundity Index (%)	100	95	94	94
Fertility Index (%)	86	83	74	71

Mating index % = (Number of males mating with at least 1 female / Number of males cohabitated with at least 1 female) x 100
Fecundity index % = (Number of males impregnating at least 1 female / Number of males mating with at least 1 female) x 100
Fertility Index % = (Number of males impregnating at least 1 female / Number of males cohabitated with at least 1 female) x 100

Table 28: Voxelotor-related Effects on F1 Females Reproductive Performance

(Excerpted from Submission)

Treatment Group	Control	15 mg/kg	50 mg/kg	250 mg/kg
Total Females	22	22	24	22
Unscheduled Deaths Prior to Cohabitation	0	0	0	0
Females Cohabited	22	22	24	22
Unscheduled Deaths During Cohabitation	0	0	0	0
Females Mated	21	21	21	20
Pregnant Females	21	20	20	18
Non Pregnant Females	1	2	4	4
Mating Index %	95	95	88	91
Fecundity Index %	100	95	95	90
Fertility Index %	95	91	83	82

Mating index % = Mated females/females cohabited (excluding females sacrificed during Cohabitation) x 100
Fecundity Index % = Pregnant females/mated females (excluding females with an undetermined pregnancy status) x 100
Fertility Index % = Pregnant females/females cohabited (excluding females sacrificed during Cohabitation or with an undetermined pregnancy status) x 100

F1 Males performance: ↓number of males (born from MD and HD dams) impregnating at least 1 female (17/24 and 15/21, respectively), resulting in lower fecundity and fertility indexes.
F1 Females performance: ↑number of females (born from MD and HD dams) that did not get pregnant (4/24 and 4/22, respectively), resulting in lower fertility index.

F1 Gestation
No voxelotor-related clinical signs, body weight gains, or food consumption noted.
No voxelotor-related macroscopic observations at necropsy or Laparohysterectomy of F1 rats.

Table 29: Voxelotor-related Effects on Laparohysterectomy Evaluations of F1 Generation

Dose (mg/kg/day) administered to parents	0	15	50	250
Number of females tested	22	22	24	22
Number of females pregnant	21	20	20	18
Dams with any resorptions N	1	1	1	1
Mean corpora lutea	17	18	16	15**
Mean no. of implantations	17	17	15*	14**
Mean pre-implantation loss (%)	1 (3.5)	1 (3.5)	1 (5.0)	2 (11.2)
Mean post-implantation loss (%)	1 (5.4)	1 (5.6)	1 (5.7)	2 (6.1)
Mean number live fetuses	16	16	14*	13**

The number of corpora lutea for F1 females (HD dams) was lower than controls, as were the number of implantations noted for F1 females (MD and HD dams), which occurred in a dose-responsive manner. Those values were near or above the upper limit of the historical control data. Gravid uterine weights were not reported.

Second F1 Male Mating to Undosed Naïve Females
To understand if these findings were voxelotor-related, F1 males were mated a second time with naïve females. No effects on male reproductive indexes or on naïve female Laparohysterectomy evaluations were observed.

5.5.5. Other Toxicology Studies

Study title / number: An Oral Dose Range-Finding Juvenile Toxicity Study of GBT440 in Rats / PRC-15-019-R

In a GLP-compliant, voxelotor was orally administered to juvenile Crl:CD(SD) Sprague-Dawley rats from Postnatal Day (PND) 7 through 35 at doses of 0, 5, 15, 50 or 350 mg/kg/day. There was an increased number of pups at the HD with suspected dehydration between PND 10 and 24. The mean body weight gain was slightly lower at different intervals during the study period (PND 7 to 35) in males at ≥15 mg/kg/day and in females at ≥50 mg/kg/day compared to controls. Total body weight gain for the study period was lower ↓10% in 50 mg/kg/day males, ↓21% in 250 mg/kg/day males, and ↓13% in HD females. Juvenile rats at the HD presented with voxelotor-related increases in red cell mass (RBC count, hemoglobin and hematocrit), reticulocyte counts and red cell distribution width, ALT, and spleen weigh (↑40-50%), and decreases in triglycerides. Juvenile males presented with increased organ-to-bodyweight ratios, heart (↑24%), lung (↑13%), and liver (↑15%) at the HD. Juvenile females presented increased heart (↑18%) at the MD and HD, and increased (↑16%) liver at the HD. No histopathology evaluations were conducted. There are no new findings in this study that were not detected previously in other studies.

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Primary Reviewer

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Team Leader (Acting)

6 Clinical Pharmacology

6.1. Executive Summary

Voxelotor inhibits the polymerization of sickle cell hemoglobin and increases hemoglobin affinity to oxygen. The proposed indication for voxelotor is the treatment of adult (b) (4) patients with sickle cell disease (SCD). The proposed dosing regimen is 1500 mg orally once daily with or without food.

The clinical pharmacology section of the NDA is supported by analyses of single and repeat dose pharmacokinetics (PK) of voxelotor in healthy subjects and SCD patients, effect of food on voxelotor PK, population PK, exposure-response relationships for efficacy and safety; a thorough QT/QTc interval prolongation study; mass balance study; effect of renal and hepatic impairment on voxelotor PK; relative bioavailability to bridge formulations during development; and drug-drug interactions (DDI) based on in vivo studies, in vitro studies, and physiologically-based PK (PBPK) modeling.

In a randomized, double-blind, placebo-controlled, multi-center trial, 274 patients were randomized to receive 1500 mg daily (n=90), 900 mg daily (n=92), or placebo (n=92). Efficacy was based on Hb response rate defined as the proportion of patients with Hb increase of > 1 g/dL from baseline to Week 24. The response rate for voxelotor 1500 mg was 51.1% (46/90) and 900 mg was 32.6% (30/92) compared to 6.5% (6/92) in the placebo group ($p < 0.0001$).

Exposure-efficacy analyses identified a positive and a statistically significant relationship between voxelotor exposure in whole blood and hemoglobin response (change from baseline, CFB). Exposure-safety analyses identified a positive relationship between Grade ≥ 1 ALT elevation and voxelotor plasma exposure; additionally, a relationship was identified for decreased white blood cell count (WBC) and diarrhea. Collectively, exposure-response analyses supported the proposed 1500 mg dose.

The key review questions focused on dose recommendations for patients with severe hepatic impairment, exposure in HbSC genotype, and drug-drug interactions based on coadministration of CYP3A4 modulators.

In subjects with severe hepatic impairment, voxelotor whole blood and plasma AUC increased by 90% compared to subjects with normal hepatic function. A dose reduction to 1000 mg daily is recommended in patients with severe hepatic impairment.

Patients with the HbSC genotype had a 50% higher whole blood AUC and 45% higher C_{max} compared to HbSS or HbSβ^0 at steady-state. No dose adjustment is recommended for patients with HbSC genotype.

CYP3A4 exhibits the most significant contribution to the metabolism of voxelotor (36% to 56%). A PBPK model based on detailed in vitro metabolism and ADME studies was utilized to predict the effect of CYP3A4 modulation on the PK of voxelotor. Concomitant administration of drugs that are strong CYP3A4 inhibitors is predicted to increase voxelotor by 40% to 80%. Concomitant administration of fluconazole (a moderate CYP3A/CYP2C9 and strong CYP2C19 inhibitor) is predicted to increase voxelotor by 73% to 100%; of note, fluconazole inhibits other enzymes that play a marginal role in the metabolism of voxelotor. Concomitant administration of strong CYP3A4 inhibitors or fluconazole should be avoided. If unavoidable, a dose reduction to 1000 mg daily is recommended for patients receiving concomitant medications that are strong inhibitors of CYP3A4 or fluconazole.

Concomitant medications that are strong or moderate inducers of CYP3A4 are predicted to decrease voxelotor exposure by 50 to 73%. Concomitant administration of strong or moderate CYP3A4 inducers should be avoided. If unavoidable, the recommended dose for patients receiving concomitant strong or moderate inducers of CYP3A4 is 2500 mg daily.

Recommendations

The proposed dosing regimen of 1500 mg once daily in adult (b) (4) patients with sickle cell disease is acceptable. From a clinical pharmacology standpoint, the NDA is approvable provided the Applicant and the FDA reach an agreement regarding the labeling language. There are no postmarketing requirements or commitments.

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	The evidence of effectiveness was obtained from the randomized trial GBT440-031 and supportive evidence was obtained from trials GBT440-007 and GBT440-001.
General dosing instructions	The recommended dosage is 1500 mg once daily taken orally without regard to food intake.
Dosing in patient subgroups (intrinsic and extrinsic factors)	• Patients with severe hepatic impairment should receive a daily dose of 1000 mg. • The co-administration of medications that are strong inhibitors of CYP3A4 or fluconazole (a moderate inhibitor of CYP3A4 and other CYP450 enzymes that are involved in voxelotor metabolism) should be avoided. If the

	concomitant administration of these medications is unavoidable, a voxelotor dose of 1000 mg daily should be administered. • The co-administration of medications that are strong or moderate inducers of CYP3A4 should be avoided. If the concomitant administration of these medications is unavoidable, a voxelotor dose of 2500 mg daily should be administered. • No dose adjustment is required based on other intrinsic or extrinsic factors.
Labeling	Labeling recommendations are summarized as follows: • The recommended voxelotor dose is 1500 mg daily taken orally without regard to food intake • The coadministration of voxelotor should avoided with medications that are known to be strong inhibitors of CYP3A4. If the coadministration of these drug is unavoidable, reduce voxelotor dose to 1000 mg daily. • The coadministration of voxelotor should be avoided with medications that are known to be strong or moderate inducers of CYP3A4. If the coadministration of these drugs is unavoidable, increase voxelotor dose to 2500 mg daily. • Patients with severe hepatic impairment should receive a reduced voxelotor dose of 1000 mg daily.
Bridge between the to-be-marketed and clinical trial formulations	During the development program, capsule formulations as well as tablet formulations were used. Relative bioavailability studies provided adequate PK bridging between those formulations and the to-be-marketed formulation.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Mechanism of Action: voxelotor is an HbS polymerization inhibitor.

Absorption: The median plasma T_{max} of voxelotor is 2 hours. T_{max} in whole blood and red blood cells (RBCs) was observed to occur between 6 and 18 hours following administration. Food increases whole blood AUC and C_{max} by approximately 45%.

Distribution: The apparent volume of distribution of voxelotor is approximately 410 L. The plasma protein binding of voxelotor is 99.8%. The blood-to-plasma ratio in patients with sickle cell disease is 15.

Elimination: The terminal half-life of voxelotor is approximately 36 hours. The voxelotor clearance in plasma in patients with SCD is 6.7 L/h.

Metabolism: Voxelotor is extensively metabolized by multiple CYP450, UGT, and SULT enzymes. A substantial fraction of voxelotor is metabolized via CYP3A4 (36% to 56%). The fraction metabolized by any individual CYP enzyme is less than 10%.

Excretion: Approximately 63% of the voxelotor dose is excreted in feces, with 33% as unchanged voxelotor, whereas the fraction of the dose excreted in urine is approximately 35%, with only 0.08% as unchanged voxelotor.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The recommended voxelotor dose is 1500 mg taken orally once daily with or without food.

Therapeutic Individualization

Patients with severe hepatic impairment should receive a reduced dose of 1000 mg once daily.

Patients should avoid concomitant medications that are strong inhibitors of CYP3A4 or fluconazole (a moderate inhibitor of CYP3A4, a moderate inhibitor of CYP2C9, and a strong inhibitor of CYP2C19). If unavoidable, patients should receive a reduced voxelotor dose of 1000 mg once daily.

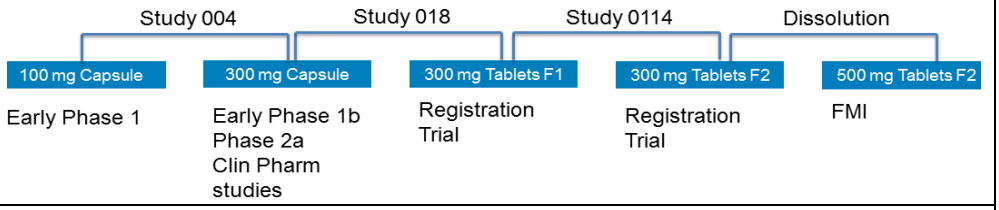
Patients should avoid concomitant medications that are strong or moderate inducers of CYP3A4. If unavoidable, patients should receive an increased voxelotor dose of 2500 mg once daily.

Outstanding Issues

None.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

PHARMACOLOGY	
Mechanism of Action	Voxelotor inhibits the polymerization of sickle cell hemoglobin, increases hemoglobin affinity to oxygen, and improves RBC deformability, thereby decreasing hemolysis.
Active Moiety	Voxelotor
QT Prolongation	In a TQT study, voxelotor did not prolong the QT interval to any clinically relevant extent at plasma concentrations approximately 1.7-fold above the therapeutic concentrations.
GENERAL INFORMATION	
Molecular Weight	337.4 g/mol
Formulation Development	A powder-in-capsule formulation (100 mg strength) was used in a healthy volunteer dose escalation study (GBT440-001). To allow for higher drug loading, common blend capsules (300 mg strength) were used in Phase I clinical studies and in the Phase 2a clinical GBT440-007 in adolescents with SCD. The voxelotor tablet formulations F1 and F2 (300 mg strength) were developed for the registration trial GBT440-031. A 500-mg F2 tablet formulation is developed for commercialization. The formulation bridging studies are highlighted in the schematic below. The GMR of the PK parameters along with the 90% CI intervals in studies GBT440-004, GBT440-018, and GBT440-0114 were within the standard BE criteria. 
Bioanalysis	Voxelotor was measured in plasma or whole blood using validated LC/MS/MS methods. A summary of the method validation is included in Appendix 19.5.1. *Summary of Bioanalytical Method Validation and Performance.*
Dose Proportionality	The PK of voxelotor exhibited a dose-proportional increase in the AUC and C_{max} in whole blood and plasma after single doses, ranging from 100 mg to 2800 mg in healthy volunteers. In SCD patients, voxelotor PK was dose-proportional in the dose range of 500 mg to 1500 mg.
Accumulation	The steady-state concentration of voxelotor in plasma and whole blood were reached by day 8 in SCD patients. The accumulation ratio of $AUC_{0\text{-}24h}$ at steady-state was approximately 3-fold.
Variability	The %CV for AUC and C_{max} of voxelotor in whole blood were below 28% in SCD patients; however, the %CV for AUC and C_{max} were slightly higher in plasma (approximately 35%).

Genotype	Steady-state whole blood AUC and C_{max} were 50% and 45% higher in HbSC genotype patients compared to HbSS or HbSβ^0 genotype patients; similarly, steady-state plasma AUC and C_{max} were 23% and 15% higher in HbSC genotype patients compared to HbSS or HbSβ^0 genotype patients.
ABSORPTION	
Absolute Bioavailability	The absolute bioavailability of voxelotor has not been characterized.
T_{max}	In patients with SCD, the median voxelotor plasma T_{max} was around 2 hours. T_{max} in whole blood was observed between 6 and 18 hours post-dose.
Food Effect	A high-fat and high-calorie meal increased voxelotor AUC (42%) and C_{max} (45%) in whole blood relative to the AUC and C_{max} in the fasted state. Similarly, AUC increased by 43% and C_{max} increased by 95% in plasma.
Acid Reducing Agents	The concomitant administration of omeprazole (a proton pump inhibitor) in Study GBT440-019 did not affect the bioavailability of voxelotor at a 900 mg dose compared to voxelotor alone. Voxelotor AUC and C_{max} increased by 15% and 9%, respectively, with concomitant administration with omeprazole compared to voxelotor alone.
Substrate Transporter Systems	Voxelotor is not a substrate of P-gp or BCRP in vitro.
DISTRIBUTION	
Volume of Distribution	The voxelotor apparent volume of distribution in the central compartment and the peripheral compartment are 338 L and 72 L, respectively.
Plasma Protein Binding	Voxelotor was highly bound to plasma proteins (99.8%) in a dose-independent manner.
Blood-to-Plasma ratio	Voxelotor exhibits preferential distribution to red blood cells. The blood-to-plasma ratio in SCD patients is 15-17.
ELIMINATION	
Mean Terminal Half-Life	The terminal half-life of voxelotor in SCD patients is approximately 36 hours with concentrations in plasma, whole blood, and RBC declining in parallel.
METABOLISM	
Primary Metabolic Pathways	Voxelotor is metabolized by cytochrome P450 (CYP450), uridine 5'-diphospho-glucuronosyltransferase (UGT), and sulfotransferase (SULT) enzymes. Specifically, voxelotor is oxidized by various CYP450 isoenzymes and glucuronidated by various UGT isoenzymes. The major metabolite is formed by oxidation and subsequent sulfate conjugation, which could be mediated through several sulfotransferase enzymes. Voxelotor is the main moiety in plasma (48.8% of total radioactivity in the mass balance study)

	and whole blood (95%). The major metabolite accounted for 17% in plasma.
Transporter Substrate	In vitro, voxelotor is not a substrate of OATP1A2, OATP1B1, OATP1B3, or BSEP. Unchanged voxelotor accounted for < 1% in urine; therefore, transport via OAT1, OAT3, OCT2, MATE1 and MATE2K can be excluded.
EXCRETION	
Primary Excretion Pathway	In the mass balance study with a 400-mg dose of ^{14}C-voxelotor, 63% of radioactivity (33% unchanged voxelotor) was recovered in feces and 35% (0.08% unchanged voxelotor) was recovered in urine.
Interaction Liability (Drug as Perpetrator)	
Inhibition/ Induction of Metabolism	Enzyme Inhibition In a cocktail study (GBT440-003) with substrates of CYP1A2 (caffeine), CYP2C9 (warfarin), CYP2C19 (omeprazole), voxelotor did not alter the exposure of these substrates. However, the exposure of midazolam was increased by approximately 75%, indicating that voxelotor is an inhibitor of CYP3A4. Voxelotor did not alter the exposure of rosiglitazone (a CYP2C8 substrate) in study GBT440-008 or metoprolol (a CYP2D6 substrate) in study GBT440-017. Enzyme Induction Voxelotor did not cause concentration-dependent increases in mRNA levels of CYP1A2 or CYP3A4/5. However, an increase in mRNA expression of CYP2B6 activity (> 2-fold change) was observed, indicating that voxelotor may be an inducer of CYP2B6.
Inhibition/ Induction of Transporter	Transporter Inhibition Voxelotor did not inhibit P-gp to a clinically significant extent in study GBT-440-0116; AUC and C_{max} of digoxin (a P-gp substrate) increased by only 12% and 17%. Voxelotor did not inhibit BCRP, OATP1B1, OATP1B3, OCT2, OAT1, OAT3, MATE1, MATE2-K, and BSEP *in vitro.*

6.3.2. Clinical Pharmacology Questions

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes, the proposed 1500 mg dose taken once daily is appropriate for the general SCD patient population.

The applicant submitted data from the Phase 1 study GBT440-001 to support dose selection in patients with SCD (**Table 29**). Additionally, the registration trial GBT440-031 and the supportive

trial GBT440-007 conducted in patients with SCD investigated two dose levels (900 mg QD and 1500 mg) in addition to placebo.

Table 30: Summary of Voxelotor Clinical Trials

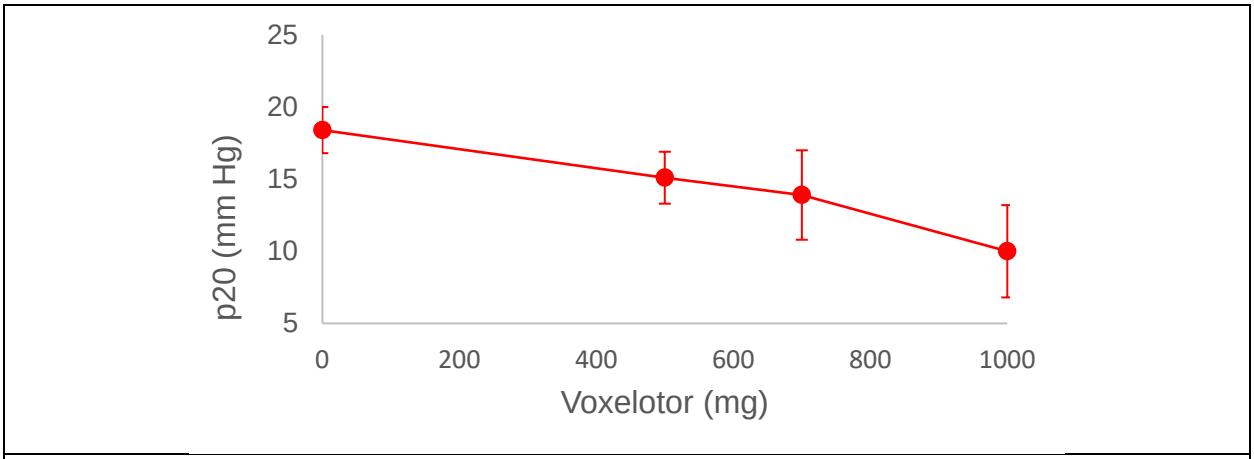
Study Identifier	Study Design	Dosage Regimen	Number of Subjects Enrolled / Treated	Subjects	Duration of Treatment
GBT440-001 Safety and tolerability; PK; food-effect	Phase 1, first-in-human, single and multiple ascending dose, placebo-controlled, double-blind	Part A: voxelotor capsule 100 mg to 2800 mg, or placebo; Single dose	Total: 40/40 Voxelotor: 30/30 Placebo: 10/10	Healthy subjects	Single dose
		Part B: voxelotor capsule 300, 600, or 900 mg, or placebo; QD	Total: 24/24 Voxelotor: 18/18 Placebo: 6/6	Healthy subjects	15 days
		Part A: voxelotor capsule 1000 mg or placebo; Single dose	Total: 8/8 Voxelotor: 6/6 Placebo: 2/2	Subjects with SCD	Single dose
		Part B: voxelotor capsule 500, 600, 700, or 1000 mg (500 mg twice daily), or placebo; QD (BID for 1000 group)	Total: 45/45 voxelotor 34/34 Placebo: 11/11	Subjects with SCD	28 days
		Part C: voxelotor capsule 700 or 900 mg, or placebo QD	Total: 16/16 Voxelotor 12/12 Placebo: 4/4	Subjects with SCD	90 to 118 days
GBT440-007 Part A: single dose PK and safety Part B: efficacy, PK, and safety Part C: efficacy and safety	Phase 2a, open- label, single- and multiple- dose	Part A: voxelotor capsule 600 mg Part B: voxelotor capsule 900 mg or 1500 mg QD Part C: voxelotor tablet 1500 mg QD	Part A: 13 (6 to < 18 years) Part B: 40 (12 to < 18 years) Part C: TBD (4 to < 18 years)	Pediatric subjects with SCD	Part A: single dose Part B: 24 weeks Part C: 48 weeks
GBT440-031 Long-term; efficacy and safety; population PK; PK/PD	Phase 3, double-blind, randomized, placebo-controlled	Voxelotor tablet 900 mg or 1500 mg, or placebo; QD	Overall: 274/271 900 mg: 92/92 1500 mg: 90/88 placebo: 92/91	Adults and adolescents with SCD	Up to 72 weeks

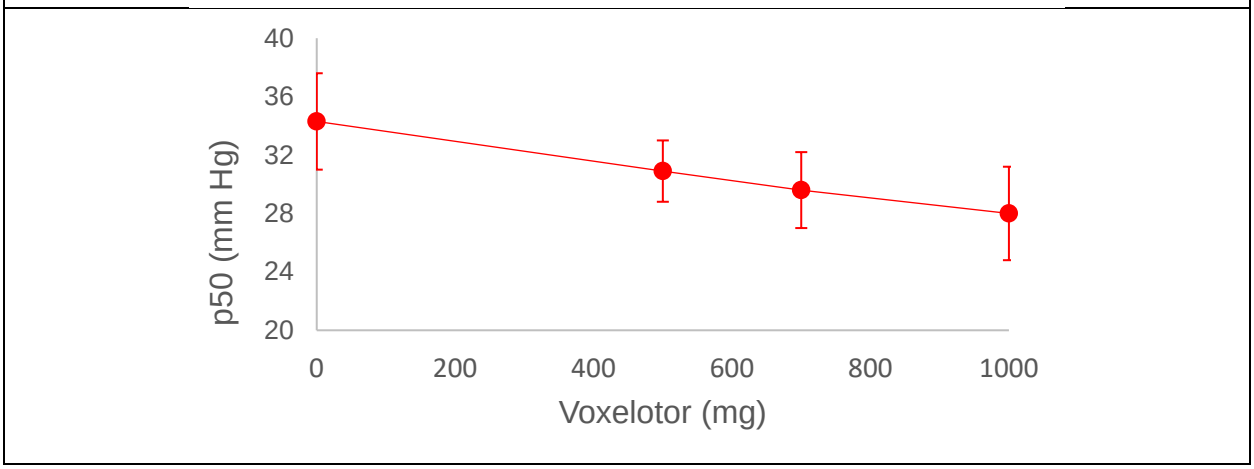
Trial GBT440-001

Part B of Trial GBT440-001 was a randomized, placebo-controlled, double-blind study of voxelotor in patients with SCD. Patients were randomized to receive 500 mg daily (n=10), 700 mg daily (n=12), or 500 mg twice daily (i.e. 1000 mg daily, n=6) dose of voxelotor for 28 days.

The pharmacodynamic endpoints in the study were oxygen partial pressure leading to 20% and 50% Hb saturation (p20 and p50) and percent modified hemoglobin (% Hb mod). Additionally, measures of hemolysis (change in bilirubin levels, LDH, and reticulocyte counts) were captured in the study.

There was a dose-dependent decrease in the p20 and p50 with increasing voxelotor doses as well as a dose-dependent increase in %Hb mod (**Figure 1**. Dose-Response Relationship of Voxelotor and Pharmacodynamic Markers. Higher voxelotor dose result in increased p20 (top panel), p50 (middle panel), and %Hb mod (bottom panel).**Figure 1**), which indicate a higher oxygen affinity with increasing voxelotor doses. Additionally, hemolysis markers decreased with increasing voxelotor doses.





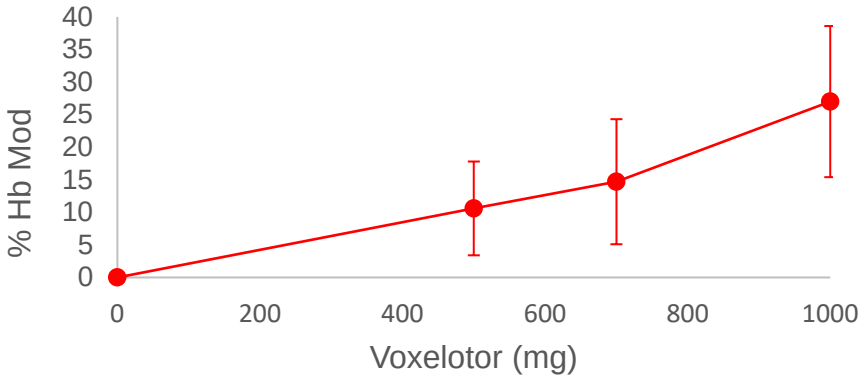


Figure 1. Dose-Response Relationship of Voxelotor and Pharmacodynamic Markers. Higher voxelotor dose result in increased p20 (top panel), p50 (middle panel), and %Hb mod (bottom panel).

The safety profile of voxelotor was characterized primarily by Grade 1 and 2 adverse events. The frequency and severity of adverse events was mainly comparable between all 3 treatment arms.

Based on the dose-dependent improvement in the pharmacodynamic markers, the applicant selected 900 mg dose for investigation in the registration trial GBT440-031 along with a higher dose level (1500 mg) to be investigated as safety lead-in phase.

Trial GBT440-031

Three cohorts receiving 3 dose levels were investigated in trial GBT440-031: 1500 mg once daily, 900 mg once daily, or placebo. The primary endpoint was the proportion of patients achieving change from baseline Hb (CFB) levels ≥ 1 g/dL. Refer to section 8 *Statistical and Clinical and Evaluation* for detailed discussion of study design.

There was a dose-dependent increase in the proportion of patients achieving CFB ≥ 1 g/dL, with 51.1% of the patients in the 1500 mg cohort achieving the primary endpoint compared to 32.6% in the 900 mg cohort and only 6.5% in the placebo arm.

The time course of Hb exhibited a mean CFB ≥ 1 g/dL that was sustained from week 2 through week 24 at the 1500 mg dose; the mean CFB was < 1 g/dL 900 mg cohort and the placebo cohort (**Figure 2**).

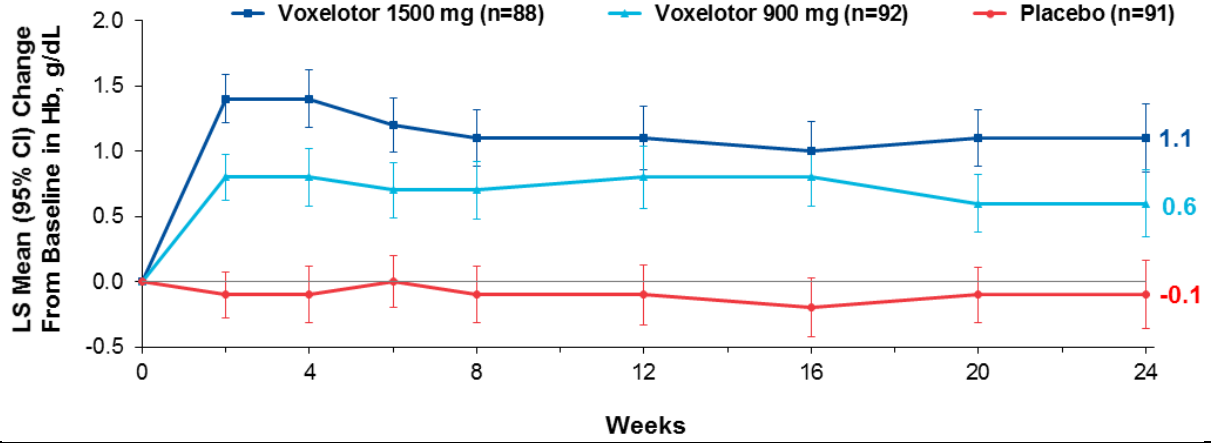


Figure 2. Time Course of Mean Hemoglobin Change from Baseline.

The frequency and severity of adverse events was comparable between the 900 mg and 1500 mg arms. Adverse events were mainly Grade 1 and Grade 2 and the rate of treatment discontinuation was low (less than 10%).

Does the clinical pharmacology program provide supportive evidence of effectiveness?

Yes, the clinical pharmacology program provides supportive evidence of effectiveness.

Exposure-Efficacy Analyses

The applicant submitted exposure-response analysis for the primary efficacy endpoint, change from baseline (CFB) Hb at Week 24. The analysis included 238 patients with SCD, including 204 adult patients from Trial GBT440-031 and 34 adolescent patients from Trial GBT440-007.

There was an increase in the CFB Hb with increasing whole blood concentrations (**Figure 3**). The CFB at the median exposure resulting from the 1500 mg dose (purple vertical line) exceeded the 1 g/dL threshold, whereas the CFB at the median exposure resulting from the 900 mg dose (green vertical line) did not (**Figure 3**). Similar trends were observed with CFB data from all visits analyzed as a function of exposure.

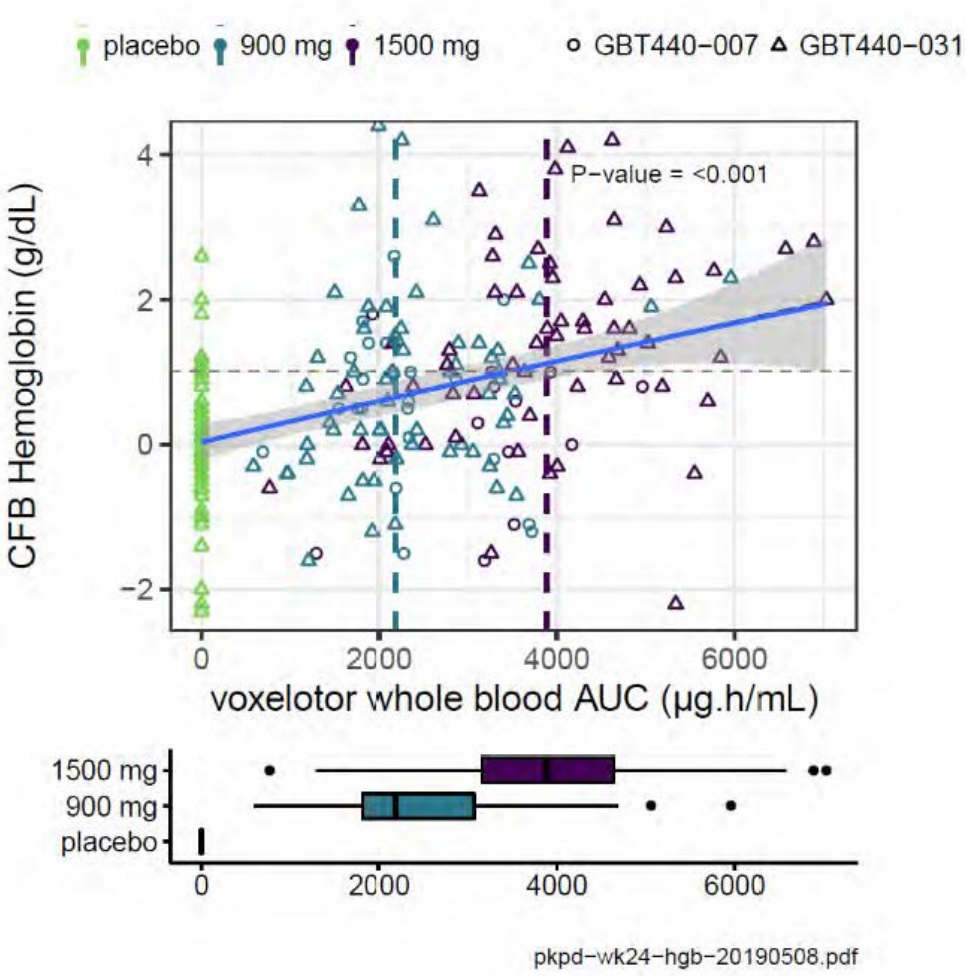
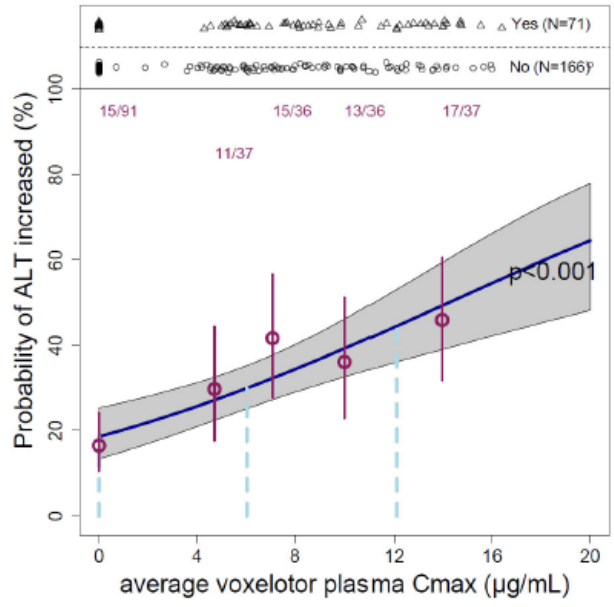


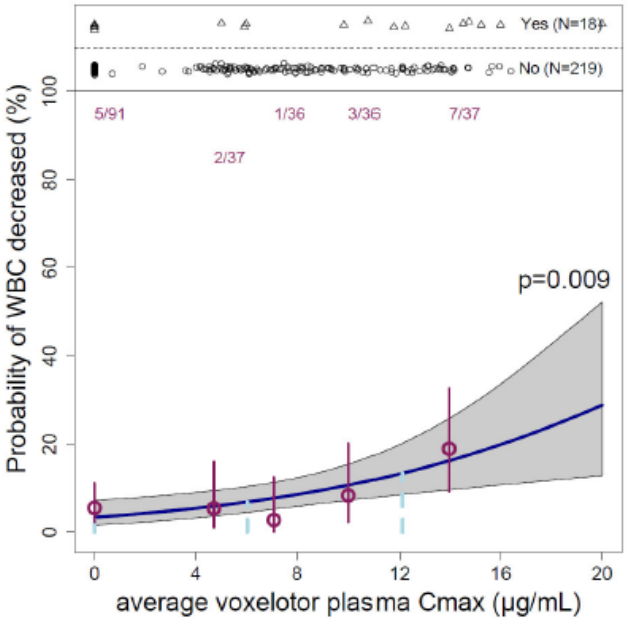
Figure 3: CFB hemoglobin at week 24 as a function of voxelotor whole blood concentrations. The green dotted vertical line represents median predicted AUC resulting from 900 mg QD dosage, whereas the purple vertical dotted line represents the median predicted AUC resulting from 1500 mg dosage.

Additionally, the relationships between measures of hemolysis (% reticulocytes, absolute reticulocyte counts, indirect bilirubin, and LDH) and time-matched whole blood concentrations were analyzed. There was a decrease in all clinical measures of hemolysis with increasing voxelotor exposure in whole blood. Details of the analysis are provided in section 19.5.3 *Exposure-Response Analysis*.

Exposure-Safety Analyses

The exposure-response analysis for safety included the relationship between voxelotor exposure in plasma and the incidence of the most frequent non-SCD-related Grade ≥ 1 adverse events: rash, arthralgia, headache, diarrhea, increased ALT, and decreased WBC. There was a flat relationship for rash and arthralgia. Logistic regression analysis identified a positive relationship for the probability of increased ALT and the probability of decreased WBC versus plasma Cmax and the probability of diarrhea versus AUC (**Figure 4**).





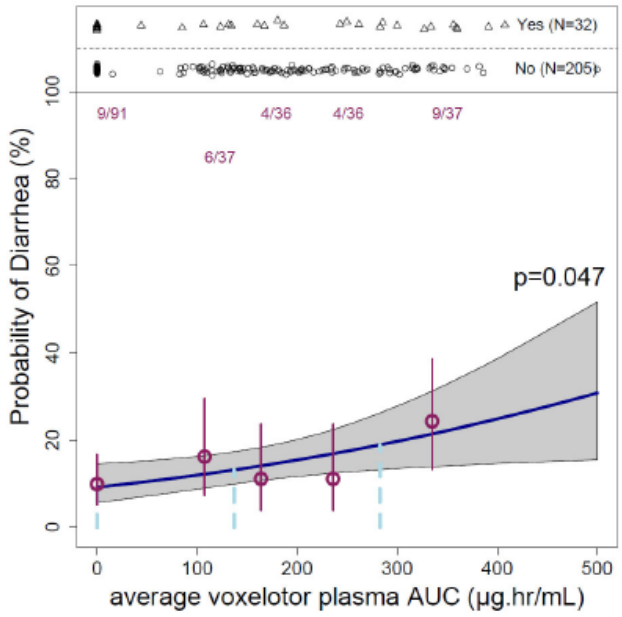


Figure 4. Exposure-Safety Relationship of Non-SCD-Related Grade ≥ 1 Adverse Events and Plasma Voxelotor Exposure. A positive relationship was identified between voxelotor Cmax in plasma and the probability of increased ALT (top panel) and the probability of decreased WBC (middle panel). Voxelotor AUC in plasma was positively correlated with the probability of diarrhea (bottom panel).

No relationship was identified between voxelotor exposure (in plasma, whole blood, or Hb occupancy) and any of the SCD-related Grade ≥2 adverse events: sickle-cell anemia with crisis, acute chest syndrome, vaso-occlusive crises or pneumonia. Details of the exposure-safety analyses are detailed in section 19.5.3 *Exposure-Response Analysis*.

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

Yes, patients with severe hepatic impairment should receive a reduced daily dose of 1000 mg. Other intrinsic factors (age [12 to 59 years], weight [28 to 135 kg], sex, mild to severe renal impairment [creatinine clearance 15-89 mL/min] and genotype) do not require an alternative dosage regimen, based on population PK analysis. Refer to section 19.5.2 Population PK Analysis for more details regarding intrinsic factors.

Hepatic Impairment

The applicant conducted study GBT440-0112 to characterize the pharmacokinetics of voxelotor in subjects with varying degrees of hepatic impairment. The study enrolled subjects with normal hepatic function (n=7) with similar to demographics to those with mild (Child-Pugh A, n=7), moderate (Child-Pugh B, n=7), and severe (Child-Pugh, n=7) hepatic impairment. Subjects with normal hepatic function as well as those with mild and moderate hepatic impairment

received a single voxelotor dose of 1500 mg, while subjects in the severe impairment cohort received a 600 mg dose.

The geometric mean ratio of the dose normalized PK parameters along with the 90% confidence interval for each hepatic impairment cohort relative to subjects with normal hepatic function are summarized in **Table 30**.

Table 31: GMR of Dose Normalized PK Parameters (90% CI) in Cohorts of Hepatic Impairment Relative to Subjects with Normal Function.

	Child Pugh A		Child Pugh B		Child Pugh C	
	AUC	**C_{max}**	**AUC**	**C_{max}**	**AUC**	**C_{max}**
Whole Blood	1.14 (0.92 - 1.42)	1.19 (0.92 - 1.53)	1.15 (0.91 - 1.46)	1.06 (0.8 - 1.4)	1.9 (1.54 - 2.36)	1.39 (1.08 - 1.79)
Plasma	1.09 (0.86 - 1.39)	1.18 (0.92 - 1.51)	1.18 (0.9 - 1.56)	1.51 (1.51 - 2)	1.93 (1.52 - 2.46)	1.45 (1.13 - 1.85)

Subjects with severe hepatic impairment exhibit a substantial increase in exposure (~90% increase) in whole blood as well as plasma compared to normal hepatic function. A dose reduction to 1000 mg daily is recommended to match exposure in subjects with normal hepatic function.

The proposed 1000 mg daily dose in subjects with severe impairment is likely to result in a 25% increase in exposure relative to subjects with normal hepatic function who receive a 1500 mg dose. Based on the favorable safety profile and the positive exposure-efficacy relationship, the proposed dose adjustment is acceptable.

No dose adjustment is necessary for patients with mild or moderate hepatic impairment. The plasma exposure, which is correlated with safety endpoints in the exposure-response analysis, exhibits a modest increase (~18%).

Renal Impairment

The Applicant conducted an abbreviated design renal impairment study (GBT440-0110) in subjects with severe renal impairment (eGFR < 30 mL/min/1.73 m^2) and subjects with normal renal function (eGFR ≥ 90 mL/min/1.73 m^2) because the route of voxelotor is mainly non-renal.

Subjects in each group received a single 900 mg dose of voxelotor. The GMR of whole blood $AUC_{0\text{-}24h}$ in subjects with renal impairment was 79.8% compared to subjects with normal function and 84% for C_{max}. The GMR of plasma $AUC_{0\text{-}24h}$ and C_{max} in subjects with severe renal impairment was 60% and 56%.

The decrease in voxelotor exposure in this patient population is likely due to higher unbound fraction and lower Hb and hematocrit values in subjects with severe renal impairment.

No dose adjustment is required for subjects with severe renal impairment.

Genotype

Sickle cell disease is caused by mutations in the *HBB* gene. The most common cause is inheriting two copies of the sickle cell gene (HbSS), but sickle cell disease may also be caused by inheriting one copy of the HbS gene plus one copy of the hemoglobin C gene (HbSC), one copy of the beta zero thalassemia gene (HbSβ^0thalassemia), or one copy of the beta plus thalassemia gene (HbSβ^+thalassemia). The underlying mutations can impact disease severity, with HbSS and HbSβ^0thalassemia patients usually having a more severe phenotype than HbSC and HbSβ^+thalassemia patients.

Study GBT440-001 Part B included 24 healthy subjects (18 received voxelotor at 300, 600, or 900 mg daily), 38 patients with HbSS or HbSβ^0thalassemia (28 received voxelotor at 500 mg daily, 700 mg daily, or 500 mg BID) and a cohort of 7 patients with HbSC and HbSβ^+thalassemia (6 received voxelotor at 600 mg daily and 1 received placebo). The data showed that voxelotor exposures were higher in healthy subjects compared to SCD patients. In addition, SCD patients with the HbSC genotype had higher exposures than patients with the HbSS genotype. Therefore, the effect of genotype on voxelotor PK was explored in the poppk analysis.

The poppk dataset included a total of 279 individuals from studies GBT 440-031, GBT440-007, and GBT440-001; 220 patients were genotype HbSS (78.9), 35 were HbS$\beta^{0\text{-}}$thalassemia (12.5%), 11 patients (3.94%) were HbSC, and other genotypes were present at less than 3% of the population for each category. In the poppk dataset, model-predicted steady state whole blood AUC and Cmax were 50 and 45% higher in HbSC patients than HbSS patients and model-predicted steady state plasma AUC and Cmax were 23% and 15% higher in HbSC patients compared to HbSS patients. No dose adjustment is recommended based on genotype; the exposure change is not likely to be clinically significant.

Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

Yes, the co-administration of drugs that are known to be strong inhibitors of CYP3A4 or fluconazole, or strong/moderate inducers of CYP3A4 should be avoided. If the coadministration of strong CYP3A4 inhibitors or fluconazole is unavoidable, subjects should receive a 1000 mg

daily dose of voxelotor. If the coadministration of strong/moderate CYP3A4 inducers cannot be avoided, patients should receive a 2500 mg daily dose of voxelotor.

Drug Interaction

Voxelotor as a Substrate

In vitro studies indicate that voxelotor is metabolized by several enzyme systems: CYP450 (73.8%), UGT (7.5%), and SULT (18.7%). Further, voxelotor is not a substrate of any transporter, possesses no CYP3A induction or TDI potential, does not undergo significant metabolism by any uncommon CYP450 isoforms or non-CYP450 enzymes, and is characterized by a low intrinsic clearance. Though several CYP enzymes (CYP3A4, CYP2C19, CYP2B6, and CYP2C9) are involved in the oxidation of voxelotor, CYP3A4 was the major enzyme that contributes to the overall clearance of voxelotor. Given these characteristics, PBPK modeling and simulation can be used to assess the potential in vivo DDI.

To accomplish this, fmCYP3A4 was rigorously assessed first with the human mass balance study and in vitro recombinant P450 kinetics study, which indicated that the contribution of each CYP enzyme to the voxelotor overall clearance was 56%, 7%, 5%, and 7% for CYP3A4, CYP2C9, CYP2C19, and CYP2B6, respectively. A second assessment based on the human mass balance study and the in vitro chemical inhibition study, indicated that the contribution of each CYP enzyme to the voxelotor overall clearance was 36%, 14%, 10%, and 14% for CYP3A4, CYP2C9, CYP2C19, and CYP2B6, respectively. Therefore, the PBPK modeling and simulation approach was used to evaluate the effect of CYP3A modulators on the PK of voxelotor employed the two estimated fmCYP3A4 values, 0.36 and 0.56.

Based on these two fmCYP3A values, the predicted voxelotor AUC increase in the presence of ketoconazole (a strong CYP3A inhibitor) was 46%-82%. Simulations with fluconazole, which inhibits CYP3A, CYP2C9, and CYP2C19, yielded a model predicted increase in voxelotor exposure of about 2-fold (i.e. 1.8-fold increase with fluconazole 200 mg QD, and 2.09-fold increase with fluconazole 400 mg QD). With induction of CYP3A, a greater than 50% reduction in voxelotor AUC was predicted with rifampicin (a strong CYP3A/CYP2C19, and moderate CYP2C9 inducer) and efavirenz (a moderate CYP3A inducer) (**Table 31**).

As there is no in vivo DDI study evaluating the effect of a strong CYP3A inhibitor on the PK of voxelotor, to confirm the estimated fmCYP3A value, potential uncertainties in estimating fmCYP3A and their impact on DDI prediction was further evaluated by the FDA. The analysis showed that the impact of uncertainty on the predicted voxelotor exposure change with CYP3A modulators is deemed insignificant due to the drug properties of voxelotor (e.g., not a substrate of any transporter, no CYP3A induction or TDI potential, no involvement of uncommon CYP450 isoforms or non-CYP450 enzymes, and low clearance). Refer to “PBPK Analyses review” for more details.

Table 32 PBPK Predicted Exposure with CYP3A4 Modulators

Perpetrator	AUC Ratio	
	56% CYP3A4 Contribution	36% CYP3A4 Contribution
Ketoconazole 400 mg QD	1.82	1.46
Fluconazole 200 mg QD	1.80	1.73
Fluconazole 400 mg QD	2.09	1.98
Efavirenz 600 mg QD	0.44	0.50
Rifampicin 600 mg QD	0.27	0.31

Based on the predicted change in exposure, patients who receive concomitant medications that are strong inhibitors of CYP3A4 or fluconazole should reduce the voxelotor dose to 1000 mg dose QD, which is predicted to result in target exposure of 90% to 120% of the nominal exposure. Similarly, patients who receive concomitant medications that are moderate or strong inducers of CYP3A4 should receive a voxelotor dose of 2500 mg, which is predicted to result in 45% to 97% of the target exposure. Even though the proposed dose adjustment (2500 mg QD) may achieve only 45% of the target exposure (based on the most conservative estimate), higher doses cannot be recommended; the highest dose administered in clinical studies was 2800 mg.

