CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216157Orig1s000

CLINICAL PHARMACOLOGY REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA:	NDA 213137 S-006 (SDN 326) & NDA 216157 (SDN 1)
Related IND:	76488
Submission Type:	Efficacy supplement
Brand Name:	Oxbryta®
Drug Name:	Voxelotor
Submission Date:	06/25/2021
PUDFA Goal Date:	12/25/2021
Priority:	Priority
Indications:	Treatment of sickle cell disease in pediatric patients 4 to <12 years of age and older
Dosage and Administration	For pediatric patients 4 to <12 years • Body weight ≥ 40 kg: 1500 mg once daily (b) (4) • Body weight 20 to < 40 kg: 900 mg once daily given as 3x300 mg tablets for oral suspension • Body weight 10 to < 20 kg: 600 mg once daily given as 2x300 mg tablets for oral suspension
Dosage Form	300 mg tablet for oral suspension
Route of Administration	Oral
Sponsor	Global Blood Therapeutics, Inc.
OCP Reviewers	Lin Zhou, Ph.D., Ye Yuan, Ph.D. (Pharmacometrics), Jianghong Fan, Ph.D (PBPK).
OCP Team Leaders	Sudharshan Hariharan, Ph.D., Liang Li, Ph.D. (Pharmacometrics), Xinyuan Zhang, Ph.D. (PBPK)
OCP Division	Division of Cardiometabolic and Endocrine Pharmacology (DCEP)
OND Division	OND/OCHEN/DNH

1. RECOMMENDATION

The review team finds this efficacy supplement approvable from a clinical pharmacology perspective. The team recommends edits to the label which are agreed upon by the Applicant.

2. BACKGROUND

Oxbrytal® (voxelotor) oral tablets, 500 mg, was granted accelerated approval for the treatment of sickle cell disease (SCD) in adults and pediatric patients 12 years of age and older on 11/25/2019. In this efficacy supplement to NDA 213137, the Applicant seeks an extension of the accelerated approval of Oxbryta to lower the indicated age limit from ≥ 12 to ≥ 4 years in pediatric patients with SCD based on data from an ongoing Phase 2a clinical study GBT440-007 in pediatric patients with SCD. The Applicant also proposes to include the following clinical pharmacology related information in the USPI:

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

The quality-related information for the new, age-appropriate dispersible tablet dosage form is provided in a separate Type 3 NDA (NDA 216157), which was submitted on the same date as this efficacy supplement and will be reviewed by CMC review team.

3. KEY REVIEW TOPICS

3.1. Weight-based Dosing for Pediatric Patients with SCD 4-11 years

The request to lower the indicated age for Oxbryta down to ≥ 4 years was mainly supported by data on 38 pediatric patients aged 4 to 11 years who received voxelotor treatment in Study GBT 440-007, Part C.

Study GBT440-007 is an ongoing Phase 2a open-label, single and multiple dose study of voxelotor in pediatric patients with SCD. Part C of this study evaluates the efficacy, safety, tolerability, and PK of multiple doses of voxelotor 1500 mg (via 5 × 300 mg oral dispersible tablets) for pediatric patients aged 12 to 17 years or weight-based dosing (Table 1) for pediatric patients aged 4 to 11 years administered once daily (QD) for up to 48 weeks.

Table 1. Body Weight-based Dosing Regimen for Voxelotor in Pediatric Patients Aged 4 to 11 Years Administered Once Daily in Study GBT440-007 Part C

Population	Voxelotor Doses*
10 to <20 kg	600 mg
20 to <40 kg	900 mg
≥ 40 kg	1500 mg

* Although the protocol stated that the patients can receive either voxelotor as either oral dispersible tablets or powder for oral suspension, as of the data cutoff date for the clinical study report (09/30/2020), all patients only received the 300 mg dispersible tablet.

Sparse PK samples (plasma and whole blood) were collected 15 min to 2 h post-dose on Day 1, pre-dose at week 4, 8, 12, 16, 20, 24, 36, 48/early termination. Whole blood and plasma concentrations of voxelotor were measured using a liquid chromatography–tandem mass spectrometry assay. Hemoglobin (Hb) response, defined as an increase in Hb > 1 g/dL, was summarized descriptively at Week 24.

Population PK analysis was performed to characterize voxelotor PK in plasma and whole blood for the pediatric patients in Part A (6 to 11 years old) and Part C (4 to 17 years old) of GBT440-007, which were summarized in Report GBT-CP-017. A two compartment PK model with first-order absorption and elimination plus allometric scaling on apparent clearance and volume of distribution and a site-of-action effect compartment was used to describe the voxelotor plasma and whole blood PK data. Since bias was identified when introducing covariates, base model was applied to predict the voxelotor exposures in pediatric patients 4 to 11 years and 12 to 17 years with SCD in Study GBT440-007 Part C.

3.1.1. Are exposures in patients aged 4-11 years similar to that in ≥12 years?

Yes. Based on the Applicant's updated population PK analysis, voxelotor PK exposures in plasma and whole blood in patients aged 4-11 years are similar to those in patients 12 years and older (Table 2). Refer to section 4.2 Pharmacometrics review for more details.

Table 2. Comparison of Voxelotor PK Exposures at Steady State in Whole-Blood and Plasma Across Different Age Groups in Studies GBT440-007 and GBT440-031