Voxelotor as a Perpetrator

In a cocktail study (GBT440-003), subjects received substrates of CYP1A2 (caffeine), CYP2C9 (warfarin), CYP2C19 (omeprazole), and CYP3A4 (midazolam) with and without voxelotor in a crossover design. The cocktail was administered to subjects on Day 0. Voxelotor was then administered at a dose of 900 mg on days 1 and 2, and at a dose of 600 mg on day 3 through day 7. On Day 4, the cocktail was administered again in the presence of voxelotor. The study showed that midazolam exposure increased by 63% and the metabolite hydroxymidazolam increased by 75%, indicating that voxelotor is an inhibitor of CYP3A4. The study also showed a less than 1.12-fold change in exposure of caffeine, warfarin, and omeprazole. After validating the model with the cocktail study results, PBPK modeling and simulation approach was used to evaluate the effect of voxelotor at the proposed dose level (1500 mg QD) at steady-state on the PK of CYP1A2 (caffeine), CYP2C9 (warfarin), CYP2C19 (omeprazole), and CYP3A4 (midazolam) substrates. About 2-fold increase in midazolam systemic exposure was predicted, while all other substrate systemic exposure were not significantly affected by concomitant voxelotor (1500 mg QD).

Food Effect

In study GBT440-005, a 900 mg oral dose of voxelotor was administered with a high fat, high calorie meal (approximately 800 to 100 calories: 150 from protein, 250 from carbohydrates, and 500 to 600 from fat) or in the fasted condition to healthy subjects. Whole blood AUC increased by 42% and C_{max} increased by 45%. Plasma AUC increased by 43% and C_{max} increased by 95%.

The effect of food on voxelotor bioavailability in SCD patients was also analyzed using population PK. The population PK analysis included patients in studies GBT440-001, GBT440-007, and GBT440-031. A total of 52 patients received voxelotor after an overnight fast, 72 patients received voxelotor with a non-high fat meal, and 121 patients had unrestricted food conditions. Patients who had a non-high fat meal had a 6% decrease in exposure compared to fasted, while those with unrestricted food conditions had a 5% increase in exposure. Of note, voxelotor was administered without regard to food in the remainder of patients in registration trial GBT440-031. As such, voxelotor can be administered with or without food.

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7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

The 1500-mg/day dosing of voxelotor was evaluated in a randomized, placebo-controlled Phase 3 study, (GBT440-031). This study will be the primary focus of determining the efficacy and safety of voxelotor in patients with sickle cell disease. In addition to study GBT440-031 Study GBT440-007 (Part B), a Phase 2a, open-label, single and multiple dose study was evaluated to support the safety of voxelotor.

Study GBT440-031 (HOPE Trial)
The study was conducted at 60 sites, of which 60 sites screened a subject and 59 sites randomized a subject. The study was conducted in 12 countries across 60 sites, of which 60 sites screened a subject and 59 sites (Canada [4], Egypt [44], France [3],Italy [1], Jamaica [4],Kenya [40],Lebanon [7], Netherlands [8], Oman [9], Turkey [11], United Kingdom [29] and United States of America [101]) randomized a subject.

Study GBT440-007
This study was conducted 10 sites, of which 5 sites screened a subject in Part A and 10 sites screened a subject in Part B. The study was conducted in 2 countries across 11 sites of which 10 sites screened a subject and 9 sites (US: Oakland, CA [3], Memphis, TN [4], Chicago, IL x 2 [4], Kansas City, MO [3], Atlanta, GA [10], New Brunswick, NJ [0], Cleveland, OH [1], and internationally: Beirut, Lebanon [9]) randomized a subject in Part B of Study GBT440-007.

Table 33: Listing of Clinical Trials Relevant to this NDA

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
		Controlled Studies to Support Efficacy and Safety						
GBT440-031	NCT03573882	A Phase 3, Double-Blind, Randomized, Placebo-Controlled, Multicenter Study Of Voxelotor Administered Orally to Patients with Sickle Cell Disease (HOPE Trial)	Voxelotor tablet 900 mg or 1500 mg, or placebo; QD; Oral	Hgb response at Week 24; Hgb response was based on the difference between the average value of hemoglobin levels at Week 20 and Week 24 and baseline hemoglobin level (Hgb).	Up to 72 weeks	Overall: 274/271 900 mg: 92/92 1500 mg: 90/88 placebo: 92/91	Adults and adolescents with SCD	60 sites; 12 countries
		Studies to Support Safety						
GBT440-007	NCT02850406	A Phase 2a, Open-Label, Single- And Multiple-Dose Study to Evaluate The Pharmacokinetics, Safety, Tolerability, And Treatment Effect of GBT440 In Pediatric Participants with Sickle Cell Disease	Part A: voxelotor capsule 600 mg Part B: voxelotor capsule 900 mg or 1500 mg QD Part C:	Treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) Clinical laboratory tests, physical	Part A: single dose Part B: 24 weeks Part C: 48 weeks	Part A: 13 (6 to < 18 years) Part B: 40 (12 to < 18 years) Part C: TBD (4 to < 18 years)	Pediatric subjects with SCD	10 sites; 2 countries

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
			voxelotor tablet 1500 mg QD; Oral	examination findings, vital signs, and electrocardiograms (ECGs)				
		Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)						
GBT440-001		Phase 1, first-in-human, single and multiple ascending dose, placebo-controlled, double-blind	Part A: voxelotor capsule 100 mg to 2800 mg, or placebo; Single dose; Oral	To evaluate the safety and tolerability of single and multiple doses of voxelotor administered to healthy subjects and subjects with sickle cell disease (SCD).	Single dose	Total: 40/40 Voxelotor: 30/30 c Placebo: 10/10	Healthy subjects	2 sites; London, UK
			Part B: voxelotor capsule 300, 600, or 900 mg, or placebo; QD; Oral		15 days	Total: 24/24 Voxelotor: 18/18 c Placebo: 6/6	Healthy subjects	
			Part A: voxelotor capsule 1000 mg or placebo; Single dose; Oral		Single dose	Total: 8/8 Voxelotor: 6/6 Placebo: 2/2	Subjects with SCD	

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
			Part B: voxelotor capsule 500, 600, 700, or 1000 mg (500 mg twice daily), or placebo; QD (BID for 1000 group); Oral		28 days	Total: 45/45 voxelotor 34/34 Placebo: 11/11	Subjects with SCD	
			Part C: voxelotor capsule 700 or 900 mg, or placebo QD; Oral		90 to 118 days	Total: 16/16 d Voxelotor 12/12 Placebo: 4/4	Subjects with SCD	
GBT440-024		An open-label single arm extension study to further evaluate the safety, tolerability and treatment response of GBT440 in patients with Sickle Cell Disease who participated in the Phase 1 Study GBT440-001	Voxelotor 900 mg QD; Oral	Long-term (6 months) extension; Safety and tolerability	6 months (including exposure in GBT440-001)	5/5	Subjects with SCD	3 sites, London, UK

7.2. Review Strategy

The Applicant submitted the application electronically. The clinical and statistical reviewers, Patricia Oneal, MD, Rosanna Setse, MD, PhD and Lola Luo, PhD, respectively, served as the primary reviewers and conducted a joint review of the efficacy data and safety data in this application, respectively. Reviewer comments are identified individually.

This clinical reviewer's strategy included:
• Review of regulatory histories of NDA 213137 and IND 121691;
• Examination of all clinical study reports and amendments
• Subjecting datasets to queries using JReview and JMP;
• Examination of approximately 300 CRFs, selected at random;
• Studying the Applicant's presentation to the FDA on 29 July 2019;
• Searching published literature relative to sickle cell disease and acute/chronic complications of sickle cell disease as well as patient experiences related to all treatment modalities used in this setting;
• Consulting the FDA Division of Scientific Investigation;
• Review of the Periodic Safety Update Reports and Annual Reports for voxelotor NDA;
• Review of guidelines and other published literature regarding the diagnosis, treatment, and monitoring of patients with sickle cell disease;
• Review of FDA reviews of previous drugs approved for the treatment of sickle cell disease;
• Review and analysis of raw data conducted throughout studies for responders on the treatment arm;
• Review of pooled safety data from the aforementioned trials to detect additional safety signals.

The safety analyses was performed using JReview 13.1 (SAS Institute, Inc). Unless specifically referenced, all analyses and presentation of findings are the work of FDA reviewers. The statistical evaluation was based on data from study GBT440-031.

Data Sources
Analysis datasets, SDTM tabulations and software codes are located on the network with the network path: \\CDSESUB1\evsprod\NDA213137\213137.enx

8 Statistical and Clinical and Evaluation

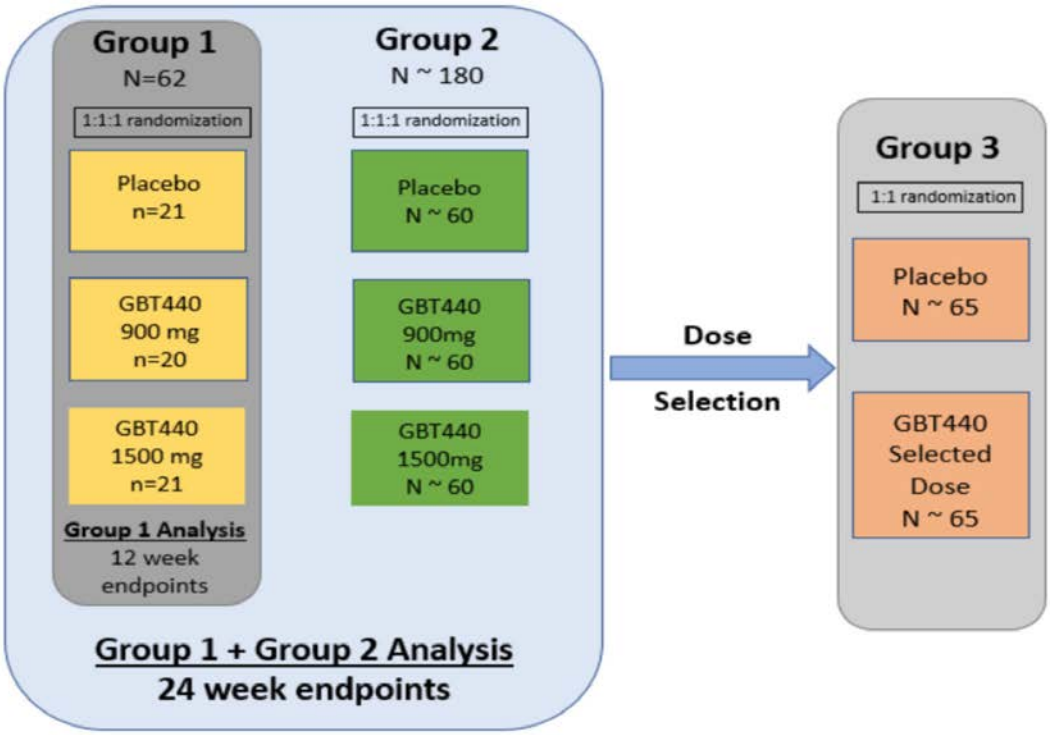
8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. GBT440-031

Trial Design

GBT440-031 is a phase 3, double-blinded, randomized, placebo-controlled, multicenter study of GBT110 (Voxelotor) administered orally to patients with sickle cell disease (SCD).

Figure 5: Study Schema



Source: Figure 1 of Applicant's CSR

Study Endpoints

Primary Efficacy Endpoint:

- Hb response at Week 24: proportion of patients with >1.0 g/dL Hb increase from baseline at 24 weeks.

Key Secondary Endpoints:

- Change from baseline in hemoglobin at Week 24
- Percent Change from baseline in hemolysis measures, including unconjugated bilirubin, reticulocytes percentage (%),and Lactate Dehydrogenase (LDH) at Week 24
- Annualized incidence rate of vaso-occlusive crisis (VOC), final analysis at 72 weeks.

Statistical Analysis Plan

Sample Size and Power:
The sample size for the primary analysis of the study was 274 randomized subjects. All randomized subjects were included in the efficacy analysis.

For the primary analysis of hemoglobin response rate comparing voxelotor 1500 mg to placebo, assuming a 10% Hb response rate in placebo, the study with approximately 90 subjects per treatment group would have >95% power to detect a targeted difference of 30%, using Fisher's exact test with a two-sided alpha of 0.0481.

Randomization was carried out centrally through an IXRS. Permuted blocks within randomization strata were used. At the time of randomization, subjects were stratified for hydroxyurea (HU) use (yes/no), geographic region (North America, Europe, Other), and age (adolescent, 12 to <18 years, and adults, 18 to 65 years).

This study was designed as a double-blinded study. The voxelotor and placebo capsules or tablets were matched for shape, size, and color.

Interim Efficacy Analysis:
Two interim analyses (IA) were performed to inform voxelotor dose selection. The first IA was performed with 62 subjects, followed by the second IA with 156 subjects. The primary analysis will be performed based on data from all randomized subjects (n=274). A Lan-DeMets alpha spending function with the O'Brien-Fleming boundary was used to determine the significance level for each IA and the primary analysis, to maintain an overall type I error rate of 5% (two-sided), resulting in the following:

Analysis	Significance level (2-sided)
IA #1 (n=62)	0.000005
IA #2 (n=156)	0.0059
Primary Analysis (n=274)	0.0481

PASS Software (version 11) was used to calculate the alpha spending for each analysis (two sample proportion).

Primary Efficacy Analysis:
The first hypothesis testing compares Hb response rate for voxelotor 1500 mg vs. placebo.

$$H_0: p_v = p_c$$
$$H_a: p_v \neq p_c$$

Where p_v is the Hb response rate in voxelotor 1500 mg group and p_c is the Hb response rate in the placebo group.

The exact Cochran-Mantel-Haenszel (CMH) general association test, stratified by baseline HU use, age and geographic region, is used for this analysis.

Secondary Efficacy Analyses:
If the null hypothesis of the primary efficacy analysis is rejected at a two-sided significance level of 0.0481, the following hierarchically ordered statistical hypotheses would be tested in the order specified below, until the first non-rejection.

<u>1500 mg vs. Placebo</u>

1. Change from baseline in Hb at Week 24: voxelotor 1500 mg vs. placebo
2. Percent change from baseline in unconjugated bilirubin at Week 24: voxelotor 1500 mg vs. placebo
3. Percent change from baseline in reticulocyte % at Week 24: voxelotor 1500 mgs vs. placebo
4. Percent change from baseline in LDH at Week 24: voxelotor 1500 vs. placebo

<u>900 mg vs. Placebo</u>

5. Hb response rate at Week 24: voxelotor 900 mg vs. placebo
6. Change from baseline in Hb at Week 24: voxelotor 900 mg vs. placebo
7. Percent change from baseline in unconjugated bilirubin at Week 24: voxelotor 900 mg vs. placebo
8. Percent change from baseline in reticulocyte % at Week 24: voxelotor 900 mg vs. placebo
9. Percent change from baseline in LDH at Week 24: voxelotor 900 mg vs. placebo

Imputation of Missing Data:
<u>Hb responder:</u>

- If Hb assessments were missed at both Week 20 and Week 24 due to dropout, VOC, or VOC hospitalization: Subject was treated as a non-responder. If Hb at one of the two time points was non-missing, Hb response assessment was based on the non-missing Hb value.

- Initiation of HU post randomization and prior to Week 24: Subject were treated as a non-responder.

- RBC transfusions: A participant who received a transfusion due to anemia within 8 weeks (12 weeks for sensitivity analysis) of the Week 24 Hb assessment was deemed a non-responder. For subjects receiving transfusion due to reasons other than anemia within 8 weeks (12 weeks for sensitivity analysis) of the Week 24 Hb assessment, Week 24 Hb was imputed with the last Hb assessment prior to the transfusion.

Hemolysis Measures Change from baseline and hemolysis reduction:

- Missing data due to subject dropout: For the primary method of analysis of this endpoint (mixed effect model for repeated measures [MMRM]), missing at random (MAR) were assumed and no imputation occurred.

- Subjects initiating HU post randomization were discontinued from the study. As such, only assessments prior to HU initiation were used in this analysis.

- Missing Week 24 hemolysis data due to VOC or VOC hospitalization: For the primary method of analysis of hemolysis measures (MMRM), missing at random (MAR) were assumed and no imputation occurred. For sensitivity analysis, the imputation rule for missed assessments due to VOC or VOC hospitalization were assigned the hemolysis measurement from the last assessment occurring prior to commencement of VOC or hospitalization for VOC (including Screening and Day 1).

- RBC transfusions: Regardless of whether data were missing, post transfusion hemolysis lab results were imputed by assigning the hemolysis measurement of the last assessment prior to transfusion (including Screening and Day 1). All hemolysis lab results starting on the transfusion date and ending 8 weeks after were imputed for the MMRM analysis of hemolysis measures and the assessment of hemolysis reduction at Week 24. All hemolysis lab results starting on the transfusion date and ending 12 weeks after were imputed for the related sensitivity analysis. The imputation for Hb was similarly applied to all measures of hemolysis for the change from baseline analyses.

Analysis Population:

Intent-to-treat (ITT) Population: all subjects who were randomized. Subjects were analyzed based upon the treatment group to which they were assigned at randomization.

Modified Intent to Treat (mITT) Population: all subjects who were randomized to a treatment group and received at least one dose of study medication.

Per-Protocol (PP) Population: randomized subjects who completed 24 weeks of study drug and did not initiate HU treatment after randomization.

Statistical Analysis for Efficacy Endpoints:

Primary Analysis of Hb Response:

Hb response was based on the difference between the average value of hemoglobin levels at Week 20 (Hb20) and Week 24 (Hb24) and baseline hemoglobin level (HbB). A subject was considered to be an Hb responder if [mean (Hb20, Hb24) – HbB] > 1 g/dL. If Hb20 or Hb24 was missing, then the calculation used the non-missing Hb level. Regardless of calculated difference, per guidelines described in the section *"Imputation of Missing Data"*, subjects were classified as non-responders if any of the non-responder criteria were met.

The Hb response rate was analyzed using an exact Cochran-Mantel-Haenszel (CMH) general association test with imputation rules outlined in the section *"Imputation of Missing Data"*. Each voxelotor dose group (900 mg and 1500 mg) was compared to placebo while stratifying for the randomization stratification factor of HU use (yes vs. no), age group (12-18 vs. >18) and geographic region (North American, Europe, other).

Change from baseline Hb to Week 24:

Change from baseline in Hb over time up to Week 24 was analyzed using a mixed effect for repeated measures (MMRM) model. The fixed effect terms included treatment, study visit, treatment by visit interaction, HU use at baseline, age group and geographic region. Baseline Hb was a covariate. Within-subject variability was modeled using an unstructured covariance matrix. Missing data due to early drop out or missed visit were not imputed for this analysis. Missing data to due to VOC, VOC hospitalization or RBC transfusion would be imputed, as described in the section *"Imputation of Missing Data"*.

The analysis of Hb response rate was repeated using observed data without imputation to assess the robustness of the data.

Change from Baseline to Week 24 in Hemolysis Related Measures:

Percent change from baseline over time up to Week 24 in unconjugated bilirubin, reticulocytes %, and LDH were analyzed with a similar MMRM model. If any of the laboratory measures reported were below the lower limit of quantitation or above the upper limit of quantitation, then the numerical limit were used in the MMRM modeling.

VOC up to Week 72:

The number of VOC events was modeled using a negative binomial model with the independent variable of treatment group and adjusted for the stratification factors used for randomization.

Protocol Amendments

The protocol amendments made in Version 3 issued on 21 September 2017are listed below:

1. Hydroxyurea use during the study was not allowed initiation during the study conduct,
2. Participants from Group 2 were included in the Group 1 analysis to include approximately 60 participants with at least 12 weeks of treatment,
3. The sample size of Group 2 increased to approximately 180 participants,
4. Total sample size of the study was increased to 435 participants,
5. Lowered the hemoglobin inclusion criteria to 5.5 g/dL and
6. Added L-glutamine to the allowed concomitant medications.

The protocol amendments made in Version 4 issued on 03 January 2019 are listed below:

1. The primary objective was changed from "improvement in anemia" to "improvement in hemoglobin" and
2. All secondary endpoints were replaced with: Change from baseline in hemoglobin at Week 24 and Change from baseline in hemolysis measures, including unconjugated bilirubin, absolute reticulocyte, reticulocytes %, and LDH at Week 24 and the annualized incidence rate of VOC.]

8.1.2. 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

<u>Phase 3 Study GBT440-031 and Phase 2a GBT440-007:</u>
Financial disclosure forms were collected for both Phase 3 Study (GBT440-031) and the Phase 2a Study (GBT440-007). No Principal Investigators or sub-investigators (if applicable) in these studies were or are a full-time or part-time employee of Global Blood Therapeutics. No principal investigators or sub investigators (if applicable) reported any disclosable financial interests or arrangements as described in 21 CFR § 54.4(a)(3). Financial disclosure forms from two investigators at the Children's Healthcare of Atlanta and Hôpital Necker in Paris, France were not obtained. These investigators did not perform any study-related activities at their sites.

Data Quality and Integrity

No issues were identified with the data quality or integrity from study GBT440-031 which could affect the efficacy results

Patient Disposition

Overall, 449 subjects were screened for this study at 60 study centers. Between January 2017 and May 2018, a total of 274 subjects were randomized at 58 study centers across 12 countries (United States, Kenya, Egypt, Great Britain, Turkey, Oman, Netherlands, Lebanon, Canada, Jamaica, France, and Italy).

All 274 randomized subjects were included in the ITT Population. A total of 271 subjects received study drug and were included in the mITT Populations. Subject disposition was generally balanced across treatment groups. Overall, 83.9% (230/274) of subjects completed the study through Week 24. As of the data cutoff date of 31 October 2018, 75.9% (208/274) of subjects were still on study and the mean duration of follow-up was approximately 40 weeks. Among the 22.6% (62/274) of subjects who discontinued early from the study, the most common reasons for discontinuation were withdrawal of consent and AEs. Subject disposition and reasons for discontinuation are summarized for the ITT Population in the table below.

Table 34: Patient Disposition Phase 3 Study GBT440-031

Subject Status	Placebo	Voxelotor 900 mg	Voxelotor 1500 mg	Total
Randomized (ITT Population), N	92	92	90	274
mITT (treated patients), n (%)	91 (98.9)	92 (100.0)	88 (97.8)	271 (98.9)
Completed 24 Weeks	76 (82.6)	79 (85.9)	75 (83.3)	230 (83.9)
Completed Study	1 (1.1)	1 (1.1)	2 (2.2)	4 (1.5)
Ongoing as of Data Cutoff	72 (78.3)	72 (78.3)	64 (71.1)	208 (75.9)
Early Discontinuation from Study, n (%)	19 (20.7)	19 (20.7)	24 (26.7)	62 (22.6)
Primary Reason for Study Discontinuation, n (%)				
Adverse Event	5 (5.4)	5 (5.4)	9 (10.0)	19 (6.9)
Withdrawal of Consent	8 (8.7)	11 (12.0)	5 (5.6)	24 (8.8)
Discretion of the Investigator	1 (1.1)	2 (2.2)	1 (1.1)	4 (1.5)
Subject is Lost to Follow-Up	0	1 (1.1)	1 (1.1)	2 (0.7)
Subject is Noncompliant	1 (1.1)	0	5 (5.6)	6 (2.2)
Pregnancy	1 (1.1)	0	0	1 (0.4)
Other	3 (3.3)	0	3 (3.3)	6 (2.2)
Duration of Follow-Up (weeks)				
N	92	92	90	274

Mean (SD)	39.2 (14.37)	38.7 (15.70)	39.5 (15.18)	39.1 (15.04)
Median	37.2	38.1	42.3	39.6
Min, Max	8.1, 72.9	4.0, 72.4	0.1, 73.3	0.1, 73.3

Protocol Violations/Deviations

The protocol violations/deviations in GBT440-031 were occurred in the eligibility and entry criteria, randomization criteria, serious adverse event criteria and the investigational product compliance.

Five patients were ineligible due to the following reasons: (1) Screen failure due to recent blood transfusion, (2) Patient had received eight red blood transfusions 45 days prior to randomization and randomized incorrectly, (3) Documentation of VOC history and analgesic use was not documented, (4) Patient received a blood transfusion within 60 days prior to ICF, and (5) Patient had a VOC during the screening period and received blood transfusion while hospitalized.

One patient was mis-randomized on the same day of screening.

Six patients were documented with a reportable serious adverse event. Those violations included the following (1) Serious adverse event of VOC which was reported and entered to the electronic record late and (2) Hospitalizations due to VOC was not reported within 24 hours of awareness.

The incorrect PK/PD kit was assigned and used with one patient.

Reviewers Comments: None of the protocol violations or deviations impacted the interpretation of the results.

Table of Demographic Characteristics

Key demographic and baseline characteristics for the ITT Population are presented in Table below. In general, demographic and baseline characteristics were similar across treatment arms, with 38.3% of subjects enrolled at sites in North America.

The mean age for the 274 subjects in the ITT Population was 28 years (range: 12–64 years). Overall, 16.8% (46/274) of enrolled subjects were adolescents (12 to < 18 years) and 83.2% (228/274) were aged 18 years or older. Fifty-eight percent of subjects were female, and 66.8% were Black or African.

Overall, 90.5% subjects had SCD genotype HbSS or HbSβ^0 thalassemia. Fifty-eight percent of subjects had at least 2 VOCs in the 12 months prior to screening. At least 1 episode of ACS within the 12 months prior to screening was reported by 8.4% (23/274) of subjects and was more common in the voxelotor 1500-mg group (11.1% [10/90 subjects]) and the voxelotor 900-mg group (10.9% [10/92 subjects]) than in the placebo group (3.3% [3/92 subjects]).

Table 35: Demographic and Baseline Characteristics - ITT Population

	Placebo (N = 92)	Voxelotor 900 mg (N = 92)	Voxelotor 1500 mg (N=90)	Total (N=274)
Age (Years)				
Mean (SD)	28 (11.5)	28 (11.8)	27 (11.7)	28 (11.6)
Median	28	24	24	24
Min, Max	12, 64	12, 59	12, 59	12, 64
Age Group, n (%)				
12 to < 18 Years	17 (18.5)	15 (16.3)	14 (15.6)	46 (16.8)
18 years or Older	75 (81.5)	77 (83.7)	76 (84.4)	228 (83.2)
Sex, n (%)				
Female	50 (54.3)	51 (55.4)	58 (64.4)	159 (58.0)
Male	42 (45.7)	41 (44.6)	32 (35.6)	115 (42.0)
Race[a], n (%)				
Arab/Middle Eastern	20 (21.7)	20 (21.7)	20 (22.2)	60 (21.9)
Asian	0	1 (1.1)	1 (1.1)	2 (0.7)
Black or African American	63 (68.5)	61 (66.3)	59 (65.6)	183 (66.8)
White	5 (5.4)	7 (7.6)	12 (13.3)	24 (8.8)
Other	6 (6.5)	5 (5.4)	2 (2.2)	13 (4.7)
Region[b], n (%)				
North America	35 (38.0)	36 (39.1)	34 (37.8)	105 (38.3)
Europe	18 (19.6)	19 (20.7)	19 (21.1)	56 (20.4)
Other	39 (42.4)	37 (40.2)	37 (41.1)	113 (41.2)
SCD Genotype, n (%)				
HbSS	74 (80.4)	71 (77.2)	61 (67.8)	206 (75.2)
HbSC	2 (2.2)	2 (2.2)	3 (3.3)	7 (2.6)
HbSβ^0 thalassemia	11 (12.0)	13 (14.1)	18 (20.0)	42 (15.3)
HbSβ+ thalassemia	3 (3.3)	2 (2.2)	7 (7.8)	12 (4.4)
Other Variants	2 (2.2)	4 (4.3)	1 (1.1)	7 (2.6)
Number of vaso-occlusive crisis (VOCs) (12 Months Prior to Screening) , n (%)				
Mean (SD)	2.5 (1.88)	2.5 (2.13)	2.5 (1.90)	2.5 (1.97)
Median	2.0	2.0	2.0	2.0
Min, Max	1, 10	1, 10	1, 10	1, 10

	Placebo (N = 92)	Voxelotor 900 mg (N = 92)	Voxelotor 1500 mg (N=90)	Total (N=274)
Number of VOCs Groups (12 Months Prior to Screening), n (%)				
1	39 (42.4)	41 (44.6)	35 (38.9)	115 (42.0)
≥ 2	53 (57.6)	51 (55.4)	55 (61.1)	159 (58.0)
Number of ACS Events (12 Months Prior to Screening), n (%)				
0	89 (96.7)	82 (89.1)	80 (88.9)	251 (91.6)
1	2 (2.2)	8 (8.7)	9 (10.0)	19 (6.9)
2	0	2 (2.2)	1 (1.1)	3 (1.1)
3	1 (1.1)	0	0	1 (0.4)
Disease Duration for SCD (years)[c]				
Mean (SD)	24.6 (13.13)	24.8 (12.53)	22.1 (12.41)	23.8 (12.71)
Median	22.0	21.2	20.0	21.2
Min, Max	2.2, 63.1	2.1, 60.1	1.1, 54.9	1.1, 63.1
Use of Hydroxyurea at Baseline, n (%)				
Yes	58 (63.0)	63 (68.5)	58 (64.4)	179 (65.3)
No	34 (37.0)	29 (31.5)	32 (35.6)	95 (34.7)

a. Subjects could be included in more than 1 race category
b. Countries labeled as Other include Egypt, Jamaica, Kenya, Lebanon, and Oman. Turkey was grouped with Europe for purposes of data summary.
c. Years since SCD diagnosis to the first date of study drug

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

Overall, baseline laboratory values were balanced across the treatment arms.

Table 36: Baseline Laboratory Values – ITT Population

	Placebo (N = 92)	Voxelotor 900 mg (N = 92)	Voxelotor 1500 mg (N=90)
Hb (g/dL), N	92	92	90
Mean (SD)	8.6 (1.06)	8.3 (1.08)	8.6 (1.10)
Median	8.6	8.3	8.7
Min, Max	6.1, 10.5	5.9, 10.8	5.9, 10.8
Indirect Bilirubin (µmol/L), N	86	89	87
Mean (SD)	50.3 (43.19)	44.2 (34.16)	45.3 (44.29)
Median	34.2	31.5	28.4
Min, Max	5.7, 259.1	7.2, 172.6	9.0, 262.1

	Placebo (N = 92)	Voxelotor 900 mg (N = 92)	Voxelotor 1500 mg (N=90)
Reticulocyte Percentage, N	92	92	90
Mean (SD)	10.9 (4.63)	11.6 (5.26)	10.5 (4.97)
Median	10.9	11.3	9.6
Min, Max	2.4, 24.9	2.9, 23.6	3.1, 24.9
Absolute Reticulocytes (10^9/L), N	92	92	90
Mean (SD)	315.8 (129.88)	319.0 (139.39)	299.0 (123.44)
Median	310.3	324.0	290.3
Min, Max	89.5, 636.5	92.0, 671.5	60.0, 705.0
Lactate Dehydrogenase (U/L), N	88	90	90
Mean (SD)	439.2 (188.70)	432.9 (179.06)	385.1 (150.61)
Median	393.8	391.8	340.8
Min, Max	161.5, 1151.0	179.5, 1210.0	185.5, 865.0
HbF (%), N	77	75	73
Mean (SD)	10.4 (10.96)	9.9 (7.47)	9.3 (6.29)
Median	7.4	8.6	8.3
Min, Max	1.2, 86.4	0.3, 30.7	0.3, 28.8

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Among the 274 patients randomized in Study GBT440, approximately 83.9% of patients completed 24 weeks of treatment (i.e. placebo, 900 mg and 1500 mg of voxelotor). Hydroxyurea (HU) therapy was allowed, provided that the dose has been stable for at least 3 months prior to signing the ICF and with no anticipated need for dose adjustments during the study. Among all subjects, there was approximately 65.3% of subjects on hydroxyurea at baseline.

The use of strong inducers of CYP2B6, CYP2C9, CYP2C19, and CYP3A4/CYP3A5 was prohibited. There were no patients on strong inducers of CYP2B6, CYP2C9, CYP2C19, and CYP3A4/CYP3A5.]

Efficacy Results – Primary Endpoint

Hb response rate at Week 24 and the results of the exact CMH general association test are summarized in table below. In the ITT Population, 46 of the 90 subjects in the voxelotor 1500-mg group achieved a > 1 g/dL increase in Hb from Baseline to Week 24, compared with 6 of the 92 subjects in the placebo group. The difference in the adjusted response rate at Week 24 for voxelotor 1500 mg vs placebo was 45.0% (95% CI: 33.4% to 56.7%) and statistically significant (P-value < 0.0001).

Table 37: Hemoglobin Response at Week24 - ITT Population

Primary Analysis	Placebo (N = 92)	Voxelotor 1500 mg (N=90)
Number of Responders	6	46
Adjusted Hb Response Rates [a] 95% CI	6.2 (1.3, 11.1)	51.2 (40.6, 61.8)
Difference in Adjusted Response Rates[b] (95%CI)	45.0 (33.4, 56.7)	
P-value from Exact CMH Test	**<0.0001**	

a. n is observed counts. Percentages and 95%CI are adjusted for baseline HU use, age group, and geographic region

b. Difference, CI, and p-value are adjusted for baseline HU use, age group, and geographic region

The following figure provides a waterfall plot of the subject level change from baseline in hemoglobin at week 24 in patients who completed the 24 weeks of treatment. Approximately 82% of patients completed the 24 weeks of treatment.

Figure 6 Subject-level Change from Baseline in Hemoglobin at Week 24 in Patients Who Completed 24 Weeks of Treatment

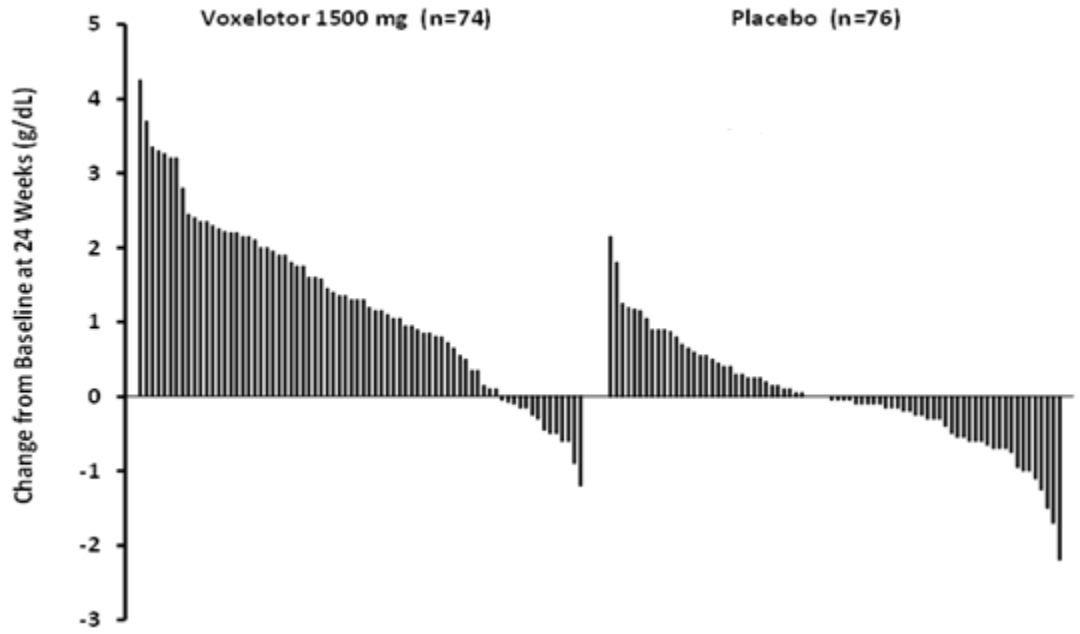


Table 37 below summarizes the reasons for subjects who did not have a Hb response at Week 24. In each treatment arm, the main reason for Hb non-response was that change from baseline was <= 1 g/dL. There were more such subjects in the placebo arm (69.6%) compared to the voxelotor 1500 mg arm (31.1%). The number of subjects who were non-responders due to missing Week 20 and Week 24 Hb values or post-randomization HU use or RBC transfusion due to anemia were relatively low and similar between the two treatment arms.

Table 38: Summary of Reason for Hb Non-response - ITT Population

	Placebo (N = 92) n (%)	Voxelotor1500 mg (N=90) n (%)
Number of subjects who did not have a Hb Response	86 (93.5)	44 (48.9)
Reasons for HB Non-Response		
Change from baseline in Hb <=1 g/dL at Week 24	64 (69.6)	28 (31.1)
Missing Week 20 and Week 24	11 (12.0)	9 (10)
➢ Due to VOC or VOC hospitalization	2 (2.2)	1 (1.1)
➢ Due to other reason	9 (9.8)	8 (8.9)
Post-randomization HU Use	3 (3.3)	1 (1.1)
RBC Transfusion due to Anemia (with 8 weeks rule)	0	2 (2.2)

Source: Table 1 of Applicant's response to FDA's IR on 28 August 2019

Sensitivity Analysis - Primary Endpoint

Sensitivity analyses were conducted as below:

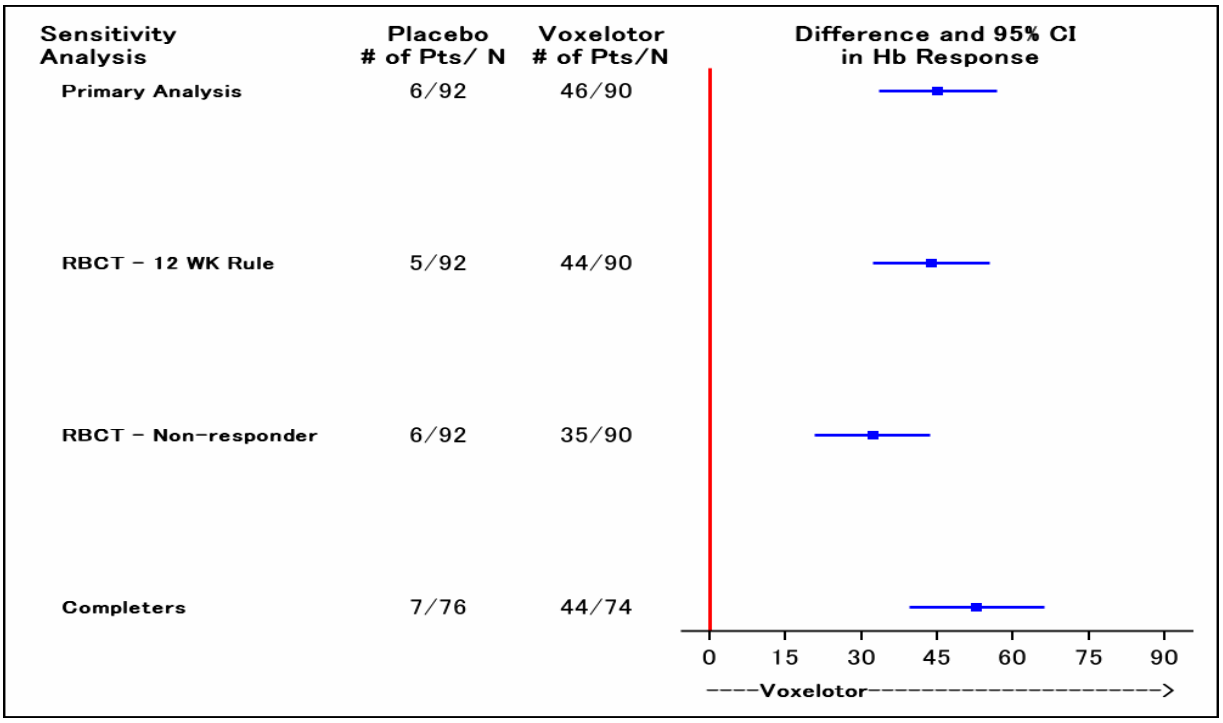
1. The first sensitivity analysis used a stricter imputation rule (12-week Imputation rule) for subjects who had RBC transfusion.

2. The secondary sensitivity analysis assumed subjects who had any RBC transfusion in the voxelotor arm were non-responders and subjects who had any RBC transfusion in the placebo arm followed the same censoring rule as the primary analysis.

3. The third sensitivity analysis included only subjects who completed 24 weeks of study drug and did not initiate hydroxyurea use after randomization.

All of the sensitivity analyses had consistent results as the primary analysis result. Therefore, the magnitude of the treatment effect of voxelotor vs placebo from the primary analysis seemed to be robust (Figure below).

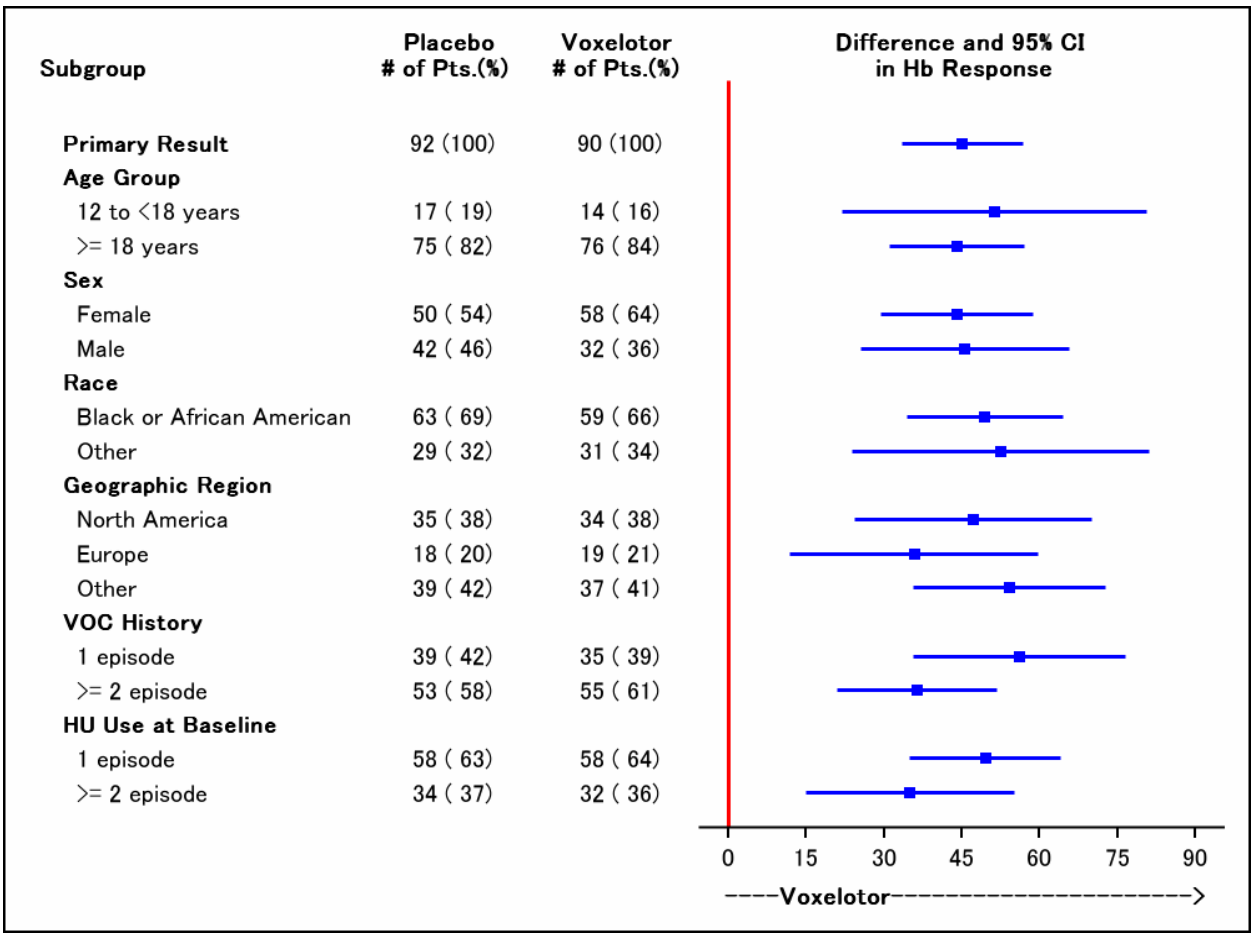
Figure 7: Forest Plot of the Sensitivity Analyses - ITT Population



Subgroup Analysis - Primary Endpoint

Hb response at Week 24 was analyzed for subgroups based on age, sex, race, geographic region, baseline VOC history and baseline HU use (Figure below). No outlier subgroups were observed, the wide CIs were due to small sample size.

Figure 8: Forest Plot of Subgroup Analysis - ITT Population



Efficacy Results – Secondary and other relevant endpoints

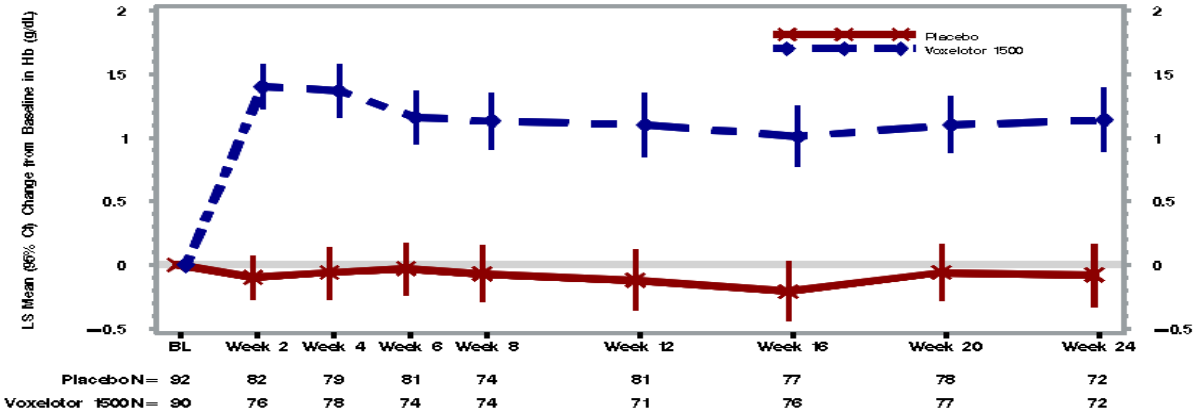
Change from Baseline in Hemoglobin at Week 24

At Week 24, the least square (LS) mean and standard error (SE) for the change from Baseline (g/dL) was 1.14 (0.133) in the voxelotor 1500 mg group and -0.08 (0.132) in the placebo group. The difference between the treatment group was 1.22 g/dL (95% CI: 0.85 to 1.59 g/dL) and statistically significant (P-value < 0.001).

Table 39: Summary Results for Change from Baseline in Hemoglobin at Week 24 - ITT Population

	Placebo (N = 92)	Voxelotor 1500 mg (N=90)
LS Mean Change in Hb from Baseline to Week 24 (SE), g/dL	-0.08 (0.133)	1.14 (0.133)
95% CI of LS Mean	(-0.34, 0.18)	(0.88, 1.40)
Difference (95% CI) in LS Mean vs. Placebo	1.22 (0.85, 1.59)	
P-value	**<0.0001**	

Figure 9: Change from Baseline in Hemoglobin Over Time - ITT Population



Percent Change from Baseline in Hemolysis Measures at Week 24

At Week 24, differences in the LS mean of percentage change from Baseline between voxelotor 1500-mg group and placebo group were

- Statistically significant for indirect bilirubin (P-value < 0.0001)
- Statistically significant for reticulocyte percentage (P-value =0.0002)
- Not Statistically significant for Lactate Dehydrogenase (LDH) (P-value = 0.1348)

Table 40: Summary of Percent Change from Baseline in Hemolysis Measures - ITT

	Voxelotor 1500 mg vs. Placebo
Indirect Bilirubin (#2)	
Difference (95% CI) in LS Mean vs. Placebo	-25.92 (-35.67, -16.16)
P-value	**<0.0001**
Reticulocytes % (#3)	
Difference (95% CI) in LS Mean vs. Placebo	-24.47 (-37.28, -11.66)
P-value	**0.0002**
LDH (#4)	
Difference (95% CI) in LS Mean vs. Placebo	-7.96 (-18.41, 2.49)
P-value	**0.1348**

The hypothesis test for LDH produced a non-statistically significant p-value. To keep the family wise type I error rate below the pre-specified 0.05, the hierarchical ordered statistical hypotheses testing stop here. Results from the subsequent hypothesis tests for the comparisons between voxelotor 900 mg and placebo are considered exploratory and may only be summarized descriptively. Any inferential conclusion from these descriptive summary are deemed not appropriate.

Table 41: Summary of Efficacy Results for Voxelotor 900 mg vs. Placebo - ITT Population

	Voxelotor 900 mg vs. Placebo
Hb Response (>1g/dL at Week 24) **(#5)**	
Difference in Adjusted Response Rates vs. Placebo, (95% CI)	26.4 (15.5, 37.3)
Change from baseline in Hb Measurement at Week 24 **(#6)**	
Difference (95% CI) in LS Mean vs. Placebo	0.66 (0.30, 1.03)
Percent Change from baseline in Indirect Bilirubin at Week 24 **(#7)**	
Difference (95% CI) in LS Mean vs. Placebo	-17.16 (-26.84, -7.49)
Percent Change from baseline in Reticulocytes % at Week 24 **(#8)**	

	Voxelotor 900 mg vs. Placebo
Difference (95% CI) in LS Mean vs. Placebo	-5.87 (-18.65, 6.92)
Percent Change from baseline in LDH at Week 24 **(#9)**	
Difference (95% CI) in LS Mean vs. Placebo	-1.99 (-12.40, 8.41)

Dose/Dose Response

Please refer to the clinical pharmacology section of this review for discussion of dose-response

Durability of Response

The durability of response was demonstrated by the significant benefit of voxelotor 1500 mg in Hb response at Week 24, and in improvement of Hb measurement from baseline at Week 24.

Persistence of Effect

Since the primary endpoint, Hb response at Week 24, was not measured once the treatment was stopped, no data were available to investigate the persistence of the treatment effect following the termination of the treatment.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

The Sickle Cell Disease Severity measure (SCDSM) total symptom score and EuroQOL 5-dimension 5-level(EQ-5D-5L) index value and visual analog scale scores were measured in this trial. There were no differences in patient-reported outcomes in the voxelotor groups compared with the placebo groups.

Reviewer Comment: The patient reported outcomes were exploratory endpoints and no formal conclusions can be drawn from these results.

Additional Analyses Conducted on the Individual Trial

Annualized Incidence Rate of vasoocclusive crisis (VOC)
The total number and annualized IR of on-treatment events of VOC in the mITT Population were similar between the two treatment groups: voxelotor1500 mg (179 events; adjusted IR of 2.77 events/year) and placebo (219 events; adjusted IR of 3.19 events/year). This analysis was limited by the relatively short observation period; the final efficacy analysis will be performed when all subjects complete 72 weeks of treatment or their final study visit.

Table 42: Annualized Incidence Rate of VOC - mITT Population

	Placebo (N = 91)	Voxelotor 1500 mg (N=88)
Subjects with Any VOCs Postbaseline, n (%)	63 (69.2)	59 (67.0)
Total Person-Years (On Treatment)	64.1	64.8
Total Number of Events	219	179
Adjusted Annualized IR (events/year) [a]	3.19 (2.50, 4.07)	2.77 (2.15, 3.57)
IRR (95% CI)	0.87 (0.61, 1.23)	

a. Based on estimates from a negative binomial model with the independent variable of treatment group and adjusted for baseline HU use, age group, and region.

Supportive Trial Information Study GBT440-007

Study GBT440-007 is an ongoing phase 2a, multicenter, open-label study of voxelotor in pediatric patients with SCD. Key eligibility criteria for Part B included male and female, age 12 to 17 years, inclusive with SCD, Hgb ≤ 10.5 g/dL during screening was designed to assess the safety, tolerability, and pharmacokinetics of voxelotor. The primary endpoint was change from baseline in hemoglobin at Week 24. This study was composed of three parts and efficacy and safety data from Part B are discussed below.

Study GBT440-007(Part B) is an open-label study which enrolled 40 adolescent subjects: 15 in the voxelotor 1500mg group and 25 in the voxelotor 900mg group. A total of 80% (12/15) of the patients in the 1500mg group and 88% (22/25) of subjects in the 900mg group completed the study with 24 weeks of dosing.

Demographics
The median age in the 900mg dose was 14 years (range 12-17) and in the 1500mg dose was 14 years (range 12-17). Eighty-eight percent of patients in the 900mg dose were on hydroxyurea and 100% of patients in the 1500mg dose cohort were on hydroxyurea.

Efficacy Results
The baseline median hemoglobin in the voxelotor 900mg and 1500mg group were 8.9 g/dL and 8.8 g/dL, respectively. The median change in hemoglobin from baseline to Week 24 in the

voxelotor 900mg group was 0.7 g/dL and in the 1500mg group was 0.5 g/dL. At Week 24, the hemoglobin response (> 1g/dL Hb increase from baseline rates were 25% (3/12) in the 1500mg voxelotor group and 26.4% (8/22) in the 900mg voxelotor groups.

Reviewer Comments:
The supportive efficacy data demonstrate similar trends that were observed in the randomized study with improvements in hemoglobin.

8.1.3 Integrated Review of Effectiveness

Primary Endpoints

In Study GBT440-031 and supportive study GBT440-007 demonstrate an improvement in hemoglobin with voxelotor treatment for both the 900mg and 1500mg dose. The percentage of subjects achieving a hemoglobin response (≥ 1g/dL Hb increase from baseline at week 24 was dose dependent with results greater with the 1500mg dose group compared to the 900mg dose group. In Study GBT440-031, 51.1% (46/90) of patients in the 1500mg dose group achieve a Hb response at Week 24 compared to 6.5% (6/92) in the placebo group and in the supportive study,(GBT440-007), 41.7% (5/12%) in the voxelotor 1500mg group achieved an Hb response at Week 24.

Secondary and Other Endpoints

Similar reductions in hemolysis parameters were observed in Study GBT440-031 and Study GBT440-007. 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 changes in hemolysis measures were maintained through week 24 for both the 900mg and 1500mg doses.

Subpopulations

Not Applicable

Conducting a pooled subgroup analysis

Not Applicable

Additional Efficacy Considerations

8.1.4 Not Applicable Integrated Assessment of Effectiveness

The Applicant has provided sufficient evidence of effectiveness for voxelotor. The response rate for voxelotor 1500mg was 51.1% (46/90) compared to 6.5% (6/92) in the placebo group ($p<0.001$). Additional efficacy evaluation included change in hemoglobin, percent change in

indirect bilirubin and percent reticulocyte count from baseline to week 24. In the voxelotor 1500mg group, the mean change from baseline to week 24 for hemoglobin, indirect bilirubin and percent reticulocyte count were 1.14g/dL, -29.08%, -19.93%, respectively. In the placebo group, the mean change from baseline to week 24 for hemoglobin, indirect bilirubin and percent reticulocyte count were -0.08g/dL, -3.16% and 4.54%, respectively. Data from the Phase 2a open-label study, GBT440-007, support the efficacy of voxelotor on increasing hemoglobin.

8.2 Review of Safety

8.2.1 Safety Review Approach

A total of twenty-two studies were conducted across the clinical development program for voxelotor. These include 6 SCD studies, 14 completed healthy-subject and clinical pharmacology studies, and 2 other studies (1 completed, 1 closed) conducted in subjects with idiopathic pulmonary fibrosis (IPF). See Table of Studies in Section 7.1 above.

The ongoing pivotal Phase 3 study in adults and adolescents -Study GBT440-031, serves as the primary source of safety data for this submission. The safety profile in adolescents is supported by data from the completed Part B of Study GBT440-007. Details of the protocol design of both studies were described in Section 8.1 above. Safety data for these 2 SCD studies were presented separately. To enable a comparison with the safety profile in adults, the Applicant pooled the adolescent data from Studies GBT440-031 and GBT440-007 Part B.

Table 43 Subjects Included in Pooled Adolescent Safety Population

	Number of Subjects		
Subjects Age 12 to < 18 Years	Placebo (N = 17)	Voxelotor 900 mg (N = 40)	Voxelotor 1500 mg (N = 29)
Study GBT440-031	17	15	14
Study GBT440-007 Part B	NA[a]	25	15

For each study, the Safety Population was defined as all subjects who received the treatment to which they were assigned.

The Applicant's safety analyses were replicated for confirmation and supplemented where necessary by the FDA. Statistical analyses by the clinical reviewer were performed using JMP 12.0 (SAS Institute, Inc., Cary, NC), and MedDRA Adverse Events Diagnostic (MAED) v1.2 (Clinical Trials & Surveys Corporation, Owings Mills, MD).

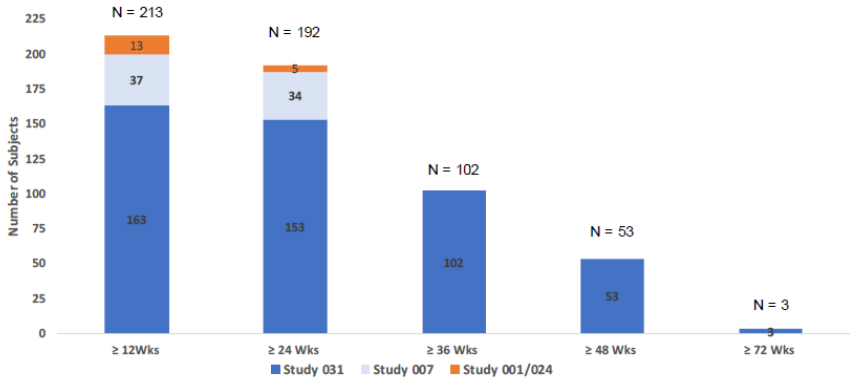
8.2.2 Review of the Safety Database

Overall Exposure

Overall, across all clinical studies in the voxelotor clinical development program, a total of 681 subjects have been exposed to at least 1 dose of voxelotor. These include 281 patients with SCD (180 patients from Study GBT440-031; 51 patients from Study GBT440-007 = 51; 42 subjects from Study GBT440-001; and 8 EAP subjects).

Overall, subjects with SCD in Studies GBT440-031, GBT440-007, GBT440-001, GBT440-024, and the EAP have been exposed for 172.0 subject-years with daily doses of voxelotor. The overall extent of exposure to voxelotor for all subjects in the SCD Studies GBT440-031, GBT440-007 Part B, GBT440-001, and GBT440-024 is shown in the figure below:

Figure 10: Voxelotor Exposure in Adult and Adolescent Subjects With SCD in Studies GBT440-031, GBT440-007, GBT440-001, and GBT440-024

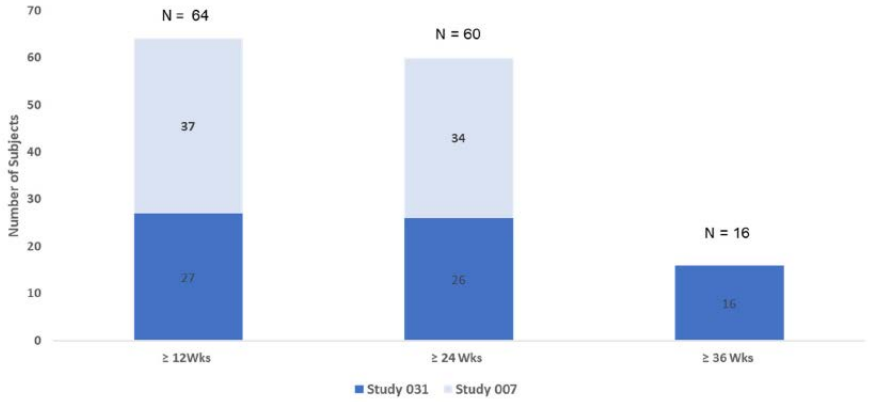


Source: Summary of Clinical Safety 2.7.4 Figure 1

In Study 034, the pivotal study supporting this application, majority of subjects (84.1%, 85.9%, and 84.6% in the voxelotor 1500-mg, voxelotor 900-mg, and placebo groups, respectively) were exposed to ≥ 24 weeks of study drug

The overall extent of exposure to voxelotor for adolescents in SCD Studies GBT440-031 and GBT440-007 Part B is shown in the figure below:

Figure 11: Voxelotor Exposure in Adolescent Subjects With SCD in Studies GBT440-031 and GBT440-007



Source: Summary of Clinical Safety 2.7.4 Figure 2

Adequacy of the safety database:

The indication sought with the current submission is approval of Voxelotor for the treatment of sickle cell disease in in adult (b) (4) patients.

The total number of subjects (n= 681, including 281 patients with SCD exposed for 172.0 subject-years with daily doses of voxelotor) exposed to voxelotor in the entire development program is adequate and meets the recommended size specified in ICH E1A guidelines for a chronically administered medication. The most substantial exposure in the SCD clinical development program comes from the pivotal study, GBT440-031 where the majority of subjects (84.1%, 85.9%, and 84.6% in the voxelotor 1500-mg, voxelotor 900-mg, and placebo groups, respectively) were exposed to ≥ 24 weeks of study drug. The demographics and disease characteristics of subjects enrolled in study 031 is reflective of the US target SCD population and allows for generalizability of the safety findings. Refer to demographic and other baseline disease characteristics of study population in Section 8.1 above.

At the time of NDA submission, the median duration of follow-up in Study 031 was 39.6. In the 90-day safety update submitted on September 24, 2019, the Applicant provided updated safety data from the voxelotor clinical development program with an additional 6 months of exposure in Study GBT440-031 (cutoff date of 07 May 2019). The cutoff date for the original NDA was October 31, 2018. The total number of subjects exposed to at least 1 dose of voxelotor increased from 681 in the original NDA to 724 in the 90-day safety update. The median duration of follow-up at this time was 63.6 weeks (range: 0.1 to 87.1 weeks).

In the 90-day safety update, additional safety data was provided for 76 enrolled subjects in Study GBT440-034. The median duration of follow-up for safety-evaluable subjects (n=53) in this study was 11.1 weeks (range: 1.3 to 48.0 weeks). The Safety-Evaluable Population was defined as subjects who received at least 1 dose of study drug in Study GBT440-034 and had at least 1 postbaseline safety assessment or reported adverse event (AE).

8.2.3 Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

This NDA was submitted on June 26, 2019 in eCTD format. FDA had no concerns regarding the submission quality of the data submitted. The applicant requested priority review. The application was filed on August 25, 2019. Expedited priority review was granted.

All studies were conducted in accordance with International Council for Harmonization Good Clinical Practice Standards – per the Applicant.

A core data fitness assessment was conducted by FDA to assess the quality & composition of data submitted to the Agency. Traceability between SDTM and Adam datasets was confirmed. No major deficiencies were identified. FDA reviewed case report forms and narratives of individual subjects who experienced severe adverse events and confirmed the consistency of the data submitted.

Categorization of Adverse Events

This section describes the Applicant's process for recording, coding, and categorizing AEs as well as FDA's approach to safety analyses.

Across all clinical studies in SCD subjects, treatment-emergent adverse events (TEAEs) were defined as any AE that emerged on or after initiation of study drug (having been absent pretreatment), or an AE that existed pretreatment and worsened on treatment (relative to the pretreatment state). AEs were recorded from the time informed consent was obtained through 28 days following the last dose of study drug. AEs were coded using MedDRA Version 19.0 and tabulated by System Organ Class (SOC) and Preferred Term (PT) at the event and subject level by treatment group. TEAEs were also summarized by investigator-assessed severity and relationship to study drug.

For these key studies (GBT440-031 and GBT440-007), the Applicant categorized all TEAEs into non- SCD–related and SCD-related TEAE. SCD-related TEAEs include: sickle cell anemia with crisis, acute chest syndrome (ACS), pneumonia, priapism, and osteonecrosis. Similarly, SAEs were categorized as non- SCD–related or SCD-related.

For adolescent subjects (12 to < 18 years) with SCD, AE data from studies GBT440-031 and GBT440-007 Part B were pooled. The justification for pooling the data was that, adolescent populations in both studies have similar characteristics (e.g., majority HU use, majority hemoglobin sickle cell disease with 2 sickle cell genes [SS] [HbSS]/HbSβ0 genotype); and the voxelotor dose regimens and safety assessments was comparable in the two studies.

In the Case Summary Report (CSR) for Study GBT440-031, MedDRA version 19.1 was used while MedDRA version 20.0 was used in the GBT44-007 CSR and for the pooled AE data for adolescent subjects in Studies GBT440-031 and GBT440-007. TEAEs were summarized by pooling each voxelotor dose levels (900 mg and 1500 mg) across studies and mapped to SOC and PT using MedDRA version 20.0. In the 90-Day safety update, AEs in Studies GBT440-031, GBT440-034 were coded using the MedDRA version 22.0.

The Applicant's safety analyses were replicated for confirmation and supplemented where necessary by FDA. Although the study design was different for studies GBT440-031 (randomized phase 3 study) and GBT440-007 Part B (open label phase 2 study), FDA agrees with the Applicants justification for pooling data in the adolescent population.

Statistical analyses by the FDA clinical reviewer were performed using JMP 12.0 (SAS Institute, Inc., Cary, NC), J Review and MedDRA Adverse Events Diagnostic (MAED) v1.2 (Clinical Trials & Surveys Corporation, Owings Mills, MD).

Routine Clinical Tests

In both Studies GBT440-031 and GBT440-007, laboratory assessments (hematology, serum chemistry, urinalysis, erythropoietin, coagulation) – were performed through a central laboratory at regular time points throughout the treatment and follow up period as per the protocol schedule of assessments. Refer to the Schedule of Assessments in Protocol GBT440-031 and Protocol GBT440-007.

In Study GBT440-031, Hb response rate at Week 24 was the primary endpoint and subjects were required to have Hb levels ≤10.5 g/dL at enrollment. Because knowledge of certain laboratory assessments (Hb, hematocrit [Hct], RBC count, total and unconjugated bilirubin, and absolute and percentage reticulocyte count) could suggest the treatment assignment, these measurements were redacted to the investigator and monitored on a regular basis by the DSMB. Clinically significant laboratory abnormalities were reported as AEs on the eCRF. Changes from baseline in Hb, reticulocyte percentage, and absolute reticulocyte count up to Week 24 were evaluated by the Applicant. Changes from Baseline for other hemolysis measures evaluated include indirect bilirubin, reticulocyte percentage, absolute reticulocytes, and lactate dehydrogenase.

The safety assessment methods and time points for both studies appear reasonable or adequate for the population, disease, and indication. An evaluation of hematology parameters

could only be provided up to Week 24 because as of the 31 October 2018 cutoff date, data for Hb or the hemolysis measures at Week 48 were only available for ≤ 25 of subjects per treatment group.

Changes in serum chemistry parameters (including Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), Alkaline phosphatase (ALK), Blood urea nitrogen (BUN), Creatinine were also evaluated. Clinically significant laboratory abnormalities were reported as AEs. Available liver function test (LFT) data were evaluated for evidence of drug-induced liver injury in all subjects.

8.2.4 Safety Results

Deaths

In the original submission filled by the Applicant in June 2019, four deaths in primary safety population (including 1 subject in each of the voxelotor groups and 2 subjects in the placebo group) were reported. Three deaths (1 in each treatment group and 1 in the placebo group), were due to a fatal sickle cell anemia with crisis. The other death in the placebo group, was due to a fatal cardiac arrest. All 4 deaths were treatment emergent. None of the deaths were considered to be related to study drug by the investigator.

In the 90-day safety update, 2 additional deaths (both in adults) were reported to have occurred in the voxelotor 1500-mg (Subject (b) (6) and 900-mg group (Subject (b) (6)) respectively.

A summary of the narrates for all treatment- emergent deaths in the voxelotor treated patients in Studies GBT440-031 and GBT440-007 are presented below.

Subject (b) (6) was a 23 year old African-American male with a history of HbSS sickle cell disease. He had 1 vaso-occlusive crisis (VOC) event in the 12 months prior to study initiation which required hospitalization. His hemoglobin was 8.4 g/dL at screening and was not taking hydroxyurea. He was enrolled in Study 031 and randomized to the voxelotor 1500mg treatment arm.

On Study Day 19, he presented with generalized body pains, headaches, and 3 episodes of diarrhea. He was diagnosed with Grade 2 malaria and Grade 2 VOC and was hospitalized. Treatment for the uncomplicated malaria included artemether and artemether-lumefantrine; treatment for painful crisis included tramadol, ceftriaxone and hydration. He improved and was discharged home on study day 20. On study day 24 & 25, the events of uncomplicated malaria and painful crisis were reportedly resolved.

On Study Day 133, the subject experienced another event of malaria and was treated with paracetamol and proguanil (Paludrine) for 2 days. On Study Day 139, the subject experienced the events of respiratory tract infection with sepsis, VOC (reported as acute sickle hepatic crisis [ASHC]), and VOC. He completed treatment with artemether-lumefantrine as well as erythromycin (empirically), paracetamol and also given intramuscular diclofenac injections for pain. The following day, (Study Day 140), the subject had chest congestion, which was reported to have occurred after starting erythromycin and resolved after discontinuing this drug. He was however noted to have facial puffiness, decreased urinary frequency and was passing of cola-colored urine. On Study Day 141, he reported to the clinic with generalized body pains and facial puffiness. He appeared ill, restless with severe pain, in respiratory distress, and had moderate pallor and moderate jaundice. Abdominal examination revealed generalized tenderness, hepatomegaly and splenomegaly. He also had tachypnea (30 breaths/minute), bronchial breath sounds, tachycardia and a flow murmur. He was started treated with IV hydration, ceftriaxone and intramuscular tramadol. Peripheral smear showed no malaria parasites. Laboratory results showed hemoglobin at 6.9 g/dL, hematocrit at 0.20 L/L, platelets at 68,000, white blood cell count at 28.67 × 109, neutrophils at 11.90, lymphocytes at 16.14, monocytes at 0.29, eosinophils at 0.20, and basophils at 0.14. He also had low potassium (3 mmol/L, reference range: 3.5-5.1 mmol/L), low chloride (92 mmol/L, range: 98-107 mmol/L), and low creatinine (43 µmol/L, range: 62-106 µmol/L); sodium, urea, and estimated filtration rate were all within normal range. His liver function tests were abnormal with elevated alkaline phosphatase, gamma-glutamyl transferase, alanine transaminases, C-reactive protein bilirubin and conjugated bilirubin. His condition deteriorated prompting transfer to another hospital. On admission, he was febrile (98.2F), tachypneic, tachycardic (126 bpm) and hypotensive (80/70mmHg). Fifteen minutes later, he went into further respiratory distress and died despite initiation of advanced cardiac life support.

The investigator assessed the events of Grade 2 malaria and Grade 2 VOC as not related to blinded study treatment. The investigator assessed the events of Grade 5 respiratory tract sepsis, Grade 5 VOC/ASHC, and Grade 5 VOC as not related to blinded study treatment.

Review Comment:

In this 23-year-old Kenyan male the diagnosis of malaria was not unexpected. Three days later following malaria treatment, he was started on a macrolide antibiotic for an acute bacterial infection and later developed symptoms suggestive of possible hypersensitivity reaction. His condition deteriorated rapidly, with a presentation suggestive of acute liver failure with shock.

The Sponsor acknowledged the temporal onset of the subject's symptoms and elevated LFTs are consistent with hepatocellular injury (Hy's Law). However, given the Coartem-erythromycin use, FDA agrees it plausible that the coartem-erythromycin combination contributed to the subject's hepatic insult and/or acted as a trigger of the subject's underlying sickle cell disease. FDA assessed the causal association between voxelotor and Grade 5 VOC as ***unlikely****.*

Subject (b) (6) was a 21 year old middle Eastern male diagnosed with HbSS sickle cell disease. He had a history of 1 VOC event in the 12 months prior to study enrollment , was taking hydroxyurea at study entry and had a screening hemoglobin of 7.1g/dl. He was enrolled in Study 031 and randomized to the voxelotor 900mg treatment arm.

On Study Day 254, the subject experienced VOC and was admitted to the hospital and transferred to the ICU for suspected pulmonary embolism and mesenteric vascular occlusion. He was treated with saline, glucose, and paracetamol and received 1 unit of blood transfusion (1 unit).He died on Study Day 256. An autopsy was not performed. He received his last dose of voxelotor on Study Day 253. The investigator and Sponsor assessed the event of Grade 5 VOC as unrelated to study treatment.

Reviewer comment:
Limited information was provided by the applicant on the course events leading up to death in this patient. In the absence of further details, the causal association between Voxelotor treatment and death in this patient is ***unclassifiable****.*

Subject (b) (6) (death reported in the 90-Day Safety Update)

Subject (b) (6) was a 39-year-old Black male with HbSS disease and a history of 6 VOC events requiring emergency room visits within the 12 months prior to study enrollment. He was taking HU (for 4 years prior to study entry) and his hemoglobin was 6.2 g/dL at screening. Reported SCD related complications prior to study entry for this patient included a history of acute chest syndrome, cholecystectomy, leg ulcers, and ongoing scleral icterus. He was enrolled in Study GBT440-031 and randomized the voxelotor 1500mg treatment arm.

On Study Day 297, the subject was found unconscious, hypothermic and unresponsive in his home by a friend. He had complained of severe sickle pain 2 days previously but refused to go to the emergency room. He was intubated and transported by EMS to a local hospital where he was found to be hypernatremic (serum sodium of 161 mmol/l), hyperkalemic (serum potassium of 6.9 mmol/dl) and reported to have a lactic acidosis. Chest x-ray showed a right lower lobe opacity, suspicious for pneumonia and cardiomegaly with pulmonary venous hypertension. An initial head CT without contrast showed a probable acute/subacute left basal ganglia lacunar infarct, no evidence of an intracranial hemorrhage or mass effect and moderate acute left maxillary sinusitis and left mastoiditis. He was diagnosed with severe hypernatremia, a right basilar pneumonia likely secondary to aspiration, acute renal failure likely secondary to rhabdomyolysis (CPK 9690) with shock liver (ALT 289, AST 133) and severe anemia (hb 7.3 g/dL declining to 4.9 g/dL), and possible cerebrovascular accident (CVA). Blood cultures and a urine toxic screen were negative. He was managed in the ICU and received iv antibiotics (Vancomycin and Zosyn), and a total of 4 units of PRBCs. He had ongoing encephalopathy and on neuro exam he was noted to have a positive Babinski sign consistent with an UMN lesion.

On Study Day 301, a repeat head CT with contrast revealed multiple brain lesions concerning for multi-focal abscesses in the setting of sepsis. On Study Day 302, he was transferred to a neurology intensive care unit for neurosurgical evaluation due to persistent encephalopathy and the new head CT findings of multifocal abscesses. Transthoracic echocardiogram on the same day showed good function without obvious vegetations. He was treated empirically with cefepime, metronidazole and continued on vancomycin. Magnetic resonance imaging of the brain with and without contrast showed multiple small ring-enhancing lesions in the brain and brainstem consistent with multiple brain abscesses. Lumbar puncture findings were consistent with a bacterial infection with: no red blood cells, WBC count of 283/µL (0-5), segmented neutrophil percentage of 84% (0-6), lymphocyte percentage of 15% (40-80), monocyte percentage of 1% (15-45), glucose of 32 mg/dL (40-70), and total protein of 121 mg/dL (15-45); no Herpes simplex virus DNA was detected; gram smear test showed 4+ mononuclear cells, 3+ polymorphonuclear cells, no organisms were seen. He was treated with levetiracetam (Keppra), meropenem, dexmedetomidine, midazolam (Versed), acetaminophen, and fentanyl. On Study Day 308, the decision was made to transition the subject to comfort care. Electroencephalogram showed right parietal dysfunction with periodic sharp waves, no ongoing epileptiform activity, severe diffuse encephalopathy. On Study Day 309, the subject died.

The investigator reported the cause of death as encephalopathy due to brain abscess. The investigator and Sponsor assessed the events of Grade 5 encephalopathy and Grade 5 brain abscess as not related to blinded study treatment.

FDA comment: *This patient was treated with voxelotor 1500mg daily and had no reported TEAEs other than grade 2 syncopal episode on Study Day 51 for which no further information is available. He was found unconscious in his home on study day 297 and had apparently complained of severe sickle cell pain 2 days prior. He was transferred to a local hospital and was initially diagnosed with severe hypernatremia, right basilar pneumonia likely secondary to aspiration, acute renal failure likely secondary to rhabdomyolysis with shock liver and severe anemia (with a decrease in hemoglobin from 7.3 g/dL declining to 4.9 g/dL), and possible CVA from an initial CT without contrast showed a probable acute/subacute left basal ganglia lacunar infarct.*

Given this patients prior complaint of severe sickle cell pain, and presentation to the hospital with severe anemia as well as chest x-ray findings suspicious for pneumonia, he likely had a VOC event with acute chest syndrome. Four days later, on Study Day 301, a head CT with contrast revealed multiple brain lesions concerning for multi-focal abscesses in the setting of sepsis. The heart was ruled out as the source of septic emboli since TEE showed good function without obvious vegetations. He was not a known IV drug abuser and urine toxicology screening was negative on admission to hospital. A likely source of his brain abscessed could be sinusitis given evidence of moderate acute left maxillary sinusitis and left mastoiditis noted on his initial CT head.

Per the sponsors assessment, this patients' clinical presentation and subsequent course is consistent with neurologic complications of his brain lesions, including loss of consciousness,

seizure, persistent encephalopathy and subsequent and resultant multi-organ failure although other concurrent neurologic events such as a CVA cannot be ruled out. The Sponsor assessed these events as unrelated to voxelotor and related to complications related to the subjects underlying sickle cell disease.

Although the immediate cause of death in this patient was likely multifocal intracerebral abscesses, the inciting event in the cascade of events leading to this patient's death is likely an acute VOC event with severe anemia, and an acute/subacute cerebral infarct with subsequent development of multiple brain abscesses from an unknown source. This reviewer accessed the events acute VOC event with severe anemia, and acute/subacute cerebral as likely related to the subjects underlying sickle cell disease.

Subject (b) (6) (death reported in the 90-Day Safety Update)
This was a 54-year-old Black female diagnosed with HbSS disease and a history of 9 VOC events, 1 requiring hospitalization, within the 12 months prior to study enrollment. She was taking hydroxyurea at study entry and her hemoglobin was 8.4 g/dL at screening. Her medical history included transient ischemic attack, non-cardiac chest pain, palpitations, osteonecrosis, osteoarthritis, ventricular extrasystoles, retinal degeneration (2007), obesity, abdominal pain and hypertension. She was enrolled in Study GBT440-031 and randomized to the voxelotor 900mg treatment arm.

Study treatment was interrupted due to an SAE of Grade 2 sickle cell anemia with crisis from Study Days 214-215. On Study Day 337, Grade 5 death due to unknown etiology was reported. She reportedly felt unwell the previous evening and was found unconscious in bed the following morning. An autopsy was declined. Her date of last study dose intake unknown.

The investigator assessed the event of Grade 2 sickle cell crisis as not related to blinded study treatment. The investigator assessed the event of Grade 5 death as not related to blinded study treatment. At the time of the assessments, the Sponsor agreed with the investigator.

***FDA comment**:*
This reviewer accessed the events of Grade 2 sickle cell anemia with crisis *as likely related to the subjects underlying sickle cell disease.*
Limited information was provided on the course events leading up to death in this patient. In the absence of further details, the causal association between Voxelotor treatment and death in this patient is ***unclassifiable****.*

Serious Adverse Events

Non-SCD related SAEs: Study 031:
SAEs in the Respiratory, Thoracic, and Mediastinal Disorders SOC occurred more commonly in the voxelotor 1500-mg group (5.7% [5/88 subjects]) than in the voxelotor 900-mg group (0.0%) or the placebo group (1.1% [1/91 subjects]). In the voxelotor 1500-mg group, these events included pleural effusion (2 subjects) and pulmonary embolism, acute respiratory failure, and

respiratory failure (in 1 subject each). The table below shows the incidence of non- SCD–related SAEs by PT in Study GBT440-031.

Table 44: Non-SCD–Related Serious Adverse Events Reported in ≥ 2 Subjects in Any Treatment Group (Safety Population – Study GBT440-031)

	GBT440 1500 mg n=88	GBT440 900 mg n=92	Placebo n=91
Subjects with at least 1 SAE - count subjects and % with data	**17 (19.3)**	**16 (17.4)**	**15 (16.5)**
Pleural effusion	2 (2.3%)	0 (0.0%)	0 (0.0%)
Malaria	1 (1.1%)	3 (3.3%)	0 (0.0%)
Anemia	0 (0.0%)	2 (2.2%)	2 (2.2%)
Pyrexia	0 (0.0%)	2 (2.2%)	2 (2.2%)
Gastritis	0 (0.0%)	2 (2.2%)	0 (0.0%)

Source: FDA analyses

The table below shows the incidence of drug-related non-SCD related SAEs by PT in Study GBT440-031.

Table 45: Study Drug–Related Non-SCD–Related SAEs (Safety Population – Study GBT440-031)

	GBT440 1500 mg n=88	GBT440 900 mg n=92	Placebo n=91
	SCD Not Related	**SCD Not Related**	**SCD Not Related**
Subjects with Drug related Non-SCD related SAESs	**3 (3.4%)**	**3 (3.3%)**	**1 (1.1%)**
Headache	1 (1.1%)	0 (0.0%)	0 (0.0%)
Pulmonary embolism	1 (1.1%)	0 (0.0%)	0 (0.0%)
Drug hypersensitivity	1 (1.1%)	0 (0.0%)	0 (0.0%)
Rash generalized	0 (0.0%)	1 (1.1%)	0 (0.0%)
Type 2 diabetes mellitus	0 (0.0%)	1 (1.1%)	0 (0.0%)
Hepatitis acute	0 (0.0%)	1 (1.1%)	0 (0.0%)
Thrombocytosis	0 (0.0%)	0 (0.0%)	1 (1.1%)

Source: FDA analyses

Review comment:

Overall, the incidence of non-SCD related SAEs was comparable across treatment groups. The incidence of drug related non-SCD related SAES was also comparable across treatment groups. No drug-related SAE was reported in more than 1 subject in any treatment group. Summary narratives of drug-related SAEs occurring in voxelotor treated subjects are provided below.

The tables below shows the incidence of non-SCD related and drug-related non-SCD related SAEs in the pooled adolescent population.

Non-SCD related SAEs: Pooled Adolescent population:

In the pooled adolescent population from Study 031 and Study 007, the only Non-SCD SAE that occurred in more than 1 subject was pyrexia occurring in 2 placebo treated patients (results not shown).

SCD related SAEs: Study 031:

The tables below shows the incidence of SCD related SAEs in the safety population (Study 031).

Table 46: SCD–Related SAEs (Safety Population – Study GBT440-031)

	GBT440 1500 mg n=88	GBT440 900 mg n=92	Placebo n=91
	SCD Related	SCD Related	SCD Related
Subjects with at least 1 SAE - count subjects and % with data	**41 (46.6%)**	**42 (45.7%)**	**40 (44.0%)**
Sickle cell anemia with crisis	39 (44.3%)	38 (41.3%)	39 (42.9%)
Acute chest syndrome	11 (12.5%)	7 (7.6%)	4 (4.4%)
Pneumonia	3 (3.4%)	3 (3.3%)	4 (4.4%)
Priapism	0 (0.0%)	1 (1.1%)	0 (0.0%)
Osteonecrosis	0 (0.0%)	0 (0.0%)	1 (1.1%)

Source: FDA analyses

Review comment:

The incidence of SCD related SAEs was similar between treatment groups (46.6%, 45.7 and 44.0%). The most common SCD related SAE was sickle cell anemia with crisis. Four subjects had drug related SCD related SAEs - all sickle cell anemia with crisis (not shown in table). The incidence of acute chest syndrome was highest in the voxelotor 1500mg treatment group. This is likely explained by the higher incidence of ACS in the voxelotor 1500mg treatment group at baseline.

SCD related SAEs: Pooled Adolescent population:

As in the adult population, in the pooled adolescent population from Studies 031 and 007, the most common SCD-related SAEs was sickle cell anemia with crisis - similar to adult population.

Table 47: SCD–Related SAEs (Safety Population – Studies GBT440-031 & GBT440-007)

	GBT440 1500 mg n=29	GBT440 900 mg n=40	Placebo n=17	Totals n=86
	SCD related	SCD related	SCD related	
Subjects with Non SCD related SAEs -	**10 (34.5%)**	**16 (40.0%)**	**7 (41.2%)**	**33 (38.4%)**

Sickle cell anemia with crisis	9 (31.0%)	15 (37.5%)	7 (41.2%)	31 (36.0%)
Priapism	2 (6.9%)	1 (2.5%)	0 (0.0%)	3 (3.5%)
Acute chest syndrome	2 (6.9%)	1 (2.5%)	1 (5.9%)	4 (4.7%)
Pneumonia	0 (0.0%)	2 (5.0%)	0 (0.0%)	2 (2.3%)
Osteonecrosis	0 (0.0%)	0 (0.0%)	1 (5.9%)	1 (1.2%)

Source: FDA analyses

Narratives of Voxelotor treated patients with Drug-Related SAEs

Subject (b) (6) was a 22-year-old Arab/Middle Eastern male with HbSS genotype sickle cell disease who was taking hydroxyurea at study entry. His sickle cell disease history included 1 VOC/acute chest syndrome event in the 12 months prior to study initiation. Hemoglobin at baseline was 9.0 g/dL at study day -6 prior to study entry. He was enrolled in Study 031 and randomized to the voxelotor 1500mg daily treatment arm.

Study treatment was interrupted for this patient on Study Days 71-79 due to an AE of Grade 1 tonsillitis. On Study Day 77, the subject experienced Grade 3 sickle cell anemia with crisis and was admitted to the hospital on Study Day 78 for management of pain crisis. Treatment received for the event included intravenous hydration, antibiotics (ceftriaxone sodium), as well as paracetamol, ibuprofen, morphine and tramadol for pain. The event of VOC was resolved on Study Day 84, and the subject was discharged from the hospital on the same day. No action was taken with study treatment due to the event. The investigator and Sponsor assessed the Grade 3 VOC as not related to blinded study treatment.

On Study Day 180, the subject experienced Grade 3 pulmonary embolism and Grade 1 pneumonia. By report, while at home, the subject had intermittent loss of consciousness for 5 minutes with dyspnea, tachypnea, chest pain, and palpitations. In the emergency department on the same day, he was noted to have generalized pallor and bluish discoloration of the lips and was hypotensive, tachycardic, and hypoxic. Laboratory results revealed decreased hemoglobin (exact value not reported) and platelets at 400,000 (units and reference ranges were not reported). The subject apparently missed 17 doses of study treatment in the 5 month period prior to Study Day 180 (exact dates are unknown).

Computed tomography (CT) angiogram of the chest demonstrated multiple pulmonary emboli, including a segmental right lower lobe embolus and subsegmental emboli in the right middle, right upper lobe, and left upper lobe; dilatation of the right ventricle and pulmonary artery, considered likely chronic in nature; and left lung base and right middle lobe consolidation considered to be infection-related and with trace left pleural effusion. Chest x-ray showed air space consolidation at the left lung base, clear right lung, and prominent cardiac silhouette. Duplex ultrasound of his lower extremities showed no evidence of deep or superficial venous thrombosis bilaterally. The subject was diagnosed with massive right-sided pulmonary embolism with no evidence of deep vein thrombosis (DVT), and a small left-sided Grade 1 pneumonia. Study treatment was discontinued (Study Day 180) and the subject was hospitalized. . Treatment received for the event included fluid resuscitation, packed red blood

cells transfusion (4.4 units), oxygen therapy, anticoagulants (heparin and enoxaparin sodium), antibiotics (ceftaroline, clarithromycin, ceftriaxone), budesonide, ipratropium bromide, prophylactic esomeprazole and pain medications including paracetamol, tramadol, morphine, fentanyl, diclofenac and gabapentin.

On Study Day 191, the Grade 3 pulmonary embolism was considered resolved and the subject was discharged from the hospital. On Study Day 223, study treatment was permanently discontinued due to the AEs of pulmonary embolism and pneumonia. The investigator assessed the event of Grade 3 pulmonary embolism as related to blinded study treatment and the sponsor agreed with the investigator at the time of assessment.

Review comment:
This patient (22 yo) with Hb SS disease had a history of SCD complications prior to study including a previous history of ACS, splenectomy and a baseline hemoglobin of 9g/dl. He was diagnosed with a massive pulmonary embolism, and acute chest syndrome 6 months after study entry.

ACS is a serious acute complication of SCD and a leading cause of mortality in both children and adults with Hb SS disease (Vichinsky, Neumayr et al. 2000). In adults with SCD, ACS is usually more severe and has a higher mortality rate than in children, is commonly precipitated by fat embolism and infection, especially community-acquired pneumonia (Maitre, Habibi et al. 2000, Vichinsky, Neumayr et al. 2000). ACS in this patient is also not unexpected given his previous history of ACS prior to study entry. A high risk/incidence of venous thromboembolism has also been reported for patients with sickle cell disease. (Brunson, Keegan et al. 2019).

Therefore, considering the known risk of ACS and venous thromboembolism in patients with SCD, the previous history of SCD in this patient and the lack of any preclinical indication of thromboembolic risk associated voxelotor, FDA assessed the event of Grade 3 pulmonary embolism as "unlikely" to be related to study treatment. FDA assessed the event of ACS as related to the patients baseline SCD.

Subject (b) (6) was a 27-year-old Not-Hispanic or Latino male with HbSS sickle cell disease. He had a reported history of 4 VOC events requiring hospitalization within the last 12 months prior to study enrollment and was taking hydroxyurea at study entry. His familial medical history included type 2 diabetes mellitus in his paternal grandmother. He was enrolled in Study 031 and randomized to the voxelotor 900mg treatment arm. He missed 2 doses of voxelotor on unspecified dates within the first month of enrollment, but otherwise received biweekly doses of voxelotor as per study protocol. On Study day 63, he presented to the emergency department with symptoms of polyuria, polydipsia, polyphagia, blurred vision, and unsteady gait. He was hyperglycemic [blood glucose level of 701 mg/dL (reference range: 75-100 mg/dL).] and subsequently admitted to hospital for hyperglycemia workup. His body mass index (BMI) was 44. He had no known history of hyperglycemia, diabetes, cardiac disorders, or

history of any recent infections. Other laboratory results during the hospitalization included blood glucose at 635 mg/dL, beta-hydroxybutyric acid at 0.95 mmol/L, lipase at 14 U/L, and C-peptide at 1.5 ng/mL (reference range: 0.8-3.5 ng/mL). He was diagnosed with new onset type 2 diabetes mellitus. Treatments administered during his hospitalization included intravenous fluids, regular insulin boluses, insulin glargine, and insulin aspart. Following successful treatment of the hyperglycemia, he was discharged home in a stable condition with continued insulin glargine and insulin aspart treatment with meals, and a carbohydrate-controlled diet was advised. Study treatment had been interrupted on Study Day 60. On Study Day 65, the subject discontinued study treatment and withdrew from study due to type 2 diabetes mellitus.

The Investigator and Sponsor assessed the event of Grade 4 type 2 diabetes mellitus as related to blinded study treatment however the Sponsor noted that the subject's risk factors of morbid obesity and family history of type 2 diabetes mellitus, provide a plausible alternative explanation for the episode of hyperglycemia.

Review comment:

FDA assessed the association between Grade 4 type 2 diabetes mellitus and voxelotor treatment as unlikely. This subjects was predisposed to development of type 2 diabetes mellitus due to his morbid obesity and family history of type 2 diabetes mellitus.

Subject (b) (6) was a 52-year-old Black or African American female diagnosed with HbSC genotype sickle cell disease. She had a history of 3 VOC events requiring hospitalization within the last 12 months prior to study enrollment. She was not taking hydroxyurea at study entry. Her hemoglobin at screening was 10.2 g/dL. She was enrolled in Study 031 and was randomized to the voxelotor 900 mg QD treatment arm.

Approximately 2 months after study treatment initiation, the subject experienced Grade 2 generalized rash – described as "dry skin/rash on hands and feet". On Study Day 67, study treatment was permanently discontinued. On Study Day 86, the subject saw a dermatologist who noted dry scaly hyperkeratotic plaques on the chest, abdomen, and arms that appeared eczematous, mainly scaling, and desquamating. The subject's hands had fissures and were peeling and noted to be more sensitive. There was no evidence of infection. There were no bullous or pustular lesions or urticaria. She was treated with topical betamethasone ointment and topical triamcinolone cream. The rash began to improve after discontinuation of study treatment but still had some remaining dry skin at the time of final follow-up. specific diagnosis for the rash was not provided.

Concomitant medications used by the subject within the enrollment period included: hydromorphone, calcium, morphine, multivitamin, docusate, folic acid, vitamin D, metoprolol tartrate, ondansetron, ranitidine, naproxen, aspirin, atorvastatin, triamcinolone 0.1% and betamethasone 0.05%

The investigator assessed the event of Grade 2 generalized rash as related to blinded study treatment. At the time of assessment, the sponsor agreed with the investigator. The Applicant noted that dry skin is not a typical presentation of drug-associated rash; and dry, scaly hyperkeratotic plaques suggest skin diseases such as eczema and psoriasis.

Review comment:
FDA assessed the event of Grade 2 generalized rash as related as likely related to voxelotor treatment. Although the subject was taking other concomitant medications during the enrolment period, the fact the rash improved after discontinuation of the study treatments lends support to a causal association between study drug use and the rash. This reviewer recommends including this finding in the label for voxelotor.

Subject (b) (6) was a 44-year-old Black and Asian female diagnosed with "other" genotype sickle cell disease. She had had 2 VOC events requiring hospitalization within the last 12 months prior to study enrollment and a history of Acute chest syndrome, cholecystectomy and scleral icterus. She was not taking hydroxyurea at study entry. Her medical history also included cardiomegaly, tricuspid regurgitation, mitral regurgitation-Grade 1, and anemia, as well as ongoing conditions including paroxysmal supraventricular tachycardia (PSVT), abnormal EKG-NSR/Q wave in lead III, metabolic acidosis, gout and herpes simplex virus infection. Her hemoglobin was 7.6 g/dL at screening. She was enrolled in Study 031 and was randomized to the voxelotor 900 mg QD treatment arm.

On Study Day 4, the subject experienced Grade 3 supraventricular tachycardia (SVT), reported as an exacerbation of underlying history of SVT. She reported to the emergency department and was treated with IV adenosine with the restoration of sinus rhythm with premature ventricular contractions (PVCs). A follow-up ECG performed on Study Day 5 showed sinus rhythm with frequent PVCs, nonspecific T-wave abnormality, and prolonged QT. This was considered a clinically significant change from baseline. On Study Day 7, the event of Grade 3 exacerbation of SVT was resolved and the subject was discharged from the hospital. No action was taken with study treatment due to this event.

On Study Day 192, the subject experienced Grade 2 back pain, suspected to be VOC related and was also treated for concomitant paroxysmal SVT. She was admitted to the hospital for pain management and treated with 2 doses of IV morphine , IVFs, and , IV ondansetron, oral APAP, subcutaneous enoxaparin, and IV adenosine. The event of back pain was considered resolved on the same day and the subject was discharged from the hospital Study Day 193. On Study Day 194, blinded study treatment was reintroduced. On Study Day 195, a day after discharge she was diagnosed with Grade 3 acute hepatitis, Grade 3 ACS, and Grade 4 worsening anemia and was hospitalized. At the time of admission, her hemoglobin (Hgb) was 5.7 g/dL (11.6-15.2 g/dL). Laboratory tests during admission showed elevated bilirubin, albumin 2.8 g/dL, AST 950 IU/L, and ALT 694 IU/L. Abdominal ultrasound showed a normal bile duct. She had leukocytosis, fever, and hypoxia, with a right lower lobe pulmonary infiltrate on chest x-ray, all attributed to

ACS. Her serum creatinine was elevated from a baseline of 1.7 mg/dL to 2.0 mg/dL. She was treated with acetaminophen, cefepime, prochlorperazine, sodium chloride, vancomycin, enoxaparin and metoprolol.

On Study Day 203, her WBC count was 10.4, and her blood chemistry showed markedly improved transaminitis (ALT of 96 and AST of 38), ALP of 193, potassium of 7, CO2 of 18, BUN of 30, GFR of 29, calcium of 8, and creatinine of 2.02 mg/dL. On Study Day 204, her vital signs were stable and the hypoxia was resolved. The investigator confirmed that the subject was clinically improved, the event of ACS was considered resolved, and the subject was discharged from the hospital. On Study Day 207, following hospitalization, the event of acute hepatitis was considered resolved. On Study Day 227, the event of worsening anemia was considered resolved.

The investigator assessed the event of:

- Grade 3 exacerbation of SVT as not related to blinded study treatment. At the time of assessment, the sponsor agreed with the investigator.
- Grade 2 back pain as not related to blinded study treatment. At the time of assessment, the sponsor agreed with the investigator.
- Grade 3 acute hepatitis as related to blinded study treatment. At the time of the assessment, the sponsor agreed with the investigator.
- Grade 3 ACS and Grade 4 worsening anemia as not related to blinded study treatment, and the sponsor agreed with the investigator.
- Grade 2 fever and Grade 3 hypoxia as not related to study treatment, and the sponsor agreed.

Review comment:
FDA assessed the events of Grade 2 back pain and Grade 3 exacerbation of PSVT as unrelated to study drug. Grade 3 exacerbation of SVT is likely due to the subject's longstanding underlying PSVT. FDA also assessed the events of Grade 3 ACS, and Grade 4 worsening anemia as likely related to the subjects underlying history of SCD.

"Acute Hepatitis" in this subject was non-viral. Markedly elevated liver enzymes were reported on study day 195 at the time when the subject also had severe anemia likely due to a VOC event, acute chest syndrome, possible right heart failure and PSVT. On study day 203, transaminitis was markedly improved. FDA is unable to determine the etiology of the event of transaminitis in this patient. Hepatic congestion, congestive hepatopathy exacerbated by her underlying cardiac disease and hepatic sequestration crises are plausible however, an idiosyncratic liver injury due to verapamil or study drug cannot be ruled out. Voxelotor treatment had been re-introduced to the patient on study day 194 Hepatic sequestration crises is unlikely given the absence of documented hepatomegaly on abdominal ultrasound. This case however, does not meet the Hy's Law criteria.

Subject (b) (6) was a 52-year-old African American female diagnosed with HbSS genotype sickle cell disease. She had a history of 2 VOC events requiring hospitalization within the last 12 months prior to study enrollment and was not taking hydroxyurea at study entry. Her hemoglobin was 9.5 g/dL at screening. She was enrolled in Study 031 and was randomized to the voxelotor 1500 mg QD treatment arm.

On study day 173, She was reported to have had severe pains complicated by hypertension and reported early signs of ACS. No other description of her symptoms was not provided. Her WBC was 14.9; electrocardiogram (ECG) showed normal sinus rhythm; and chest x-ray showed bilateral infiltrative changes and left lung base consolidation. Treatments received included IV fluids, antibiotics (ceftriaxone and clarithromycin), pain medications (fentanyl, gabapentin, morphine sulfate, paracetamol, ibuprofen) and antihypertensives(amlodipine, bisoprolol and doxazosin). She also received 1 unit of PRBCs on Study Day 173 and 6 units for an exchange transfusion with packed red blood cells on Study Day 175. The event of grade 3 VOC was considered resolved on study Day 182 and she was discharged from hospital on the same day. Study treatment was interrupted during her hospitalization due to Grade 3 sickle cell anemia with crisis and resumed on Study Day 189. Treatment was on-going at the time of data cutoff for submission. The investigator assessed the event of Grade 3 sickle cell anemia with crisis as related to blinded study treatment. The sponsor assessed the event as not related to blinded study treatment.

On Study Day 218, the subject presented to the Emergency department and was diagnosed with Grade 3 vitreous hemorrhage and Grade 3 blindness in the right eye. On Study Day 252, she underwent the following emergency surgery: right sided vitrectomy, right cryotherapy retinopexy, right injection of gas, and right laser retinopexy and was prescribed chloramphenicol 0.5% eye drops and dexamethasone eye drops 0.1%. Following surgery, the subject's vision improved but was worse than at baseline. On Study Day 252, both events were considered resolved with sequelae of partial loss of vision in right eye. The etiology of the event was reported as due to retinal detachment, not due to sickle retinopathy. No action was taken with the blinded study treatment due to these events. The investigator and sponsor assessed the events of Grade 3 vitreous hemorrhage and Grade 3 blindness as not related to blinded study treatment.