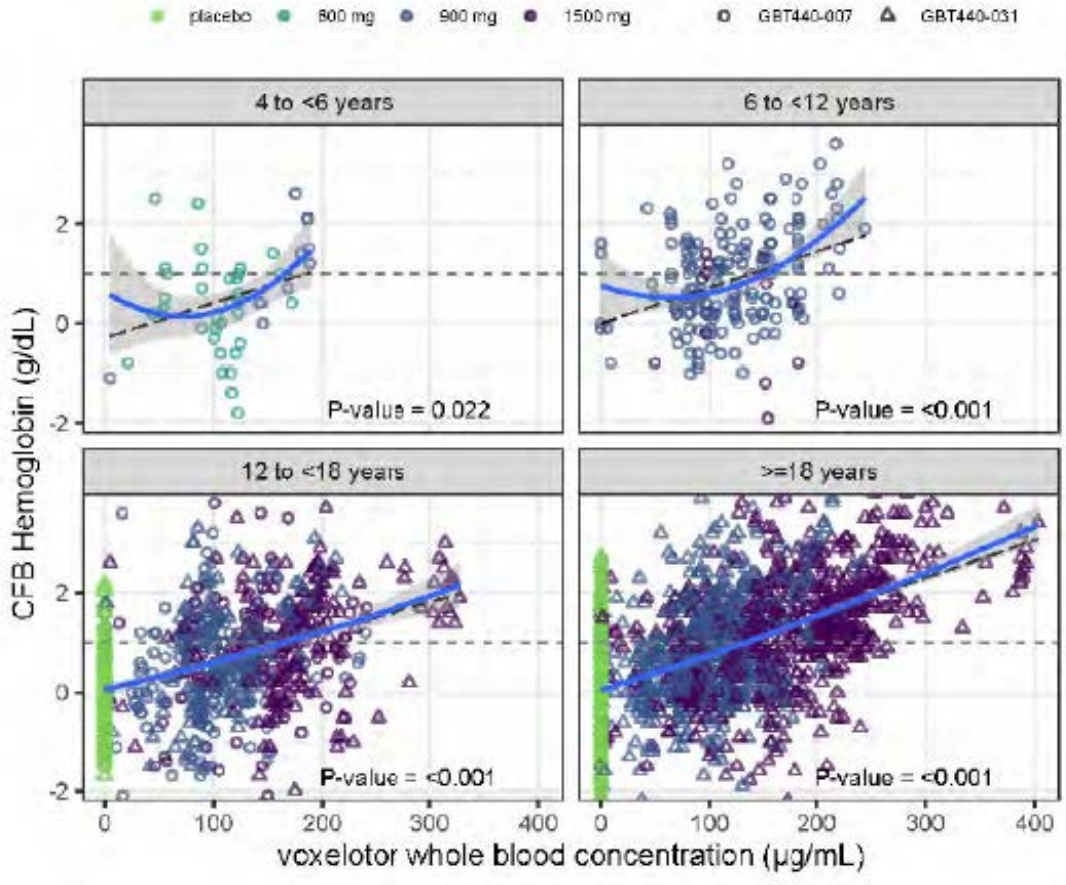
Voxelotor PK Exposures		Study GBT440-007 Part C[1]		Study GBT440-007 A&B + GBT440-031, 1500 mg QD[2]	
		4-11 years [n=38]	12-17 years [n=11]	Adolescent[3] 12-17 years [n=29]	Adult 18 - 59 years [n=68]
Cmax [mcg/mL]	Plasma	10.29 (32.9)	10.84 (27.8)	13.7 (27)	13.7 (24)
	Whole Blood	148.3 (30.2)	133.5 (33.5)	172 (30)	177 (32)
Cmin [mcg/mL]	Plasma	7.709 (40.1)	8.126 (30.2)	8.47 (39)	9.14 (34)
	Whole Blood	117.8 (35)	105.9 (36.6)	122 (38)	132 (40)
AUC [mcg*h/mL]	Plasma	221.8 (34.4)	233 (27.4)	265 (32)	274 (28)
	Whole Blood	3257 (31.2)	2925 (34)	3610 (33)	3780 (35)

Geometric mean (%CV)
[1]: Based on PPK model described in report GBT-CP-017; data source is Table 6; 4-11y BW-based dosing and 12-17y 1500 mg QD
[2]: Based on PPK model described in report GBT-CP-013; data source is Table 10
[3]: GBT440-007 Part A: 12-17y (only cohort 1 included); GBT440-007 Part B: 12-17y; GBT440-031: 12-17y
Source: Study Report GBT-CP-017 Table 6 and Study Report GBT-CP-013 Table 10

3.1.2. Are the exposure-response (E-R) analyses for both efficacy and safety acceptable to support the Applicant's proposed body weight-based dosing regimen for voxelotor in patients aged 4 to 11 years?

Yes. The Applicant's E-R analysis for efficacy suggested a linear relationship ($p < 0.001$) between Hb change from baseline (CFB) and time-matched whole blood voxelotor concentrations. Refer to 4.2.2 E-R Analysis for Efficacy for more information. Subgroup analysis showed similar trend in E-R relationship for Hb CFB (Figure 1) across different age groups (4 to <6 years, 6 to <12 years, 12 to <18 years, and ≥18 years). The Applicant stated that the slope of the E-R relationship appears slightly lower in pediatric patients 4 to <6 years compared to other age groups. However, the reviewer's independent analysis indicated the difference in slope was minor (4-<6 years: 0.00703 [95% CI: 0.00068 - 0.01337] vs. overall: 0.00738 [95% CI: 0.00687 - 0.00789]) and may be due to limited sample size (n=9) in this age group. Overall, these analyses suggested the E-R relationship for Hb CFB is comparable between pediatric patients 4 to 11 years and patients 12 years and older, which further supports the Applicant's proposed body weight-based dosing regimen for voxelotor in patients aged 4 to 11 years.

Figure 1. CFB Hb Versus Time-Matched Voxelotor Whole Blood Concentration Facetted by Age



Source: Study Report GBT-CP-018 Figure 2

The Applicant's E-R analyses for safety were performed for both SCD-related AEs (e.g., VOCs, acute chest syndrome [ACS], and pneumonia) and non-SCD-related AEs (e.g., arthralgia, back pain, abdominal pain, headache, diarrhea, nausea, fatigue, pyrexia, rash, increased ALT, and decreased WBC). Similar to the previous analysis in the original NDA submission, there was no significant E-R relationship for the evaluated safety measures, except decreased WBC. The Applicant identified a positive E-R relationship for Grade ≥1 decreased WBC. The reviewer's multivariate analysis showed age was not a significant covariate, demonstrating comparable E-R for Grade ≥ 1 decreased WBC between patients 4 - 11 years and patients ≥12 years. Overall, the E-R relationships for safety measures were comparable between patients 4 - 11 years and patients ≥12 years. Refer to 4.2.3 E-R Analysis for Safety for more information.

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

3.2 Labeling Updates based on Population PK Analyses

3.2.1 Are the Applicant's updated population PK analyses acceptable to inform the labeling change in Section 12.3 of USPI?

Yes. Based on reviewers' assessment and independent analyses, the Applicant's updated population PK analyses (Report GBT-CP-013 and Report GBT-CP-017) generally described the voxelotor PK in plasma and whole blood in adults and pediatric patients aged 4 - 17 years. Refer to 4.2.1 Summary of Applicant's Population PK Analysis for more information. Therefore, the Applicant's population PK analyses are acceptable to support the following labeling changes in Section 12.3 of USPI.

3.3. Labeling Changes regarding DDI Based on Dedicated DDI Study with Itraconazole and updated PBPK Modeling and Simulation

At the time of the original NDA submission, the evaluation of the effect of a CYP3A4 modulator on the PK of voxelotor was conducted by physiologically based pharmacokinetic (PBPK) analysis which was developed based on voxelotor ADME (absorption, distribution, metabolism, and excretion) properties, the in vitro chemical inhibition study, in vitro phenotyping study, human mass balance study, single-dose and multiple-dose PK studies in human. The contribution of CYP3A4 to the total metabolism of voxelotor was estimated to be in the range of 27% to 56%. Therefore, the current USPI includes the following recommendations regarding concomitant administration with a CYP3A modulator.

- Strong CYP3A4 inhibitors or fluconazole: avoid concomitant use; if unavoidable, reduce the dose of voxelotor to 1000 mg once daily
- Strong or moderate CYP3A4 inducers: avoid concomitant use; if unavoidable, increase the dose of voxelotor to 2500 mg once daily

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

The model predicted rifampin (600 mg QD, a strong CYP3A inducer) and efavirenz (a moderate CYP3A inducer) to decrease voxelotor AUC by approximately 32%-40%, and 21%-28%, respectively, at steady state which only considered CYP3A4 induction. Additional simulations were conducted by considering the induction potential towards CYP2C9, CYP2C19 and CYP2B6 for rifampin, and CYP2C9 and CYP2B6 for efavirenz. These simulations suggests that voxelotor doses of 2500 mg with rifampin and 2000 mg with efavirenz would provide similar exposure compared to when voxelotor is administered alone. Refer to Appendix 4.3 PBPK review for additional details and simulation strategy. Therefore, the recommended voxelotor doses are 2500 mg with a strong CYP3A4 inducer and 2000 mg with a moderate CYP3A4 inducer, respectively, if unavoidable.

The Applicant's PBPK analysis is inadequate to evaluate the effect of fluconazole (a moderate CYP3A4, CYP2C9 and strong CYP2C19 inhibitor), and fluvoxamine (a moderate CYP3A4, strong CYP2C19 inhibitor and weak CYP2C9 inhibitor) on the PK of voxelotor because contribution of the non-CYP3A pathways to the voxelotor metabolism has not been validated. However, the DDI potential

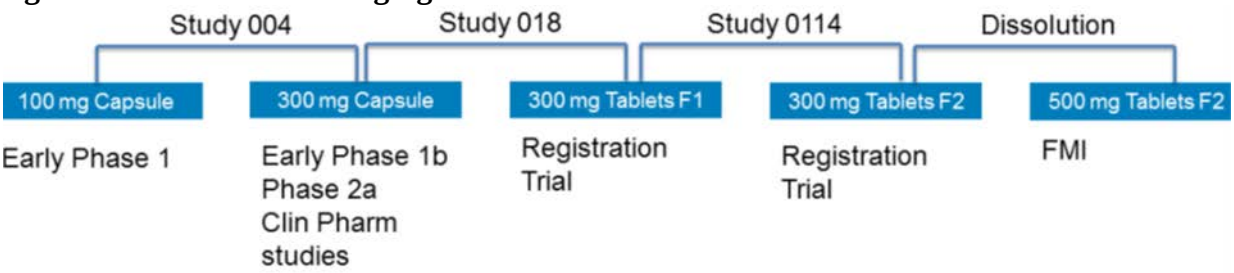
of voxelotor as a victim of any individual CYP2C9 or CYP2C19 inhibitor is expected to be low assuming a similar rank order of non-CYP3A enzymes in the metabolism of voxelotor as observed in the in vitro phenotyping study.

More details on the PBPK analysis can be found in Appendix 4.3.

3.4. Bridge between the Dispersible Tablet and the Approved Tablet

During the clinical development program of voxelotor, different strength and dosage forms were developed (as shown in Figure 2). The voxelotor tablet formulations F1 and F2 (300 mg strength) were developed for the registration trial GBT440-031. The 500-mg F2 tablet formulation was the to-be-marketed formulation when the original NDA for voxelotor was approved. The geometric mean ratio (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.

Figure 2. Formulation bridging studies for NDA 213137



Source: page 93/259 of the multidiscipline review for NDA 213137

The Applicant conducted a relative bioavailability study (Study 0113) to demonstrate that the dispersible tablet (900 mg) is bioequivalent to the F1 tablet (300 mg) (Table 3). While the 90% CIs of the GMR of Cmax passed BE criteria, the lower 90% CI of the GMR of AUCt and AUCinf was 0.795 and 0.798, respectively. The Cmax, AUCt, and AUCinf were all approximately 10% lower for voxelotor when administered as a single 900-mg dispersible tablet compared to 3 × 300-mg tablets.

Table 3. Statistical Analysis of Whole Blood Voxelotor Pharmacokinetic Data in Study 0113

Comparison		PK Parameter	No. of Subjects		Geometric LS Mean		Ratio of Geometric LS Mean (Test/Reference)	90% CI
Test	Reference		Test	Reference	Test	Reference		
900 mg Dispersible tablet	3 × 300 mg F1 tablets	C_{max} (µg/mL)	19	20	37.0	40.8	0.909	0.821, 1.005
		AUC_t (µg•h/mL)	19	20	4632	5179	0.894	0.795, 1.006
		AUC_∞ (µg•h/mL)	19	20	4694	5221	0.899	0.798, 1.012

Source: Adapted from Table 11.2 of Study 0113 CSR.

The 10% lower overall exposure following administration of the voxelotor dispersible tablet is not expected to have any clinical relevance.

In addition, for this efficacy supplement, the sponsor is seeking approval of the 300-mg dispersible tablets because only the 300-mg dispersible tablets were tested in Study 007 (Part C, 4-17 yrs old), the pivotal study in pediatric patients with sickle cell disease. Although Study 0113 tested the 900-mg

dispersible tablet strength, not the 300-mg, the 300-mg dispersible tablet and the 900-mg dispersible tablet strengths are adequately bridged because they are compositionally proportional and have comparable dissolution profiles.

The Applicant also provided data from Study 0114 to support the bioequivalence between the F2 tablet (900 mg) and the F1 tablet (300 mg) (Table 4). The Cmax, AUCt, and AUCinf were all similar for voxelotor when administered as a single 900-mg F2 ablet compared to 3 × 300-mg F1 tablets. Study 0114 was reviewed during the original NDA and found to be acceptable.