Review comment:
Although this patient did not meet protocol definition for ACS, the reported events of severe VOC, chest x-ray findings of bilateral infiltrative changes and left lung base consolidation and exchange blood transfusion are consistent with this diagnosis. FDA assessed the events of Grade 3 sickle cell anemia with crisis and likely acute chest syndrome as related to the patients baseline sickle cell disease.

FDA assessed the events of Grade 3 vitreous hemorrhage and Grade 3 blindness as unrelated to study treatment. Vitreous hemorrhage and visual loss resulting from non-SCD-related retinal

detachment are unexpected for voxelotor. Also , the subject recovered from this event though with some sequelae (partial loss of vision in right eye) without changes to study treatment during the event.

Subject (b) (6) was a 21 year old African American female with HbSS genotype sickle cell disease. Her sickle cell disease history included 3 VOC events in the 12 months prior to study entry and splenic sequestration. She was not taking hydroxyurea at study entry. Her hemoglobin was 8.7 g/dL at screening/baseline. She was enrolled in Study 031 and was randomized to the voxelotor 1500 mg QD treatment arm.

On Study Day 57, she was hospitalized and underwent planned laparoscopic cholecystectomy. The event of laparoscopic cholecystectomy was resolved on Study Day 59, and the subject was discharged from the hospital on the same day. No action was taken with the study treatment due to this event. The investigator and sponsor assessed the event of Grade 2 cholecystectomy as not related to blinded study treatment.

On Study Day 164, she was hospitalized for a 7-day history of central abdominal pain that localized to the right iliac fossa after 3 days. On Study Day 165, diagnostic tests including an ultrasound scan of abdomen, revealed appendicitis for which laparoscopic appendectomy was performed on Study Day 166. Treatments received included enoxaparin subcutaneously, amoxicillin sodium-clavulanate potassium, lactulose fentanyl and morphine. The investigator assessed the event of Grade 3 appendicitis as not related to blinded study treatment. At the time of the assessment, the sponsor agreed with the investigator.

One day following laparoscopic appendectomy, the subject experienced sickle cell anemia with crisis (VOC-chest), which prolonged her hospitalization. Computer tomography pulmonary angiography ruled out a pulmonary embolus. Treatments received for this event included morphine sulphate solution, codeine, diamorphine, normal saline and anticoagulant citrate dextrose solution, and the subject was transfused with 1 unit of packed red blood cells. The event of sickle cell anemia with crisis was resolved on Study Day 172, and the subject was discharged from the hospital on the same day. Study treatment was interrupted on Study Day 167 and resumed on Study Day 171.

On Study Day 289, the subject presented to the hospital and was diagnosed with another event of Grade 3 sickle cell anemia with crisis. She was treated with morphine and discharged. She returned to hospital again on Study Day 290 with ongoing pain. She was admitted and treated for pain with morphine and chlorphenamine. On Study Day 291 the event of VOC was considered resolved, and the subject was discharged from the hospital.

The investigator assessed the events Grade 3 sickle cell anemia with crisis as not related to blinded study treatment. At the time of the assessment, the sponsor agreed with the investigator.

Review comment: *FDA assessed the events of Grade 3 appendicitis, Grade 2 cholecystectomy and grade 3 VOC as unrelated to study drug. This patient experienced multiple VOC events which are not unexpected with her underlying sickle cell disease.*

Subject (b) (6) was a 41 year old Black male with HbSS genotype sickle cell disease. He was taking hydroxyurea at study start and his SCD history included 3 VOC events in the previous 12 months prior to study initiation. His hemoglobin was 10.1 g/dL at screening. His medical history included osteonecrosis, insomnia and obesity. He was enrolled in Study 031 and was randomized to the voxelotor 1500 mg QD treatment arm.
On Study Day 53, the subject presented to the accident and emergency department with severe headache (Grade 3) and was admitted. He denied any rashes, nausea, vomiting, or joint pain, and had no history of migraines or other types of headache. On examination, the subject was in severe pain with eyes closed in pain and holding his head in his hands. He had a normal neurologic exam; the Glasgow Coma Scale showed 14/15 (eyes closed). His last dose of study treatment was received on Study Day 52.

Laboratory tests results included normal oxygen saturation 95%, hemoglobin of 11.8 g/dL, WBC count of 10.7, platelets of 200, estimated glomerular filtration rate > 90, alanine transaminase of 117, and C-reactive protein of 6. CT imaging of his head showed no acute intracranial or osseous findings. He was started on a treatment dose of tinzaparin due to concern for venous sinus thrombosis.

On Study Day 55, the subject experienced Grade 4 type 2 respiratory failure with acute oxygen desaturation (SpO2 of 78%) for which he was started on continuous positive airway pressure. On Study Day 56, he was transferred to the intensive care unit (ICU) for bilevel positive airway pressure ventilation (BiPAP) due to worsening hypercapnia. Chest x-ray results showed cardiac enlargement and slightly congested lung fields with no focal lung lesions however, he had a fever and was therefore started on cefuroxime. His clinical course was thought to be likely due to an atypical chest crisis and he underwent exchange transfusion (8 units of packed red blood cells). His respiratory status improved and BiPAP was discontinued on Study Day 58. Empirical antimicrobial therapy including ceftriaxone and acyclovir was initiated.

The subject continued to experience severe headaches with significant relief with a fentanyl patient-controlled analgesia (PCA). On Study Day 63, MRI of the head showed no acute intracranial abnormality, specifically no infarct or hemorrhage. On Study Day 70, the headaches were considered resolved and the subject was discharged. Voxelotor was interrupted on Study Day 52 and then permanently discontinued.

The investigator assessed the event of Grade 3 headache as related to blinded study treatment and the Grade 4 respiratory failure as not related to blinded study treatment. At the time of assessment, the sponsor agreed with the investigator.

FDA reviewer comment: *The etiology of grade 3 headache in this patient with no history of headaches or migraines in this patient is intriguing. Differential diagnosis of headache in this patient include - a VOC event involving the skull, hyperviscosity possibly due an increase in Hb, a cerebral-vascular event, or the remote possibility of a side effect of opiates (concomitant medications for this patient include oxycodone). A VOC involving the skull may present with headache in patients with sickle cell disease. However, a VOC as the inciting event for this patient's headache is unlikely given his hemoglobin of 11.8 g/dL (up from a baseline hb of 10.1g/dl) and the absence of laboratory evidence of hemolysis on the day of presentation. MRI of the head ruled out an acute intracranial event, specifically no infarct or hemorrhage.*

Therefore, FDA assessed the event of grade 3 headache as possibly due to study treatment with voxelotor. Headache was also the most frequently reported non -SCD related AE in voxelotor treated patients in Study GBT440-031. This reviewer recommends including headache as one of the common side effects of voxelotor in the PI for voxelotor.

Regarding the episode of Grade 4 respiratory failure, this reviewer agrees with the Applicant that this patient had multiple risk factors that may have contributed to the event: obesity and snoring (possibly associated with sleep apnea) and opiate use, which, combined with obesity and pain, likely led to hypoventilation. He also likely had an event of acute chest syndrome consistent with his history of sickle cell disease.

Subject (b) (6) was a 26-year-old female of unspecified race diagnosed with HbSS genotype sickle cell disease. She had a history of 3 VOC events requiring hospitalization within the last 12 months prior to study enrollment and one blood transfusion. She was taking hydroxyurea at study entry and her medical history included osteonecrosis, secondary osteoarthritic changes, and right femoral shaft bone infarction. Her hemoglobin was 10 g/dL at screening. She was enrolled in Study 031 and was randomized to the voxelotor 1500 mg QD treatment arm. Study treatment was interrupted due to an AE of drug hypersensitivity from Study Day 49 to Study Day 51 and resumed on Study Day 52 at a reduced dose of 4 tablets per day. Study treatment was further reduced to 3 tablets per day on Study Day 55.

On Study Day 40, the subject was diagnosed with Grade 2 drug hypersensitivity reaction to study treatment, with onset of a maculopapular skin rash on arms, hands, and legs. On Study Day 49, the rash was persistent with increased severity to Grade 3, with facial swelling, urticaria, and shortness of breath. The subject had no history of rash, active dermatitis, or any known allergies. Study treatment was interrupted in response to this event. Treatment received included pheniramine maleate, dexamethasone, and fexofenadine. On 14 Study Day 52, the SAE of worsening of hypersensitivity reaction to study treatment was considered resolved, and study treatment resumed at a reduced dose (4 capsules per day). Subsequently, the subject had multiple reoccurrence of drug hypersensitivity events (Grade 1 – 3) with re-introduction of study treatment. Treatments received for these events included pheniramine maleate,

dexamethasone and mometasone furoate. On Study day 58, a complete blood count revealed neutropenia and eosinophilia. Her mild neutropenia was attributed to hydroxyurea and hydroxyurea was discontinued. The last dose of voxelotor was received on Study Day 56. On Study Day 67 the event of hypersensitivity resolved. On the same day, study treatment was permanently discontinued due to the AE of drug hypersensitivity.

The investigator and sponsor assessed the events of Grade 1-3 drug hypersensitivity as related to blinded study treatment.

Review comment: *FDA agrees with the sponsor's assessment that the events of* Grade 1-3 drug hypersensitivity *are related to study treatment and consistent with a delayed-type hypersensitivity reaction to voxelotor with a positive dechallenge/rechallenge and the development of eosinophilia. This reviewer recommends including drug hypersensitivity in the warnings and precautions section of the label for voxelotor.*

Subject (b) (6) was a 30-year-old Black or African American female diagnosed with HbSS genotype sickle cell disease. Her sickle cell disease history included 2 VOC) events in the previous 12 months prior to study entry requiring treatment in the emergency department. Sickle cell disease complications included ACS, hematuria, kidney dysfunction, and ongoing scleral icterus. Her medical history included hyperthyroidism, Grade 2 systolic murmur rheumatoid arthritis, and an unspecified vascular disorder. Her hemoglobin was 8.2 g/dL at screening. She was enrolled in Study 031 and was randomized to the voxelotor 1500 mg QD treatment arm.

Study drug use for this patient was characterized by frequent episodes of missed doses that began within the first month after starting study treatment. She experienced 3 SAEs of sickle cell anemia with crisis over a 2-month time course which required hospitalization on Study Days 81, 102, and 129. Due to recurrence of sickle cell crisis events in this patient, study treatment was reduced progressively on Study Days 102-112, Study Days 113-119, Study Days 127-129 and then permanently discontinued study treatment on Study Day 129. She was transfused with 1 unit of packed red blood cells on Study day 134 during her 3rd VOC event, which led to permanent study treatment discontinuation.

The investigator assessed the event of Grade 3 sickle cell anemia with crisis as related to blinded study treatment because "there appeared to be a positive relationship between stopping the drug abruptly and the onset of new painful crisis". The sponsor assessed the event of Grade 3 sickle cell anemia with crisis as not related to blinded study treatment, but to their underlying SCD.

Review comment: *FDA agrees with the sponsor's assessment that the VOC episodes in this patient with poor adherence to study treatment, a history of 2 VOC episodes in the 11 months*

prior to study entry, as well as ACS and concurrent rheumatoid arthritis requiring immunosuppressive therapy – is related to her underlying disease.

Subject (b) (6) was a 14-year-old White male diagnosed with HbSS genotype sickle cell disease. His sickle cell disease history included 1 VOC event requiring hospitalization within the 12 months prior to study enrollment, as well as acute chest syndrome and splenic sequestration. He was taking hydroxyurea at study enrollment. He was enrolled in Study GBT440-007 and was randomized to the voxelotor 900 mg QD treatment arm. His hemoglobin was 10.20 g/dL at screening.

On Study Day 162, he presented with cough, right lower lobe infiltrates and chest pain, and was admitted to the hospital for acute chest syndrome. On Study Day 144, his hemoglobin was 10.50 g/dL. Right lower lobe consolidation was found on chest x-ray. Cultures were negative, and results of diagnostic and additional laboratory tests performed were not reported. The event of ACS was resolved on Study Day 167, and he was discharged from the hospital on the same day. The study treatment was interrupted due to this event on Study Day 164 and resumed on Study Day 170. His last dose of voxelotor was received at completion of the study on Study Day 170. The investigator assessed the event of Grade 3 ACS as possibly/probably related to voxelotor, secondary to increased hemoglobin. The sponsor assessed the event of Grade 3 ACS as not related to voxelotor.

Review comment: *FDA agrees with the sponsor's assessment that the VOC episodes in this patient with a history of acute chest syndrome prior to study entry is likely related to his underlying disease and unrelated to voxelotor treatment.*

Dropouts and/or Discontinuations Due to Adverse Effects

Safety Population: Study GBT440-031

Overall, 83.9% (230/274) of subjects completed Study GBT440-031 through Week 24. The tables below show reasons for discontinuations and TEAEs leading to study drug discontinuation among subjects enrolled in Study 031.

Table 48: Reasons for discontinuation of treatment Subjects - Study GBT440-031

Reason for treatment discontinuation	GBT440 1500 mg n=88	GBT440 900 mg n= 92	Placebo n=91
	n (%)	n(%)	n(%)
Adverse Event	9 (10.0)	6 (6.5)	5 (5.4)
Withdrawal By Subject	5 (5.6)	9 (9.8)	6 (6.5)
Non-Compliance	6 (6.7)	0 (0.0)	3 (3.3)
Other	3 (3.3)	1 (1.1)	4 (4.3)
Investigator Decision Lost To Follow-Up Pregnancy	1 (1.1) 0 (0.0) 0 (0.0)	2 (2.2) 1 (1.1) 0 (0.0)	1 (1.1) 0 (0.0) 1 (1.1)

Source: FDA analyses

Table 49: TEAEs leading to study drug discontinuation - Study GBT440-031

	GBT440 1500 mg n=88	GBT440 900 mg n=92	Placebo n=91
DRUG WITHDRAWN	**7 (8.0%)**	**1 (1.1%)**	**4 (4.4%)**
Sickle cell anemia with crisis	2 (2.3%)	0 (0.0%)	1 (1.1%)
Nausea	1 (1.1%)	0 (0.0%)	2 (2.2%)
Chest pain	1 (1.1%)	0 (0.0%)	0 (0.0%)
Angina pectoris	1 (1.1%)	0 (0.0%)	0 (0.0%)
Paresthesia	1 (1.1%)	0 (0.0%)	0 (0.0%)
Pneumonia	1 (1.1%)	0 (0.0%)	0 (0.0%)
Pulmonary embolism	1 (1.1%)	0 (0.0%)	0 (0.0%)
Pulmonary sepsis	1 (1.1%)	0 (0.0%)	0 (0.0%)
Abdominal pain	1 (1.1%)	0 (0.0%)	0 (0.0%)
Rash generalized	0 (0.0%)	1 (1.1%)	0 (0.0%)
Diarrhea	0 (0.0%)	0 (0.0%)	1 (1.1%)
Vomiting	0 (0.0%)	0 (0.0%)	1 (1.1%)
Cardiac arrest	0 (0.0%)	0 (0.0%)	1 (1.1%)

Source: FDA analyses

The most common SCD-related TEAE that led to study drug discontinuation in more than 1 subject across treatment groups was sickle cell anemia with crisis (2 subjects in the voxelotor 1500-mg group and 1 subject in the placebo group. The most common non-SCD related TEAE that led to discontinuation of more than 1 subject across treatment groups was nausea.

Reviewer's Comment: Discontiniations due to adverse reactions(study drug related adverse reactions) occurred in 5% of the patients in the 1500mg arm.

The table below shows TEAEs leading to study drug modification (interruption or dose reduction) in study 031.

Table 50: Adverse Events Leading to Modification of Study Drug - Study GBT440-031

	GBT440 1500 mg n=88	GBT440 900 mg n=92	Placebo n=91
TEAEs leading to dose modification	**36 (40.9%)**	**22 (23.9%)**	**23 (25.3%)**
DRUG INTERRUPTED	**26 (29.5%)**	**20 (21.7%)**	**21 (23.1%)**
Sickle cell anemia with crisis	17 (19.3%)	12 (13.0%)	12 (13.2%)
Acute chest syndrome	5 (5.7%)	1 (1.1%)	3 (3.3%)
Vomiting	2 (2.3%)	2 (2.2%)	1 (1.1%)
Pneumonia	1 (1.1%)	1 (1.1%)	3 (3.3%)
Headache	1 (1.1%)	1 (1.1%)	2 (2.2%)

	GBT440 1500 mg n=88	GBT440 900 mg n=92	Placebo n=91
Abdominal pain	1 (1.1%)	1 (1.1%)	0 (0.0%)
Pyrexia	0 (0.0%)	2 (2.2%)	0 (0.0%)
Gastritis	0 (0.0%)	2 (2.2%)	0 (0.0%)
Bone pain	0 (0.0%)	1 (1.1%)	1 (1.1%)
Cough	0 (0.0%)	1 (1.1%)	0 (0.0%)
Abdominal pain upper	0 (0.0%)	1 (1.1%)	1 (1.1%)
Nausea	0 (0.0%)	1 (1.1%)	3 (3.3%)
Transaminases increased	0 (0.0%)	1 (1.1%)	1 (1.1%)
DOSE REDUCED	**13 (14.8%)**	**2 (2.2%)**	**2 (2.2%)**
Diarrhea	3 (3.4%)	0 (0.0%)	0 (0.0%)
Rash	2 (2.3%)	0 (0.0%)	0 (0.0%)
Sickle cell anemia with crisis	2 (2.3%)	1 (1.1%)	0 (0.0%)
Rash generalized	2 (2.3%)	0 (0.0%)	0 (0.0%)
Nausea	1 (1.1%)	0 (0.0%)	1 (1.1%)

Source: FDA analyses

TEAEs that led to modification of study drug dosing occurred most commonly in the voxelotor 1500-mg group (40.9% [36/88 subjects]). Overall, the most common TEAE that led to modification of dosing (interruption or dose reduction) was sickle cell anemia with crisis: in 21.6% (19/88) of the subjects in the voxelotor 1500-mg group, 15.2% (14/92) of the subjects in the voxelotor 900-mg group, and 14.3% (13/91) of the subjects in the placebo group

Significant Adverse Events

Drug Hypersensitivity: Across all studies in the voxelotor clinical development program, 2 TEAEs of drug hypersensitivity were assessed by the investigator as related to voxelotor occurred: 1 subject with SCD in Study GBT440-031 and 1 subject with IPF in Study GBT440-006

The event of drug hypersensitivity in the subject with SCD in Study 031 was reported as an SAE and the narrative for this patient is presented in Section 8.2.4 above. The time of onset of this event relative to treatment was Study Day 40 for the subject with SCD and Study Day 10 for the subject with IPF. Narratives for these events were provided by the Applicant and reviewed by FDA. No events of anaphylaxis or anaphylactoid reactions occurred.

Review comment: *The incidence rate of drug hypersensitivity across the voxelotor clinical development program was 0.29% (2/681 voxelotor-treated subjects). Although both cases were confounded by the use of other medications with known risk of drug hypersensitivity reactions (platelet-rich plasma for hair growth in the subject with SCD and anti-fibrotics [nintedanib or pirfenidone] for the subject with IPF); a causal association between study drug exposure and the event of hypersensitivity cannot be excluded because of the temporal association and*

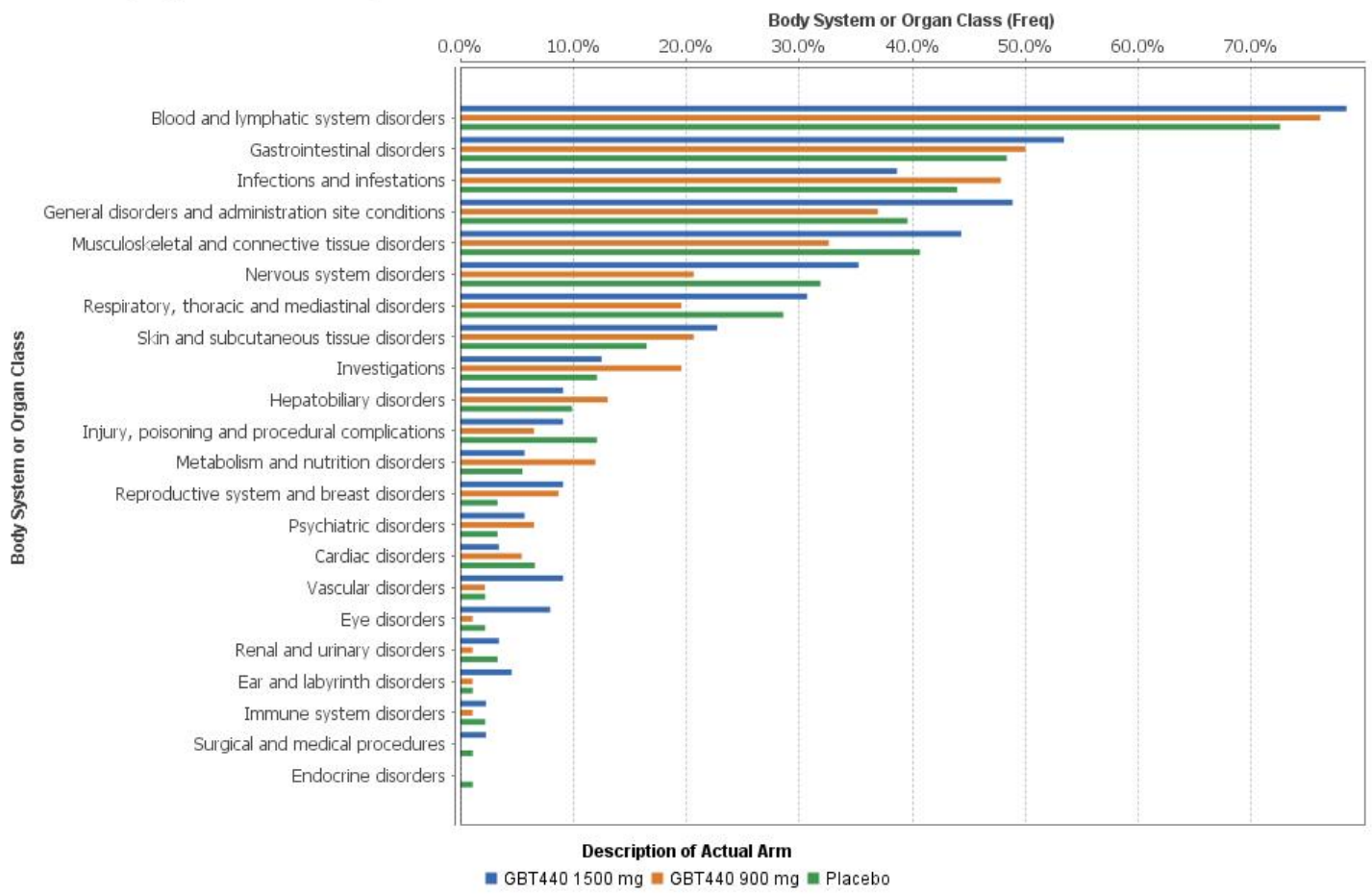
recurrence observed after reintroduction of voxelotor in the SCD subject. Therefore, this reviewer recommends including a warning of hypersensitivity in the label for voxelotor.

Rash: The table below shows the incidence of rash (grouped PT) in Study GBT440-031. Overall, the incidence of rash in Study GBT440-031 was slightly higher in the voxelotor groups than in the placebo group.
Approximately one-half of the subjects with reports of rash in the voxelotor 1500-mg (58.3% [7/12 subjects]) and placebo (44.4% [4/9 subjects]) groups had events that were considered by the investigator to be related to study drug (Table 15); 20.0% (2/10) of the subjects in the voxelotor 900-mg group had events of rash that were related to study drug.

Treatment Emergent Adverse Events and Adverse Reactions

Overall, the incidence of TEAEs was comparable among subjects treated with voxelotor 1500mg (94.3%), voxelotor 900mg (93.5%) and placebo (89.0%). The figure below shows TEAEs that occurred in ≥ 10% of voxelotor and placebo treated patients by SOC.

Figure 12: TEAEs reported in Voxelotor versus placebo treated patients by SOC



Source: FDA analyses

Gastrointestinal Disorders was the most commonly reported SOC in each treatment group: 53.4% (47/88), 50.0% (46/92), and 48.4% (44/91) of the subjects in the voxelotor 1500-mg, voxelotor 900-mg, and placebo groups, respectively.

TEAEs in the Skin and Subcutaneous Tissue Disorders SOC was higher in the voxelotor 1500-mg treatment group (22.7% [20/88] subjects]) and the voxelotor 900-mg (20.7% [19/92 subjects]) groups than in the placebo (16.5% [15/91 subjects]) group.

Non-SCD–related TEAEs that occurred in ≥ 10% of subjects in any treatment group are summarized by PT in the table below:

Table 51: TEAEs reported in Voxelotor versus placebo treated patients by PT, Study GBT440-031

Non SCD related TEAE	GBT440 1500 mg n=88	GBT440 900 mg n=92	Placebo n=91
Headache	23 (26.1%)	14 (15.2%)	20 (22.0%)
Diarrhea	18 (20.5%)	16 (17.4%)	9 (9.9%)
Abdominal pain (Grouped PTs)*	18 (20.4%)	24 (26.1%)	13 (14.3%)
Nausea	15 (17.0%)	15 (16.3%)	9 (9.9%)
Arthralgia	13 (14.8%)	11 (12.0%)	11 (12.1%)
Fatigue	12 (13.6%)	12 (13.0%)	9 (9.9%)
Upper respiratory tract infection	12 (13.6%)	17 (18.5%)	10 (11.0%)
Rash (Grouped PTs)**	12 (13.6)	10 (10.9)	9 (9.9)
Pyrexia	11 (12.5%)	10 (10.9%)	6 (6.6%)
Pain in extremity	10 (11.4%)	18 (19.6%)	16 (17.6%)
Back pain	10 (11.4%)	13 (14.1%)	10 (11.0%)
Vomiting	10 (11.4%)	12 (13.0%)	11 (12.1%)
Pain	8 (9.1%)	10 (10.9%)	6 (6.6%)
Non-cardiac chest pain	7 (8.0%)	12 (13.0%)	8 (8.8%)

Source: FDA analyses

*Abdominal pain (grouped PTs) includes abdominal pain and abdominal pain, upper.
**Rash (grouped PTs) includes the following PTs: rash, urticaria, rash generalized, rash maculo-papular, rash pruritic, rash papular, rash erythematous, rash vesicular, and rash macular.

The most common TEAEs in subjects treated with voxelotor 1500mg was headache 23 (26.1%). TEAEs that occurred with higher incidence (by ≥3 percentage points) in the voxelotor 1500mg group compared to the placebo group were headache (26%), diarrhea (21%), abdominal pain (20%), nausea (17.0%), fatigue (14%), rash (14%) and pyrexia (12%).

The overall incidence of rash (grouped PT) in Study GBT440-031 was slightly higher in the voxelotor groups than in the placebo group. Events that were reported in the voxelotor groups but not in the placebo group included urticaria, rash generalized, rash maculo-papular, rash erythematous and rash vesicular.

The overall incidence of non-SCD–related TEAEs in the pooled adolescent population is shown below.

Table 52: Non-SCD–related TEAEs - Pooled adolescent population

	GBT440 1500 mg n=29	GBT440 900 mg n=40	Placebo n=17
Subjects with Non SCD related TEAEs -	**28 (96.6%)**	**33 (82.5%)**	**15 (88.2%)**
Arthralgia	7 (24.1%)	5 (12.5%)	3 (17.6%)
Abdominal pain	7 (24.1%)	8 (20.0%)	2 (11.8%)
Back pain	6 (20.7%)	8 (20.0%)	5 (29.4%)
Headache	6 (20.7%)	10 (25.0%)	5 (29.4%)
Upper respiratory tract infection	5 (17.2%)	6 (15.0%)	2 (11.8%)
Nausea	5 (17.2%)	11 (27.5%)	1 (5.9%)

	GBT440 1500 mg n=29	GBT440 900 mg n=40	Placebo n=17
Pain in extremity	5 (17.2%)	12 (30.0%)	1 (5.9%)
Oropharyngeal pain	4 (13.8%)	1 (2.5%)	1 (5.9%)
Pyrexia	3 (10.3%)	2 (5.0%)	4 (23.5%)
Cough	3 (10.3%)	2 (5.0%)	1 (5.9%)
Vomiting	3 (10.3%)	8 (20.0%)	1 (5.9%)
Ocular icterus	2 (6.9%)	3 (7.5%)	4 (23.5%)
Non-cardiac chest pain	2 (6.9%)	5 (12.5%)	3 (17.6%)
Tonsillitis	2 (6.9%)	1 (2.5%)	2 (11.8%)

Source: FDA analyses

Table 53: Drug related Non-SCD–Related TEAEs, Study GBT440-031

	GBT440 1500 mg n=88	GBT440 900 mg n=92	Placebo n=91
Drug related Non-SCD related TEAEs	**34 (38.6%)**	**29 (31.5%)**	**23 (25.3%)**
Diarrhea	11 (12.5%)	8 (8.7%)	3 (3.3%)
Nausea	6 (6.8%)	6 (6.5%)	5 (5.5%)
Abdominal pain	6 (6.8%)	6 (6.5%)	1 (1.1%)
Headache	5 (5.7%)	3 (3.3%)	3 (3.3%)
Vomiting	1 (1.1%)	3 (3.3%)	4 (4.4%)
Rash	4 (4.5%)	0 (0.0%)	3 (3.3%)
Abdominal pain upper	2 (2.3%)	2 (2.2%)	2 (2.2%)
Rash generalized	3 (3.4%)	1 (1.1%)	0 (0.0%)
Dizziness	0 (0.0%)	0 (0.0%)	3 (3.3%)
Pyrexia	0 (0.0%)	2 (2.2%)	0 (0.0%)
Fatigue	0 (0.0%)	2 (2.2%)	0 (0.0%)
Decreased appetite	0 (0.0%)	2 (2.2%)	0 (0.0%)
Aspartate aminotransferase increased	0 (0.0%)	2 (2.2%)	0 (0.0%)
Pruritus	0 (0.0%)	1 (1.1%)	1 (1.1%)
Migraine	1 (1.1%)	0 (0.0%)	1 (1.1%)
Paresthesia	0 (0.0%)	1 (1.1%)	1 (1.1%)
Dermatitis acneiform	1 (1.1%)	1 (1.1%)	0 (0.0%)
Hypoesthesia	1 (1.1%)	0 (0.0%)	1 (1.1%)

Source: FDA analyses

The overall incidence of drug-related non-SCD–related TEAEs was higher in the voxelotor treatment groups than in the placebo group. This was driven primarily by the higher incidence of drug related GI TEAEs (diarrhea and abdominal pain) in the voxelotor groups..

Drug related TEAEs: Pooled Adolescent population:

Study drug related TEAEs in the pooled adolescent is shown in the table below.

Table 54: Study Drug related TEAEs: Adolescents- Study GBT440-031 and 007

	GBT440 1500 mg n=29	GBT440 900 mg n=40	Placebo n=17
Subjects with TEAEs related to study drug	**13 (44.8%)**	**7 (17.5%)**	**4 (23.5%)**
Nausea	5 (17.2%)	3 (7.5%)	1 (5.9%)
Diarrhea	2 (6.9%)	1 (2.5%)	0 (0.0%)
Headache	2 (6.9%)	2 (5.0%)	1 (5.9%)
Body tinea	1 (3.4%)	0 (0.0%)	0 (0.0%)
Back pain	1 (3.4%)	0 (0.0%)	0 (0.0%)
Abdominal pain upper	1 (3.4%)	0 (0.0%)	0 (0.0%)
Abdominal pain	1 (3.4%)	1 (2.5%)	0 (0.0%)
Pruritus	1 (3.4%)	0 (0.0%)	0 (0.0%)
Rash generalized	1 (3.4%)	0 (0.0%)	0 (0.0%)
Retinopathy sickle cell	1 (3.4%)	0 (0.0%)	0 (0.0%)
Vomiting	0 (0.0%)	2 (5.0%)	0 (0.0%)
Nasal congestion	0 (0.0%)	1 (2.5%)	0 (0.0%)
Acute chest syndrome	0 (0.0%)	1 (2.5%)	0 (0.0%)
Rash papular	0 (0.0%)	1 (2.5%)	0 (0.0%)
Transaminases increased	0 (0.0%)	1 (2.5%)	0 (0.0%)
Urticaria	0 (0.0%)	1 (2.5%)	0 (0.0%)
Dizziness	0 (0.0%)	1 (2.5%)	0 (0.0%)
Insomnia	0 (0.0%)	0 (0.0%)	1 (5.9%)
Rash	0 (0.0%)	0 (0.0%)	1 (5.9%)
Sickle cell anemia with crisis	0 (0.0%)	0 (0.0%)	1 (5.9%)
Thrombocytosis	0 (0.0%)	0 (0.0%)	1 (5.9%)

Source: FDA analyses

The overall incidence of SCD-related and non-SCD related TEAEs in the combined adolescents was generally comparable to the observed incidences in adult subjects in Study GBT440-031.

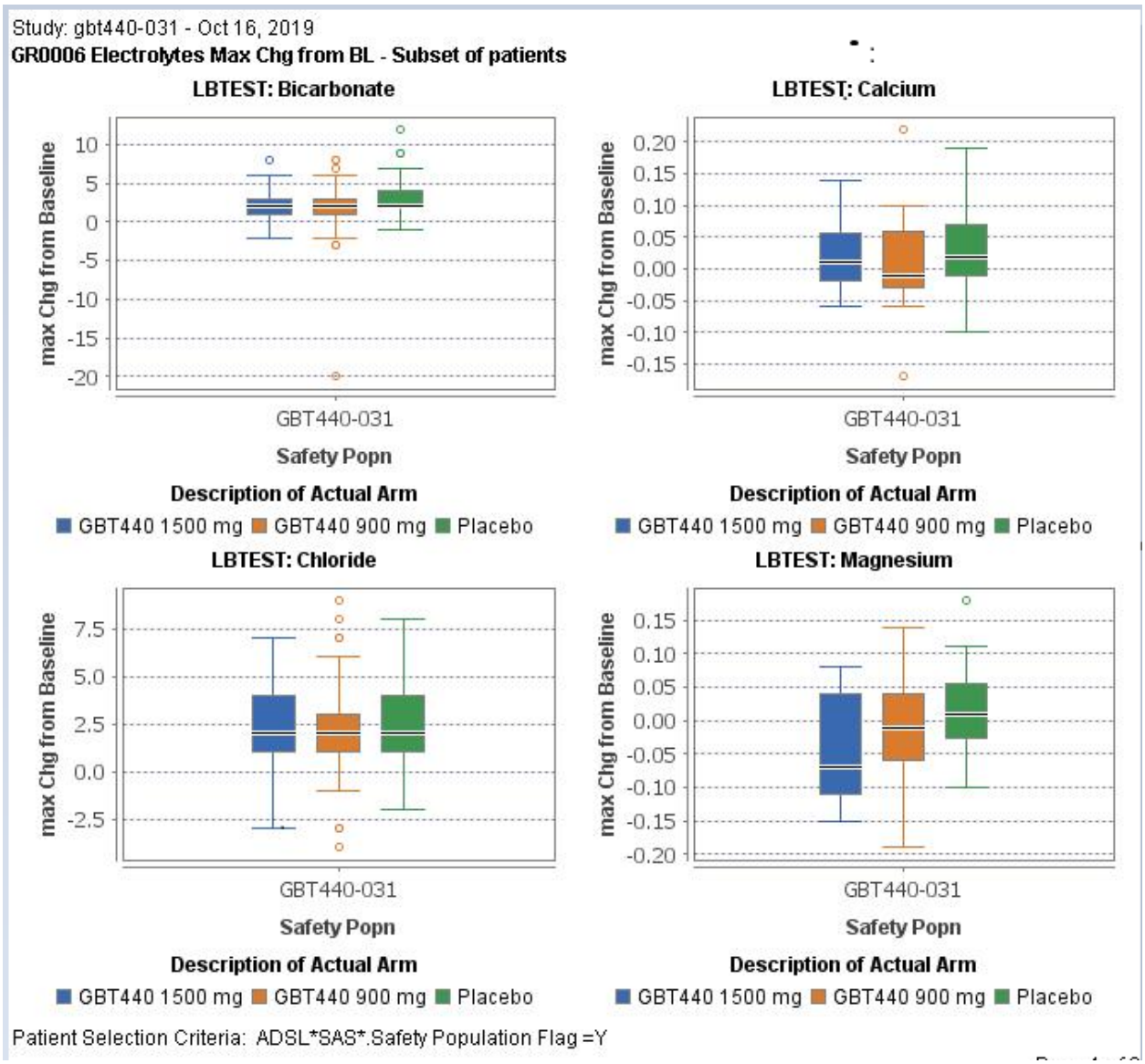
Laboratory Findings

This section provides a summary of changes in clinical chemistry, non–hematological and hematology laboratory parameters in the primary safety population (Study GBT440-031) and in the pooled adolescent population from study GBT440-031 and GBT440-007.

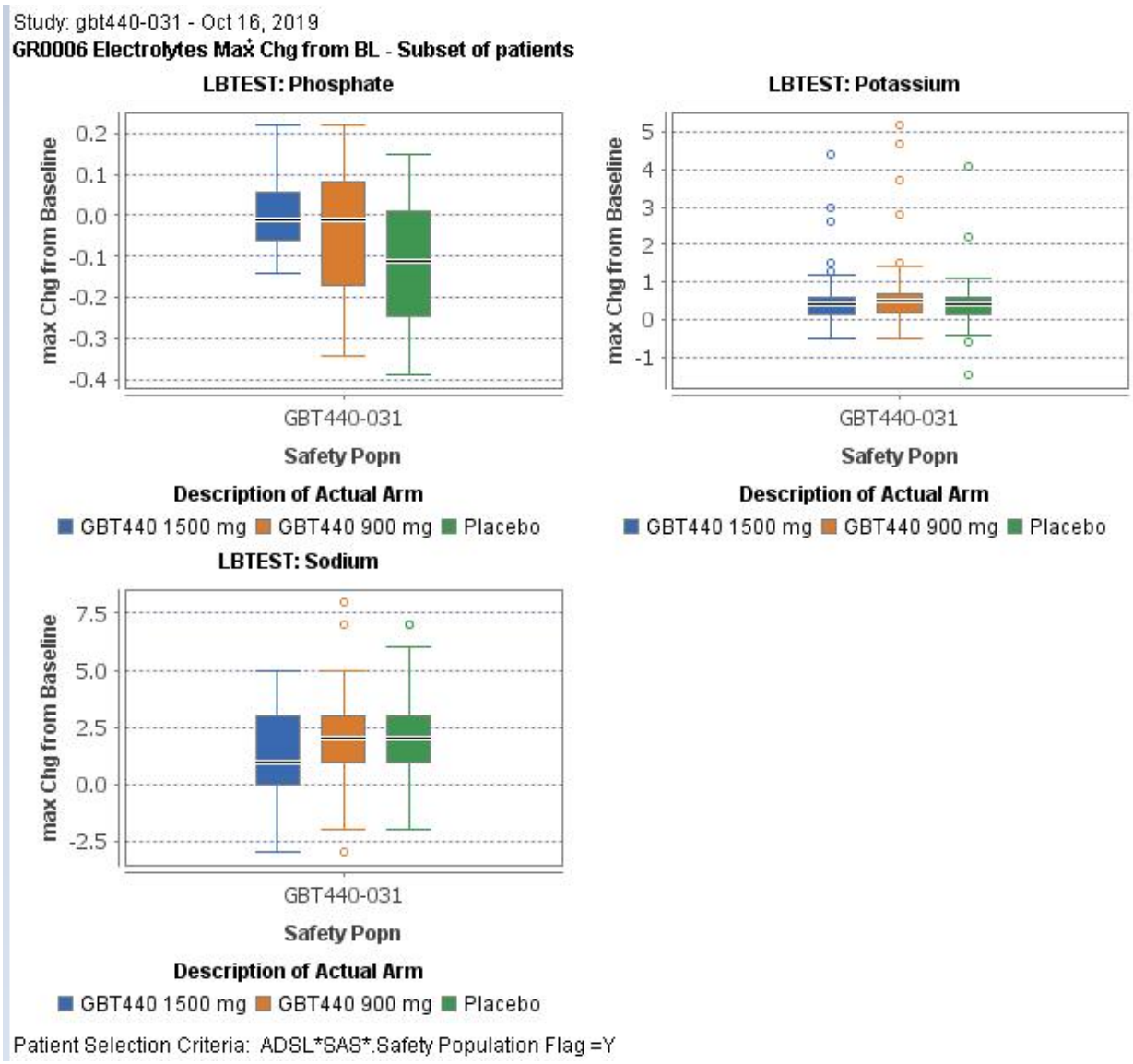
Safety Population: Study GBT440-031

The figures below show the maximum change from baseline in chemistry parameters from Baseline to Week 24 in treatment period by treatment group.

Figure 13: Summary of Clinical Chemistry Parameters, Safety Population: Study GBT440-031)



Source: FDA analyses

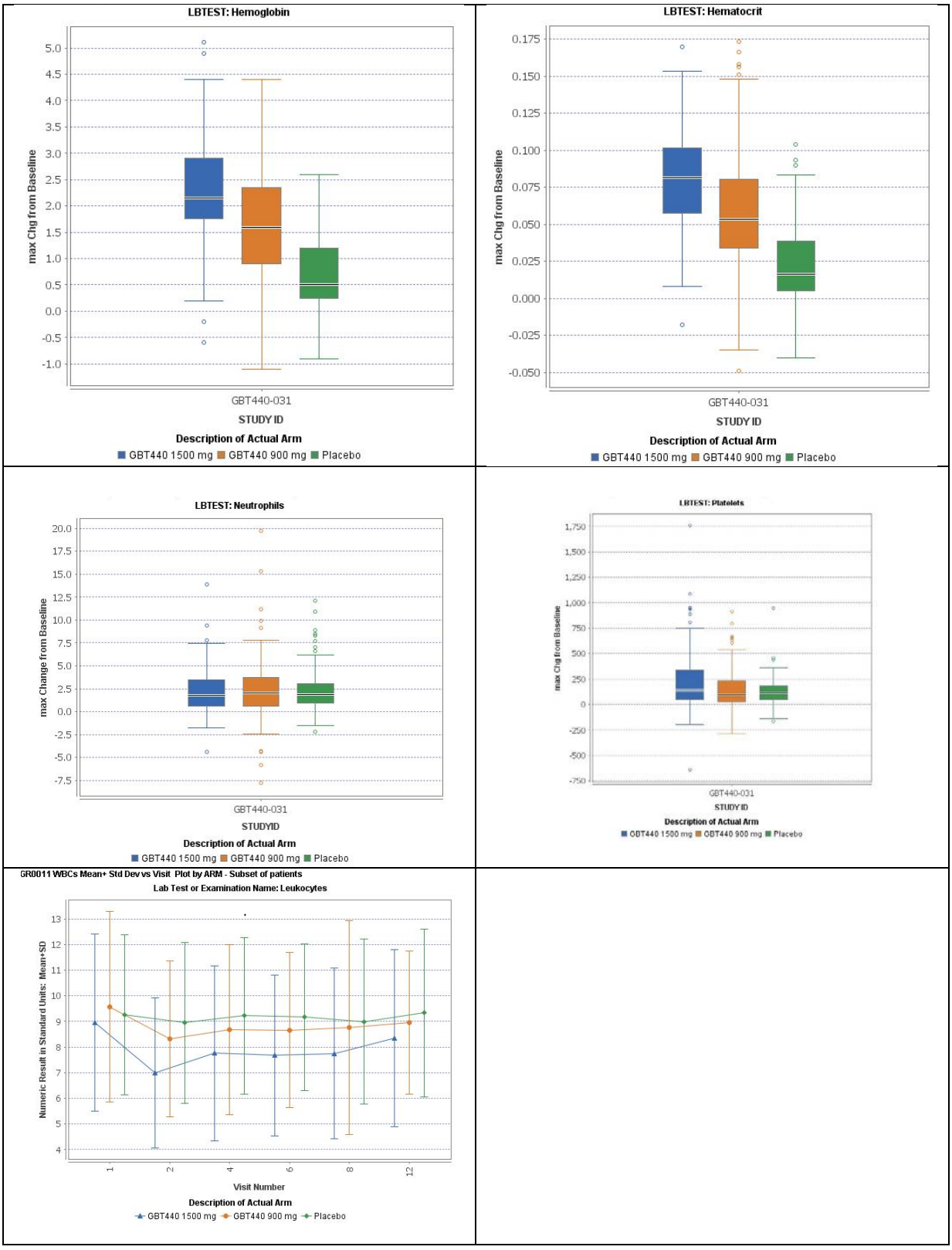


Source: FDA analyses

Review Comment: *At baseline, clinical chemistry parameters were similar for voxelotor and placebo treated patients. No notable differences or safety signal associated with the hepatic or renal parameters were observed between treatment groups over the course of the treatment period.*

The figures below show the maximum change from baseline to Week 24 for hematology parameters by treatment group.

Figure 14: Summary of Hematology Parameters, Safety Population (Study GBT440-031)

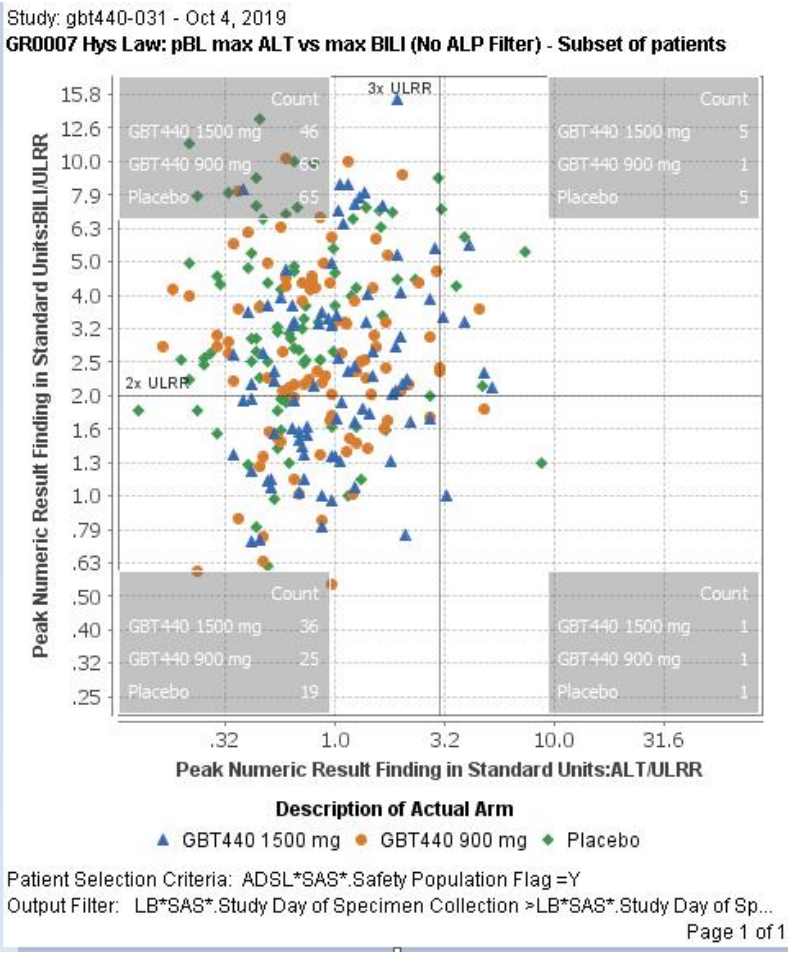


Source: FDA analyses

Review Comment: *As expected, mean changes in hemoglobin and hematocrit were highest in the voxelotor 1500mg treatment group. Mean changes in neutrophil and platelets counts from baseline to Week 24 were generally small and not clinically meaningful. Overall, the mean white blood cells (WBC) count was consistently lower across visits in subjects with voxelotor that in the placebo group. The Applicant reported that, exposure response analysis showed a statistically significant relationship with Grade 1 but not Grade 2 decreases in WBCs. Because mean WBCs in the voxelotor treatment groups remained within the normal range these changes are not considered clinically meaningful by FDA.*

Potential Drug-induced liver injury Assessment
FDA evaluated the liver function test results of subjects in Study GBT440-031 for the occurrence of potential drug-induced liver injury (DILI) cases.