Table 4. Statistical Analysis of Whole Blood Voxelotor Pharmacokinetics Data in Study 0114

		Geometric LS Mean		Ratio of Geometric LS Means (Test to Ref)	90% CI for Geometric LS Mean Ratio (Test to Ref)
PK Parameter	Comparison	Test	Ref		
C_{max} (µg/mL)	A (Test) vs B (Ref)	47.2	47.0	1.004	(0.863, 1.167)
AUC_t (h*µg/mL)	A (Test) vs B (Ref)	5640	5463	1.032	(0.882, 1.208)
AUC_{inf} (h*µg/mL)	A (Test) vs B (Ref)	5706	5520	1.034	(0.885, 1.208)

A: 1 X 900 mg tablet of F2 (same formulation as the marketed tablet); B: 3 x 300 mg tablets of F1
Source: Table 11.2 of Study 0114 CSR.

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

4. APPENDICES

4.1. Bioanalytical Assay

Validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) methods used for the determination of voxelotor in human whole blood and human plasma were initially described in NDA 213137 SN0003 26 June 2019, Module 2.7.1, and were found to be acceptable during the original NDA review cycle. The same methods were used to determine voxelotor concentration in human whole blood and plasma for studies supporting this efficacy supplement. In addition, a method to measure itraconazole in human plasma was validated and implemented for analysis of samples from the DDI Study GBT440-0118.

Bioanalytical reports for the biopharmaceutic Studies GBT440-0113, drug-drug interaction Study GBT440-0118, and Phase 3 Study GBT440-031 were provided in Module 5.3.1.4. of NDA 213137 SN0070 25 June 2021. Study GBT440-007 is an ongoing study; the bioanalytical report for Study GBT440-007 Part A, B, and C were submitted on SN0080 (06 August 2021) and SN0082 (19 August 2021).

The validation parameters and performance of the methods used for the determination of voxelotor in human whole blood and plasma are summarized in Table 5 and Table 6. The validation parameters and performance of the methods used for the determination of itraconazole in human plasma in summarized in Table 7.

Table 5. Summary of Assay Validations and Performance for Voxelotor in Human Whole Blood

Method Description	Human K2-EDTA whole blood (50 µL) containing voxelotor and the internal standard GBT1592 (voxelotor-D7) was extracted using liquid-liquid extraction and analyzed by a Sciex API 4000 LC-MS/MS equipped with an HPLC column. The peak area of the m/z 338.1 → 158.1 voxelotor product ion was measured against the peak area of the m/z 345.1 → 159.1 GBT1592 (voxelotor-D7) internal standard product ion
Range of quantitation	120 to 300,000 pg/mL
Stability	7 days in human whole blood at room temperature (22°C) and 4°C; 4 cycles in whole blood at -20°C; 1183 days in whole blood at -20°C and at -70°C.
Performance in Individual Studies	Study 0113: 6 of 7 runs (86%) met the run acceptance criteria. Out of the 58 samples re-analyzed, 100% met the pre-specified criteria. Study 0118: 12 of 12 runs (100%) met the run acceptance criteria. Out of the 94 samples re-analyzed, 90 samples (95.7%) met the pre-specified criteria. Study 031: 32 of 32runs (100%) met the run acceptance criteria. Out of the 179 samples re-analyzed, 176 samples (98.3%) met the pre-specified criteria. Study 007 Part A&B: 17 of 17 runs (100%) met the run acceptance criteria. Out of the 61 samples re-analyzed, 59 samples (96.7%) met the pre-specified criteria. Study 007 Part C: 9 of 10 runs (100%) met the run acceptance criteria. Out of the 37 samples re-analyzed, 29 samples (78.4%) met the pre-specified criteria. For all aforementioned studies, the long-term storage stability covered corresponding sample storage periods.

Source: Table 13 of Summary of Biopharmaceutical and Associated Analytical Methods

Table 6. Summary of Assay Validations and Performance for Voxelotor in Human Plasma

Method Description	Human K2-EDTA plasma (50 µL) containing voxelotor and the internal standard GBT1592 (voxelotor-D7) was extracted using liquid-liquid extraction and analyzed by a Sciex API 4000 LC-MS/MS equipped with an HPLC column. The peak area of the m/z 338.1 → 158.1 voxelotor product ion was measured against the peak area of the m/z 345.2 → 159.1 GBT1592 (voxelotor-D7) internal standard product ion.
Range of quantitation	6.00 to 15,000 ng/mL
Stability	7 days in human plasma at room temperature (22°C); 5 cycles in plasma at -20°C; 1151 days in plasma at -20°C and at -70°C.
Performance in Individual Studies	Study 0118: 12 of 12 runs (100%) met the run acceptance criteria. Out of the 94 samples re-analyzed, 94 samples (100%) met the pre-specified criteria.

	Study 031: 31 of 37 runs (84%) met the run acceptance criteria. Out of the 181 samples re-analyzed, 178 samples (98.3%) met the pre-specified criteria. Study 007 Part A&B: 17 of 17 runs (100%) met the run acceptance criteria. Out of the 52 samples re-analyzed, 52 samples (100%) met the pre-specified criteria. Study 007 Part C: 11 of 11 runs (100%) met the run acceptance criteria. Out of the 43 samples re-analyzed, 43 samples (100%) met the pre-specified criteria. For all aforementioned studies, the long-term storage stability covered corresponding sample storage periods.

Source: Table 14 of Summary of Biopharmaceutical and Associated Analytical Methods

Table 7.Summary of Assay Validations and Performance for Itraconazole in Human Plasma

Method Description	Human sodium heparin plasma (100 µL) containing itraconazole and the internal standard, itraconazole-D9, was extracted by liquid-liquid extraction. Following sample processing, an aliquot of the extract was injected onto a Sciex API 4000 LC-MS/MS equipped with an HPLC column. The peak area of the m/z 705→392 itraconazole product ion was measured against the peak area of the m/z 714→401 itraconazole-D9 internal standards product ion.
Range of quantitation	2.00 to 1000 ng/mL
Stability	24 hours in human plasma at room temperature (22°C); 5 cycles in plasma at -20°C; 48 days in plasma at -20°C and 85 days in plasma at -70°C.
Performance in Individual Studies	Study 0118: 3 of 3 runs (100%) met the run acceptance criteria. Out of the 20 samples re-analyzed, 20 samples (100%) met the pre-specified criteria. The long-term storage stability covered corresponding sample storage periods.

Source: Table 15 of Summary of Biopharmaceutical and Associated Analytical Methods

4.2. Pharmacometrics review

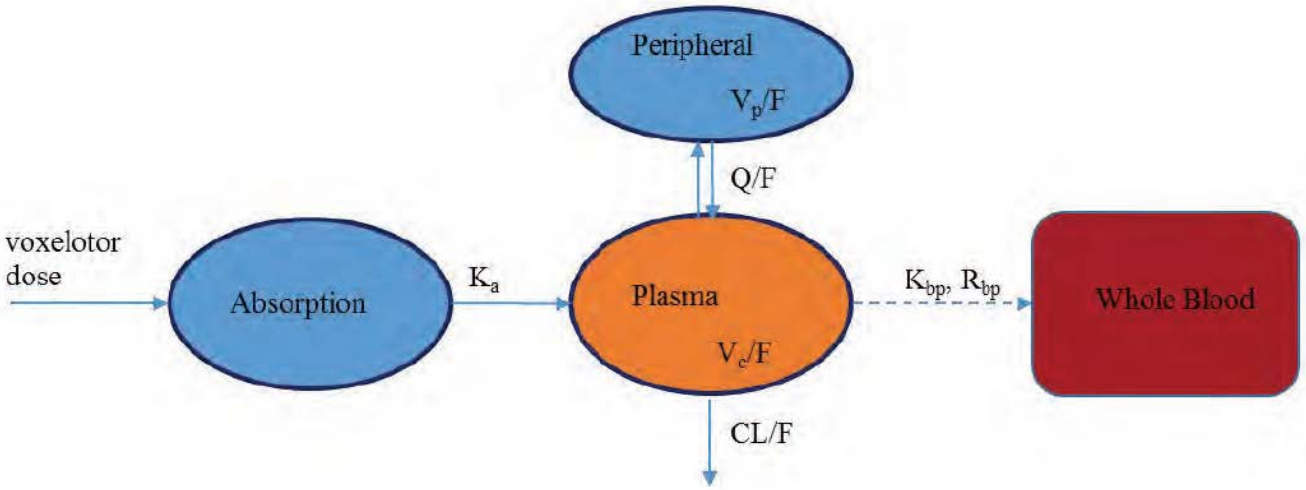
4.2.1 Summary of Applicant's Population PK Analysis

A previous PPK analysis (Study Report GBT-CP-013) was submitted on 9/25/2020 as a part to fulfill the PMR 3746-2 entitled "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".

The PPK analysis was conducted based on 2266 plasma PK observations and 2279 whole blood PK observations from 267 PK-evaluable patients in Study GBT440-031 with at least 72 weeks of study data, all available PPK data from patients with SCD in Study GBT440-001, and data from Part A and Part B of Study GBT440-007. The PPK model was a joint model describing the PPK of voxelotor in plasma and whole blood based on data from adult and adolescent patients with SCD. The joint model described voxelotor plasma PK as a two-compartment model with first-order absorption and first-order

elimination. Voxelotor whole blood PK was modeled as an effect compartment model with a rate constant (Kbp) describing the observed delay between plasma and whole blood concentrations, and a ratio (Rbp) describing the voxelotor concentration in whole blood relative to plasma. The model structure is summarized in Figure 3.

Figure 3. Population PK Model Structure



CL/F = apparent clearance, K_a = absorption rate constant, K_{bp} = rate constant for transfer between plasma and whole blood, Q/F = apparent inter compartmental clearance, R_{bp} = ratio of blood to plasma concentration, V_p/F = apparent volume of the peripheral compartment, V_c/F = apparent volume of the central compartment

Source: Study Report GBT-CP-013 Figure 1

The PK parameter estimates of the final model are list in Table 8.The statistically significant covariates include blood volume on apparent volume of distribution (Vc/F), CYP3A4 inducer on apparent central clearance (CL/F), and hematocrit and nominal dose on ratio of whole blood concentration over plasma concentration. With concomitant use of a weak CYP3A4 inducer, CL/F increased 47% from 6.14 L/hr to 9.05 L/hr. Age, sex, food intake, renal function as well as concomitant use of HU had no clinically significant impact on exposure.

Table 8 Final Model Parameter Estimates in Study Report GBT-CP-013

Parameter	Description	Estimate [a]	RSE (%)	95% CI [b]	Shrinkage
THETA1	CL/F (L/hr)	6.14	2.77	(5.56 - 6.78)	NA
THETA2	Vc/F (L)	333	0.520	(314 - 353)	NA
THETA4	Q/F (L/hr)	0.388	1.93	(0.374 - 0.402)	NA
THETA5	Vp/F (L)	72.3	0.811	(67.5 - 77.3)	NA
THETA6	K_{bp} (1/hr)	0.427	6.56	(0.382 - 0.476)	NA
THETA7	R_{bp}	16.6	0.487	(16.2 - 17.1)	NA
THETA8	KA (1/hr)	2.38	FIXED	FIXED	NA
THETA9	Blood volume on Vc/F, $(BLV/3.89)^{TH}$	0.738	14.1	(0.534 - 0.942)	NA
THETA10	Hematocrit on R_{bp}, $(HCT/27.8)^{TH}$	0.765	8.55	(0.637 - 0.894)	NA
THETA11	CYP3A4 inducer on CL/F, exp(TH)	0.388	4.90	(0.351 - 0.425)	NA
THETA12	Nominal dose on R_{bp}, $(dose/900)^{TH}$	-0.370	10.8	(-0.449 - -0.292)	NA
OMEGA(1,1)	BSV CL/F, %CV	34.1	5.32	(0.0919 - 0.14)	10.4
OMEGA(1,2)	CL-Vc BSV Correlation	10.0	123	(-0.0105 - 0.0253)	NA
OMEGA(2,2)	BSV Vc/F, %CV	21.7	7.65	(0.0331 - 0.0614)	31.5
OMEGA(6,6)	BSV K_{bp}, %CV	43.8	10.4	(0.114 - 0.270)	43.4
OMEGA(6,7)	K_{bp}-R_{bp} BSV Correlation	-10.2	124	(-0.0233 - 0.00966)	NA
OMEGA(7,7)	BSV R_{bp}, %CV	15.2	7.60	(0.0162 - 0.0299)	21.3
OMEGA(9,9)	BOV on CL/F, %CV	56.3	3.60	(0.272 - 0.362)	28.5 [c]
SIGMA(1,1)	Proportional error, plasma (%)	24.0	2.09	(0.0530 - 0.0624)	NA
SIGMA(3,3)	Proportional error, whole blood (%)	17.0	3.21	(0.0251 - 0.0324)	NA
SIGMA(4,4)	Additive error, whole blood (ng/mL)	880	12.5	(3.95e5 - 1.15e6)	NA

[a] Estimates for CL/F, Vc/F, Q/F, Vp/F, K_{bp}, R_{bp}, and Ka are reported as exp(TH). Parameters were estimated as MU referenced variables [5]. The relative standard errors (RSE) are reported on the theta estimate. The %CV for omega is calculated as 100*sqrt(omega).