Figure 15: Assessment for Potential DILI cases, Safety Population (Study GBT440-031)



Source: FDA analyses

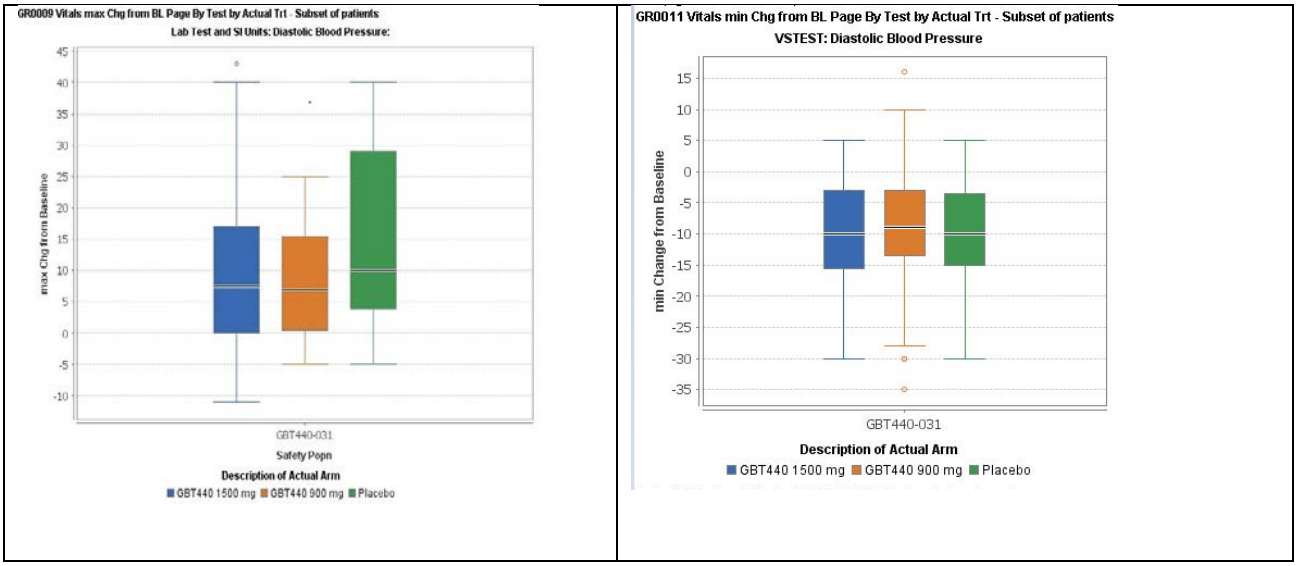
As shown in the figure above, 5 subjects (see top right quadrant of figure) treated with Voxelotor 1500mg, 1 subject treated with voxelotor 900mg and 1 placebo treated subject met the criteria for potential DILI as defined by an AST >3 times ULN, total bilirubin > 2 times ULN at any time post baseline.

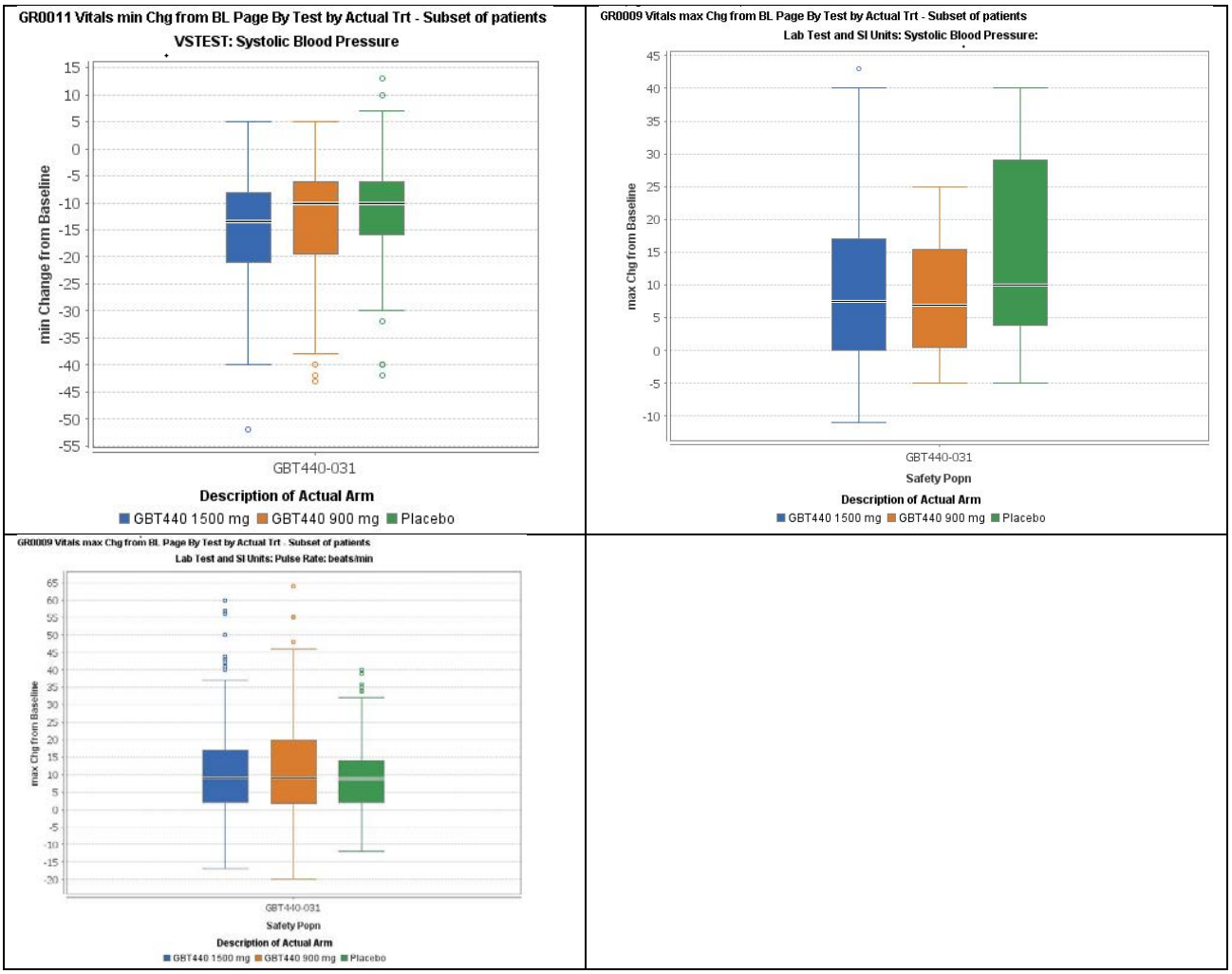
FDA reviewed the patient profiles for voxelotor treated subjects who met the criteria for potential DILI. In all 6 cases(3 adolescents and 3 adults: Patient IDs 031-(b) (6) (b) (6) ; 031-(b) (6) 031-(b) (6) 031-(b) (6) and 031-(b) (6) total bilirubin (reference range: 5 to 17) was above ULN at baseline.

Review Comment: *Due to chronic hemolysis, elevations in bilirubin are expected in patients with SCD population. All cases are also confounded by concomitant medication use including acetaminophen and NSAIDs which can induce liver injury. Given the presence of other alternative explanations for these LFT abnormalities, DILI appears unlikely in these cases.*

Vital Signs

Figure 16: Changes From Baseline In Vital Signs, Safety Population (Study GBT440-031)





Source: FDA analyses

No clinically meaningful changes from baseline in vital signs were observed in adults and adolescents with SCD in Study GBT440-031.

Electrocardiograms (ECGs)

Clinically significant ECG results were reported as TEAEs in Study GBT440-031. All TEAEs related to ECG results were assessed as not related to study drug by the investigator and sponsor. None were considered serious or led to study drug discontinuation. Overall, no clinically meaningful changes from baseline in ECG results and no clinically meaningful changes between treatment groups were reported.

QT

The effect of voxelotor was evaluated by the Applicant in thorough QT study in healthy adult subjects (Study # GBT440-0115).

DHP obtained a consult from FDA's Interdisciplinary Review Team for QT Studies. See consult report from Dr Girish Bende in Darrts dated 08/23/2019. In summary, no significant QTc prolongation effect of voxelotor 1500 mg once daily was detected in this QT assessment.

Immunogenicity

Not Applicable

8.2.5 Analysis of Submission-Specific Safety Issues

8.2.5.1 Effect of Voxelotor on Tissue Oxygen Availability

Voxelotor (formerly known as GBT440), is a small-molecule HbS polymerization inhibitor developed for the treatment of adults and adolescents with SCD. Voxelotor' s mechanism of action is expected 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. The Applicant hypothesizes that, by maintaining approximately 30% of Hb in the nonpolymerizing state, Voxelotor may be an effective therapeutic approach for SCD. This is supported by clinical data from Study A2201 which suggests voxelotor increases hemoglobin levels and decreases hemolysis, consistent with an inhibition of polymerization.

There is however a risk that at a certain percentage of Hb occupancy, offloading of O2 from voxelotor-bound Hb in the tissues could be decreased leading to possibly end-organ tissue hypoxia. In a recent article (Hebbel and Hedlund 2018), Hebbel and Hedlund express 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 deoxyHbS. Therefore, the GBT440 effect will result in a significantly increased proportionate oxy-to-deoxyHb conversion, and no overall improvement in deoxyHbS concentration. The authors express further concern that, while the rising hemoglobin does increase blood viscosity, the modest increase in hb attained by voxelotor is inadequate to make up for the loss of 30% of oxygen delivery capability caused by giving the drug and the functional hemoglobin drop would be abrupt if full drug dosing is started immediately. Particularly in hypoxemic patients, the express concern that the GBT-modified tetramers would falsely bolster measured oxygen saturation measures, but this would not translate to oxygen delivery benefit and would be dangerous. 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.

A commentary (Estepp 2018) in response to the article by Hebbel and Hedlund noted that, in two of seven patients with severe SCD who received voxelotor for up to 17 months under

GBT4040's compassionate use program, oxygenation improved after 24 weeks of voxelotor treatment. In one of these patients, One individual 6-minute walk tests were conducted at baseline and then following 14 and 24 weeks of voxelotor. During this interval, the 6-minute walk tests improved with declining pulse rates and rising SpO2 on room air.
In Study GBT031, severely anemic patients (Hb < 5.5 g/dL), were excluded. The median Hb in patients with SCD treated with voxelotor 1500mg and 900mg was 8.7g/dl and 8.3g/dl (range 5.9, 10.8) respectively.

FDA exploratory safety analyses did not find a difference in the safety profile in subjects more anemic at baseline.

No confirmed case of cerebrovascular injury occurred in Study GBT031. In the 90-Day safety update, the Applicant reported a possible treatment emergent CVA event and death in a 39-year-old male with HbSS sickle cell disease who had a history of 6 vaso-occlusive crisis the 12 months prior to study enrollment. The diagnosis of CVA in this patient was however unconfirmed and his death was attributed to encephalopathy due to multifocal intracerebral abscesses by the investigator. Further studies on the effect of voxelotor on cerebrovascular blood flow and oxygen delivery to the brain are warranted and will be required forvoxeletor as a confirmatory study.

8.2.6 Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

In the phase 3 Study GBT440-031, the Sickle Cell Disease Severity Measure (SCDSM), a self-administered 9-item subject questionnaire of SCD core symptoms, including pain severity, frequency, and type, as well as fatigue and mental acuity, on a 4-point response scale was completed daily using a handheld electronic device. The SCDSM was developed by the sponsor. Daily intake of prescribed study drug , use of opioid drugs, including the frequency and amount; and the days of school or work that were missed were recorded by subjects in an eDiary. Subjects also completed the EuroQol health questionnaire (EQ-5D-5L), standardized instrument for use as a measure of health outcome, at the start of clinic visits every 4 weekly and the investigator provided an assessment of the subject's overall condition using the Clinical Global Impression of Change (CGIC) at specific time points.

Rate of opioid use, changes in the SCDSM, EQ-5D-5L, CGIC and School and/or work attendance as recorded in the eDiary were evalutated as exploratory endpoints in Study 031 but did not inform safety/tolerability.

There were no additional COA data related to safety included in the application.

8.2.7 Safety Analyses by Demographic Subgroups

Age:

As noted in Section 8.1 above, in general, demographic and baseline characteristics were similar across treatment groups in Study 031 and representative of the characteristics of patients with sickle cell disease in North America. The overall higher proportion of blacks or African American patients in the study population was not unexpected. Enrolled subjects ranged in age from 12 to 64 and 16.8% (46/274) of enrolled subjects were adolescents (12 to < 18 years).

Phase 2a Study GBT440-007 only included adolescents With SCD (12 to < 18 Years). As detailed in Section 8.1, adolescents (12 to < 18 years old) in the pivotal Phase 3 study GBT440-031 and Part B of the Phase 2a Study GBT440-007 were pooled together for analysis. The adolescent populations in studies 031 and Study GBT440-007 were generally similar, except for higher rates of VOC events the 12 months prior to enrollment in Study GBT440-031.

Overall, there were no meaningful differences in the overall incidence of non-SCD–related TEAEs between treatment groups in the adolescent population (Pooled Studies GBT440-031 and GBT440-007) compared to the adult population (Study GBT440-031).

In the adolescent population, study drug related TEAEs occurred more frequently in the voxelotor 1500mg group (44.8%) compared to the voxelotor 900mg (7.5%)and placebo groups (23.5%)- (See table below). However, study 007 was not randomized so no meaningful conclusions can be drawn.

The most frequently reported non-SCD–related TEAEs (≥ 10%) in the pooled adolescents voxelotor 1500-mg group was were arthralgia, abdominal pain, back pain and headache. The majority of events had a maximum severity of Grade 1 or 2, consistent with the adult population.

Table 55: Adult Subjects From Study GBT440-031 and Pooled Adolescent Subjects (12 to < 18 Years) with SCD: Overview of Non-SCD–Related Treatment-Emergent Adverse Events (Safety Population)

	Number (%) of Subjects					
	Adults (GBT440-031)			Adolescents (Pooled GBT440-031 and GBT440-007 Part B)		
	Placebo (N = 74)	Voxelotor 900 mg (N = 77)	Voxelotor 1500 mg (N = 74)	Placebo (N = 17)	Voxelotor 900 mg (N = 40)	Voxelotor 1500 mg (N = 29)
Subjects with Any TEAE	66 (89.2)	73 (94.8)	70 (94.6)	15 (88.2)	33 (82.5)	28 (96.6)
Maximum Severity Grade = 5	1 (1.4)	0	1 (1.4)	0	0	0
Maximum Severity Grade = 4	2 (2.7)	2 (2.6)	1 (1.4)	0	0	0
Maximum Severity Grade = 3	15 (20.3)	16 (20.8)	19 (25.7)	6 (35.3)	7 (17.5)	8 (27.6)
Subjects with Any Serious TEAE	11 (14.9)	14 (18.2)	15 (20.3)	4 (23.5)	3 (7.5)	6 (20.7)
Study Drug–Related	0	3 (3.9)	3 (4.1)	1 (5.9)	0	0
Leading to Treatment Discontinuation	1 (1.4)	3 (3.9)	3 (4.1)	0	0	1 (3.4)[a]
Subjects with Any Drug-Related TEAE	19 (25.7)	29 (37.7)	29 (39.2)	4 (23.5)	7 (17.5)	13 (44.8)
Subjects with Any TEAE Leading to Treatment Discontinuation	3 (4.1)	5 (6.5)	8 (10.8)	1 (5.9)	0	1 (3.4)[a]

Source: Applicants Summary of Clinical Safety, Table 37

Table 56: Adult Subjects From Study GBT440-031 and Pooled Adolescent Subjects (12 to < 18 Years) with SCD: Overview of SCD-Related Treatment-Emergent Adverse Events (Safety Population)

	Number (%) of Subjects					
	Adults (GBT440-031)			Adolescents (Pooled GBT440-031 and GBT440-007 Part B)		
	Placebo (N = 74)	Voxelotor 900 mg (N = 77)	Voxelotor 1500 mg (N = 74)	Placebo (N = 17)	Voxelotor 900 mg (N = 40)	Voxelotor 1500 mg (N = 29)
Subjects with Any TEAE	54 (73.0)	56 (72.7)	59 (79.7)	12 (70.6)	26 (65.0)	14 (48.3)
Maximum Severity Grade = 5	1 (1.4)	1 (1.3)	1 (1.4)	0	0	0
Maximum Severity Grade = 4	1 (1.4)	0	0	0	0	0
Maximum Severity Grade = 3	35 (47.3)	41 (53.2)	38 (51.4)	10 (58.8)	14 (35.0)	11 (37.9)
Subjects with Any Serious TEAE	33 (44.6)	36 (46.8)	36 (48.6)	7 (41.2)	16 (40.0)	10 (34.5)
Study Drug-Related	1 (1.4)	0	3 (4.1)	0	1 (2.5)	0
Leading to Treatment Discontinuation	1 (1.4)	2 (2.6)	2 (2.7)	0	0	0
Subjects with Any Drug-Related TEAE	3 (4.1)	2 (2.6)	4 (5.4)	1 (5.9)	1 (2.5)	0
Subjects with Any TEAE Leading to Treatment Discontinuation	1 (1.4)	2 (2.6)	3 (4.1)	0	0	0

Source: Applicants Summary of Clinical Safety, Table 38

The overall lower incidence of SCD-related TEAEs for adolescents in the voxelotor 1500-mg group compared to adults treated with voxelotor 1500-mg in Study GBT440-031 [48.3% (14/29) vs 79.7% (59/74)] is noteworthy but largely unexplained. In general, a higher frequency of SC crises events and TEAEs would be expected in younger patients with SCD.

As with adults, the most commonly reported SCD-related TEAEs across all treatment groups was sickle cell anemia with crisis: 44.8% (13/29), 57.5% (23/40), and 70.6% (12/17) in the voxelotor 1500-mg, voxelotor 900-mg, and placebo groups, respectively. No study drug discontinuations due to SCD-related TEAEs were reported in the pooled adolescent subjects.

The incidence of SCD related SAEs was generally balanced across treatment groups in the adolescent population: 34.5% (10/29), 40.0% (16/40), and 41.2% (7/17) in the voxelotor 1500-mg, voxelotor 900-mg, and placebo groups, respectively. One adolescent subject in the voxelotor 900-mg group experienced an SCD-related SAE (Grade 3 ACS) assessed as related to study drug (discussed above).

No deaths were reported in adolescent subjects.

Sex:
Among all treated subjects in Study GBT440-031, similarly proportions of female and male voxelotor-treated subjects experienced TEAEs (93.5% vs 94.4%), respectively.

Race:
In Study GBT440-031, majority of subjects were Arab/Middle Eastern (22.1%) and Black or African American (66.8%). The overall incidence of TEAEs by treatment group was similar between these 2 racial groups with 87.5% of Arab/Middle Eastern and 95.8% of Black or African American voxelotor treated subjects experiencing a TEAE.

HU use:
Hydroxyurea use was a stratification variable in Study 031. Therefore, the proportion of subjects who were HU users was balanced across treatment groups in Study 031. Overall, 65.3% of the study population were HU users. The overall incidence of TEAEs was similar among the HU users and non-HU users.

Review Comment: *No clinically significant differences were observed by HU use with respect to safety. The safety of concomitant use of HU and voxelotor is provided by findings from the PPK analysis of Study GBT-CP-005 which showed no significant difference in voxelotor exposure in subjects who used HU concomitantly and those taking voxelotor alone.*

8.2.8 Specific Safety Studies/Clinical Trials

Hepatic Impairment
In Study GBT440-031, only 12/247 (4.4%) subjects had a history of renal impairment or

dysfunction at baseline and no subjects had hepatic impairment. Therefore, the safety of voxelotor in these populations could not be evaluated in the pivotal study.

The applicant conducted study GBT440-0112 to characterize the pharmacokinetics of voxelotor in subjects with varying degrees of hepatic impairment. In this study (GBT440-0112), enrolled subjects with normal hepatic function (n=7), mild (Child-Pugh A, n=7), moderate (Child-Pugh B, n=7), and severe (Child-Pugh, n=7) hepatic impairments. Subjects with normal hepatic function and those with mild and moderate hepatic impairment received a single voxelotor dose of 1500 mg, while subjects in the severe impairment cohort received a 600 mg dose. A substantial increase in exposure in whole blood as well as plasma was observed in subjects with severe compared to normal hepatic function. Eleven subjects reported a total of 17 TEAEs (mild to moderate in severity). These included 8 drug related TEAES (in 7 subjects) per investigator assessment. Drug-related TEAEs included diarrhea (7 events), headache (1 event), and dyspepsia (1 event). The Applicant recommended a dose reduction to 1000 mg daily in patients with severe hepatic impairment to match exposure in subjects with normal hepatic function. No dose adjustment is recommended for patients with mild or moderate hepatic impairment. See discussion in Section 6.3 above.

Renal Impairment

The Applicant conducted an abbreviated design renal impairment study (GBT440-0110) in subjects with severe renal impairment (eGFR < 30 mL/min/1.73 m^2) and subjects with normal renal function (eGFR ≥ 90 mL/min/1.73 m^2). A total of 3 TEAEs (all mild in severity) were reported in 2 subjects with severe renal impairment. Two of these 3 TEAEs (abdominal pain and headache) occurred in 1 subject and were assessed as treatment-related by the investigator. The Applicant recommended no dose adjustment for subjects with severe renal impairment.

Review comment: *Renal and/or hepatic impairment is common in patients with SCD. FDA agrees with the Applicant that a dose reduction to 1000 mg daily is necessary for patients with severe hepatic impairment. The renal impairment study (GBT440-0110) conducted by the Applicant was very limited in size and scope. However, voxelotor is mainly metabolized and excreted in feces, and renal impairment status does not affect exposure (See Clin pharm discussion in section 6.3 above); therefore no further renal impairment studies are warranted for safety.*

Drug Interactions with Laboratory Tests

Voxelotor administer may interfere with measurement of Hb subtypes(adult hemoglobin HbA, HbS, and HbF) by high performance liquid chromatography (HPLC) (Rutherford 2018). If precise quantitation of Hb species is required, HPLC should not be performed during voxelotor therapy.

8.2.9 Additional Safety Explorations

Human Carcinogenicity or Tumor Development

See PharmTox reviewer discussion Section 5.5 above.

Human Reproduction and Pregnancy

No clinical studies of Voxelotor in pregnant women or lactating women have been conducted or planned. One pregnancy occurred in study GBT440-031 (Subject (b) (6) This was an 18 year old Black female randomized to the placebo treatment arm. who became pregnant 5.5 months after study initiation. The subject discontinued the placebo, and then 2 weeks later voluntarily terminated the pregnancy.

Pediatrics and Assessment of Effects on Growth

No clinical studies of the effect voxelotor on pediatric growth have been conducted.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

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

The sponsor evaluated SCD symptom exacerbation (the occurrence of VOC events) during the 28-day follow-up period after study drug discontinuation in Study GBT440-031. There was no evidence of rebound following withdrawal or discontinuation of voxelotor. At the time of the data cutoff (31 October 2018), 62 subjects had discontinued study drug. During the 28-day period after treatment discontinuation, the estimated incidence rate of post-treatment VOC events was 4.6 per subject-year and 4.3 per subject-year in the voxelotor 1500-mg and 900-mg groups, respectively, and 7.0 per subject-year in the placebo group.

The Applicant evaluated the number of VOCs that occurred in the 12 months prior to study participation, while on treatment, and after treatment discontinuation in subjects who discontinued study drug. No pattern of symptom exacerbation associated with voxelotor discontinuation was observed. Similarly, in Study GBT440-007, an analysis of VOC events did not reveal a temporal pattern for increased VOC risk after study drug discontinuation

8.2.10 Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Voxelotor has not been marketed in any country.

Expectations on Safety in the Postmarket Setting

The safety of Voxelotor in SCD patients with severe anemia will be of interest.

8.2.11 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 3 randomized study in adult and adolescent patients with SCD with the safety profile in adolescents supported by data from Part B of the open-label Phase 2a study, GBT440-007. 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. A total of 5 deaths were reported in the pivotal phase 3 study (GBT440-031) and the supportive Phase 2a study (GBT440-007). None of these deaths were assessed as related to voxelotor treatment by FDA.

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.

SCD-Related Safety Profile

In the pivotal study GBT440-031, the incidence of non-SCD–related TEAE was comparable in the voxelotor 1500-mg (94.3%), voxelotor 900-mg (93.5), and placebo groups (89.0%). The incidence of SCD-related TEAEs was also comparable - 76.1%, 72.8%, and 72.5% in the voxelotor 1500-mg, voxelotor 900-mg, and placebo groups, respectively. The majority of non-SCD–related TEAEs were predominantly of low-grade severity. The most commonly reported TEAEs occurred in the Gastrointestinal Disorders SOC (53.4%, 50.0%, and 48.4% in the voxelotor 1500-mg, voxelotor 900-mg, and placebo groups, respectively) and included diarrhea, nausea, and abdominal pain. The incidence of non-SCD related SAEs and SCD-related was also was balanced across treatment groups. Non-SCD–related SAEs related to study drug were few occurring in 3.4%, 3.3%, and 1.1% of subjects in the voxelotor 1500-mg, voxelotor 900-mg, and placebo groups, respectively. These events included drug hypersensitivity, headache, and pulmonary embolism in 1 subject each in the voxelotor 1500-mg group; hepatitis acute, type 2 diabetes mellitus, and rash generalized in 1 subject each in the voxelotor 900-mg group, and thrombocytosis in 1 subject in the placebo group.

SCD-Related Safety Profile

SCD related TEAEs occurred frequently in Studies GBT440-031 and GBT440-007. In the pivotal study, the incidence of SCD-related TEAEs and SAES was similar for the voxelotor and placebo treatment groups (46.6%, 45.7%, and 44.0% in the voxelotor 1500-mg, voxelotor 900-mg, and placebo groups, respectively for SCD related SAEs). The most common SCD-related TEAE in both Studies GBT440-031 and GBT440-007 was sickle cell anemia with crisis, majority of which were categorized as serious and resulted in hospitalization. The incidence of ACS was notably higher in the voxelotor 1500mg group than in the other treatment groups: 13.6% (12/88 subjects) in the voxelotor 1500 mg group; 7.6% (7/92 subjects) in the voxelotor 900-mg group, and 5.5%

(5/91 subjects) in the placebo group. The higher incidence ACS events in the voxelotor 1500mg group is likely explained by the imbalance in the incidence of ACS across treatment groups at baseline in study GBT440-031 despite randomization. An imbalance in priapism incidence was also observed across treatment groups in male subjects in Study GBT440-031: 3/31 (9.7%), 6/41 (14.6%), and 1/42 (2.4%) in the voxelotor 1500-mg, voxelotor 900-mg, and placebo groups, respectively. However, this is likely due to chance considering the small numbers of subjects involved. Since VOC crises is the most typical presentation of SCD an improvement in the VOC event rate in the study treatment arm would have been reassuring, however, an improvement in VOC rate was not expected as a proximal effect of voxelotor and study GBT440-031 was neither designed or powered to detect an improvement in the VOC events.

TEAEs leading to study drug discontinuation

In the pivotal study GBT440-031, TEAEs leading to study drug discontinuation was highest in the voxelotor 1500mg group but overall, low across treatment groups (10.2%, 6.5%, and 5.5% in the voxelotor 1500-mg, voxelotor 900-mg, and placebo groups, respectively). Majority of TEAES were assessed as not related to study drug but as related to underlying SCD. Across the SCD clinical studies, the majority of dose modifications were due to dosing interruptions during adverse events, not dose reductions; a small percentage of subjects discontinued study drug due to TEAEs (≤ 10%). TEAEs that led to modification of study drug dosing were most common in the voxelotor 1500-mg group (40.9% [36/88] of subjects versus 29.3% (27/92) in the voxelotor 900-mg group and 28.6% (26/91) in the placebo group). The most common TEAE that led to modification of dosing in all treatment groups was sickle cell anemia with crisis reported in 21.6% (19/88) of subjects in the voxelotor 1500-mg group compared with 15.2% (14/92) in the voxelotor 900-mg group and 14.3% (13/91) in the placebo group.

Across all studies in the voxelotor clinical development program, 2 TEAEs of drug hypersensitivity assessed as related to voxelotor occurred. No events of anaphylaxis or anaphylactoid reactions were reported. Overall across the voxelotor clinical studies, mean changes over time in safety hematology and serum chemistry variables were small and not clinically meaningful. TEAEs were largely consistent across subgroups based on age, sex, race, and hydroxyurea use. Results of the pooled adolescent analyses demonstrated that the overall safety profile of voxelotor was similar in nature and incidence for adolescents and adults with SCD.

Across all clinical studies included in this NDA, voxelotor demonstrated an acceptable safety and tolerability profile that supports the proposed registration dose of 1500 mg QD. In patients with severe hepatic impairment a reduced dose of 1000mg daily is recommended.

8.3 Statistical Issues

No major statistical issues were identified in the review.

8.4 Conclusions and Recommendations

For the efficacy results presented in this Study GBT440-031, we found that there were significantly more subjects in voxelotor 1500 mg arm than in placebo arm who achieved an Hb response at Week 24 ($p < 0.0001$) and results from the sensitivity analyses support the primary analysis result. Furthermore, no outlier subgroups were observed.

Per the pre-specified hierarchical hypothesis testing order, statistically significant treatment effects of voxelotor 1500-mg compared with placebo were observed for the primary efficacy endpoint (Hb response at Week 24) and for the three of the four key secondary efficacy endpoints: (1) the change from Baseline in Hb at Week 24, (2) the percentage change from Baseline in indirect bilirubin at Week 24, and (3) percentage change from Baseline in reticulocyte percentage at Week 24. The voxelotor 1500 mg did not demonstrate a statistically significant improvement in percent change from baseline in LDH at Week 24. This non-significant finding prevented any inferential claims of the treatment effect of voxelotor 900 mg in any of the efficacy endpoints.

In conclusion, from the study result, voxelotor was shown to significantly improve Hb and reduce some clinical measures of hemolysis in adult and adolescent subjects with SCD. Across all clinical studies included in this NDA, voxelotor demonstrated an acceptable safety and tolerability profile.

The most common non-SCD related TEAEs in Voxelotor treated patients that occurred with an incidence ≥ 3 percentage points in the voxelotor 1500mg treatment group compared to placebo group were headache (26%), diarrhea (21%), abdominal pain (20%), nausea (17.0%), fatigue (14%), rash (14%) and pyrexia (12%).

X see signature page
Lola Luo, PhD
Primary Statistical Reviewer

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Yeh-Fong Chen, PhD
Statistical Team Leader

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Patricia Oneal, MD
Primary Clinical Reviewer

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Rosanna Setse, MD, PhD
Primary Clinical Reviewer

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Tanya Wroblewski, MD
Clinical Team Leader

APPEARS THIS WAY ON ORIGINAL

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

11.2 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	Hemoglobin S polymerization inhibitor indicated for the treatment of sickle cell disease in adults and (b) (4) pediatric patients 12 years of age and older. (b) (4)	Hemoglobin S polymerization inhibitor indicated for the treatment of sickle cell disease in adults (b) (4) pediatric patients 12 years of age and older.
Dosage and Administration	Recommended dosage: •1,500 mg taken orally once daily with or without food	Recommended dosage: •1,500 mg taken orally once daily with or without food Recommended dosage for severe hepatic impairment: •1,000 mg taken orally once daily in patients with severe hepatic impairment (Child Pugh C)
Warnings and Precautions	(b) (4)	Hypersensitivity Reactions: Generalized rash, urticaria, shortness of breath, facial swelling and eosinophilia may occur. Observe for signs and symptoms and manage promptly (5.1). Laboratory Test Interference: Perform quantification of hemoglobin species when patient is not receiving OXBRYTA.

Clinical Trials Experience	(b) (4)	Include the adverse reactions by percentage. Serious adverse reactions and permanent discontinuation due to an adverse reactions were highlighted.
Clinical Studies	Included the graphical waterfall plot on subject-level change from baseline in hemoglobin at Week 24, indirect bilirubin and percent reticulocyte count changes from baseline to Week 24 compared to placebo	Waterfall plot is noted as Figure 1 in Section 14. Additional efficacy results on changes from baseline to Week 24 in hemoglobin and clinical measures of hemolysis were included.

The Applicant's submitted proposed Prescribing Information (PI) and Patient Labeling were reviewed for consistency with the labeling regulations and guidance's; to ensure that the PI is a useful communication tool for healthcare providers; and uses clear, concise language. All disciplines contributed to the revisions of the PI. As labeling negotiations are ongoing, these recommendations should be considered preliminary and may not represent DHP's final recommendations for the voxelotor labeling.

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 Commitment

The following postmarketing requirements are recommended:

PMR-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 (based on primary analysis):	07/2025
Study/Trial Completion:	03/2026
Final Report Submission:	09/2026

PMR-2 (Accelerated Approval PMR)
Complete follow-up of patients (on treatment) enrolled in Study GBT440-031: A Phase 3, Double-Blind, Randomized, Placebo-Controlled, Multicenter Study of Voxelotor Administered Orally to Patients with Sickle Cell Disease (HOPE Trial).
Conduct an updated safety and efficacy analysis and submit datasets at the time of final clinical study report submission.

Study/Trial Completion:	12/2019
Final Report Submission:	09/2020

PMC
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 Division Director (DHOT)

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Haleh Saber, PhD

15 Division Director (OCP)

X see signature page

Brian Booth, PhD

16 Division Director (OB) Comments

X see signature page

Thomas Gwise, PhD

17 Division Director (Clinical) Comments

I concur with the recommendation for approval and the post-marketing requirements including that for subpart H. For additional details, see my summary review.

X see signature page

Ann T. Farrell, MD

18 Office Director (or designated signatory authority) Comments

This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.

X

Marc Theoret, MD

19 Appendices

19.2 References

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19.3 Financial Disclosure

The financial disclosure for conducting the two clinical trials are listed below.

Covered Clinical Study (Name and/or Number): Studies GBT440-031 and GBT 440-034

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 278		
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)

19.4 Nonclinical Pharmacology/Toxicology

19.5 OCP Appendices (Technical documents supporting OCP recommendations)

19.5.1 Summary of Bioanalytical Method Validation and Performance

Two validated bionanalytical methods were used to determine the voxelotor concentrations in human plasma and whole blood using liquid chromatography-tandem mass spectrometry (LC-MS/MS). The method used GBT440-D_7 as an internal standard. As summarized in Table 55 , the both methods satisfied the criteria for method validation and application to routine analysis as outline in the Guidance for Industry: Bioanalytical Method Validation.

Table 57: Voxelotor Method Validation Summary

Parameter	Details
Method	LC/MS/MS
Analyte	Voxelotor (GBT440)
Internal Standard	GBT440-D_7

Calibration Range	120 to 300,000 ng/mL
Validation Range	120; 360; 10,000; 24,000; 600,000 ng/mL
Intra-Day Reproducibility	CV% less than 10.8% and RE% less than 15 for all concentrations
Inter-Day Reproducibility	CV% less than 11% and RE% less than 18% for all concentrations
LLOQ	120 ng/mL
Dilution Factor	Demonstrated for 10-fold
Stability	
Freeze/Thaw Cycles	Demonstrated stability after 5 cycles at -20 °C and -80 °C
Short Term Stability	Demonstrated stability for 25 hours at room temperature
Long Term Stability	Demonstrated stability up to 443 days at -20 °C and -70 °C
Standard Solution Stability	Demonstrated stability up to 117 days in DMSO at 1 °C to 8 °C

19.5.2 Population PK Analysis

The Applicant's population PK analysis was conducted based on a pooled dataset of observed 1848 plasma and 1869 whole blood voxelotor concentrations in 245 patients from studies GBT440-001, GBT440-007, and GBT440-031. Summary statistics of the continuous and categorical covariates that were evaluated in the population PK analysis are shown in Table 56 and
Table 57, respectively.

Table 58 Summary Statistics for the Continuous Covariates in the Population PK Analysis

Covariate	GBT440-001	GBT440-007	GBT440-031	All Studies
N	52	47	180	279
	Median (range)			
Age (y)	33 (20-56)	14 (12-17)	23.5 (12-59)	22 (12-59)
Baseline Weight (kg)	68.6 (54.4-92.5)	49.5 (30.2-93.3)	60.68 (28-135)	60.6 (28-135)
Baseline Height (cm)	171.4 (155-194)	156.1 (136-187)	165 (130-193)	164.9 (130-194)
Baseline Albumin (g/L)	42 (31-50)	44 (36-51)	43 (33-50)	43 (31-51)
Baseline Alkaline Phosphatase (U/L)	73.5 (36-112)	158 (60-318)	92 (34-513)	91 (34-513)
Baseline Alanine Transferase (U/L)	27.5 (11-100)	22 (6-88)	19 (6-134)	21 (6-134)
Baseline Aspartate Aminotransferase (U/L)	42 (20-119)	41 (17-89)	33 (10-113)	36 (10-119)
Baseline Direct Bilirubin (µmol/L)	10 (3-17)	5.13 (1.71-34.2)	10.85 (3.6-48.9)	9.747 (1.71-48.9)
Baseline Total Bilirubin (µmol/L)	35.85 (9.1-136)	46.17 (13.7-222)	44.2 (8.5-256)	42.75 (8.5-256)
Baseline Indirect Bilirubin (µmol/L)	28 (4.9-121)	41.04 (8.72-188)	30.35 (7.2-234)	29.7 (4.9-234)
Baseline Creatinine (mg/dL)	0.661 (0.452-1.03)	0.4 (0.21-0.8)	0.513 (0.211-2.38)	0.52 (0.21-2.38)
Baseline Hematocrit (%)	24.7 (19.1-32)	26 (17-36)	27.7 (17.9-39.8)	27 (17-39.8)
Baseline Hemoglobin (g/dL)	8.55 (7-11.4)	8.8 (6.2-12)	8.4 (5.6-11)	8.5 (5.6-12)
Baseline Lactate Dehydrogenase (U/L)	856 (206-2120)	505 (220-1280)	370 (164-1220)	438 (164-2120)
Baseline Reticulocytes (10^9/L)	234.2 (51-726)	--	286 (0-783)	270.2 (0-783)
Baseline Percent Reticulocytes (%)	6.67 (2.37-26.4)	9.4 (3.17-26.3)	10.1 (1.3-23.2)	9.2 (1.3-26.4)

Covariate	GBT440-001	GBT440-007	GBT440-031	All Studies
N	52	47	180	279
Baseline WBC (10^9/L)	9.1 (3.5-14.9)	9.75 (3.13-19.1)	8.855 (3.05-23.6)	9.06 (3.05-23.6)
Baseline Erythropoietin (mU/mL)	86.8 (19.3-835)	98.3 (27.8-297)	78.5 (9-1140)	83.25 (9-1140)
Baseline Fetal Hemoglobin (%)	5 (0.6-27.8)	11.95 (3.7-29)	8.4 (0.2-30.7)	7.8 (0.2-30.7)
Baseline Cystatin C (mg/L)	--	--	0.83 (0.47-2.58)	0.83 (0.47-2.58)
Baseline Creatinine Clearance (mL/min)	169.7 (82.2-267)	217.9 (94.2-396)	206.8 (57.5-473)	195.5 (57.5-473)
Blood Volume (L)	4.471 (3.39-5.75)	3.355 (2.1-6)	3.903 (2.02-6.85)	3.925 (2.02-6.85)
Estimated Glomerular Filtration Rate (mL/min/SSA)	140.9 (79-200)	154.8 (74.9-314)	145 (40-236)	146 (40-314)
Baseline Body Mass Index (kg/m^2)	23.02 (17.2-35.2)	19.91 (15-29.8)	22.1 (13.9-45.3)	21.9 (13.9-45.3)
Maximum Hematocrit (%)	28.3 (20.2-35)	30.6 (20-52.8)	34.1 (21.1-50.5)	32.2 (20-52.8)
Maximum Hemoglobin (g/dL)	9.6 (7.3-12.3)	9.7 (7.1-13.5)	9.6 (5.6-14.3)	9.6 (5.6-14.3)

WBC = white blood cell, SSA = standard surface area

Source: Population PK Report GBT-CP-005, Table 5.

Table 59 Summary Statistics for the Categorical Covariates in the Population PK Analysis

Covariate	Category	GBT440-001	GBT440-007	GBT440-031	All Studies
N		52	47	180	279
		N (%)			
Sex	Female	28 (53.8%)	25 (53.2%)	108 (60%)	161 (57.7%)
	Male	24 (46.2%)	22 (46.8%)	72 (40%)	118 (42.3%)
Race	Missing	--	--	1 (0.556%)	1 (0.358%)
	White	--	15 (31.9%)	12 (6.67%)	27 (9.68%)
	Black or African American	52 (100%)	32 (68.1%)	118 (65.6%)	202 (72.4%)
	Arab/Middle Eastern	--	--	34 (18.9%)	34 (12.2%)
	Other	--	--	7 (3.89%)	7 (2.51%)
	Asian	--	--	1 (0.556%)	1 (0.358%)
	Multiple	--	--	7 (3.89%)	7 (2.51%)
Ethnicity	Not Hispanic or Latino	52 (100%)	45 (95.7%)	166 (92.2%)	263 (94.3%)

Covariate	Category	GBT440-001	GBT440-007	GBT440-031	All Studies
N		**52**	**47**	**180**	**279**
	Hispanic or Latino	--	2 (4.26%)	7 (3.89%)	9 (3.23%)
	Not Reported	--	--	7 (3.89%)	7 (2.51%)
Region	North America	--	33 (70.2%)	69 (38.3%)	102 (36.6%)
	Mid-Southern Africa	--	--	31 (17.2%)	31 (11.1%)
	Mid-East	--	14 (29.8%)	50 (27.8%)	64 (22.9%)
	Europe	52 (100%)	--	28 (15.6%)	80 (28.7%)
	Caribbean	--	--	2 (1.11%)	2 (0.717%)
Hydroxyurea Use	No use	42 (80.8%)	5 (10.6%)	60 (33.3%)	107 (38.4%)
	Use	10 (19.2%)	42 (89.4%)	120 (66.7%)	172 (61.6%)
Age Group	Adolescent	--	47 (100%)	29 (16.1%)	76 (27.2%)
	Adult	52 (100%)	--	151 (83.9%)	203 (72.8%)
Concomitant Proton Pump Inhibitor	No	50 (96.2%)	47 (100%)	164 (91.1%)	261 (93.5%)
	Yes	2 (3.85%)	--	16 (8.89%)	18 (6.45%)
Formulation	300 mg F1 or F2 Tablets	--	--	178 (98.9%)	178 (63.8%)
	100 mg PIC	52 (100%)	--	--	52 (18.6%)
	300 mg CB Capsules	--	47 (100%)	2 (1.11%)	49 (17.6%)
Sickle Cell Disease Genotype	HbSS	46 (88.5%)	43 (91.5%)	131 (72.8%)	220 (78.9%)
	HbSC	6 (11.5%)	NA	5 (2.78%)	11 (3.94%)
	HbSβ0	--	4 (8.51%)	31(17.2%)	35 (12.5%)
	HbSβ+ THAL	--	--	8 (4.44%)	8 (2.87%)
	Missing/Other	--	--	5 (2.78%)	5 (1.79%)
Fed	Fasted	52 (100%)	3 (6.38%)	--	55 (19.7%)
	Non High-Fat Meal	NA	37 (78.7%)	40 (22.2%)	77 (27.6%)
	Not Specified	--	7 (14.9%)	140 (77.8%)	147 (52.7%)
Number of Capsules	Not dosed	--	--	4 (2.22%)	4 (1.43%)
	0 [a]	--	--	12 (6.67%)	12 (4.3%)
	2	--	7 (14.9%)	--	7 (2.51%)
	3	--	25 (53.2%)	83 (46.1%)	108 (38.7%)
	5	16 (30.8%)	15 (31.9%)	80 (44.4%)	111 (39.8%)

Covariate	Category	GBT440-001	GBT440-007	GBT440-031	All Studies
N		52	47	180	279
	6	6 (11.5%)	--	--	6 (2.15%)
	7	18 (34.6%)	--	--	18 (6.45%)
	9	6 (11.5%)	--	--	6 (2.15%)
	10	6 (11.5%)	--	1 (0.556%)	7 (2.51%)
Number of VOCs Previous 12 Months	Missing	52 (100%)	47 (100%)	--	99 (35.5%)
	1	--	--	75 (41.7%)	75 (26.9%)
	2	--	--	44 (24.4%)	44 (15.8%)
	3	--	--	24 (13.3%)	24 (8.6%)
	4	--	--	16 (8.89%)	16 (5.73%)
	5	--	--	7 (3.89%)	7 (2.51%)
	6	--	--	3 (1.67%)	3 (1.08%)
	7	--	--	1 (0.556%)	1 (0.358%)
	8	--	--	4 (2.22%)	4 (1.43%)
	9	--	--	4 (2.22%)	4 (1.43%)
	10	--	--	2 (1.11%)	2 (0.717%)

[a] The 12 patients with 0 capsules include 11 patients for whom no PK observations were available and 1 patient.
HbSS = homozygous hemoglobin S, HbSC = hemoglobin sickle cell, HbS β+ thalassemia = the combination of sickle cell mutation and beta-thalassemia (β-thal) mutations, HbS β 0 thalassemia = the combination of sickle cell mutation and null beta-thalassemia (β-thal) mutations, PIC = powder in capsule, CB = 300 mg capsule formulation, F1 = 300 mg tablet formulation, F2 = 300 mg tablet formulation, VOC = vaso-occlusive crisis, NA = not applicable

Source: Population PK Report GBT-CP-005, Table 6.

The PK of voxelotor in plasma and whole blood was best characterized by a two-compartment model with first order absorption and fist-order elimination for plasma, coupled with an effect-compartment for whole blood. The between subject variability (BSV) was estimated as log-normally distributed with a non-zero covariance on apparent clearance (CL/F), apparent volume of distribution (Vc/F), relative bioavailability (Frel), and ratio of drug in whole blood to plasma (Rbp), while the between occasion variability (BOV) was estimated on CL/F.

Covariate analysis identified 5 statistically significant covariates, including the effect of baseline albumin (31-51 g/L) on CL/F, the effect of blood volume (2.0-6.9 L) on V/F, and the effects of baseline Hb (5.6-12 g/dL), nominal dose (500, 600, 700, 900, 1000 or 1500 mg) and baseline hematocrit (17%-39.8%) on Rbp. No statistically significant effect on voxelotor PK was found for sex, age (12-59 yrs), age group (adult vs. adolescent), race (Black or African-American, Arab or Middle-Eastern, or White), geographic region (Africa, Europe, Middle East, or North America),

direct bilirubin (1.7-48.9 µmol/L), drug product formulation (100 mg powder-in-capsule, 300 mg CB capsule, or F1/F2 tablets), number of capsules/tablets, food intake (fasted, non-high-fat meal, or unrestricted meal), concomitant proton pump inhibitor (PPI) use, and hydroxyurea (HU) use. The final voxelotor PK model parameter estimates are presented in Table 58.

Table 60 Population PK Parameters of Voxelotor from the Final PK Model

Parameter	Description	Estimate	RSE (%)	95% CI [a]	Shrinkage
THETA1	CL/F (L/hr)	6.693	2.701	(6.339 - 7.048)	NA
THETA2	Vc/F (L)	338.1	2.847	(319.3 - 357)	NA
THETA3	KA (1/hr)	3.115	37.85	(0.8039 - 5.427)	NA
THETA4	Proportional error, plasma (%)	25.48	4.27	(23.35 - 27.61)	NA
THETA6	Q/F (L/hr)	0.3812	8.155	(0.3203 - 0.4422)	NA
THETA7	Vp/F (L)	72.17	6.502	(62.97 - 81.37)	NA
THETA11	Kbp (1/hr)	0.364	8.921	(0.3004 - 0.4277)	NA
THETA12	Rbp	16.96	1.481	(16.47 - 17.45)	NA
THETA13	Proportional error, whole blood (%)	19.24	4.597	(17.5 – 20.97)	NA
THETA14	Additive error, whole blood (ng/mL)	732.2	11.58	(566.1 - 898.4)	NA
THETA15	Baseline albumin on CL/F	-0.0163	33.83	(-0.0271 - -0.005491)	NA
THETA16	Baseline hemoglobin on Rbp	0.04772	22.57	(0.02661 - 0.06882)	NA
THETA17	Nominal dose on Rbp	-0.00032	10.64	(-0.0003877 - -0.0002539)	NA
THETA18	Hematocrit on Rbp	0.02638	12.07	(0.02014 - 0.03262)	NA
THETA19	Blood volume on Vc/F	0.1426	23.98	(0.07556 - 0.2096)	NA
OMEGA(1,1)	BSV CL/F, %CV	24.6	12.56	(0.03067 - 0.09014)	26.0
OMEGA(2,2)	BSV Vc/F, %CV	26.1	11.95	(0.03628 - 0.1002)	40.1
OMEGA(3,3)	BSV Frel, %CV	21.4	12.46	(0.0234 - 0.06809)	32.5
OMEGA(4,4)	BSV Rbp, %CV	12.3	9.374	(0.009572 - 0.02069)	31.7
OMEGA(9,9)	BOV on CL/F, %CV	47.5	6.069	(0.1721 - 0.2795)	31.8 [b]

[a] The relative standard errors for omega (BSV and BOV) are reported on the approximate standard deviation scale (SE/variance estimate)/2. The 95% CI for omega (BSV and BOV) are calculated based on the parameter estimate of omega. The %CV is calculated as 100*sqrt(omega).

[b] The shrinkage shown is the median of the eight defined occasions. The individual estimates were 29.7, 36.3, 33.9, 64.0, 37.5, 19.7, 23.7, and 27.9. The occasion with 64% shrinkage was Day 25, which was limited to 87 observations in study GBT440-001 subjects.