[b] The RSEs 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) and for sigmas are reported based on the parameter estimate of omega or sigma.

[c] The shrinkage is the median of the thirteen defined occasions. The individual estimates ranged from 6.07% at Week 72 to 40.6% on Day 25. The Day 25 occasion, which was limited to 29 plasma and 29 whole blood observations in study GBT440-001 subjects.

BOV = between occasion variability, BSV = between subject variability, CL/F = apparent clearance, K_{bp} = rate transfer constant from plasma to whole blood, R_{bp} = 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 rate constant, %CV = percentage of coefficient of variance, RSE = relative standard error, CI = confidence interval, THETA = typical population value of parameter, OMEGA = inter-individual variability, NA = not applicable

Note: All continuous covariate effects in the model were parameterized as power functions, e.g., $P = \theta_k \cdot ((X_i/M(X_i))^{\theta_j})$, 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 subject 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: Study Report GBT-CP-013 Table 9

In the current submission (Study Report GBT-CP-017), data from patients in Study GBT440-007 were updated to include all available study data from Part A, B and C of the study, as a cutoff date of 30 September 2020. Additional data from Study GBT440-007 Part C included 158 plasma PK observations and 173 whole blood PK observations from 49 pediatric patients aged 4 - 17 years who were administered voxelotor as dispersible tablets once daily. The previous joint model in Study Report GBT-CP-013 was re-estimated with the updated dataset. The joint model was further improved by incorporating the study effect of Part C on Ka, fixing the exponents the standard allometric scaling values of 0.75 for CL/F and 1.0 for Vc/F. Model parameter estimates of the base model are provided in Table 9. Covariate analysis identified additional significant covariates, including study effect of Part C on Kbp and Rbp, effects of blood volume (BLV) on Kbp. The parameter estimates of the final model are provided in Table 10.

Table 9 Parameter Estimates of Base Model in Study Report GBT-CP-017

Variable	Parameter	Estimate [a]	RSE (%)	Fixed?
THETA1	CL (L/hr)	6.913	NA	TRUE

Variable	Parameter	Estimate [a]	RSE (%)	Fixed?
THETA2	V2 (L)	332.7	NA	TRUE
THETA3	Ka (1/hr)	2.305	NA	TRUE
THETA4	Q (L/hr)	0.3824	NA	TRUE
THETA5	V3 (L)	73.08	NA	TRUE
THETA6	Kbp	0.4271	NA	FALSE
THETA7	Rbp	17.01	NA	FALSE
THETA8	Blood volume on Vc/F, $(BLV/3.89)^{TH}$	1	NA	TRUE
THETA9	Hematocrit on R_{bp}, $(HCT/27.8)^{TH}$	0.7974	NA	FALSE
THETA10	CYP3A4 inducer on CL/F, exp(TH)	0.3881	NA	TRUE
THETA11	Nominal dose on R_{bp}, $(dose/900)^{TH}$	-0.2593	NA	FALSE
THETA12	Blood volume on CL/F, $(BLV/3.89)^{TH}$	0.75	NA	TRUE
THETA13	007C Study effect on Ka, $\exp(TH_{Ka} + TH_{13})$	-2.46	NA	TRUE
OMEGA(1,1)	etaCL (%CV)	34.1	NA	TRUE
OMEGA(2,1)	corrCL-V2	17.9	NA	TRUE
OMEGA(2,2)	etaV2 (%CV)	22.2	NA	TRUE
OMEGA(3,3)	etaKA (%CV)	120	NA	TRUE
OMEGA(6,6)	etaKbp (%CV)	32.2	NA	FALSE
OMEGA(7,6)	corrKbp-Rbp	-46.9	NA	FALSE
OMEGA(7,7)	etaRbp (%CV)	17.1	NA	FALSE
OMEGA(8,8)	BOV on CL/F (%CV)	57.5	NA	TRUE
SIGMA(1,1)	Plasma Proportional Error (%CV)	0.237	NA	FALSE
SIGMA(3,3)	Whole Blood Proportional Error (%CV)	0.151	NA	FALSE
SIGMA(4,4)	Whole Blood Additive Error (ng/mL)	1118	NA	FALSE

[a] Estimates for CL/F, Vc/F, Q/F, Vp/F, K_{bp}, R_{bp}, and Ka are reported as exp(TH). Parameters were estimated as MU referenced variables. The relative standard errors (RSE) are reported on the theta estimate. The %CV for omega is calculated as 100*sqrt(omega).

[b] The RSEs 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) and for sigmas are reported based on the parameter estimate of omega or sigma.

BOV = between occasion variability, BSV = between subject variability, CL/F = apparent clearance, K_{bp} = rate transfer constant from plasma to whole blood, R_{bp} = 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 rate constant, %CV = percentage of coefficient of variance, RSE = relative standard error, CI = confidence interval, THETA = typical population value of parameter, OMEGA = inter-individual variability, NA = not applicable

Note: All continuous covariate effects in the model were parameterized as power functions, e.g., $P = \theta_k \cdot ((X_i/M(X_i))^{\theta_j})$, 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 subject 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: Study Report GBT-CP-017 Appendix 9.5