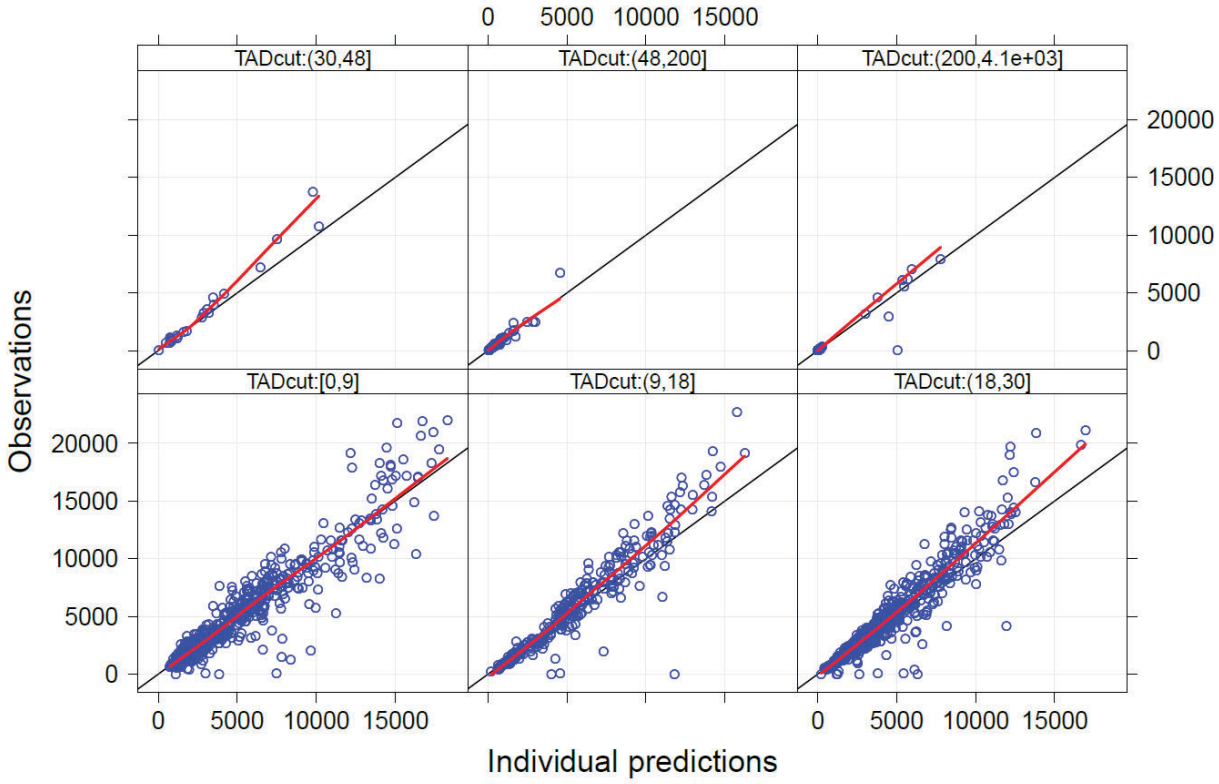
BOV = between occasion variability, BSV = between subject variability, CL/F = apparent clearance, Frel = relative bioavailability, Kbp = rate transfer constant from plasma to whole blood, Rbp = ratio of voxelotor concentration in whole blood to plasma, Vc/F = apparent central volume, Vp/F = apparent peripheral volume, Q/F = intercompartmental clearance, KA = absorption constant, %CV = percentage of coefficient of variance, Frel = relative bioavailability, RSE = relative standard error, CI = confidence interval, THETA = typical population values of pharmacokinetics or pharmacodynamics parameter, OMEGA = inter-individual variability, NA = not applicable

Note: All covariate effects in the model were parameterized as linear effects on the parameter, e.g., $P = \theta_k \cdot (1 + \theta_j \cdot (X_i - M(X_i)))$, where P is the population estimate of a parameter, Xi is the covariate of subject i for the parameter P, M(Xi) is the median of covariate X for the patient population, θk is the typical value of the parameter P, and θj is a coefficient that reflects the covariate's effect on the parameter.

Source: Population PK Report GBT-CP-005, Table 8.

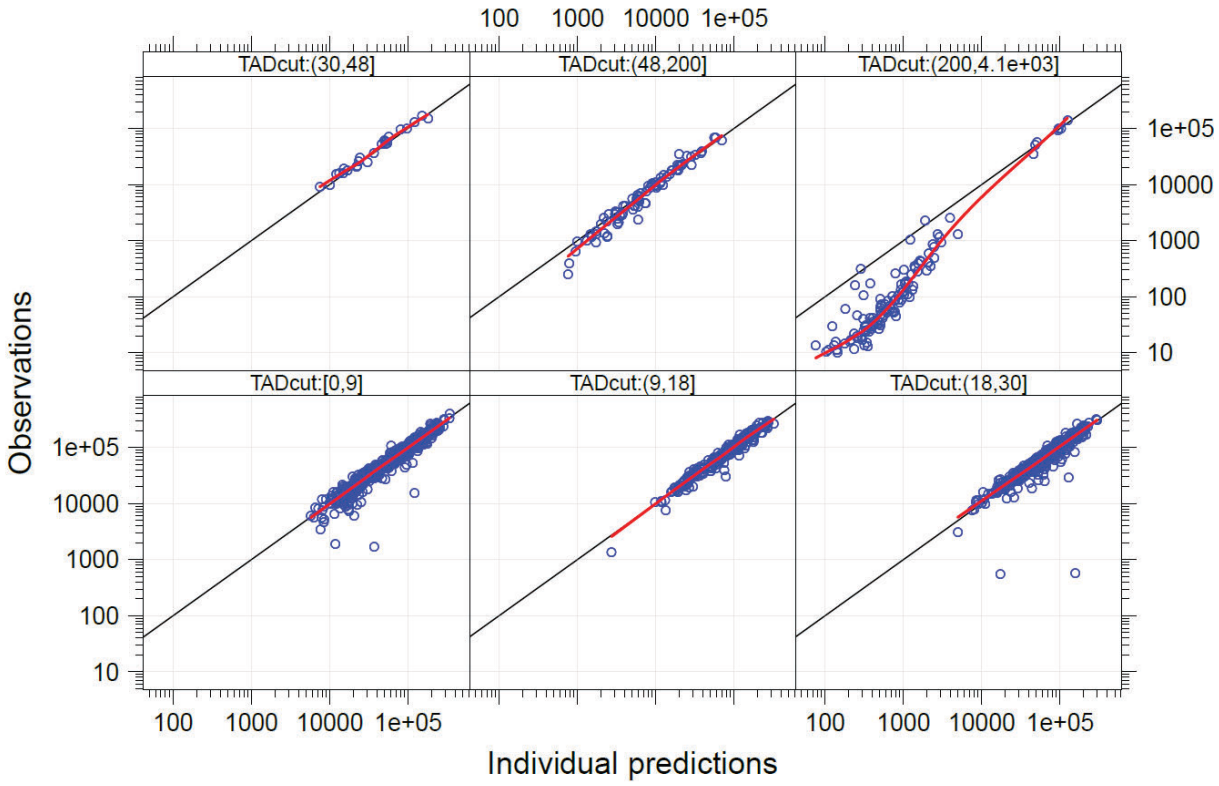
The goodness-of-fit plots overall showed that the final voxelotor PK model describes both the plasma and whole blood PK data reasonably well. When stratified by time after dose, plots of observed versus individual predictions of voxelotor concentrations in plasma (Figure 14) and whole blood (Figure 15) show that the observations in the first nine hours post dose ("TADcut:[0,9])" are well described by the model, with no apparent over- or under-prediction. However, later time intervals suggest some slight under-prediction of voxelotor concentrations in plasma and some over-prediction of voxelotor concentrations in whole blood, especially in the latest time after dose interval (200 to 4100 hours). The Sponsor argued that the under-prediction of voxelotor plasma concentrations in later time intervals was likely due to undetected errors in recorded sample times (i.e., post dose samples recorded as troughs), while the over-prediction of voxelotor whole blood concentrations in the latest time interval was likely due to extremely low concentrations (<1000 ng/mL) collected from patients in study GBT440-001 during the long follow-up period. The Applicant also argued that the low concentrations in the latest time interval unlikely represent any clinically relevant concentration range, because previous estimates of EC_{50} for relevant markers of hemolysis are substantially higher (e.g., >30 µg/mL).

Figure 17 Observed versus individual predictions of voxelotor concentrations in plasma for the final model, stratified by time after dose



Source: Population PK Report GBT-CP-005, Figure 5.

Figure 18 Observed versus individual predictions (log-log) of voxelotor concentrations in whole blood for the final model, stratified by time after dose

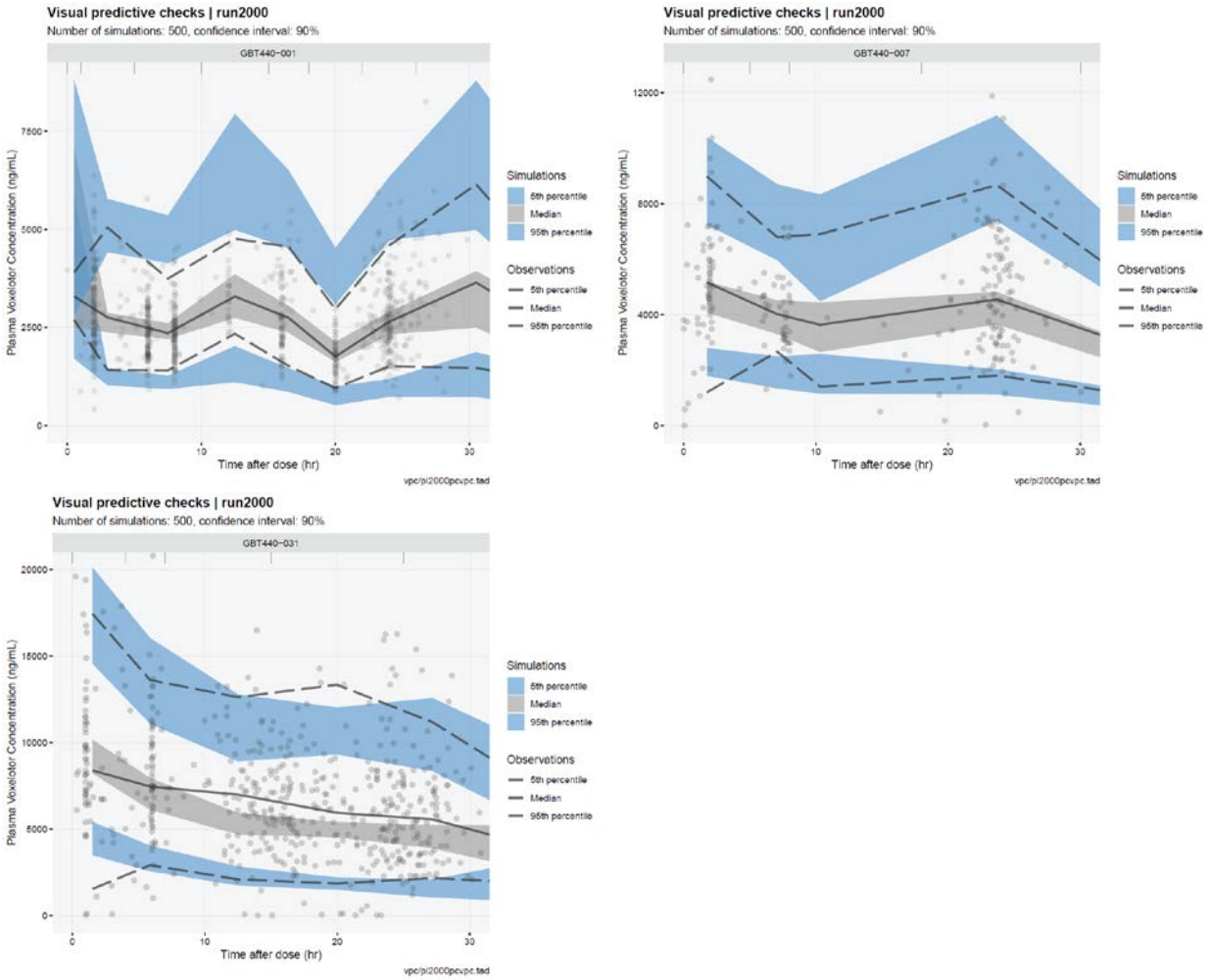


Source: Population PK Report GBT-CP-005, Figure 6.

The bootstrap analysis of the final voxelotor PK model based on 500 runs showed a successful minimization rate of 86.8%. The parametric and bootstrap median estimates were similar, with the largest differences observed for estimates BSV on Rbp (-5.8%) and BSV on Vc/F (-4.3%). All remaining differences were less than ±3%. Confidence intervals (CI) were mostly similar, with the exception of the CI on Ka, which was likely due to limited data collected during the absorption phase in Study GBT440-007 and GBT440-031.

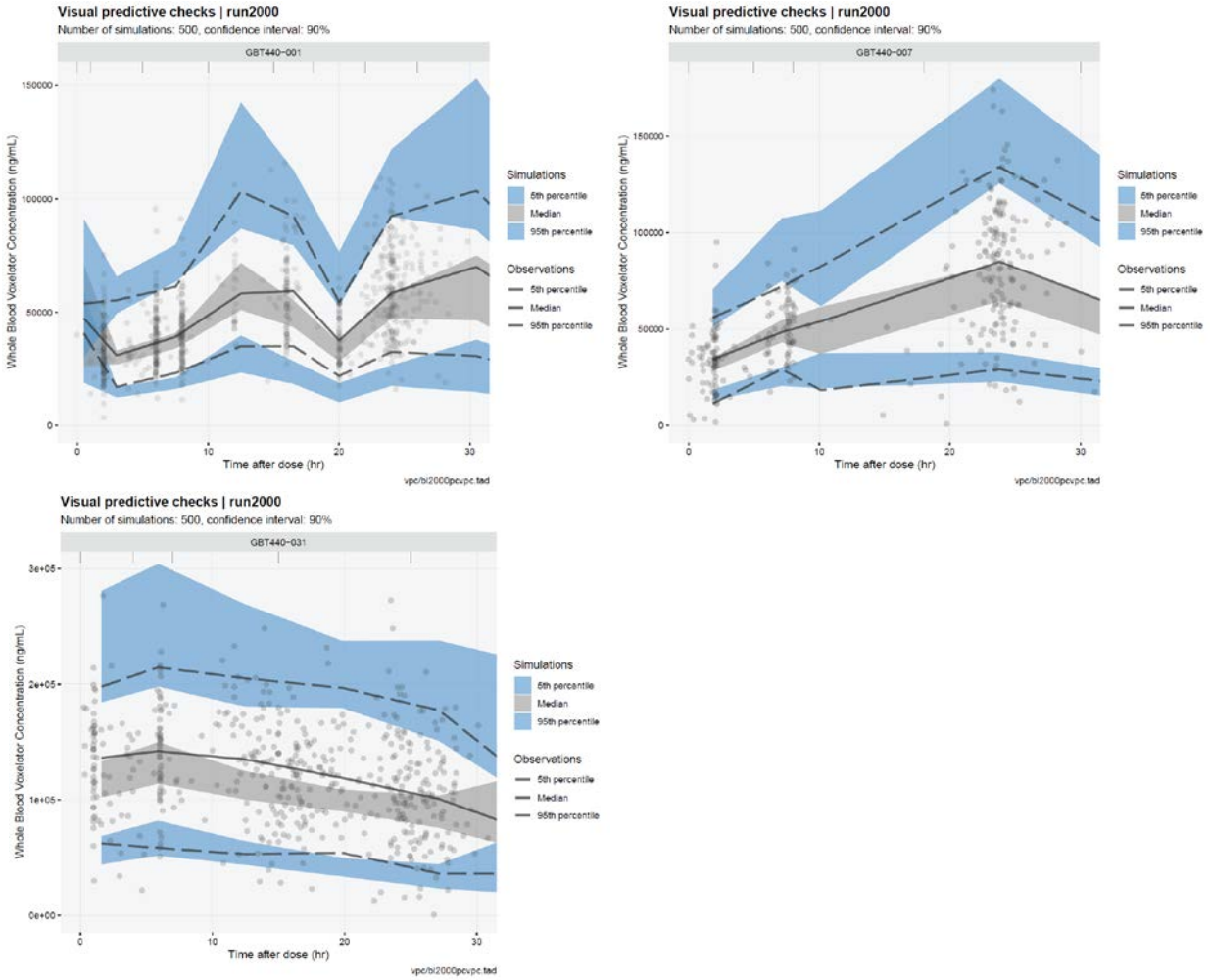
The prediction-corrected visual predictive check (pcVPC) stratified by study are shown in Figure 16 for plasma PK data and in Figure 17 for whole blood PK data. The median observed PK data in plasma and whole blood from the studies with intensive data (GBT440-001 and GBT440-007) were well described by the model. For Study GBT440-031, however, the early observations (<10 hour after dose) in plasma and whole blood were reasonably well described, the model showed a slight under-prediction of trough concentrations in plasma and whole blood (between 10 and 30 hours after dose). The under-prediction was consistent with the trends observed in the diagnostic plots. The same under-prediction was not observed around the trough observations in GBT440-001 and GBT440-007, suggesting that the apparent under-prediction may be study-related (e.g., potential errors in sample time records and the impact of unreported non-compliance).

Figure 19 Prediction Corrected Visual Predictive Check for the Final Voxelotor Model in Plasma Stratified by Study



Source: Population PK Report GBT-CP-005, Figure 9.

Figure 20 Prediction Corrected Visual Predictive Check for the Final Voxelotor Model in Whole Blood Stratified by Study



Source: Population PK Report GBT-CP-005, Figure 10.

The covariate model included statistically significant covariate effects of baseline Hb, baseline albumin, blood volume, baseline hematocrit and nominal dose on CL/F, Vc/F, and Rbp. Simulations based on the final voxelotor PK model in patients following a 1500 mg nominal dose at steady-state showed that, compared to the typical median patient:

- patients with baseline Hb in the top quartile (9.5 to 12 g/dL) had ~0.2% lower AUC_{SS}, ~2% lower $C_{max,SS}$, and ~2% higher $C_{min,SS}$ in plasma, and ~23% higher AUC_{SS}, 22% higher $C_{max,SS}$, and 25% higher $C_{min,SS}$ in whole blood;
- patients with baseline albumin in the top quartile (45 to 51 g/dL) had ~2% higher AUC_{SS}, $C_{max,SS}$ and $C_{min,SS}$ in plasma, and ~8% higher AUC_{SS}, $C_{max,SS}$ and $C_{min,SS}$ in whole blood;

- patients with blood volume in the top quartile (4.5 to 6.2 L) had ~8% lower AUC_{SS}, ~10% lower $C_{max,SS}$ and ~4% lower $C_{min,SS}$ in plasma, and ~8% lower AUC_{SS}, ~9% lower $C_{max,SS}$ and ~6% lower $C_{min,SS}$ in whole blood;
- patients with baseline hematocrit in the top quartile (30% to 40%) had ~2% higher AUC_{SS}, ~0.4% lower $C_{max,SS}$ and ~5% higher $C_{min,SS}$ in plasma, and ~16% higher AUC_{SS}, ~15% higher $C_{max,SS}$ and ~18% higher $C_{min,SS}$ in whole blood.

In addition, the covariate analysis also showed that patients with genotype HbSC (n=11) had ~23% higher AUC_{SS}, ~15% higher $C_{max,SS}$ and ~33% higher $C_{min,SS}$ in plasma, and ~50% higher AUC_{SS}, ~45% higher $C_{max,SS}$ and ~60% higher $C_{min,SS}$ in whole blood, compared to patients with genotye HbSS.

Reviewer's Comments: *The Applicant's population PK model appears adequate to describe the voxelotor PK profiles in plasma and whole blood following the administration of voxelotor ranged from 500 mg QD to 1500 mg QD in patients with SCD. Although there were some model mis-specifications of voxelotor concentrations in plasma and whole blood during the latest time after dose interval (200 to 4100 hours), it is not expected to significantly affect the prediction of AUC_{SS} nor considered as clinically significant because voxelotor concentrations in the latest time interval were lower than the previous estimates of EC_{50} (e.g., >30 µg/mL) for relevant markers of hemolysis, thus unlikely represent any clinically relevant concentration range. Therefore, the final PK model is generally acceptable to simulate post-hoc voxelotor exposure metrics, e.g. AUC_{SS}, $C_{max,SS}$ and $C_{min,SS}$ for the E-R analyses for efficacy and safety measurements.*

Covariate analysis identified 5 statistically significant and clinically relevant covariates, including baseline albumin on CL/F, blood volume on V/F, and baseline Hb, baseline hematocrit , and nominal dose on Rbp. However, the impacts of these covariates on voxelotor plasma and whole blood exposures were limited with < 20% alterations and hence not clinically significant. Sex, age, age group, race, geographic region, direct bilirubin, drug product formulation, number of capsules/tablets, food intake, concomitant PPI use, and HU use were found no statistically significant ($p<0.05$) effects on voxelotor PK. Therefore, no dose adjustment is needed for the above-mentioned specific populations.

Although patients with genotype HbSC had ~23% higher AUC_{SS}, ~15% higher $C_{max,SS}$ in plasma, and ~50% higher AUC_{SS}, ~45% higher $C_{max,SS}$ in whole blood, compared to patients with genotye HbSS, such alterations in voxelotor exposures are not considered clinically significant, given the positive E-R relationship for the primary efficacy endpoint (change from baseline in Hb at week 24), and the relative flat E-R relationship for Grade≥2 SCD-related safety endpoints and the mild non-SCD-related safety profile. Refer to 19.5.3 Exposure-Response Analyses for further information. Therefore, no dose adjustment is warranted in patients with genotype HbSC.

Since patients with SCD are hyperfiltrating, typical renal function markers, such as creatinine clearance (CL_{CR}) and estimated glomerular filtration rate (eGFR) may not be accurate indicators of renal function. Similarly, NCI-ODWG criteria and Child-Pugh criteria may also not be accurate

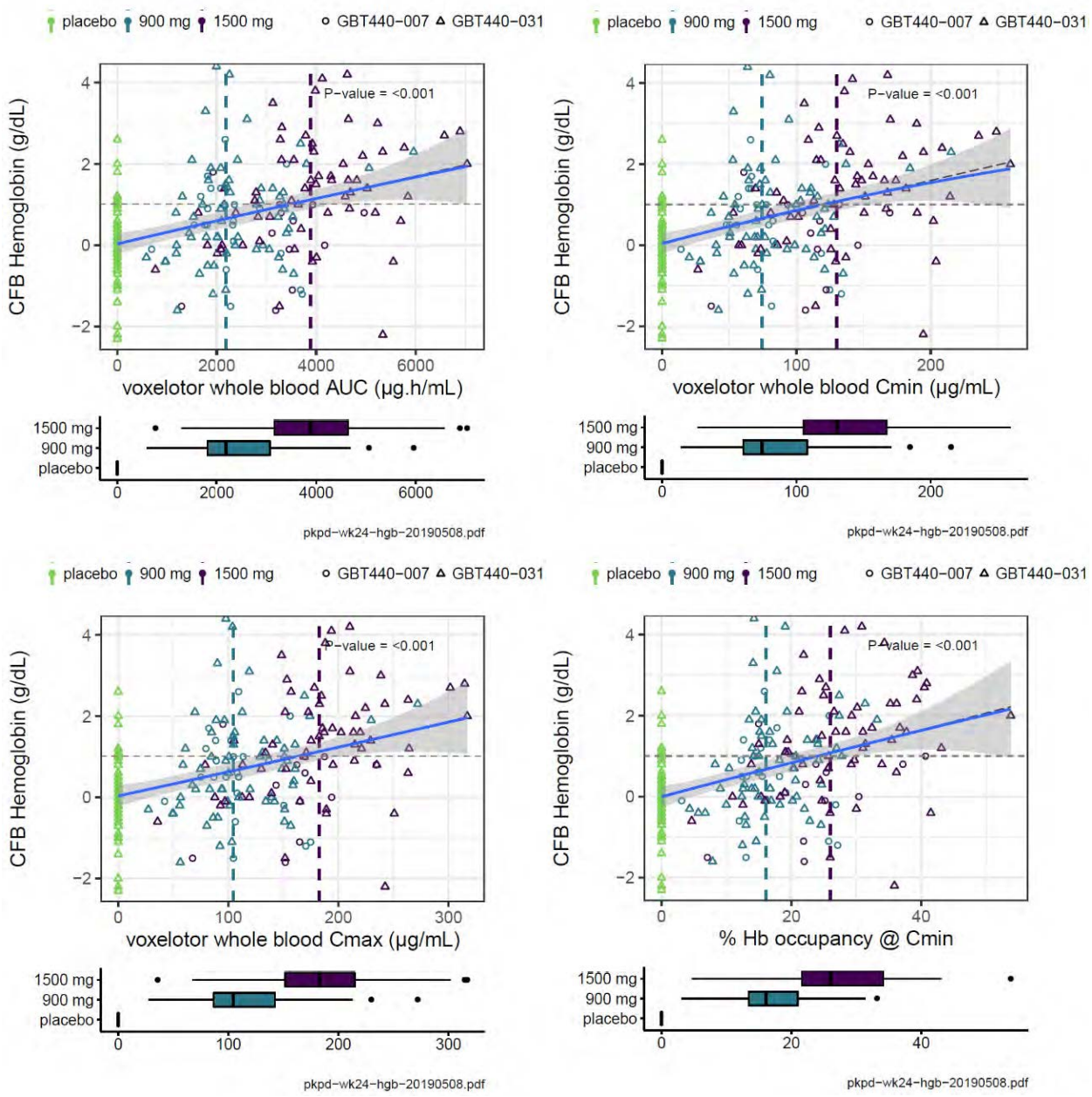
indicators of hepatic impairment, because patients with SCD have abnormal total bilirubin level due to hemolysis. Therefore, population PK analysis may not be an appropriate approach to evaluate the effects of renal/hepatic impairment on voxelotor PK in patients with SCD. Refer to Section 6.3.2 for the recommendations on dose adjustment in patients with SCD and renal/hepatic impairment.

19.5.3 Exposure-Response Analysis

Applicant's Exposure-Response for Efficacy

The exposure-response (E-R) analysis was conducted for the primary efficacy endpoint, change from baseline (CFB) Hb at Week 24 in 238 patients with SCD, including 204 adult patients from Trial GBT440-031 and 34 adolescent patients from Trial GBT440-007. In Trial GBT440-031, 76, 66 and 62 adult patients were treated with placebo, 900 mg and 1500 mg voxelotor, respectively. In Trial GBT440-007, 22 and 12 adolescent patients were treated with 900 mg and 1500 mg voxelotor, respectively. The exposure metrics used for E-R analysis included average AUC_{SS}, $C_{max,SS}$, $C_{min,SS}$ in whole blood, as well as % Hb occupancy at $C_{min,SS}$. Figure 18 shows positive relationships between the CFB Hb at week 24 and voxelotor whole blood PK parameters or % Hb occupancy. As the four exposure metrics were highly correlated, the four relationships with CFB Hb were similar. At the median for each exposure parameter in the 1500 mg patients (vertical, purple dashed line), the second degree polynomial regression line (solid blue line) falls at or marginally above the target line, indicating that the mean increase in Hb following 24 weeks of treatment at voxelotor 1500 mg QD meets or exceeds the 1g/dL target increase. The covariate analysis showed that no differences in the E-R relationship were observed with or without HU use, in male or female patients, in different body weight quantiles, or in patients of HbSS or HbSβ0 genotype. Limited conclusions can be drawn for the HbSC genotype, as the analysis population at week 24 only included five patients in GBT440-031 and none in GBT440-007.

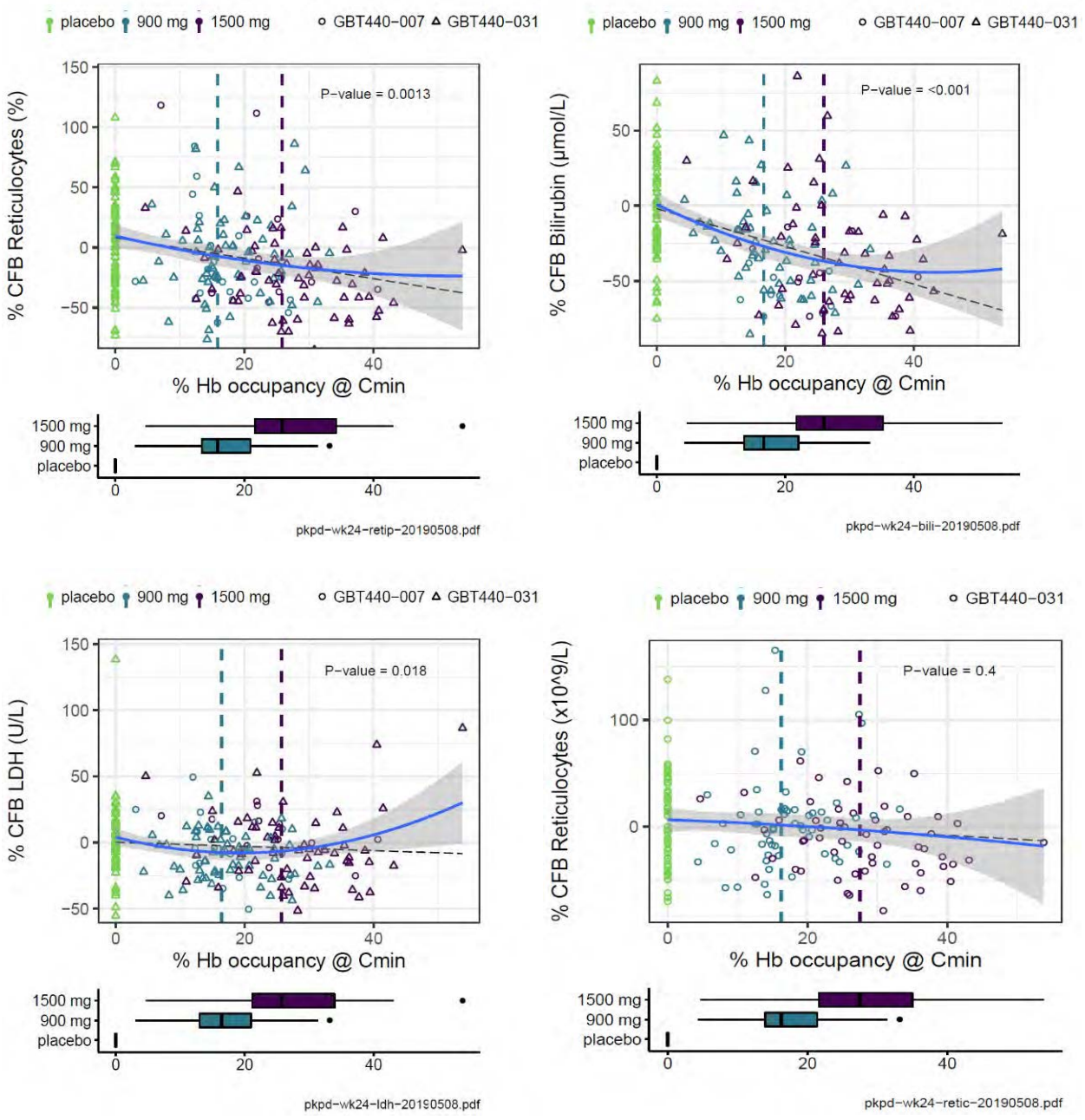
Figure 21 Relationship between Voxelotor Serum Exposure and Probability of Achieving RBC-TI ≥ 8 Consecutive Weeks in Week 1 to Week 15



Source: Exposure-Response and PK/PD Relationships Report GBT-CP-006, Figure 1.

Consistent with the E-R relationships between CFB Hb at week 24 and voxelotor exposures, the E-R analyses for the clinical measures of hemolysis also showed that the decrease from baseline in indirect bilirubin (p<0.001), % reticulocytes (p=0.0013), absolute reticulocytes (p=0.4) and LDH (p=0.018) was greater with increasing % Hb occupancy.

Figure 22 Relationships Between CFB at Week 24 and Voxelotor Whole Blood Exposures or % Hb Occupancy for Clinical Measures of Hemolysis



Source: Exposure-Response and PK/PD Relationships Report GBT-CP-006, Figure 4.

Reviewer's Comments: *The applicant's exposure-response analyses for efficacy are acceptable. The greater increase in CFB Hb (≥ 1g/dL) at 24 weeks and decrease in the clinical measures of hemolysis supported the Applicant's proposed dosing regimen of 1500 mg QD for voxelotor in patients with SCD from the efficacy perspective.*

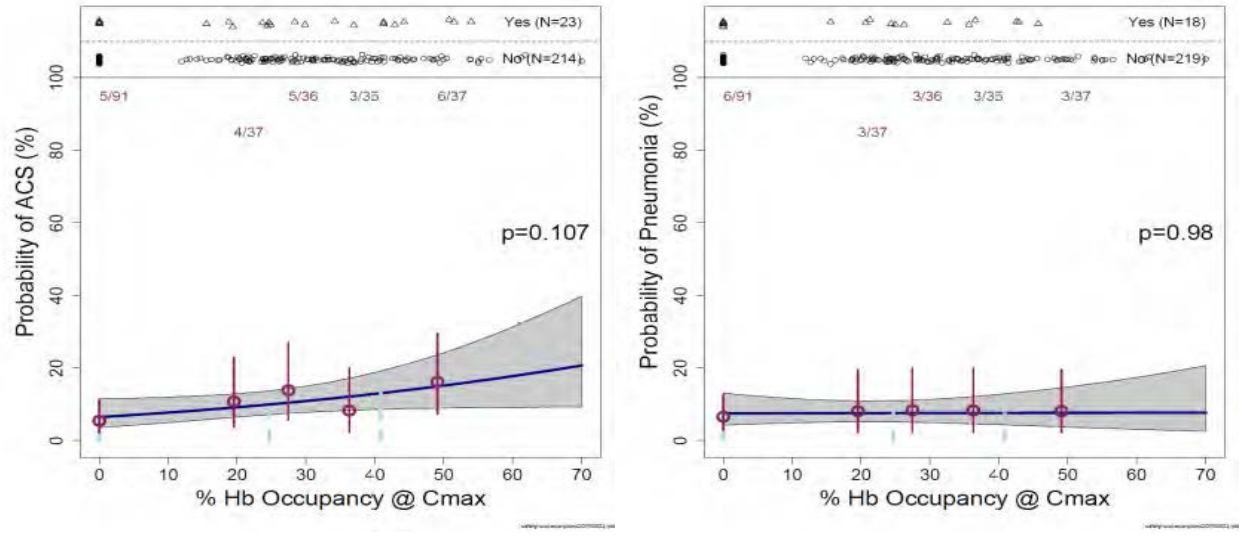
Applicant's Exposure-Response for Safety

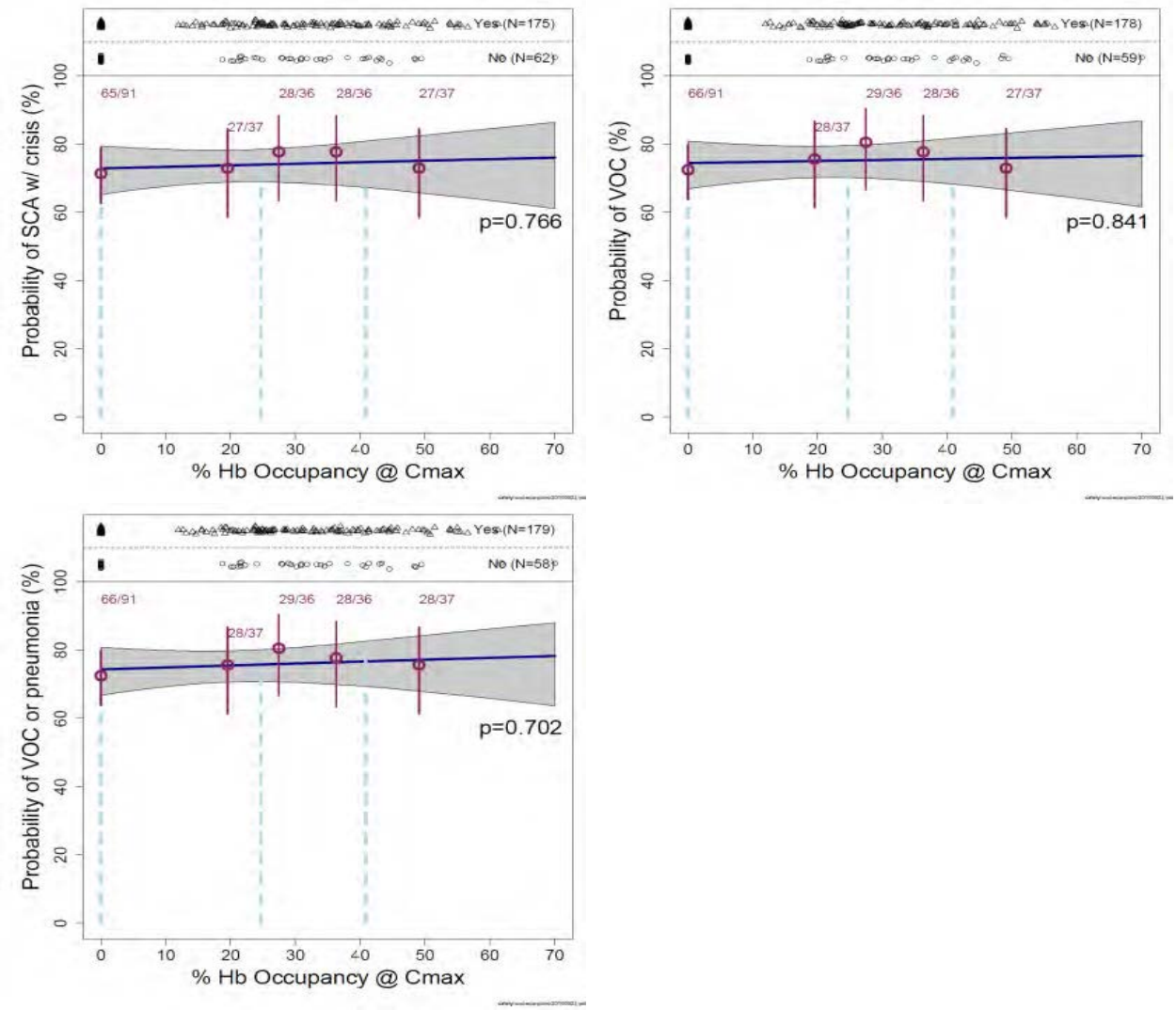
The E-R analyses for safety measurements were conducted based on data from 237 adult patients with SCD (91 placebo, 74 voxelotor 900 mg and 72 voxelotor 1500 mg) from Trial GBT440-031.

SCD-related Safety Endpoints

For Grade≥2 SCD-related TEAEs, ER relationships with voxelotor whole blood and plasma AUC_{SS} and $C_{max,SS}$, and % Hb occupancy at $C_{max,SS}$ were evaluated. ER relationships for SCD-related TEAEs as a function of % Hb occupancy are shown in Figure 20. The E-R relationships were similar for other PK metrics due to the high correlation between PK metrics. No statistically significant ER relationships were observed for acute chest syndrome (ACS), sickle-cell anemia with crisis (SCA), pneumonia, VOC (as ACS or SCA), or VOC or pneumonia. No statistically significant covariate effects were identified on the slope of the relationships.

Figure 23 Exposure-safety Analyses of Safety Measurements as a Function of % Hb Occupancy





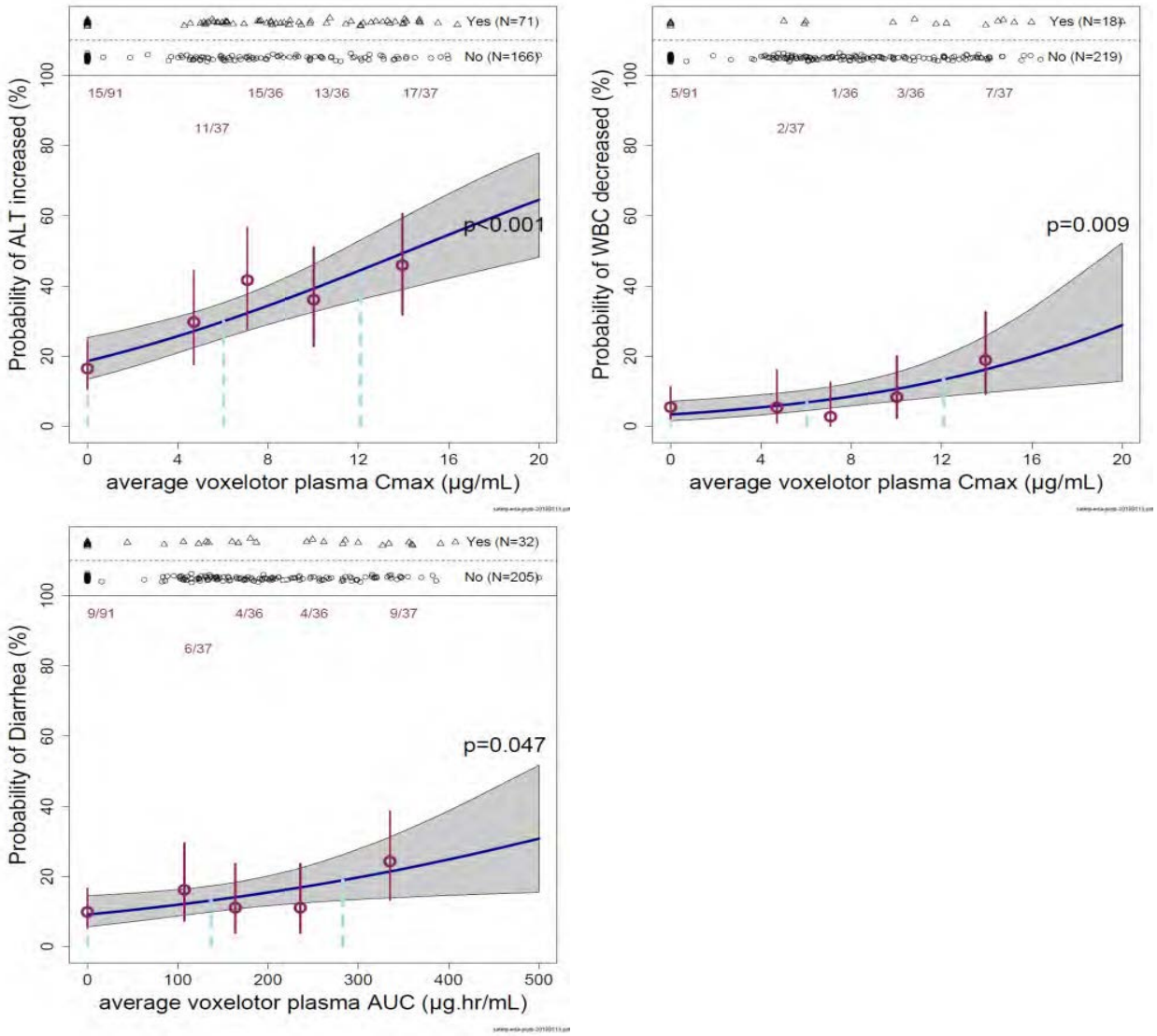
Source: Exposure-Response and PK/PD Relationships Report GBT-CP-006, Figures 11 and 12.

Non-SCD-related Safety Endpoints

For all non-SCD-related safety endpoints, ER relationships with voxelotor whole blood and plasma $C_{max,SS}$ and AUC_{SS}, and % Hb occupancy at $C_{max,SS}$ were evaluated, but given the high correlations between exposure metrics and similarity of results, only analyses with plasma $C_{max,SS}$ are presented here. The one exception is diarrhea, where $C_{max,SS}$ was not statistically significant, but AUC_{SS} was (p=0.047).

Statistically significant E-R relationships were identified for increased ALT, decreased white blood cells (WBC), and diarrhea (Figure 21). No statistically significant ER relationships were observed for rash or arthralgia. Insufficient events were observed to analyze increased creatinine.

Figure 24 Exposure-safety Relationships for Increased Alanine Aminotransferase, Decreased White Blood Cells, and Diarrhea



Source: Exposure-Response and PK/PD Relationships Report GBT-CP-006, Figures 13, 14 and 16.

Reviewer's Comments: *The applicant's exposure-response analyses for safety measurements are acceptable. The relatively flat E-R relationships for Grade≥2 SCD-related TEAEs and overall mild safety profile observed in Trial GBT440-031 supported the Applicant's proposed voxelotor 1500 mg QD for patients with SCD from the safety perspective.*

19.5.4 Physiologically Based Pharmacokinetic Modeling Review

Executive Summary

The objective of this review is to evaluate the adequacy of the Applicant's following PBPK reports to support the intended uses.

- GBT-CP-001: Part A_Quantitative Prediction of the Systemic Exposure of GBT440 in Adults and Paediatric Patients with Sickle Cell Disease;
- GBT-CP-002: Part B_DDI Liability of GBT440 as Perpetrator of CYP- and Transporter- Mediated Drug- Drug Interactions;
- GBT-CP-007: Estimation of Relative Contributions of CYP Enzymes and UGTS to the Overall Clearance of GBT440;
- GBT-CP-009: Assessment of CYP3A4-Mediated DDI Liability of Voxelotor in Healthy Subjects and Patients with Sickle Cell Disease: Impact of CYP3A4 Contribution to Clearance of Voxelotor; and
- GBT-CP-010: Assessment of CYP3A4-Mediated DDI Liability of Voxelotor in Healthy Subjects and Patients with Sickle Cell Disease: Impact of CYP3A4 Auto Inactivation.

The Division of Pharmacometrics has reviewed the PBPK reports, supporting modeling files, and the Applicant's responses to FDA's information requests (IRs) submitted on August 12 and 23, September 5, 12, and 15, 2019, and concluded the followings.

- The voxelotor PBPK model is adequate to predict the PK in healthy subjects and patients with sickle cell disease (SCD).
- The voxelotor PBPK model is adequate to predict the effect of voxelotor on midazolam (a sensitive CYP3A substrate) PK following multiple dose administration of voxelotor in healthy subjects and patients with SCD. The predicted midazolam AUC ratio is 2.05 in the presence and absence of voxelotor (1500mg QD) in healthy subjects.
- The voxelotor PBPK model is adequate to predict the effect of voxelotor on caffeine (a CYP1A2 substrate), omeprazole (a CYP2C19 substrate), warfarin (a CYP2C9 substrate), rosiglitazone (a CYP2C8 substrate), and metoprolol (a CYP2D6 substrate) PK following multiple dose administration of voxelotor (1500mg, QD) in healthy subjects and patients with SCD. Model predicted changes in the AUC of caffeine, omeprazole, warfarin, rosiglitazone, and metoprolol were less than 1.07-fold in healthy subjects when they were co-administered with multiple dose of voxelotor (1500mg, QD).
- The voxelotor PBPK model is adequate to predict the effect of ketoconazole (a strong CYP3A inhibitor), fluconazole (a moderate CYP3A/CYP2C9 and strong CYP2C19 inhibitor) and fluvoxamine (a moderate CYP3A, weak CYP2C9, and strong CYP2C19 inhibitor) on voxelotor PK. The model predicted voxelotor geometric mean ratios of AUC (with/without an inhibitor) were between 1.46 and 1.82 with ketoconazole (400 mg, QD), between 1.73 and 1.80 with fluconazole (200 mg, QD), between 1.98 and 2.09 with fluconazole (400 mg, QD), or between

1.10 and 1.16 with fluvoxamine (50 mg, QD) in healthy subjects using the fmCYP values estimated by in vitro rhCYP kinetic study or in vitro chemical inhibition study.

- The voxelotor PBPK model is adequate to predict the effect of rifampicin (a strong CYP3A/CYP2C19, and moderate CYP2C9 inducer) and efavirenz (a moderate CYP3A inducer) on the voxelotor PK. The model predicted voxelotor geometric mean ratios of AUC (with/without an inducer) were between 0.44 and 0.50 with efavirenz (600 mg, QD) and between 0.27 and 0.31 with rifampicin (600 mg, QD) in healthy subjects using the fmCYP values estimated by in vitro rhCYP kinetic study or in vitro chemical inhibition study.
- There is uncertainty in the prediction of voxelotor exposure in patients younger than 6 years of age because the Applicant's model did not incorporate the age-dependent changes in absorption and there is no PK data available for model validation.

Part A: DDI assessment

Applicant's PBPK Modeling Effort

PBPK software

Simcyp V16 (Simcyp Ltd, UK) was used to develop the PBPK models and predict the effects of voxelotor on the PK of midazolam, caffeine, warfarin, omeprazole, rosiglitazone, and metoprolol in healthy subjects and sickle cell disease (SCD) patients. Simcyp V17 (Simcyp Ltd, UK) was used to predict the effects of ketoconazole, fluconazole, fluvoxamine, rifampin and efavirenz on the PK of voxelotor.

Model development

Voxelotor

Healthy subjects

The fraction absorbed (fa) was estimated to be 0.65 based on the percent of administered dose that the unchanged parent drug in feces accounted for. To recover the observed Tmax of approximately 4 hours at steady state, the absorption rate constant (ka) was optimized and a value of 1.0 h^{-1} was applied in the final model.

A B:P ratio of 33.16 in healthy subjects was used for voxelotor in the model based on the Cmax and AUC values in the whole blood relative to plasma after oral administration of voxelotor in healthy subjects. The protein binding in plasma was reported to be 99.8% at a concentration of 50 µM and a fraction unbound (fu) value of 0.002 was applied in the voxelotor model using albumin as the main binding protein.

The apparent volume of distribution during terminal elimination (VZ/F) (565 L) was obtained from Study GBT440-005 after oral administration of a single dose of 900 mg voxelotor under fasted condition. After correction for the fa value of 0.65 and normalization with body weight, a Vz value

of 4.53 L/kg was obtained and applied in the model. The minimal PBPK model without single-adjusting compartment was used to simulate the voxelotor PK.

A mean CL/F value of 5.16 L/h was obtained from clinical data. Unchanged voxelotor accounted for 0.08% of the administered dose in urine in the mass balance study. After correction for the fa of 0.65, a renal CL value of 0.0027 L/h was applied in all simulations.

A metabolic intrinsic clearance value of 423.87 µL/min/mg protein was obtained for voxelotor using clinical clearance data and the retrograde approach. The mass balance study results were used to estimate the contribution of metabolic pathways to voxelotor overall clearance (oxidation: 73.46%, reduction:18.92%, and direct conjugation: 7.62%). The contribution of CYP enzymes and UGTs to the overall clearance of voxelotor were estimated based on the in vitro metabolism study involving recombinant enzymes and in vitro chemical inhibition study results. Refer to result section "Can voxelotor PBPK model predict the effect of CYP modulators on voxelotor PK?" for more details.
The in vitro Ki values for CYP1A2 (35.0 µM), CY2C8 (0.8 µM), CYP2C9 (9.5 µM), CYP2C19 (11.1 µM), and CYP2D6 (96.1 µM) were used in the voxelotor model. The Ki value for CYP3A4 was optimized and a value of 0.2 µM was used in the model to allow accurate recovery of the observed midazolam AUC ratio.

SCD patients

A lower B:P ratio of 15.5 and a higher fu of 0.003 were used in the simulations in SCD patients to reflect the reduced hematocrit (0.214) and lower albumin level in SCD patients. Other potential differences between these two populations were not incorporated into the SCD patients' model.

Perpetrator drug models

The default PBPK models of ketoconazole, fluconazole, fluvoxamine, efavirenz and rifampicin in SimCYP were used without any modification for DDI prediction.

Victim drug models

The default PBPK models of caffeine, omeprazole, warfarin, midazolam, rosiglitazone, and metoprolol in SimCYP were used without any modification for DDI prediction.

FDA's assessment

- The in vitro study indicated that voxelotor may be a time dependent inhibitor (TDI) of CYP3A4 However, the Applicant's model did not incorporate the voxelotor mediated CYP3A4 TDI effect. An information request was issued requesting the Applicant to evaluate the effect of CYP3A4 TDI on the DDI prediction between voxelotor and midazolam at steady state. Refer to 'Results' for detailed FDA's assessment of the Applicant's response.
- In the Applicant's original PBPK submission, the effects of CYP3A modulators on voxelotor PK were not evaluated. In response to FDA's information requests, the Applicant provided PBPK

analyses to evaluate the effects of CYP3A modulators on voxelotor PK. Refer to 'Results' for FDA's assessment of the Applicant's responses.

PBPK model verification

Voxelotor

The voxelotor model was verified against the observed PK data following a single and multiple dose administration of voxelotor in healthy subjects and SCD patients, and the DDI study results between voxelotor and caffeine, omeprazole, warfarin, midazolam, rosiglitazone, and metoprolol in healthy subjects.

PBPK model application

The developed PBPK models were used to simulate the DDIs for voxelotor in the following scenarios.

- To predict the effect of voxelotor (1500 mg, QD) on caffeine (a CYP1A2 substrate), omeprazole (a CYP2C19 substrate), warfarin (a CYP2C9 substrate), midazolam (a CYP3A4 substrate), rosiglitazone (a CYP2C8 substrate), and metoprolol (a CYP2D6 substrate) PK at steady-state in healthy subjects and SCD patients.
- To predict the effect of ketoconazole (a strong CYP3A4 inhibitor), fluconazole (a moderate CYP3A/CYP2C9 and strong CYP2C19 inhibitor), fluvoxamine (a moderate CYP3A, weak CYP2C9, and strong CYP2C19 inhibitor), rifampicin (a strong CYP3A/CYP2C19, and moderate CYP2C9 inducer) and efavirenz (a moderate CYP3A inducer) on voxelotor PK at steady-state in healthy subjects and SCD patients.

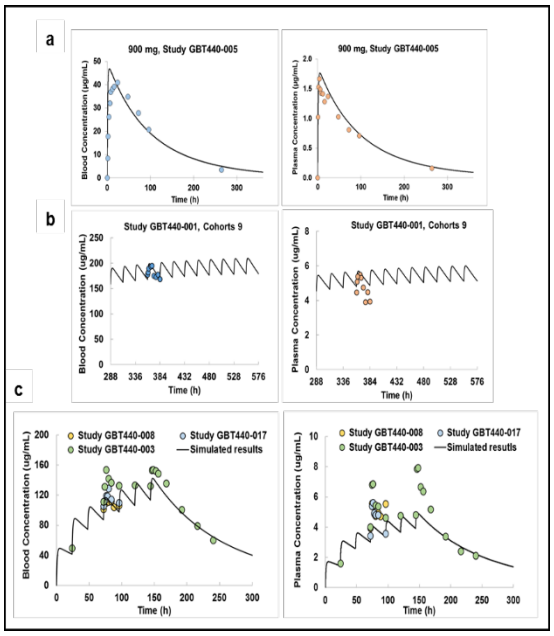
Results

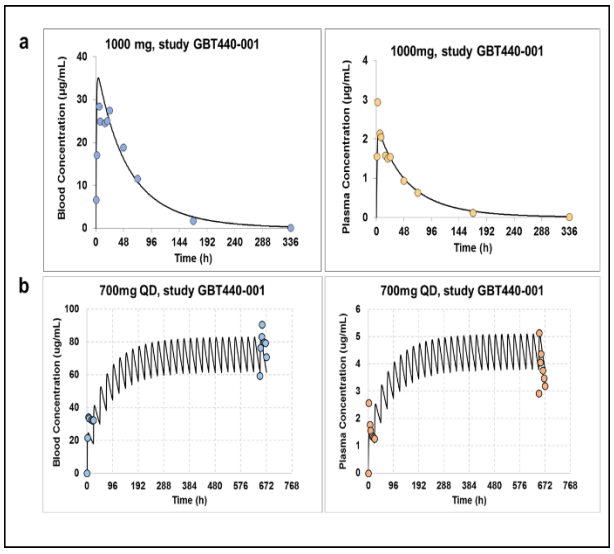
1. Can voxelotor PBPK model describe voxelotor PK in adults?

Yes. The simulated and observed voxelotor plasma and blood concentration-time profiles and PK parameters are presented in Figure 22 and Table 59. The simulated blood and plasma C_{max} and AUC values are within 0.6-1.2-fold of the corresponding observed values in healthy subjects and in SCD patients except for the plasma data on day 4 following multiple dose administration of voxelotor in healthy subjects (Study GBT440-003) where the predicted versus observed Cmax and AUC ratios were 0.49 and 0.59, respectively. The Applicant's original model did not incorporate the voxelotor mediated CYP3A4 TDI. Based on the evaluation of the Applicant's response to the FDA's information requests and reviewer's analysis, it was concluded that the clinical observed DDI between voxelotor and midazolam highly likely caused by the voxelotor mediated CYP3A competitive inhibition and the impact of voxelotor mediated clinical CYP3A4 TDI is expected to be negligible. Refer to result section "Can voxelotor PBPK model predict its effect on midazolam (a sensitive CYP3A substrate) PK?" for more details.

Figure 25 Mean observed (dots) and simulated (lines) voxelotor plasma (right panel) and blood (left panel) concentration-time profiles following a single or multiple dose administration of voxelotor in healthy subjects (**A**) and SCD patients (**B**).

A **B**





A: a, single dose, 900 mg; b, multiple dose QD, 600 mg; c, multiple dose, 900 mg on day 1 & 2, and 600 mg, QD on day 4 and day 5; B: a, single dose, 1000 mg; b, multiple dose QD, 700 mg
Source: A: reviewer's simulations using the measured B:P ratio based on the Cmax and AUC values in the whole blood relative to plasma. B: Applicant's PBPK submission package

Table 61 Observed and simulated voxelotor whole blood and plasma C_{max} and AUC and the predicted versus observed Cmax and AUC ratios following a single or multiple oral administration of voxelotor in healthy subjects and SCD patients

		Cmax (μg/mL)			AUC (μg*h/mL)			B:P ratio	Sources
		Obs.	Pred.	$R_{Pred/Obs}$	Obs.	Pred.	$R_{Pred/Obs}$		
Healthy Subjects[a]									
Single dose, 900 mg	Blood	42.0	46.5	1.11	4811	4895	1.02	29	Study GBT440-005
	Plasma	1.78	1.74	0.98	162	183	1.13		
Multiple dose, 900 mg on day 1 & 2, and 600 mg, QD on day 4 and day 5, PK on **day 4**	Blood	117	115	0.98	2547	2538	0.99	31.6	Study GBT440-008
	Plasma	5.79	3.96	0.68	115	87.2	0.76		
	Blood	121	115	0.95	2666	2538	0.95	31.6	Study GBT440-017
	Plasma	5.40	3.96	0.73	102	87.2	0.85		
	Blood	160	115	0.72	3471	2538	0.73	31.6	Study GBT440-003
	Plasma	8.10	3.96	0.49	148	87.2	0.59		

Multiple dose, 600 mg, PK on **day 1**	Blood	39.0	36.4	0.93	748	786	1.05	38	Study GBT440-001, Cohort 9
	Plasma	1.12	1.04	0.93	18.9	22.5	1.19		
Multiple dose, 600 mg, PK on **day 15**	Blood	207	189	0.91	4330	4202	0.97	38	Study GBT440-001, Cohort 9
	Plasma	5.73	5.4	0.94	113	120	1.06		
SCD Patients[b]									
Single dose, 1000 mg	Blood	34.4	35.5	1.03	2390	2281	0.95	15.5	Study GBT440-001, Cohort 7
	Plasma	2.87	2.18	0.76	131	140	1.07		
Multiple dose, 700 mg, PK on **day 28**	Blood	77.1	83.4	1.08	1850	1758	0.95	15.5	Study GBT440-001, Cohort 11
	Plasma	4.86	4.77	0.98	92.3	98.4	1.07		

Source: a: reviewer's simulations using the measured B:P ratio based on the Cmax and AUC values in the whole blood relative to plasma. b: Applicant's PBPK submission package

2. Can voxelotor PBPK model predict its effect on midazolam (a sensitive CYP3A substrate) PK?

Yes, the final voxelotor PBPK model with the incorporation of CYP3A competitive inhibition (optimized Ki of 0.2 μM) can be used to predict the effect of voxelotor on midazolam PK.

In the original PBPK submission, voxelotor mediated CYP3A competitive inhibition was incorporated into the Applicant's model. The parameter sensitive analysis was conducted for the CYP3A competitive inhibition constant (K_i) and a value of 0.2 μM was used to recover the observed midazolam AUCR and C_{max}R on day 4 following multiple dose administration of 600 mg voxelotor. Of note, in vitro K_i value was 112.1 μM using midazolam as the substrate, and 1.3 μM using testosterone as the substrate.

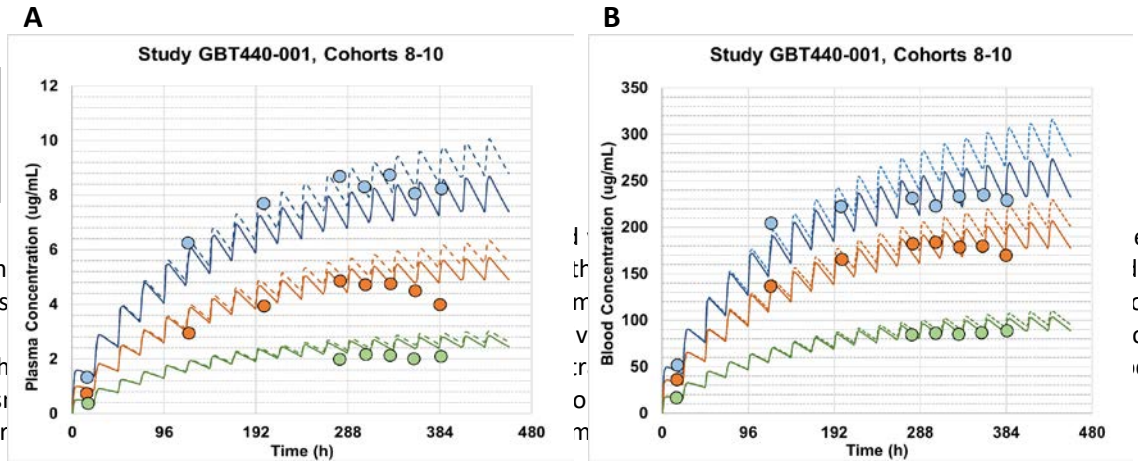
As the in vitro study indicated that voxelotor might be a time dependent inhibitor of CYP3A4 and the original Applicant's model did not incorporate the voxelotor mediated CYP3A4 TDI, FDA sent an information request and asked the Applicant to evaluate the effect of voxelotor mediated CYP3A4 TDI on the DDI prediction between voxelotor and midazolam. In the refined model, the in vitro measured Ki (112.1 μM) for the competitive inhibition and optimized K_I (20 μM) and in vitro measured k_{inact} (3 h^{-1}) were used to recover the observed effect of voxelotor on midazolam PK. Of note, the in vitro measured K_I is 4.0 μM. In this refined mode, the contribution of the CYP3A4 competitive inhibition to the overall inhibition effect can be neglected. The revised model was then called the 'CYP3A4 TDI only' model.

The reviewer evaluated the magnitude of voxelotor mediated CYP3A4 TDI. As shown in Figure 23, both plasma and blood trough concentrations reached steady-state after about five half-lives, and the simulated PK profiles using the final voxelotor model better recovered the observed data compared to the CYP3A4 TDI only model. In addition, the 'CYP3A4 TDI only model' significantly prolonged the time for voxelotor concentration to reach steady-state (around 30 days) compared to the observed 8-12 days or the final voxelotor model predicted 18 days. Thus, both clinical and

model simulation results indicated that the impact of voxelotor mediated clinical CYP3A4 TDI is negligible.

In conclusion, the clinical observed DDI between voxelotor and midazolam was highly likely caused by the voxelotor mediated CYP3A competitive inhibition. Using the final voxelotor model, the predicted midazolam CmaxR and AUCR following multiple dose administration of 1500 mg voxelotor are 1.76 and 2.05, respectively in healthy subjects; and 1.64 and 1.92, respectively in SCD patients.

Figure 26 Observed voxelotor trough concentrations and simulated voxelotor concentration-time profiles following multiple dose administration of voxelotor in healthy subjects.



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3. Can voxelotor PBPK model predict its effect on the PK of caffeine (a CYP1A2 substrate), omeprazole (a CYP2C19 substrate), warfarin (a CYP2C9 substrate), rosiglitazone (a CYP2C8 substrate), and metoprolol (a CYP2D6 substrate)?

Yes, the Applicant's voxelotor PBPK model is adequate to predict the effect of voxelotor on the PK of caffeine, omeprazole, warfarin, rosiglitazone, and metoprolol in healthy subjects and SCD patients. The in vitro K_i values for CYP1A2 (35.0 µM), CY2C8 (0.8 µM), CYP2C9 (9.5 µM), CYP2C19 (11.1 µM), and CYP2D6 (96.1 µM) were used in the voxelotor model. The model predicted DDI effects were verified against the clinical DDI studies (GBT440-003, 8 and 17) (Table 60).

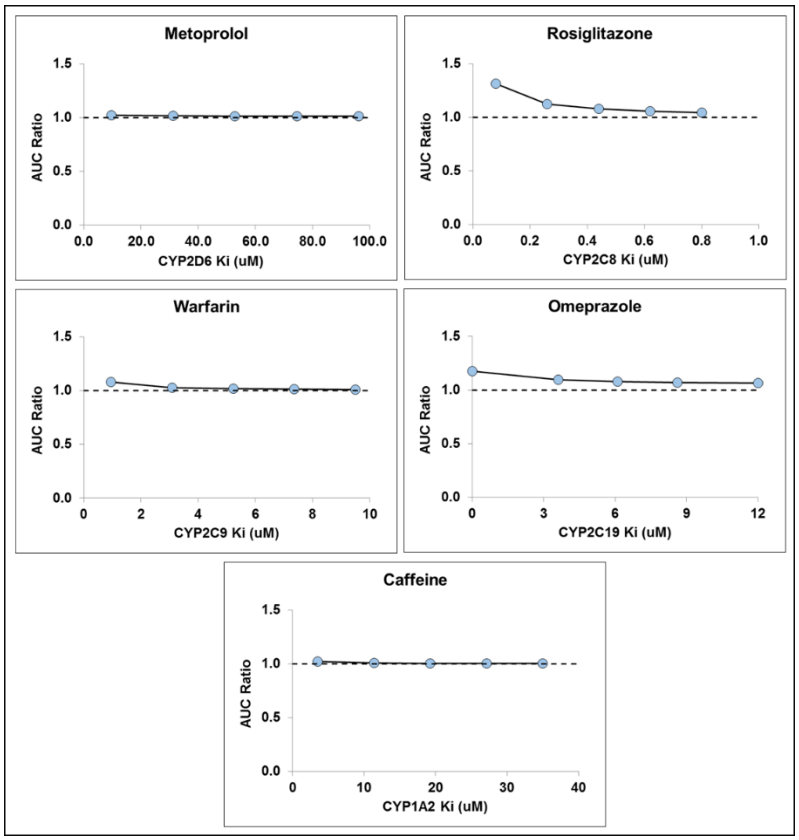
Table 62 Simulated and observed geometric mean ratios for Cmax and AUC of CYP substrates in the presence and absence of voxelotor in healthy subjects

Substrate	Substrate Dose (mg)	Pathway	Observed		Predicted		Predicted	
			CmaxR[a]	AUCR[a]	CmaxR	AUCR	CmaxR	AUCR
Midazolam	2	CYP3A	1.23[a]	1.63[a]	1.50[a]	1.59[a]	1.76[c]	2.05[c]
Caffeine	100	CYP1A2	0.91[a]	0.96[a]	1.00[a]	1.00[a]	1.00[c]	1.00[c]
Warfarin	10	CYP2C9	1.04[a]	1.12[a]	1.00[a]	1.00[a]	1.00[c]	1.01[c]
Omeprazole	20	CYP2C19	0.95[a]	0.96[a]	1.03[a]	1.03[a]	1.07[c]	1.07[c]
Rosiglitazone	4	CYP2C8	0.90[b]	0.95[b]	1.00[b]	1.02[b]	1.01[c]	1.04[c]
Metoprolol	50	CYP2D6	1.14[b]	1.14[b]	1.01[b]	1.01[b]	1.01[c]	1.02[c]

Voxelotor dose:
a: 900 mg QD on days 1 and 2, 600 mg QD on days 3-7
b: 900 mg QD on days 1 and 2, 600 mg QD on day 3-5
c: 1500 mg, QD for 30 days
Sources: observed data were from study GBT440-003 (Cocktail study), GBT440-008, and GBT440-017; predicted data were from Applicant's PBPK submission package.

The reviewer conducted sensitivity analyses on the CYP Ki values in a range of 0.1 to 1-fold of the in vitro values in healthy subjects (Figure 24) and SCD patients (data not shown). The simulated plasma AUC ratios were 1.00, 1.17, 1.02, 1.31 and 1.02 for caffeine, omeprazole, warfarin, rosiglitazone, and metoprolol, respectively, when the K_i values were lowered by 10-fold, suggesting the inhibition effect of voxelotor is low towards CYP1A2, CYP2C8, CYP2C9, CYP2C19 and CYP2D6.

Figure 27 Sensitivity analysis of voxelotor CYP2D6, 2C8, 2C9, 2C19 and 1A2 K_i on the simulated metoprolol, rosiglitazone, warfarin, omeprazole and caffeine AUC following multiple dose administration of 1500 mg voxelotor in healthy subjects.



Source: FDA reviewer's analysis.

The verified model was then used to simulate the effect of voxelotor at a dose of 1500 mg QD on the PK of metoprolol, rosiglitazone, warfarin, omeprazole and caffeine. The model predicted AUCRs were less than 1.07 for all the substrates (Table 60).

4. Can voxelotor PBPK model predict the effect of CYP modulators on voxelotor PK?

Yes, the voxelotor PBPK model can be used to simulate a range of voxelotor PK change in the presence of a CYP3A modulator.

To accurately assess the magnitude of exposure change of a victim drug due to the modulation of its metabolic clearance, it is important to understand the fraction of drug cleared by the specific metabolic pathway and the fractional contribution of metabolizing enzyme to its overall metabolism clearance (fmCYP). The clearance is another important factor for a victim drug DDI evaluation following oral administration. The following listed the Applicant's approaches to clearance pathway identification, fmCYP estimation, along with the PBPK modeling and simulation strategy in predicting the victim DDI liability of voxelotor due to the modulation of metabolizing enzymes and followed by the reviewer's investigation and comments.

a. Metabolic pathways identification

In the voxelotor mass balance study, the average total recovery of the administered radioactivity over 23 days was 98.0%, of which 35.4% and 62.6% were recovered in the urine and feces, respectively (Clinical Study GBT440-002). Unchanged voxelotor accounted for 33.3% of the administered dose in feces. Thus, it appears that at least 64.7% (=98.0%-33.3%) of the dose was absorbed (fa).

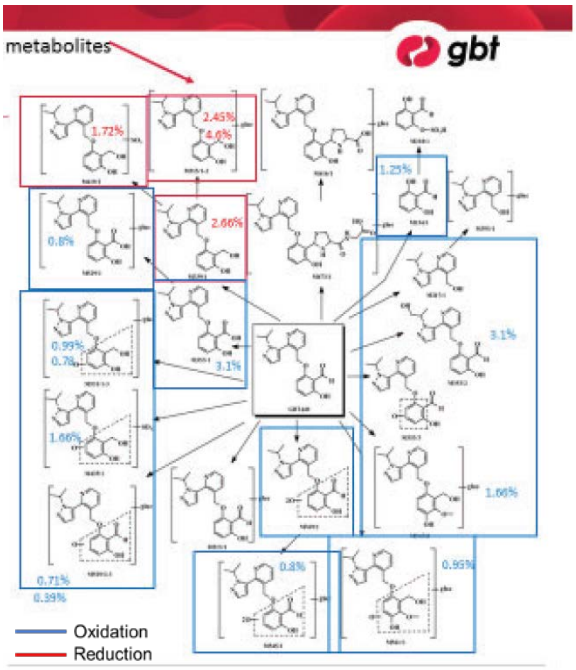
The metabolite profiles in feces and urine were used to assign the clearance routes (Figure 25). It appears that oxidation, reduction and direct conjugation accounted for 16.9%, 11.43% and 4.60% of the voxelotor dose recovered, respectively (Table 61). The 28.20% of the voxelotor dose recovered, for which the structures were not determined, was assigned as 'others' at the beginning. After evaluation of the structural characterization of voxelotor and the identified metabolites, the Applicant assigned the 28.20% of the voxelotor dose recovered as oxidative metabolites to provide a conservative estimate of DDI risk. The total oxidation was therefore considered to account for 44.39% (=16.19%+28.20%) of the voxelotor dose recovered. After correction for the radioactivity recovery and fraction absorbed, total oxidation, reduction and direct conjugation account for 73.78%, 18.70% and 7.52%, respectively of total clearance (Table 61).

Table 63 Estimated contributions of different metabolic pathways to the overall voxelotor clearances

	% of dose	% of dose (100)	fm (metabolism)
Unchanged faeces	33.30%	**35.53%**	NA
Oxidation	**16.19%**	**17.27%**	NA
Reduction	11.43%	**12.20%**	**18.92%**
Direct conjugation	4.60%	**4.91%**	**7.62%**
Others	28.20%	**30.09%**	NA
Total oxidation (oxidation + others)	**44.39%**	**47.36%**	**73.46%**
TOTAL	**93.72%**	100.00%	100%

Source: Table 2 in Response to Clinical Pharmacology Information Request Dated 14Aug2019 - Data Regarding Study GBT-CP-001 (16 August 2019)

Figure 28 Voxelotor metabolic profiles in feces and urine following multiple dose administration of voxelotor in healthy subjects



Source: GBT-CP-007_ Estimation of Relative Contributions of CYP Enzymes and UGTS to the Overall Clearance of GBT440

b. fmCYP estimation

In vitro metabolism studies involving recombinant enzymes indicated that CYP3A4, CYP1A1, CYP3A5, CYP2C9, CYP2C19 and CYP2B6 were responsible for the oxidative metabolism of

voxelotor. The Applicant used two methods to estimate fmCYPs, recombinant P450 kinetics method and in vitro chemical inhibition method.

Recombinant CYP450 kinetics method

The enzyme kinetic parameters for the metabolism of voxelotor were determined using recombinant human P450 enzymes (rhCYPs) and the obtained rhCYP intrinsic clearance (CL_{int}) for each individual enzyme was scaled to human liver microsome (HLM) CL_{int} via an intersystem extrapolation factor (ISEF) approach to account for differences in the expression/activity of the CYP enzymes between in vitro recombinant enzyme system and in vitro HLM system. Then the fmCYP values were estimated (Table 62). CYP1A1 was not considered in the voxelotor PBPK model as the contribution of CYP1A1 to the voxelotor overall clearance was negligible due to the very low CYP1A1 abundance in the liver. A metabolic intrinsic clearance value of 423.87 µL/min/mg protein was calculated using the retrograde approach based on the clinical clearance data. Based on this total intrinsic clearance and the estimated fmCYP values, the intrinsic clearance for each pathway was calculated (Table 62). It should be noted that the estimation was based on the assumption that the metabolic intrinsic clearance of 423.87 µl/min per mg protein was represent of a CYP3A5 non-expressor, as the majority of subjects recruited into the clinical studies were Caucasian and only 13% of the Caucasian population express CYP3A5.

In vitro chemical inhibition method

The rhCYP450 kinetics study showed that the CYP3A mediated metabolism of voxelotor was the major metabolic pathway. The Applicant conducted in vitro chemical inhibition study to evaluate the effect of ketoconazole (a strong CYP3A inhibitor) on CYP3A mediated metabolic pathway. The study result indicated that 48% of voxelotor metabolism was inhibited by ketoconazole. The fmCYP3A was subsequently calculated to be 0.36 after considering the fractional contribution of oxidation pathway to the voxelotor overall metabolism clearance (Table 62).

Worse-case scenario analysis

It was assumed that CYP3A is the only enzyme responsible for the oxidative metabolism of voxelotor. Thus, fmCYP3A4 was estimated to be 0.738 in this worst-case scenario. The DDI evaluation in the worst-case scenario indicated that the predicted voxelotor AUC ratios with CYP modulators were not sensitive to the increase in fm values as only 2.5-fold increase in voxelotor AUC was predicted with ketoconazole (a strong CYP3A inhibitor) (Table 62).

Table 64 Relative contributions of each pathway to the overall clearance of voxelotor. fmCYP estimation was based on method A: recombinant P450 kinetics, method B: chemical inhibition with ketoconazole and method C: worse-case scenario analysis

Metabolic Pathways	Enzymes	Contribution of Metabolic pathways to overall clearance	$CL_{uH,int}$ (µl/min /mg)	A: Recombinant P450 kinetics		B: Chemical inhibition with ketoconazole		C: worse-case scenario analysis	
				fm	$CL_{uH\ int}$ (µl/min/mg)	fm	$CL_{uH\ int}$ (µl/min/mg)	fm	$CL_{uH\ int}$ (µl/min/mg)
Oxidation	CYP3A4	0.738	312.72	0.56	234.54	0.36	150.11	0.738	312.72
	CYP3A5			0	0	0	0	0	0
	CYP2C9			0.07	28.15	0.14	59.9	0	0
	CYP2C19			0.05	21.89	0.099	42.8	0	0
	CYP2B6			0.07	28.15	0.14	59.9	0	0
Conjugation	UGT1A1	0.075	31.90	0.04	15.19	0.04	15.19	0.04	15.19
	UGT1A9			0.04	16.71	0.04	16.71	0.04	16.71
Reduction		0.187	79.26	0.19	79.26	0.19	79.26	0.19	79.26
Total		1.0	423.87	1.0	423.87	1.0	423.87	1.0	423.87

Sources: GBT-CP-010_ Assessment of CYP3A4-Mediated DDI Liability of Voxelotor in Healthy Subjects and Patients with Sickle Cell Disease_Impact of CYP3A4 Auto Inactivation, PRC-19-022_ In Vitro Assessment of the Contribution of CYP3A4 to the Total Metabolism of GBT440 using Pooled Human Liver Microsomes and Chemical Inhibitor Ketoconazole, and Response to Clinical Pharmacology Information Request Dated 16Sep2019 - Regarding Study GBT-CP-009 (20 September 2019)

c. DDI evaluation

PBPK simulations were performed to estimate the systemic exposure change of voxelotor in the presence and absence of CYP3A modulators assuming fmCYP3A4 values of 0.36, 0.56 or 0.738.

The simulated voxelotor plasma AUC ratios (Table 63) were similar to the voxelotor whole blood AUC ratios (data not shown) in the presence and absence of CYP3A modulators. The voxelotor exposure change in the presence and absence of CYP3A modulators in healthy subjects (Table 63) were also similar to those in SCD patients (data not shown). The effect of a strong CYP3A inhibitor on the PK of voxelotor is likely within 2-fold. A strong or moderate CYP3A inducer may decrease the systemic exposure of voxelotor by more than 50%.

It should be noted that the CYP3A modulators used in the simulations interacted with not only CYP3A, but also CYP2C9 (e.g. ketoconazole, fluconazole, fluvoxamine, and rifampicin), CYP2C19 (e.g. fluconazole, fluvoxamine, and rifampicin), and CYP2B6 (e.g. efavirenz and rifampicin). The model accounted for multiple inhibitory or induction effects by these CYP3A modulators. This explains the simulated larger effect on voxelotor PK by fluconazole compared to the strong CYP3A inhibitor, ketoconazole.

Table 65 Model predicted voxelotor geometric mean AUCR in the presence and absence of CYP modulators

CYP3A modulators	fmCYP3A4: 0.36[b]	fmCYP3A4: 0.56[a]	fmCYP3A4: 0.738[a]
Ketoconazole, 400 mg QD	1.46	1.82	2.51
Fluconazole, 200 mg QD	1.73	1.80	1.98
Fluconazole, 400 mg QD	1.98	2.09	2.42
Fluvoxamine, 50 mg QD	1.16	1.10	1.04

Efavirenz, 600 mg QD	0.50	0.44	0.41
Rifampicin, 600 mg QD	0.31	0.27	0.23

a: Applicant's simulations: GBT-CP-009_ Assessment of CYP3A4-Mediated DDI Liability of Voxelotor HVs and Patients with Sickle Cell Disease_ Impact of CYP3A4 Contribution to Clearance of Voxelotor, and Response to Clinical Pharmacology Information Request Dated 16Sep2019 - Regarding Study GBT-CP-009 (20 September 2019)
b: Reviewer's simulations. In the Applicant's model, clearance for CYP2C9, CYP2C19 and CYP2B6 were grouped and assigned to $CL_{int,others}$ (additional systemic clearance). Since some CYP3A modulators may also interact with CYP2C9, CYP2C19 or CYP2B6 in addition to CYP3A, the reviewer assigned CL_{int} to CYP2C9, CYP2C19 and CYP2B6 and rerun the simulations.

To summarize, the mass balance study provided basis to estimate metabolic pathway contributions to voxelotor overall clearance (73.46% oxidation, 18.92% reduction, and 7.62% direct conjugation). The rhCYP study estimated a fmCYP3A of 0.56 and the in vitro chemical inhibition study estimated a fmCYP3A of 0.36. As there is no in vivo DDI study evaluating the effect of a strong CYP3A inhibitor on the PK of voxelotor to confirm the fmCYP3A, potential uncertainties in estimating fmCYP3A and their impact on DDI prediction are summarized in Table 64.

Table 66 Sources of uncertainties estimating fmCYP3A, their impact on DDI evaluation and analysis for voxelotor

Sources of uncertainty[1,2,3,4]	**Impact on DDI prediction**	**Voxelotor**	**References**
Alternative routes of metabolism	Over-prediction	No evidence showing the involvement of uncommon P450 isoforms or non-P450 enzymes in the metabolism of voxelotor.	PRC-14-016-R
A substrate of efflux transporter	Over-prediction	Not a substrate of any transporter	PRC-14-013-R PRC-15-012-R
A substrate of uptake transporter	Under-prediction	Not a substrate of any transporter	PRC-14-013-R PRC-15-012-R
CYP3A time dependent inhibition	Over-prediction	Voxelotor mediated CYP3A TDI is unlikely to have an appreciable effect.	Reviewer's analysis
CYP3A induction	Under-prediction	no evidence showing that voxelotor is a CYP3A inducer	PRC-14-017-R

[1] Peters SA, Schroeder PE, Giri N, Dolgos H. Evaluation of the use of static and dynamic models to predict drug-drug interaction and its associated variability: impact on drug discovery and early development. Drug Metab Dispos. 2012 Aug;40(8):1495-507.
[2] Bohnert T, Patel A, Templeton I et al. International Consortium for Innovation and Quality in Pharmaceutical Development (IQ) Victim Drug-Drug Interactions Working Group. Evaluation of a New Molecular Entity as a Victim of Metabolic Drug-Drug Interactions-an Industry Perspective. Drug Metab Dispos. 2016 Aug;44(8):1399-423.
[3] Youdim KA1, Zayed A, Dickins M, et al. Application of CYP3A4 in vitro data to predict clinical drug-drug interactions; predictions of compounds as objects of interaction. Br J Clin Pharmacol. 2008 May;65(5):680-92.
[4] Fowler S, Morcos PN, Cleary Y et al. Progress in Prediction and Interpretation of Clinically Relevant Metabolic Drug-Drug Interactions: a Minireview Illustrating Recent Developments and Current Opportunities. Curr Pharmacol Rep. 2017;3(1):36-49.

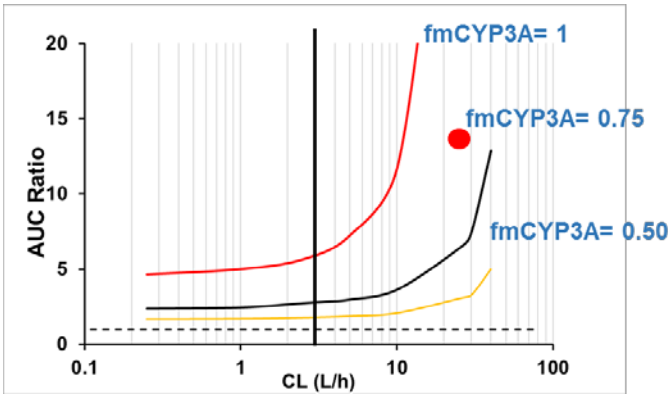
Clearance	Following oral administration: o High clearance → predicted AUCR is more sensitive to fmCYP3A o Low clearance → predicted AUCR is less sensitive to fmCYP3A	Voxelotor is a low clearance drug	Reviewer's analysis

To further evaluate the risks associated with the uncertainty in the fmCYP3A estimation and consequently DDI liability estimation, the reviewer further evaluated the relationship among the total clearance, fmCYP3A, and predicted AUCRs in the presence and absence of ketoconazole for hypothetical CYP3A substrate drugs following oral administration. As shown in Figure 26, the predicted AUCRs decrease with the decrease in clearance. As the clearance decreased to a certain level, the AUCR reached 'steady state' for drugs having the same fmCYP3A value.

For drugs having the same clearance, the drug with a higher fmCYP3A value generally has a higher predicted AUCR. The predicted AUCRs for low clearance drugs were less sensitive to the change in fmCYP3A values compared to the drugs having a high clearance.

Voxelotor is a low clearance drug. The clearance of voxelotor after correction for the fraction absorbed (64.7%) is 3.35 L/h (the vertical solid back line in Figure 26) which falls into the clearance range where the predicted AUCRs were less sensitive to the change in fmCYP3A values. Therefore, even if there were certain uncertainties that were not considered in previous analysis (Table 64), due to the low clearance characteristics of voxelotor, the impact of uncertainties on predicted AUCR would be consider less than significant.

Figure 29 Relationship between drug clearance and predicted AUCR in the presence and absence of ketoconazole for hypothetical drugs with different fmCYP3A values following oral administration.



The black vertical line represents the clearance of voxelotor. The red dot represents midazolam, a sensitive CYP3A substrate having a fmCYP3A of 0.93, for which the predicted AUCR with ketoconazole was sensitive to the change in

fmCYP3A values. The red, black and yellow lines represent the drugs with a fmCYP3A value of 1.0, 0.75 and 0.5, respectively.

To conclude, combining the human mass balance study, in vitro rhCYP kinetic study, in vitro chemical inhibition study, and PBPK analyses, the estimated voxelotor AUC increase in the presence of ketoconazole (a strong CYP3A inhibitor) was 46%-82%. Due to the inhibition of fluconazole on CYP3A, CYP2C9, and CYP2C19, model predicted about 2-fold increase (1.73-1.8-fold increase with fluconazole 200mg QD, and 1.98-2.09-fold increase with fluconazole 400 mg, QD) in voxelotor AUC. In addition, a greater than 50% reduction in voxelotor AUC was predicted with rifampicin (a strong CYP3A/CYP2C19, and moderate CYP2C9 inducer) and efavirenz (a moderate CYP3A inducer).

Part B: Dose Selection in Pediatric Patients with SCD

Applicant's PBPK Modeling Effort

PBPK software

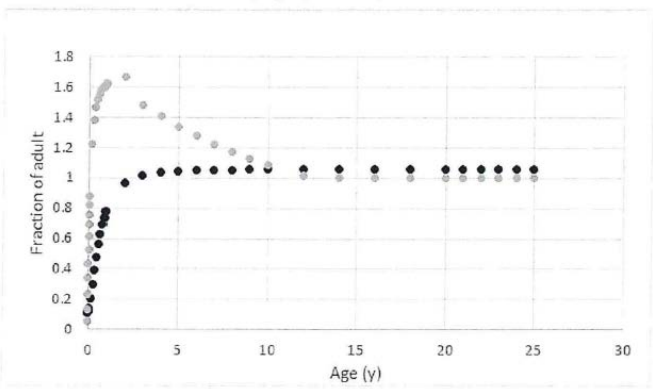
Simcyp V16 (Simcyp Ltd, UK) was used to develop the PBPK model and predict the voxelotor exposure in healthy pediatric subjects and pediatric patients with SCD.

Model development

Voxelotor adult PBPK model has been developed and verified with clinical single and multiple dose PK data in healthy adult subjects and adult patients with SCD (Part A: DDI assessment in this review). The adult PBPK model was then extrapolated to the pediatric population by incorporating ontogeny and maturation processes using Simcyp Pediatric Simulator to predict the voxelotor exposure in neonates, infants and children. The Simulator includes developmental physiology (liver size, renal function, liver blood flow) and biochemistry (albumin CYP ontogeny). The default CYP3A4 ontogeny function within Simcyp pediatric population and an alternative CYP3A4 ontogeny function reported by Upreti and Wahlstrom (Upreti, 2016[5]) were used to predict the voxelotor exposure in pediatric subjects (Figure 27). The first-order absorption model in Simcyp was selected with the fa and ka parameter values estimated based on the voxelotor PK in adults and fixed across all the pediatric age groups.

1 [5] Upreti VV, Wahlstrom JL. Meta-analysis of hepatic cytochrome P450 ontogeny to underwrite the prediction of pediatric pharmacokinetics using physiologically based pharmacokinetic modeling. J Clin Pharmacol. 2016 Mar;56(3):266-83.

Figure 30 CYP3A4 ontogeny profiles based on Simcyp (black circles) and Upreti and Wahlstrom (2016) (grey circles)



Source: Applicant's PBPK submission package

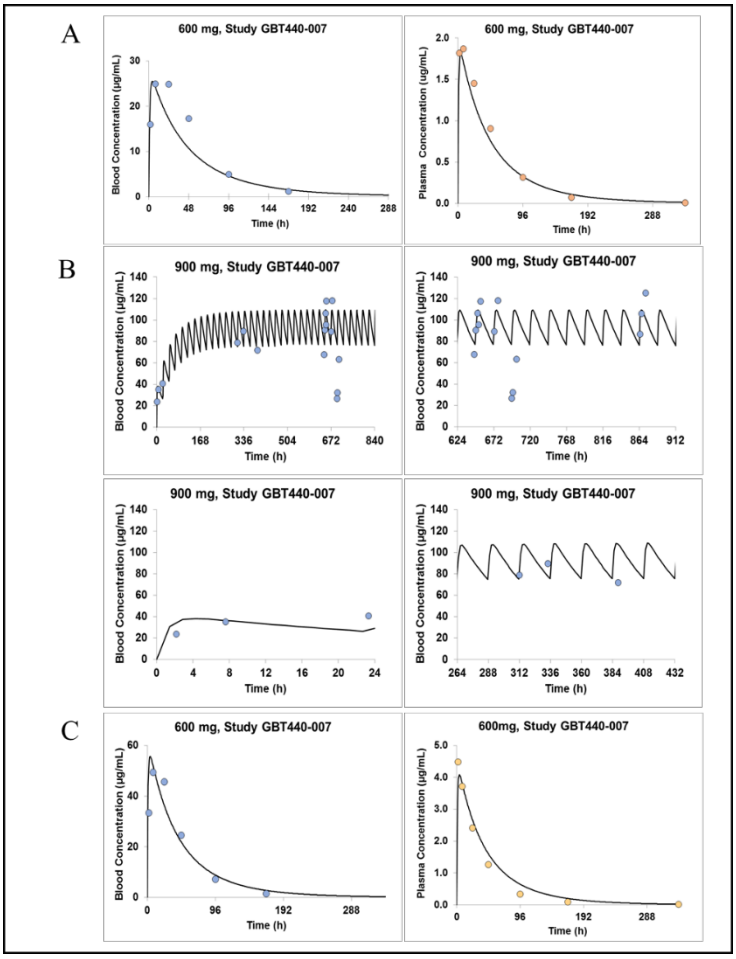
PBPK model verification

Model verification in adolescents aged 12 to < 18 years with SCD and children aged 6< to 12 years with SCD

The lower B:P ratio of 15.5 was used and age-related changes integrated within the pediatric module were applied in the simulations. Figure 28A and Figure 28B showed the simulated and observed voxelotor plasma and blood concentration-time profiles following a single (600 mg) or multiple (900 mg, QD) oral administration of voxelotor in adolescents aged 12 to < 18 years with SCD. Figure 28C showed the simulated and observed voxelotor blood concentration-time profiles following a single (600 mg) oral administration of voxelotor in children aged 6 to < 12 years (using Simcyp CYP3A4 ontogenies), with SCD. The plasma and blood C_{max} and AUC values obtained from model simulation and clinical studies in pediatric patients with SCD were summarized in Table 65.

Reviewer's comments: The simulated C_{max} and AUC values are within 0.75-1.2-fold of the observed data following a single or multiple oral administration of voxelotor in adolescents aged 12 to < 18 years with SCD and children aged 6 < to 12 years with SCD.

Figure 31 Observed (dots) and simulated (lines) voxelotor PK profiles following a single or multiple dose administration of voxelotor children with SCD.



A: single dose, 600 mg, aged 12 to < 18 years; B: multiple dose 900 mg QD, aged 12 to < 18 years; C: single dose, 600 mg, aged 6 to <12 years; Source: Applicant's PBPK submission package

Table 67 Observed and simulated voxelotor whole blood and plasma C_{max} and AUC and the C_{max} and AUC ratios following a single or multiple oral administration of voxelotor in adolescents aged 12 to < 18 years with SCD and children aged 6 to <12 years with SCD.

Age	Dosing regimen	Matrix	Cmax (µg/mL)			AUC (µg*h/mL)		
			Obs.	Pred.	$R_{Pred/Obs}$	Obs.	Pred.	$R_{Pred/Obs}$
12 to < 18 years with SCD	Single dose, 600 mg[a]	**Whole Blood**	24.3	25.4	0.96	1520	1344	1.13
		Plasma	1.88	1.80	1.04	101	95	1.06
		Whole Blood	97.4	102	0.95	2000	2018	0.99

	Multiple dose, 900 mg[a]	**Plasma**	6.89	7.59	0.91	126	157	0.80
	Multiple dose, 1500 mg[b]	**Whole Blood**	151	186	0.81	3110	3719	0.84
		Plasma	12.0	13.2	0.91	221	264	0.84
6 to < 12 years with SCD	Single dose, 600 mg[a]	**Whole Blood**	47.3	55.4	0.85	2570	2716	0.95
		Plasma	3.39	4.05	0.84	150	198	0.76

Source: a: Applicant's PBPK submission package; b: reviewer's simulations; observed PK from Study GBT440-007

PBPK model application

In support of dose selection in pediatric patients with SCD in clinical studies, the developed PBPK model was used to predict whole blood concentration of voxelotor in infants aged 9 months to <2 years (using the Simcyp and Upreti CYP3A4 ontogenies), children aged 2 to <6 and 6 to <12 years, adolescents aged 12 to <18 years and adults with SCD following multiple oral administration of voxelotor.

Results

Dose Projections in Children with SCD

Predicted geometric mean whole blood Cmax and AUC for infants aged 9 months to <2 years (using Simcyp and Upreti CYP3A4 ontogenies), children aged 2 to <6 (using Simcyp CYP3A4 ontogenies) and 6 to <12 years (using Simcyp CYP3A4 ontogenies), adolescents aged 12 to <18 years and adults with SCD following administration of multiple oral doses of voxelotor (900 mg, QD) are shown in Table 66. Then the predicted fold differences in voxelotor exposure in children relative to adults receiving 900 mg QD at steady-state were used to determine dose adjustments in children with SCD. Table 67 shows the model predicted dose that needs to be administered to each group to generate voxelotor exposure in whole blood that were matching those in adults following 1500 mg QD administration.

Table 68 Simulated geometric mean whole blood Cmax and AUC values for voxelotor following multiple oral doses of voxelotor (900 mg QD)

	C_{min}	C_{max}	AUC(0,24)	C_{min}	C_{max}	AUC(0,24)
Populations (n=70)	(ng/mL)	(ng/mL)	(ng/mL.h)	Ratios (relative to adult)		
9 months to 2 years - Simcyp ontogeny	332	532	10500	5.64	6.05	5.9
9 months to 2 years - Upreti ontogeny	196	396	7150	3.33	4.51	4.02
2 to <6 years	205	337	6571	3.48	3.83	3.69
6 to <12 years	124	201	3946	2.11	2.29	2.22
12 to <18 years	70.00	109	2180	1.19	1.24	1.22
adults	58.9	87.9	1780	1.00	1.00	1.00

Source: Applicant's PBPK submission package

Table 69 Simulated geometric mean whole blood Cmax and AUC values for voxelotor following multiple oral doses of voxelotor (1500 mg QD) in adults with SCD and equivalent doses in infants and Children with SCD

	Dose equivalent (mg)	C_{min}	C_{max}	AUC(0,24)	C_{min}	C_{max}	AUC(0,24)
Populations (n=70)	(1500 mg in adults)	(ng/mL)	(ng/mL)	(ng/mL.h)	(ng/mL)	Ratios (relative to adult)	
9 months to 2 years - Simcyp ontogeny	300	111	177	3493	1.13	1.20	1.18
9 months to 2 years - Upreti ontogeny	300	65.4	132	2383	0.67	0.90	0.80
2 to <6 years	400	90.9	150	2920	0.93	1.02	0.98
6 to <12 years	600	82.5	134	2631	0.84	0.91	0.89
12 to <18 years	1500	117	182	3632	1.19	1.24	1.22
adults	1500	98.1	147	2971	1.00	1.00	1.00

Source: Applicant's PBPK submission package

Reviewer's comments:

The Applicant's voxelotor PBPK model assumed first order absorption kinetics for voxelotor and the fixed fa and ka parameter values were used across all the pediatric age groups.

The age-dependent changes in gastrointestinal fluid composition, motility, absorptive surface area, and pH ranges along the gastrointestinal tract were not incorporated in the Applicant's model. The age-dependent drug absorption may affect voxelotor PK in children and the Applicant's model could not capture the effect of age on voxelotor absorption. Although the Applicant's model reasonably described the voxelotor PK in adolescents aged 12 to < 18 years with SCD and children aged 6 to <12 years with SCD, the prediction of voxelotor exposure in younger pediatric patients than 6 years may be biased.

19.6 Additional Clinical Outcome Assessment Analyses

Brunson, A., T. Keegan, A. Mahajan, R. White and T. Wun (2019). "High incidence of venous thromboembolism recurrence in patients with sickle cell disease." Am J Hematol **94**(8): 862-870.

Estepp, J. H. (2018). "Voxelotor (GBT440), a first-in-class hemoglobin oxygen-affinity modulator, has promising and reassuring preclinical and clinical data." Am J Hematol **93**(3): 326-329.

Hebbel, R. P. and B. E. Hedlund (2018). "Sickle hemoglobin oxygen affinity-shifting strategies have unequal cerebrovascular risks." Am J Hematol **93**(3): 321-325.