Table 10 Parameter Estimates of Final Model in Study Report GBT-CP-017

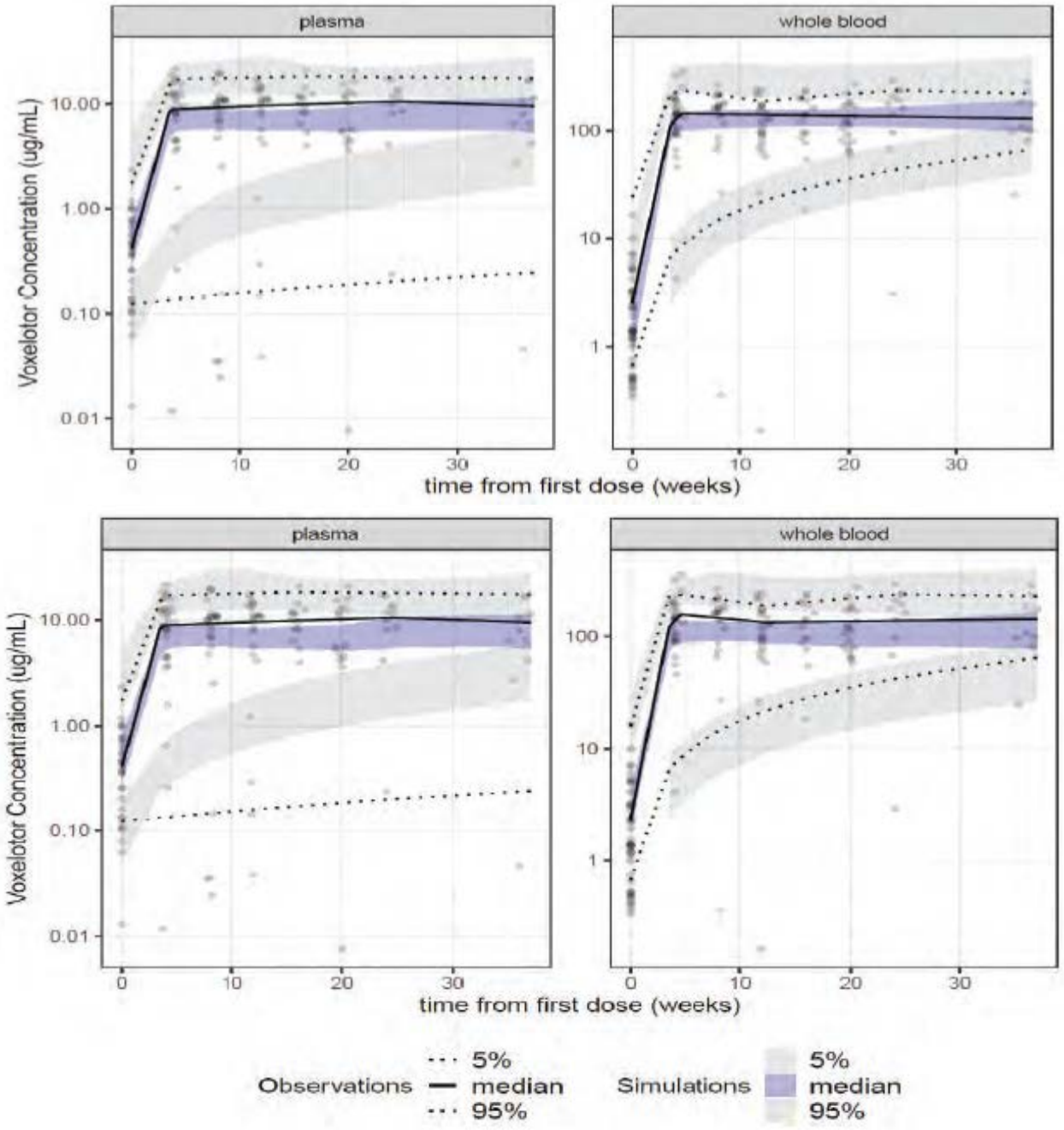
Variable	Parameter	Estimate	RSE (%)	Fixed?
THETA1	CL (L/hr)	6.913	NA	TRUE
THETA2	V2 (L)	332.7	NA	TRUE
THETA3	Ka (1/hr)	2.305	NA	TRUE
THETA4	Q (L/hr)	0.3824	NA	TRUE
THETA5	V3 (L)	73.08	NA	TRUE
THETA6	Kbp	0.3825	6.40	FALSE
THETA7	Rbp	17.77	0.618	FALSE
THETA8	Blood volume on Vc/F, $(BLV/3.89)^{TH}$	1	NA	TRUE
THETA9	Hematocrit on R_{bp}, $(HCT/27.8)^{TH}$	0.87436	6.95	FALSE
THETA10	CYP3A4 inducer on CL/F, exp(TH)	0.38808	NA	TRUE
THETA11	Nominal dose on R_{bp}, $(dose/900)^{TH}$	-0.22037	17.6	FALSE
THETA12	Blood volume on CL/F, $(BLV/3.89)^{TH}$	0.75	NA	TRUE
THETA13	KA007C	-2.4599	NA	TRUE
THETA14	RBPBLV	0	NA	TRUE
THETA15	RBP007C	-0.21194	18.2	FALSE
THETA16	KBPBLV	0.35134	9.97	FALSE
THETA17	KBP007C	1.9887	4.76	FALSE
OMEGA(1,1)	etaCL	34.1	NA	TRUE
OMEGA(2,1)	corrCL-V2	17.9	NA	TRUE
OMEGA(2,2)	etaV2	22.2	NA	TRUE
OMEGA(3,3)	etaKA	120	NA	TRUE
OMEGA(4,4)	etaQ	3.16	NA	TRUE
OMEGA(5,5)	etaV3	3.16	NA	TRUE
OMEGA(6,6)	etaKbp	19.7	73.3	FALSE
OMEGA(7,6)	corrKbp-Rbp	-35.4	114	FALSE
OMEGA(7,7)	etaRbp	14.7	14.9	FALSE
OMEGA(8,8)	BOV on CL/F	57.5	NA	TRUE
SIGMA(1,1)	Plasma Proportional Error (%CV)	0.23412	0.102	FALSE
SIGMA(3,3)	Whole Blood Proportional Error (%CV)	0.15836	0.0419	FALSE
SIGMA(4,4)	Whole Blood Additive Error (ng/mL)	799.54	0.343	FALSE

Source: Study Report GBT-CP-017 Appendix 9.9

The pcVPC for the base model and the final covariate model are shown in Figure 4. The pcVPC

for the final covariate model shows that the model under predicts the observed whole blood data in Part C (right, lower panel), while the median of the observed data falls well within the median prediction interval for the base model. The plasma data are slightly under predicted in both models, potentially due to the fixed allometric scaling on CL/F and Vc/F.

Figure 4. PcVPC for the Base Model (Upper Panel) and the Final Model (Lower Panel)



Source: Study Report GBT-CP-017 Figure 5

Due to the under predicted whole blood concentration in the final model, the base model was selected for simulating exposures in subjects with SCD from Study GBT440-007 Part C. Voxelotor exposures in plasma and whole blood were predicted following a single nominal dose at steady-state for patients

in Study GBT440-007 Part C. The geometric mean and range of voxelotor exposures in plasma and whole blood in patients 4 to 11 years old, and 12 to 17 years old from Study GBT440-007 Part C are summarized in Table 11, and compared to that in adolescent and adult patients from Study GBT440-007 Parts A&B and Study GBT440-031.