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Nonclinical Reviewer	Pedro Del Valle, PhD, ATS	Office of Oncologic Diseases/Division of Hematology Oncology Toxicology	Sections: 5	**Select one:** ■ Authored ☐ Approved
	Signature: Pedro L. Del Valle -A — Digitally signed by Pedro L. Del Valle -A DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001000884, cn=Pedro L. Del Valle -A Date: 2019.11.25 07:10:22 -05'00'			
Nonclinical Team Leader	Brenda Gehrke, PhD	Office of Oncologic Diseases/Division of Hematology Oncology Toxicology	Sections: 5	**Select one:** ▪ Authored ■ Approved
	Signature: Brenda Gehrke -S — Digitally signed by Brenda Gehrke -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Brenda Gehrke -S, 0.9.2342.19200300.100.1.1=0012062023 Date: 2019.11.25 09:03:21 -05'00'			
Nonclinical Team Division Director	Haleh Saber PhD, MS	Office of Oncologic Diseases/Division of Hematology Oncology Toxicology	Sections: 5	**Select one:** ☐ Authored ■ Approved
	Signature: Haleh Saber -S — Digitally signed by Haleh Saber -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Haleh Saber -S, 0.9.2342.19200300.100.1.1=1300212858 Date: 2019.11.25 08:14 27 -05'00'			
Clinical Pharmacology Reviewer	Salaheldin Hamed, PhD	Office of Clinical Pharmacology/Division of Cancer Pharmacology I	Sections: 6, 19.5	**Select one:** ■ Authored ☐ Approved
	Signature: Salaheldin S. Hamed -S — Digitally signed by Salaheldin S. Hamed -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9 2342.19200300.100.1.1=2000952138, cn=Salaheldin S. Hamed -S Date: 2019.11.25 09:11:34 -05'00'			
Clinical Pharmacology Team Leader	Ruby Leong, PharmD	Office of Clinical Pharmacology/Division of Cancer Pharmacology I	Sections: 6, 19.5	**Select one:** ☐ Authored ■ Approved
	Signature: Ruby Leong -S — Digitally signed by Ruby Leong -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Ruby Leong -S, 0.9.2342.19200300.100.1.1=2000548953 Date: 2019.11 25 09:18:46 -05'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Pharmacology Division Director	Brian P Booth, PhD	Office of Clinical Pharmacology/Division of Cancer Pharmacology I	Sections: 6, 19.5	**Select one:** ☐Authored ■Approved
	Signature:			
Pharmacometrics Reviewer	Jianghong Fan, PhD	Office of Clinical Pharmacology/ Department of Pharmacometrics	Sections: 6, 19.5	**Select one:** ■Authored ☐Approved
	Signature: Jianghong Fan -S Digitally signed by Jianghong Fan -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Jianghong Fan -S, 0.9.2342.19200300.100.1.1=2001454698 Date: 2019.11.25 10:04:27 -05'00'			
Pharmacometrics Team Leader	Xinyuan Zhang, PhD	Office of Clinical Pharmacology/ Department of Pharmacometrics	Sections: 6, 19.5	**Select one:** ☐Authored ■Approved
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Pharmacometrics Division Director	Yaning Wang, PhD	Office of Clinical Pharmacology/ Department of Pharmacometrics	Sections: 6, 19.5	**Select one:** ☐Authored ■Approved
	Signature: Hao Zhu -S Digitally signed by Hao Zhu -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Hao Zhu -S, 0 9.2342.19200300.100.1.1=1300405208 Date: 2019.11.25 12:27 28 -05'00'			
Clinical Reviewer	Patricia Oneal, MD	Office of Drug Evaluation I Division of Hematology Products	Sections: 1, 2, 3, 4, 7, 8	**Select one:** ■Authored ☐Approved
	Signature: Patricia O'neal -S Digitally signed by Patricia O'neal -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=0011182769, cn=Patricia O'neal -S Date: 2019.11.25 11:50 20 -05'00'			
Clinical Reviewer	Rosanna Setse, MD, PhD	Office of Drug Evaluation I Division of Hematology Products	Sections: 2, 7 8.2 8.4	**Select one:** ■Authored ☐Approved
	Signature: Rosanna W. Setse -S Digitally signed by Rosanna W. Setse -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1000634340, cn=Rosanna W. Setse -S Date: 2019.11.25 11:54:00 -05'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Team Leader	Tanya Wroblewski, MD	Office of Drug Evaluation I Division of Hematology Products	Sections: 1, 2, 3, 4, 7, 8	**Select one:** ☐Authored ■Approved
	Signature: Tanya M. Wroblewski -S3 Digitally signed by Tanya M. Wroblewski -S3 DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=0011605845, cn=Tanya M. Wroblewski -S3 Date: 2019.11.25 11:51:33 -05'00'			
Statistical Reviewer	Lola Luo, PhD	Office of Biostatistics/ DBIX	Sections: 8.1, 8.3, 8.4	**Select one:** ■Authored ☐Approved
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Statistical Team Leader	Yeh-Fong Chen, PhD	Office of Biostatistics/ DBIX	Sections: 8.1, 8.3, 8.4	**Select one:** ■Authored ■Approved
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Cross-Disciplinary Team Leader (CDTL)	Tanya Wroblewski, MD	Office of Drug Evaluation I Division of Hematology Products	Sections: 1, 2, 3, 4, 7, 8	**Select one:** ☐Authored ■Approved
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Division Director (Clinical)	Ann T Farrell, MD	Office of Drug Evaluation I Division of Hematology Products	Sections: 1,2,3,4,5,6,7,8,9,10,11, 12,13	**Select one:** ☐Authored ■Approved
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Division Director (OB)	Thomas E Gwise, PhD	Office of Biostatistics/ DBIX	Sections: 8.1, 8.3, 8.4	**Select one:** ☐Authored ■Approved
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DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Pharmacometrics Reviewer	Liang Li, PhD	Office of Clinical Pharmacology / Division of Pharmacometrics	Sections: 6, 19.5	**Select one:** ☒ Authored ☐ Approved
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Pharmacometrics Team Leader	Lian Ma, PhD	Office of Clinical Pharmacology / Division of Pharmacometrics	Sections:	**Select one:** ☒ Authored ☒ Approved
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Genomics reviewer	Robert Schuck, PharmD, PhD	Office of Clinical Pharmacology/ Division of Translational and Precision Medicine	Sections:	**Select one:** ☒ Authored ☐ Approved
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GenomicsTeam Leader	Christian Grimstein, PhD	Office of Clinical Pharmacology/ Division of Translational and Precision Medicine	Sections:	**Select one:** ☐ Authored ☒ Approved
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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Science
Office of Biostatistics

Statistical Review and Evaluation

CARCINOGENICITY STUDY

IND/NDA Number:	NDA213137
Drug Name:	Voxelotor (GBT440)
Indication:	Treatment of Sickle Cell Disease (SCD)
Applicant:	Global Blood Therapeutics, Inc. 171 Oyster Point Blvd., Suite 300 South San Francisco, CA 94080 Test Facility for mice Study: (b) (4) UNITED STATES OF AMERICA
Documents Reviewed:	Study report (PRC-17-006) and Electronic data submitted on March 29, 2019 via NDA213137/0001;
Biometrics Division:	Division of Biometrics -6
Statistical Reviewer:	Zhuang Miao, Ph.D.
Concurring Reviewers:	Feng Zhou, MS Karl Lin, Ph.D.
Medical Division:	Division of Hematology Products
Reviewing Pharmacologist:	DelValle, Pedro, Ph.D.
Keywords:	Carcinogenicity, Dose response

Table of Contents

1. Summary

In this submission the sponsor included the report of one animal carcinogenicity study 001178-T (hemizygous) RasH2 mice. This study was intended to assess the carcinogenic potential of GBT440 when administered orally by gavage at appropriate drug levels for 26 weeks in mice.

Mouse Study: One hundred and twenty five RasH2 mice of each sex were randomly assigned to the treated, vehicle, and water control groups in equal size of 25 mice per group. There are 10 mice of each sex in the positive control group. The dose levels for the GBT440 treated groups were 50, 150, and 500 mg/kg/day. The mice in the vehicle control group received the vehicle (0.5% (w/w) Methocel± E50 in reverse osmosis water containing 0.01% (w/w) polysorbate 80 and 10 mM phosphate buffer (pH 7 ± 0.2)). The mice in the water control group received the reverse osmosis water. The mice in the positive control group received acidified physiological saline (150 mM sodium chloride and 15 mM sodium citrate in reverse osmosis water, adjusted to pH 4.5 ± 0.1 with 1 N hydrochloric acid) injection once on Day 1 at the dose of 75 mg/kg. The study was designed to continue for up to 26 weeks for both sexes, however in accordance with study termination criteria, all surviving mice were sacrificed during Week 27.

Survival analysis showed that no GBT440-related effects on survival or mortality occurred. The pairwise comparisons showed statistically significant increases in mortality in the positive control group when compared to the vehicle control and to the water control for the male and female mice.

Tumor analysis showed that no GBT440-related clinical pathology findings suggested an effect on the occurrence of neoplasia. There were significant tumor findings for the positive control group when compared with vehicle or water control groups:

1. For male mice, the pairwise comparisons between the vehicle control and the positive control showed statistically significant increases in incidence of Lymphoma in Hemolympho-reticu (P-value<0.001), Squamous cell Papilloma in Stomach, nonglandu (P-value<0.001), Squamous cell Carcinoma in Stomach, nonglandu (P-value=0.0071), Combined tumors of Squamous cell Papilloma+Carcinoma in Skin/Subcutis (P-value=0.0423).
2. For male mice, the pairwise comparisons between the water control and the positive control showed statistically significant increases in incidence of Lymphoma in Hemolympho-reticu (P-value<0.001), Squamous cell Papilloma in Stomach, nonglandu (P-value<0.001), Squamous cell Carcinoma in Stomach, nonglandu (P-value=0.0071), Combined tumors of Squamous cell Papilloma+Carcinoma in Skin/Subcutis (P-value=0.0423).
3. For female mice, the pairwise comparisons between the vehicle control and the positive control showed statistically significant increases in incidence of Lymphoma in Hemolympho-reticu (P-value<0.001), Squamous cell Papilloma in Stomach, nonglandu (P-value<0.001), Squamous cell Papilloma in Skin/Subcutis (P-value=0.0345), Combined tumors of Squamous cell Papilloma+Carcinoma in Skin/Subcutis (P-value=0.0345).
4. For female mice, the pairwise comparisons between the water control and the positive control showed statistically significant increases in incidence of Lymphoma in Hemolympho-reticu (P-value<0.001), Squamous cell Papilloma in Stomach, nonglandu (P-value<0.001), Squamous cell Papilloma in Skin/Subcutis (P-value=0.0369), Combined tumors of Squamous cell Papilloma+Carcinoma in Skin/Subcutis (P-value=0.0369).

2. Background

In this submission the sponsor included the report of one animal carcinogenicity study in 001178-T (hemizygous) RasH2 mice. This study was intended to assess the carcinogenic potential of GBT440, when administered orally by gavage at appropriate drug levels for 26 weeks in mice. Results of this review have been discussed with the reviewing pharmacologist Dr. Pedro DelValle. This review analyzed the SAS data sets of this study received from the sponsor on March 29, 2019 via NDA213137/0001.

In this review the phrase "dose response relationship" refers to the linear component of the effect of treatment, and not necessarily to a strictly increasing or decreasing mortality or tumor incidence rate as the dose increases.

3. Mouse Study

Two separate experiments were conducted, one in males and one in females. In each of these two experiments there were three treated groups, one vehicle control group, one water control group and one positive control group. One hundred and twenty five RasH2 mice of each sex were randomly assigned to the treated, vehicle and water control groups in equal size of 25 mice per group. There are 10 mice of each sex in the positive control group. The dose levels for treated groups were 50, 150, and 500 mg/kg/day for mice that received GBT440. The mice in the vehicle control group received the vehicle (0.5% (w/w) Methocel± E50 in reverse osmosis water containing 0.01% (w/w) polysorbate 80 and 10 mM phosphate buffer (pH 7 ± 0.2)). The mice in the water control group received the reverse osmosis water. The study was designed to continue for up to 26 weeks for both sexes, however in accordance with study termination criteria, all surviving mice were sacrificed during Week 27. The mice in the positive control group received acidified physiological saline (150 mM sodium chloride and 15 mM sodium citrate in reverse osmosis water, adjusted to pH 4.5 ± 0.1 with 1 N hydrochloric acid) injection once on Day 1 at the dose of 75 mg/kg.

Table 1: Study Design in Mouse Study

Protocol Group No.	Dose Levels (mg/kg/day)	Identification	Number of Animals Enrolled	
			Males	Females
1	0	Water	25	25
2	0	Vehicle	25	25
3	50	Low	25	25
4	150	Mid	25	25
5	500	High	25	25
6	75	Positive	10	10

3.1. Sponsor's analyses

3.1.1. Survival analysis

The data were analyzed in accordance with current FDA guidelines (Food and Drug Administration, 2001). For all analyses, the two sexes were kept separate. Actual dose levels were used in the statistical analysis. Tests to compare survival were performed, with a two-sided risk for increasing and decreasing mortality with dose. Kaplan-Meier product-limit estimates and log-rank and Wilcoxon tests were performed for dose response (vehicle control and dosed groups only) and to compare water controls and each dosed group against vehicle controls. These were performed using the LIFETEST procedure in Statistical Analysis System (SAS). The time to death or euthanasia (in weeks, calculation detailed in the following) was the dependent variable. The

dosed groups were included as the strata. Animals with a death or euthanasia status recorded as a scheduled euthanasia (interim or terminal) or accidental death were censored in the analysis.

Sponsor's findings: The sponsor's analysis showed 0 (0%), 1 (4%), 1 (4%), 2 (8%), 0 (0%), and 5 (50%) mortalities in male mice, and 2 (8%), 1 (4%), 2 (8%), 2 (8%), 1 (4%), and 9 (90%) mortalities in female mice in water control, vehicle control, 50 mg/kg/day, 150 mg/kg/day, 500 mg/kg/day and positive control group, respectively.

There were no statistically significant differences in survival rates in either males or females in any treated groups when compared with the vehicle control group or water control group.

3.1.2. Tumor data analysis

Observable or palpable (superficial as in mammary or skin) tumors were analyzed using the methods previously described for analyzing survival, using the time to death or time of detection of the tumor (in weeks) as a surrogate for the tumor onset time. The comparisons between the vehicle control and dosed groups were performed with a one-sided risk for increasing incidence with dose. The water and vehicle control groups were compared using two-sided tests.

Unadjusted P-values were reported for tumors. An indication of a possible dose effect was assessed on the basis of whether the tumor was a rare or common type, in line with the current FDA guidelines (Food and Drug Administration, 2001). The incidence rate for defining whether a tumor type was rare or common was based on site-specific background historical data. The study Pathologist determined whether a tumor type was rare or common.

Sponsor's findings: The sponsor's tumor data analysis did not find any carcinogenic effects related to GBT440 administration.

3.2. Reviewer's analyses

To verify sponsor's analyses and to perform additional analyses suggested by the reviewing pharmacologist, this reviewer independently performed survival and tumor data analyses. Data used in this reviewer's analyses were provided by the sponsor electronically on March 29, 2019 via NDA213137/0001. The significance level for all statistical tests was set at 0.05.

3.2.1. Survival analysis

The survival distributions of three treated groups, one vehicle control group, one water control group and one positive control group were estimated using the Kaplan-Meier product limit method. The dose response relationship in survival was tested using the likelihood ratio test and the homogeneity of survival distributions was tested using the log-rank test. The Kaplan-Meier curves for survival rates are given in Figures 1 and 2 in the appendix for male and female mice, respectively. The intercurrent mortality data are given in Tables 6 and 7 in the appendix for male and female mice, respectively. Results of the tests for dose response relationship and homogeneity of survivals among the vehicle control, the treated groups and positive control, among the water control, the treated groups and positive control are given in Tables 8, 9, 10 and 11 in the appendix for male and

female mice, respectively.

Reviewer's findings: This reviewer's analysis showed the numbers (percent) of death 0 (0%), 1 (4%), 1 (4%), 2 (8%), 0 (0%), and 5 (50%) mortalities in male mice, and 2 (8%), 1 (4%), 2 (8%), 2 (8%), 1 (4%), and 9 (90%) mortalities in female mice in water control, vehicle control, low, medium, high dose groups and positive control group, respectively.

The survival analyses did not show any statistically significant dose response relationships in mortality across vehicle control and treated groups or across the water control and the treated groups for either males or females. The pairwise comparisons did not show any statistically significant differences in mortality between the vehicle control and each of the treated groups or between the water control and each of the treated group for either males or females.

The pairwise comparisons showed statistically significant increases in mortality in the positive control group when compared to the vehicle control and to the water control for the male and female mice. For male mice, the p-values for Likelihood Ratio test are 0.0016 and 0.0002 and the p-values for Log-Rank test are 0.00004 and <0.00001, respectively. For female mice, the p-values for Likelihood Ratio test are <0.00001 and <0.00001 and the p-values for Log-Rank test are <0.00001 and <0.00001, respectively.

3.2.2. Tumor data analysis

The tumor data were analyzed for the positive dose response relationships and the positive pairwise comparison increases between each of the treated groups with control group. Both the dose response relationship tests and pairwise comparisons were performed using the Poly-K method described in the paper of Bailer and Portier (1988) and Bieler and Williams (1993). In this method an animal that lives the full study period ($w_{\max}$) or dies before the terminal sacrifice but develops the tumor type being tested gets a score of s_h =1. An animal that dies at week w_h without a tumor before the end of the study gets a score of $s_h = \left(\frac{w_h}{w_{\max}} \right)^k < 1$. The adjusted group size is defined as Σs_h. As an interpretation, an animal with score s_h =1 can be considered as a whole animal while an animal with score $s_h < 1$ can be considered as a partial animal. The adjusted group size Σs_h is equal to N (the original group size) if all animals live up to the end of the study or if each animal that dies before the terminal sacrifice develops at least one tumor, otherwise the adjusted group size is less than N. These adjusted group sizes are then used for the dose response relationship (or the pairwise) tests using the Cochran-Armitage test. One critical point for Poly-k test is the choice of the appropriate value of k, which depends on the tumor incidence pattern with the increased dose. For long term 104 week standard rat and mouse studies, a value of k=3 is suggested in the literature. Hence, this reviewer used k=3 for the analysis of this data. For the calculation of p-values the exact permutation method was used. The tumor rates and the p-values for the positive dose response relationship tests and pairwise comparisons are listed in Tables 11 and 12 in the appendix for male and female rats, respectively.

The tumor rates and the p-values for the positive dose response relationship tests and pairwise comparisons between vehicle control and three treated groups, between water control and three treated groups, between vehicle control and positive control and between water control and positive control are listed in Tables 12, 13,

14, 15, 16, 17, 18, and 19 in the appendix for male and female mice, respectively.

Adjustment for multiple testing: For the adjustment of multiple testing of dose response relationship for the transgenic mouse study in a submission with only one transgenic mouse study, the more recently revised draft (January, 2013) FDA guidance for the carcinogenicity studies suggests the use of test levels $\alpha = 0.05$ for both common tumors and rare tumors for the mouse study. For pairwise, the same guidance document suggests the use of test levels $\alpha = 0.05$ for both common tumors and rare tumors for the mouse study.

It should be noted that the FDA guidance for multiple testing for dose response relationship is based on a publication by Lin and Rahman (1998). In this work the authors investigated the use of this rule for Peto analysis. However, in a later work Rahman and Lin (2008) showed that this rule for multiple testing for dose response relationship is also suitable for Poly-K tests.

Reviewer's findings: The tumor types in Table 2, 3, 4, and 5 (pairwise comparisons between vehicle and positive control and between water control and positive control for male mice and female mice, respectively) below showed p-values less than or equal to 0.05.

Table 2: Tumor Types with P-Values ⩽ 0.05 for Comparisons between Vehicle Control and Positive Control-Male Mice

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=25)	Positive (N=10) P-value - Vehicle vs. Positive
HEMOLYMPHO- RETICU	M-MALIGNANT LYMPHOMA	0/25 (25)	6/7 (6) <0.001
STOMACH, NONGLANDU	B-PAPILLOMA, SQUAMOUS CELL	0/25 (25)	6/10 (9) <0.001
	M-CARCINOMA, SQUAMOUS CELL	0/25 (25)	3/10 (7) 0.0071
Skin Subcutis	C_Squamous cell Papilloma+Carcinoma	0/25 (25)	2/10 (7) 0.0423

Table 3: Tumor Types with P-Values ⩽ 0.05 for Comparisons between Water Control and Positive Control-Male Mice

Organ Name	Tumor Name	0 mg/kg/day Water (N=25)	Positive (N=10) P-value - Water vs. Positive
HEMOLYMPHO- RETICU	M-MALIGNANT LYMPHOMA	0/25 (25)	6/7 (6) <0.001
STOMACH, NONGLANDU	B-PAPILLOMA, SQUAMOUS CELL	0/25 (25)	6/10 (9) <0.001
	M-CARCINOMA, SQUAMOUS CELL	0/25 (25)	3/10 (7) 0.0071
Skin Subcutis	C Squamous cell Papilloma+Carcinoma	0/25 (25)	2/10 (7) 0.0423

Table 4: Tumor Types with P-Values ⩽ 0.05 for Comparisons between Vehicle Control and Positive Control-Female Mice

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=25)	Positive (N=10) P-value - Vehicle vs. Positive
HEMOLYMPHO- RETICU	M-MALIGNANT LYMPHOMA	0/25 (24)	10/10 (10) <0.001
SKIN/SUBCUTIS	B-PAPILLOMA, SQUAMOUS CELL	0/25 (24)	2/10 (6) 0.0345
STOMACH, NONGLANDU	B-PAPILLOMA, SQUAMOUS CELL	0/25 (24)	5/10 (7) <0.001
Skin Subcutis	C Squamous cell Papilloma+Carcinoma	0/25 (24)	2/10 (6) 0.0345

Table 5: Tumor Types with P-Values ⩽ 0.05 for Comparisons between Water Control and Positive Control-Female Mice

Organ Name	Tumor Name	0 mg/kg/day Water (N=25)	Positive (N=10) P-value - Water vs. Positive
HEMOLYMPHO- RETICU	M-MALIGNANT LYMPHOMA	0/25 (23)	10/10 (10) <0.001
SKIN/SUBCUTIS	B-PAPILLOMA, SQUAMOUS CELL	0/25 (23)	2/10 (6) 0.0369
STOMACH, NONGLANDU	B-PAPILLOMA, SQUAMOUS CELL	0/25 (23)	5/10 (7) <0.001
Skin Subcutis	C Squamous cell Papilloma+Carcinoma	0/25 (23)	2/10 (6) 0.0369

Reviewer's findings: Based on the criteria of adjustment for multiple testing discussed in the mouse data analysis section, we make the following conclusions:

1. For male mice, the pairwise comparisons between the vehicle control and the positive control showed statistically significant increases in incidence of Lymphoma in Hemolympho-reticu (P-value<0.001), Squamous cell Papilloma in Stomach, nonglandu (P-value<0.001), Squamous cell Carcinoma in Stomach, nonglandu (P-value=0.0071), Combined tumors of Squamous cell Papilloma+Carcinoma in Skin/Subcutis (P-value=0.0423).
2. For male mice, the pairwise comparisons between the water control and the positive control showed statistically significant increases in incidence of Lymphoma in Hemolympho-reticu (P-value<0.001), Squamous cell Papilloma in Stomach, nonglandu (P-value<0.001), Squamous cell Carcinoma in Stomach, nonglandu (P-value=0.0071), Combined tumors of Squamous cell Papilloma+Carcinoma in Skin/Subcutis (P-value=0.0423).
3. For female mice, the pairwise comparisons between the vehicle control and the positive control showed statistically significant increases in incidence of Lymphoma in Hemolympho-reticu (P-value<0.001), Squamous cell Papilloma in Stomach, nonglandu (P-value<0.001), Squamous cell Papilloma in Skin/Subcutis (P-value=0.0345), Combined tumors of Squamous cell Papilloma+Carcinoma in Skin/Subcutis (P-value=0.0345).
4. For female mice, the pairwise comparisons between the water control and the positive control showed statistically significant increases in incidence of Lymphoma in Hemolympho-reticu (P-value<0.001), Squamous cell Papilloma in Stomach, nonglandu (P-value<0.001), Squamous cell Papilloma in Skin/Subcutis (P-value=0.0369), Combined tumors of Squamous cell Papilloma+Carcinoma in Skin/Subcutis (P-value=0.0369).

4. Conclusion

In this submission the sponsor included the report of one animal carcinogenicity study 001178-T (hemizygous) RasH2 mice. This study was intended to assess the carcinogenic potential of GBT440 when administered orally by gavage at appropriate drug levels for 26 weeks in mice.

Mouse Study: One hundred and twenty five RasH2 mice of each sex were randomly assigned to the treated, vehicle and water control groups in equal size of 25 mice per group. There are 10 mice of each sex in the positive control group. The dose levels for treated the GBT44 groups were 50, 150, and 500 mg/kg/day. The mice in the vehicle control group received the vehicle (0.5% (w/w) Methocel± E50 in reverse osmosis water containing 0.01% (w/w) polysorbate 80 and 10 mM phosphate buffer (pH 7 ± 0.2)). The mice in the water control group received the reverse osmosis water. The mice in the positive control group received acidified physiological saline (150 mM sodium chloride and 15 mM sodium citrate in reverse osmosis water, adjusted
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Tumor analysis showed that no GBT440-related clinical pathology findings suggested an effect on the occurrence of neoplasia. There were significant tumor findings for the positive control group when compared with vehicle or water control groups:

1. For male mice, the pairwise comparisons between the vehicle control and the positive control showed statistically significant increases in incidence of Lymphoma in Hemolympho-reticu (P-value<0.001), Squamous cell Papilloma in Stomach, nonglandu (P-value<0.001), Squamous cell Carcinoma in Stomach, nonglandu (P-value=0.0071), Combined tumors of Squamous cell Papilloma+Carcinoma in Skin/Subcutis (P-value=0.0423).
2. For male mice, the pairwise comparisons between the water control and the positive control showed statistically significant increases in incidence of Lymphoma in Hemolympho-reticu (P-value<0.001), Squamous cell Papilloma in Stomach, nonglandu (P-value<0.001), Squamous cell Carcinoma in Stomach, nonglandu (P-value=0.0071), Combined tumors of Squamous cell Papilloma+Carcinoma in Skin/Subcutis (P-value=0.0423).
3. For female mice, the pairwise comparisons between the vehicle control and the positive control showed statistically significant increases in incidence of Lymphoma in Hemolympho-reticu (P-value<0.001), Squamous cell Papilloma in Stomach, nonglandu (P-value<0.001), Squamous cell Papilloma in Skin/Subcutis (P-value=0.0345), Combined tumors of Squamous cell Papilloma+Carcinoma in Skin/Subcutis (P-value=0.0345).
4. For female mice, the pairwise comparisons between the water control and the positive control showed statistically significant increases in incidence of Lymphoma in Hemolympho-reticu (P-value<0.001), Squamous cell Papilloma in Stomach, nonglandu (P-value<0.001), Squamous cell Papilloma in Skin/Subcutis (P-value=0.0369), Combined tumors of Squamous cell

Papilloma+Carcinoma in Skin/Subcutis (P-value=0.0369).

Zhuang Miao, Ph.D.
Mathematical Statistician

Concur:
Feng Zhou, MS
Mathematical Statistician, Biometrics-6

Karl Lin, Ph.D.
Mathematical Statistician, Team Leader, Biometrics-6

cc:
Yi Tsong, Ph.D.
DelValle, Pedro, Ph.D.

5. Appendix

Table 6: Intercurrent Mortality Rate -Male Mice

	Water 0 mg|kg|day (N=25)		Vehicle 0 mg|kg|day (N=25)		50 mg|kg|day (N=25)		150 mg|kg|day (N=25)		500 mg|kg|day (N=25)		Positive (N=10)	
Week	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**
0 - 13	.	.	.	.	.	.	.	.	.	.	1	10.00
14 - 26	.	.	1	4.00	1	4.00	2	8.00	.	.	4	50.00
Ter. Sac.	25	100.00	24	96.00	24	96.00	23	92.00	25	100.00	5	50.00

Cum. %: Cumulative percentage except for Ter. Sac.

Table 7: Intercurrent Mortality Rate -Female Mice

	Water 0 mg|kg|day (N=25)		Vehicle 0 mg|kg|day (N=25)		50 mg|kg|day (N=25)		150 mg|kg|day (N=25)		500 mg|kg|day (N=25)		Positive (N=10)	
Week	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**
0 - 13	1	4.00	1	4.00	.	.	1	4.00	1	4.00	.	.
14 - 26	1	8.00	.	.	2	8.00	1	8.00	.	.	9	90.00
Ter. Sac.	23	92.00	24	96.00	23	92.00	23	92.00	24	96.00	1	10.00

Cum. %: Cumulative percentage except for Ter. Sac.

Table 8: Intercurrent Mortality Comparison between the Treated Groups and Vehicle Control, Positive Control and Vehicle Control -Male Mice

Test	Statistic	P_Value Vehicle vs Treated Groups Dose Response	P_Value Vehicle vs. Low	P_Value Vehicle vs. Med	P_Value Vehicle vs. High	P_Value Vehicle vs. Positive
Dose-Response	Likelihood Ratio	0.6635	1.0000	0.5362	0.2390	0.0016
Homogeneity	Log-Rank	0.5429	1.0000	0.5396	0.3173	0.0004

Table 9: Intercurrent Mortality Comparison between the Treated Groups and Water Control, Positive Control and Vehicle Control -Male Mice

Test	Statistic	P_Value Water vs Treated Groups Dose Response	P_Value Water vs. Low	P_Value Water vs. Med	P_Value Water vs. High	P_Value Water vs. Positive
Dose-Response	Likelihood Ratio	0.6114	0.2390	0.0935	.	0.0002
Homogeneity	Log-Rank	0.2814	0.3173	0.1531	.	<0.0001

Table 10: Intercurrent Mortality Comparison between Treated Groups and Vehicle Control, Positive Control and Vehicle Control --Female Mice

Test	Statistic	P_Value Vehicle vs Treated Groups Dose Response	P_Value Vehicle vs. Low	P_Value Vehicle vs. Med	P_Value Vehicle vs. High	P_Value Vehicle vs. Positive
Dose-Response	Likelihood Ratio	0.9954	0.5678	0.5521	0.9885	<0.0001
Homogeneity	Log-Rank	0.8789	0.5717	0.5557	0.9885	<0.0001

Table 11: Intercurrent Mortality Comparison between Treated Groups and Water Control, Positive Control and Water Control --Female Mice

Test	Statistic	P_Value Water vs Treated Groups Dose Response	P_Value Water vs. Low	P_Value Water vs. Med	P_Value Water vs. High	P_Value Water vs. Positive
Dose-Response	Likelihood Ratio	0.6530	0.9667	0.9834	0.5521	<0.0001
Homogeneity	Log-Rank	0.9310	0.9667	0.9834	0.5557	<0.0001

Table 12: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons between Vehicle Control and the Treated Groups -Male Mice

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=25) P-value - Trend	50 mg/kg/day Low (N=25) P-value - Vehicle vs. Low	150 mg/kg/day Med (N=25) P-value - Vehicle vs. Med	500 mg/kg/day High (N=25) P-value - Vehicle vs. High
HARDERIAN GLAND	B-ADENOMA	0/25 (25) 0.1855	0/25 (25) NC	1/25 (24) 0.4898	1/25 (25) 0.5000
HEMOLYMPHO-RETICU	M-MALIGNANT LYMPHOMA	0/25 (25) 0.7475	1/25 (25) 0.5000	0/25 (24) NC	0/25 (25) NC
LIVER	B-ADENOMA, HEPATOCELLULAR	1/25 (25) 0.8093	0/25 (25) 1.0000	1/25 (24) 0.7449	0/25 (25) 1.0000
LUNG	B-ADENOMA, BRONCHIOLO-ALVEO*	0/25 (25) 0.1318	1/25 (25) 0.5000	1/25 (24) 0.4898	2/25 (25) 0.2449
MUSCLE, SKELETAL,	M-HEMANGIOSARCOMA	0/25 (25) 0.2525	0/25 (25) NC	0/25 (24) NC	1/25 (25) 0.5000
SKIN/SUBCUTIS	B-MELANOMA	0/25 (25) 0.2551	0/24 (24) NC	0/25 (24) NC	1/25 (25) 0.5000
	M-HEMANGIOSARCOMA	1/25 (25) 0.9369	1/24 (24) 0.7449	0/25 (24) 1.0000	0/25 (25) 1.0000
SPLEEN	B-HEMANGIOMA	0/25 (25) 0.3422	2/25 (25) 0.2449	2/25 (24) 0.2347	1/25 (25) 0.5000
	M-HEMANGIOSARCOMA	0/25 (25) 0.6238	1/25 (25) 0.5000	1/25 (24) 0.4898	0/25 (25) NC
STOMACH, NONGLANDU	M-CARCINOMA, SQUAMOUS CELL	0/25 (25) 0.6238	1/25 (25) 0.5000	1/25 (24) 0.4898	0/25 (25) NC
Whole Body	C_Hemangiosarcoma+hemangioma	1/25 (25) 0.4360	4/25 (25) 0.1743	3/25 (24) 0.2890	2/25 (25) 0.5000

Table 13: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons between Water Control and the Treated Groups -Male Mice

Organ Name	Tumor Name	0 mg/kg/day Water (N=25) P-value - Trend	50 mg/kg/day Low (N=25) P-value - Water vs. Low	150 mg/kg/day Med (N=25) P-value - Water vs. Med	500 mg/kg/day High (N=25) P-value - Water vs. High
HARDERIAN GLAND	B-ADENOMA	0/25 (25) 0.1855	0/25 (25) NC	1/25 (24) 0.4898	1/25 (25) 0.5000
HEMOLYMPHO-RETICU	M-MALIGNANT LYMPHOMA	0/25 (25) 0.7475	1/25 (25) 0.5000	0/25 (24) NC	0/25 (25) NC
LIVER	B-ADENOMA, HEPATOCELLULAR	1/25 (25) 0.8093	0/25 (25) 1.0000	1/25 (24) 0.7449	0/25 (25) 1.0000
LUNG	B-ADENOMA, BRONCHIOLO-ALVEO*	1/25 (25) 0.3422	1/25 (25) 0.7551	1/25 (24) 0.7449	2/25 (25) 0.5000
MUSCLE, SKELETAL,	M-HEMANGIOSARCOMA	0/25 (25) 0.2525	0/25 (25) NC	0/25 (24) NC	1/25 (25) 0.5000
SKIN/SUBCUTIS	B-MELANOMA	0/25 (25) 0.2551	0/24 (24) NC	0/25 (24) NC	1/25 (25) 0.5000
	M-HEMANGIOSARCOMA	0/25 (25) 0.7449	1/24 (24) 0.4898	0/25 (24) NC	0/25 (25) NC
SPLEEN	B-HEMANGIOMA	0/25 (25) 0.3422	2/25 (25) 0.2449	2/25 (24) 0.2347	1/25 (25) 0.5000
	M-HEMANGIOSARCOMA	1/25 (25) 0.8438	1/25 (25) 0.7551	1/25 (24) 0.7449	0/25 (25) 1.0000
STOMACH, NONGLANDU	M-CARCINOMA, SQUAMOUS CELL	0/25 (25) 0.6238	1/25 (25) 0.5000	1/25 (24) 0.4898	0/25 (25) NC
Whole Body	C_Hemangiosarcoma+hemangioma	1/25 (25) 0.4360	4/25 (25) 0.1743	3/25 (24) 0.2890	2/25 (25) 0.5000

Table 14: Tumor Rates and P-Values for Comparisons between Vehicle Control and Positive Control-Male Mice

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=25)	Positive (N=10) P-value - Vehicle vs. Positive
HEMOLYMPHO-RETICU	M-MALIGNANT LYMPHOMA	0/25 (25)	6/7 (6) <0.001
LIVER	B-ADENOMA, HEPATOCELLULAR	1/25 (25)	0/10 (7) 1.0000
SKIN/SUBCUTIS	B-PAPILLOMA, SQUAMOUS CELL	0/25 (25)	1/10 (7) 0.2188
	M-CARCINOMA, SQUAMOUS CELL	0/25 (25)	1/10 (7) 0.2188
	M-HEMANGIOSARCOMA	1/25 (25)	0/10 (7) 1.0000
Skin Subcutis	C_Squamous cell Papilloma+Carcinoma	0/25 (25)	2/10 (7) 0.0423
SPLEEN	M-HEMANGIOSARCOMA	0/25 (25)	1/10 (7) 0.2188
STOMACH, NONGLANDU	B-PAPILLOMA, SQUAMOUS CELL	0/25 (25)	6/10 (9) <0.001
	M-CARCINOMA, SQUAMOUS CELL	0/25 (25)	3/10 (7) 0.0071

Table 15: Tumor Rates and P-Values for Comparisons between Water Control and Positive Control-Male Mice

Organ Name	Tumor Name	0 mg/kg/day Water (N=25)	Positive (N=10) P-value - Water vs. Positive
HEMOLYMPHO-RETICU	M-MALIGNANT LYMPHOMA	0/25 (25)	6/7 (6) <0.001
LIVER	B-ADENOMA, HEPATOCELLULAR	1/25 (25)	0/10 (7) 1.0000
LUNG	B-ADENOMA, BRONCHIOLO-ALVEO*	1/25 (25)	0/10 (7) 1.0000
SKIN/SUBCUTIS	B-PAPILLOMA, SQUAMOUS CELL	0/25 (25)	1/10 (7) 0.2188
	M-CARCINOMA, SQUAMOUS CELL	0/25 (25)	1/10 (7) 0.2188
SPLEEN	M-HEMANGIOSARCOMA	1/25 (25)	1/10 (7) 0.3952
STOMACH, NONGLANDU	B-PAPILLOMA, SQUAMOUS CELL	0/25 (25)	6/10 (9) <0.001
	M-CARCINOMA, SQUAMOUS CELL	0/25 (25)	3/10 (7) 0.0071
Skin Subcutis	C Squamous cell Papilloma+Carcinoma	0/25 (25)	2/10 (7) 0.0423
Whole Body	C_Hemangiosarcoma+hemangioma	1/25 (25)	1/10 (7) 0.3952

Table 16: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons between Vehicle Control and the Treated Groups - Female Mice

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=25) P-value - Trend	50 mg/kg/day Low (N=25) P-value - Vehicle vs. Low	150 mg/kg/day Med (N=25) P-value - Vehicle vs. Med	500 mg/kg/day High (N=25) P-value - Vehicle vs. High
HARDERIAN GLAND	B-ADENOMA	1/25 (24) 0.6211	0/25 (25) 1.0000	0/25 (23) 1.0000	1/25 (24) 0.7553
LUNG	B-ADENOMA, BRONCHIOLO-ALVEO*	0/25 (24) 0.6211	1/25 (25) 0.5102	1/25 (23) 0.4894	0/25 (24) NC
OVARY	B-HEMANGIOMA	1/25 (24) 1.0000	0/25 (25) 1.0000	0/25 (23) 1.0000	0/25 (24) 1.0000
SPLEEN	B-HEMANGIOMA	1/25 (24) 0.4921	0/25 (25) 1.0000	1/25 (23) 0.7447	1/25 (24) 0.7553
THYMUS	B-THYMOMA	0/25 (24) 0.1854	0/24 (24) NC	1/25 (23) 0.4894	1/25 (24) 0.5000
	M-MESOTHELIOMA	0/25 (24) 0.7474	1/24 (24) 0.5000	0/25 (23) NC	0/25 (24) NC
Whole Body	C_Hemangiosarcoma+hemangioma	1/25 (24) 0.4921	0/25 (25) 1.0000	1/25 (23) 0.7447	1/25 (24) 0.7553

Table 17: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons between Water Control and the Treated Groups - Female Mice

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=25) P-value - Trend	50 mg/kg/day Low (N=25) P-value - Water vs. Low	150 mg/kg/day Med (N=25) P-value - Water vs. Med	500 mg/kg/day High (N=25) P-value - Water vs. High
HARDERIAN GLAND	B-ADENOMA	0/25 (23) 0.2526	0/25 (25) NC	0/25 (23) NC	1/25 (24) 0.5106
LUNG	B-ADENOMA, BRONCHIOLO-ALVEO*	1/25 (23) 0.8496	1/25 (25) 0.7757	1/25 (23) 0.7556	0/25 (24) 1.0000
MUSCLE, SKELETAL,	M-HEMANGIOSARCOMA	1/25 (24) 1.0000	0/25 (25) 1.0000	0/25 (23) 1.0000	0/25 (24) 1.0000
SPLEEN	B-HEMANGIOMA	1/25 (23) 0.5020	0/25 (25) 1.0000	1/25 (23) 0.7556	1/25 (24) 0.7660
THYMUS	B-THYMOMA	0/25 (23) 0.1894	0/24 (24) NC	1/25 (23) 0.5000	1/25 (24) 0.5106
	M-MESOTHELIOMA	0/25 (23) 0.7553	1/24 (24) 0.5106	0/25 (23) NC	0/25 (24) NC
UTERUS	M-CHORIOCARCINOMA	1/25 (23) 1.0000	0/25 (25) 1.0000	0/25 (23) 1.0000	0/25 (24) 1.0000
Whole Body	C_Hemangiosarcoma+hemangioma	2/25 (24) 0.7391	0/25 (25) 1.0000	1/25 (23) 0.8752	1/25 (24) 0.8830

Table 18: Tumor Rates and P-Values for Comparisons between Vehicle Control and Positive Control- Female Mice

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=25)	Positive (N=10) P-value - Vehicle vs. Positive
HARDERIAN GLAND	B-ADENOMA	1/25 (24)	0/10 (4) 1.0000
HEMOLYMPHO-RETICU	M-MALIGNANT LYMPHOMA	0/25 (24)	10/10 (10) <0.001
OVARY	B-HEMANGIOMA	1/25 (24)	0/10 (4) 1.0000
SKIN/SUBCUTIS	B-PAPILLOMA, SQUAMOUS CELL	0/25 (24)	2/10 (6) 0.0345
	M-CARCINOMA, SQUAMOUS CELL	0/25 (24)	1/10 (5) 0.1724
SPLEEN	B-HEMANGIOMA	1/25 (24)	0/10 (4) 1.0000
STOMACH, NONGLANDU	B-PAPILLOMA, SQUAMOUS CELL	0/25 (24)	5/10 (7) <0.001
Skin Subcutis	C Squamous cell Papilloma+Carcinoma	0/25 (24)	2/10 (6) 0.0345
Whole Body	C_Hemangiosarcoma+hemangioma	1/25 (24)	0/10 (4) 1.0000

Table 19: Tumor Rates and P-Values for Comparisons between Water Control and Positive Control-Female Mice

Organ Name	Tumor Name	0 mg/kg/day Water (N=25)	Positive (N=10) P-value - Water vs. Positive
HEMOLYMPHO-RETICU	M-MALIGNANT LYMPHOMA	0/25 (23)	10/10 (10) <0.001
LUNG	B-ADENOMA, BRONCHIOLO-ALVEO*	1/25 (23)	0/10 (4) 1.0000
MUSCLE, SKELETAL,	M-HEMANGIOSARCOMA	1/25 (24)	0/10 (4) 1.0000
SKIN/SUBCUTIS	B-PAPILLOMA, SQUAMOUS CELL	0/25 (23)	2/10 (6) 0.0369
	M-CARCINOMA, SQUAMOUS CELL	0/25 (23)	1/10 (5) 0.1786
SPLEEN	B-HEMANGIOMA	1/25 (23)	0/10 (4) 1.0000
STOMACH, NONGLANDU	B-PAPILLOMA, SQUAMOUS CELL	0/25 (23)	5/10 (7) <0.001
Skin Subcutis	C_Squamous cell Papilloma+Carcinoma	0/25 (23)	2/10 (6) 0.0369
UTERUS	M-CHORIOCARCINOMA	1/25 (23)	0/10 (4) 1.0000
Whole Body	C_Hemangiosarcoma+hemangioma	2/25 (24)	0/10 (4) 1.0000

Figure 1: Kaplan-Meier Survival Functions for Male Mice

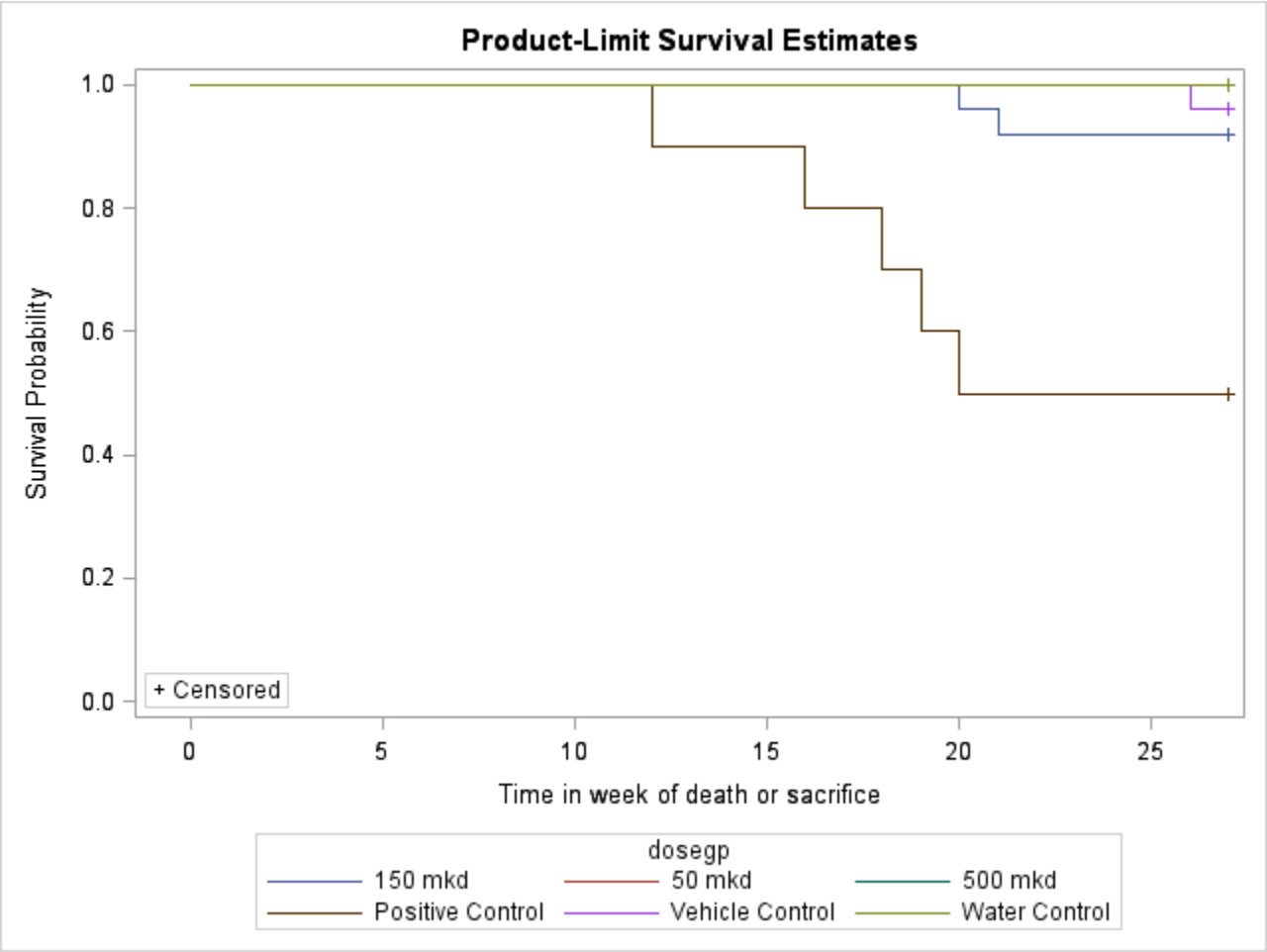
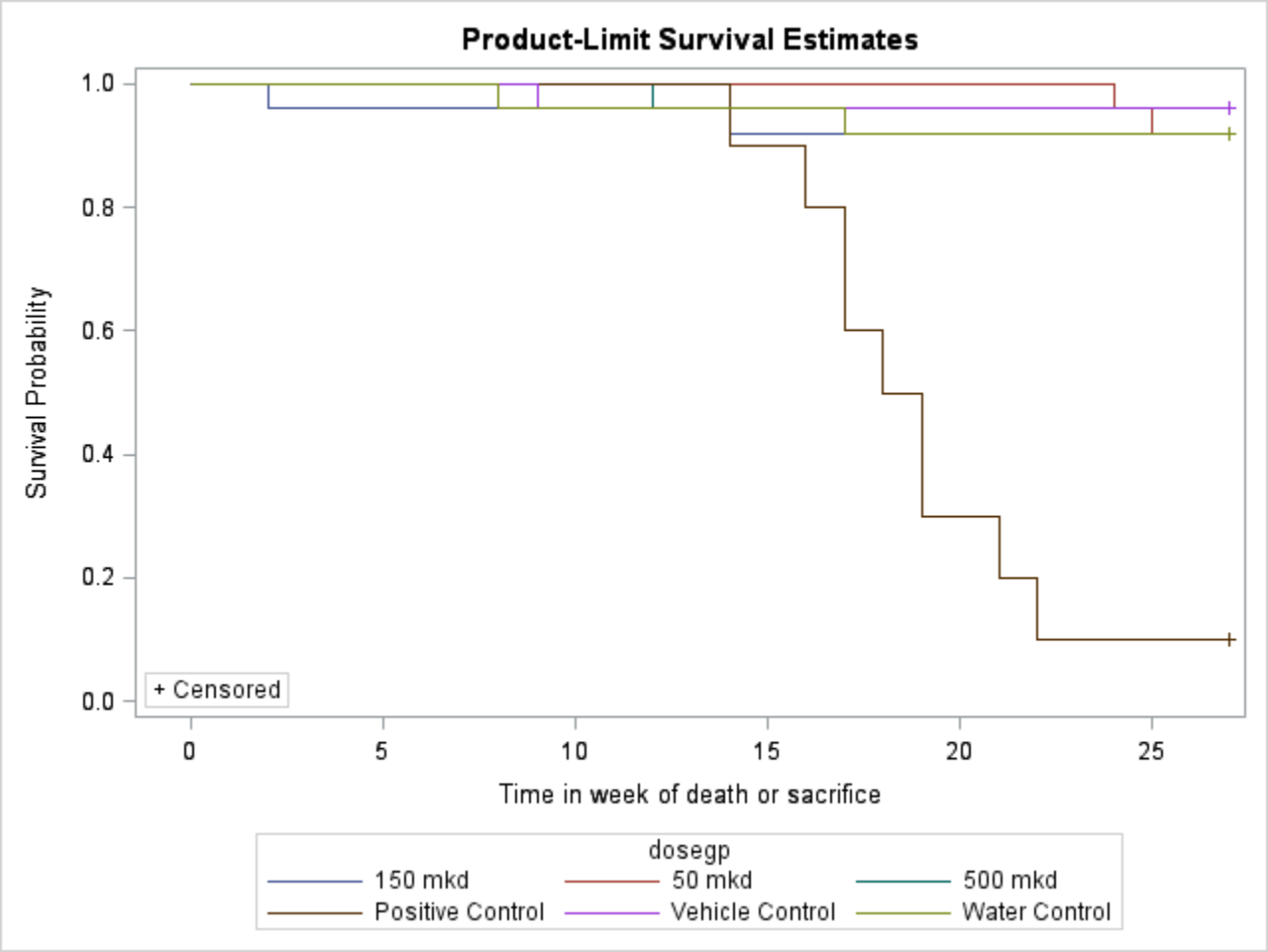


Figure 2: Kaplan-Meier Survival Functions for Female Mice



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