Table 11. Comparison of Voxelotor PK Exposures at Steady State in Whole-Blood and Plasma Across Different Age Groups in Studies GBT440-007 and GBT440-031.

Voxelotor PK Exposures		Study GBT440-007 Part C[1]		Study GBT440-007 A&B + GBT440-031, 1500 mg QD[2]	
		4-11 years [n=38]	12-17 years [n=11]	Adolescent[3] 12-17 years [n=29]	Adult 18 - 59 years [n=68]
Cmax [mcg/mL]	Plasma	10.29 (32.9)	10.84 (27.8)	13.7 (27)	13.7 (24)
	Whole Blood	148.3 (30.2)	133.5 (33.5)	172 (30)	177 (32)
Cmin [mcg/mL]	Plasma	7.709 (40.1)	8.126 (30.2)	8.47 (39)	9.14 (34)
	Whole Blood	117.8 (35)	105.9 (36.6)	122 (38)	132 (40)
AUC [mcg*h/mL]	Plasma	221.8 (34.4)	233 (27.4)	265 (32)	274 (28)
	Whole Blood	3257 (31.2)	2925 (34)	3610 (33)	3780 (35)

Geometric mean (%CV)
[1]: Based on PPK model described in report GBT-CP-017; data source is Table 6; 4-11y BW-based dosing and 12-17y 1500 mg QD
[2]: Based on PPK model described in report GBT-CP-013; data source is Table 10
[3]: GBT440-007 Part A: 12-17y (only cohort 1 included); GBT440-007 Part B: 12-17y; GBT440-031: 12-17y
Source: Study Report GBT-CP-017 Table 6 and Study Report GBT-CP-013 Table 10

Compared to voxelotor exposures in adults and pediatrics following steady-state dosing at 1500 mg QD in the Study GBT440-031 Week-72 PPK model application, exposures in plasma and whole blood are slightly lower in patients aged 4 to 11 years and patients aged 12 to 17 years in Study GBT440-007 Part C. However, the PK exposures of patients aged 4 to 11 years and patients aged 12 to 17 years in Study GBT440-007 Part C are generally comparable (less than 12% difference in exposures between the two age groups).

Reviewer's comments:
The reviewer reproduced the PPK model analysis described in Study Report GBT-CP-013. The PK parameters estimated by the PPK model have been verified, thus supporting the labeling update in Section 12.3 Pharmacokinetics.

The reviewer also reproduced the base and final PPK analyses described in Study Report GBT-CP-017. The Applicant's population PK model appears adequate to describe the voxelotor PK profiles in plasma and whole blood for pediatric patients in Study GBT440-007 Part C. Since the final covariate model showed evidence of bias introduced with the addition of covariates to the model, the base model was selected to simulate the PK profile for the pediatric patients Study GBT440-007 Part C. The base PK model is generally acceptable to simulate post-hoc voxelotor exposure metrics, e.g., AUCSS, Cmax,SS and Cmin,SS for the E-R analyses for efficacy and safety measurements.

Compared to voxelotor exposures in adults and pediatrics ≥12 years following steady-state dosing at 1500 mg QD in the Study GBT440-031, the exposures in plasma and whole blood were slightly lower for pediatric patients 4 - 17 years in Study GBT440-007 Part C. This could be partly due to the different formulation (dispersible) used in trial Part C. Since the bioequivalence between the dispersible formulation and the marketed formulation was demonstrated in Study GBT440-0113 and Study GBT440-0114, we conclude that voxelotor exposures in patients aged 4-11 years at the proposed body weight-based dosing regimen were comparable to those in patients ≥12 years.

Despite the slightly underprediction of PK in whole blood in Applicant's final covariate model, the reviewer's simulations showed that voxelotor exposures estimated from the Applicant's final PPK model in whole-blood and plasma were generally close to those predicted by base PPK model (Table 11 and Table 12). Similar to base PPK model, the final model predicted PK exposure parameters for pediatric patients 4 to <12 years were comparable to those of patient 12 years and older (Table 11 and Table 12).

Table 12. PK Parameters in Whole-Blood and Plasma Estimated Using Final PPK Model Simulations for Patients in Study GBT440-007 Part C

PK Exposure		4-11y [n=39]	12-17y [n=11]
Cmax [mcg/mL]	Plasma	8.9 (38%)	10.1 (44%)
	Whole Blood	126 (41%)	115 (54%)
Cmin [mcg/mL]	Plasma	6 (47%)	7.5 (55%)
	Whole Blood	85 (51%)	86 (66%)
AUC [mcg*h/mL][4]	Plasma	189 (41%)	218 (48%)
	Whole Blood	2658 (45%)	2481 (58%)

Geometric mean (%CV)
Source: Reviewer's analysis.

4.2.2 Summary of Applicant's E-R Analysis for Efficacy

The full exposure-response (E-R) efficacy analysis dataset comprised 381 patients (110 from GBT440-007 and 271 treated and placebo subjects from GBT440-031). The PK evaluable E-R efficacy analysis dataset comprised 366 patients (109 patients from GBT440-007, and 166 PK evaluable patients and 91

placebo patients from GBT440-031). The 381 patients in the efficacy analysis dataset comprise 156 pediatric patients (110 from GBT440-007 and 46 from GBT440-031) and 225 adults. Median baseline hemoglobin (Hb) was similar in 3 dose groups of GBT440-007 (8.5 g/dL in 600mg group, 8.6 g/dL in 900mg group, and 8.8 in 1500mg group). and the 1500 mg of GBT440-031 (900 mg: 8.3 g/dL and 1500 mg: 8.75 g/dL). The median baseline Hb in placebo patients (8.45 g/dL) of GBT440-031 was the same as the overall median (8.5 g/dL), and the median in the 900 mg dose group (8.3 g/dL) in GBT440-031 was lower than that in the 1500 mg dose group (8.75 g/dL). The key continuous and categorical baseline characteristics for the patients involved in E-R analyses (both efficacy and safety) were shown in Table 8 and Table 9, respectively. There is no substantial imbalance for the baseline characteristics for the patients involved in E-R analysis for efficacy and safety.

Table 13. Key Baseline Continuous Characteristics

	GBT440-007			GBT440-031			Total
Covariate	600 mg (N=22)	900 mg (N=61)	1500 mg (N=27)	Placebo (N=91)	900 mg (N=92)	1500 mg (N=88)	(N=381)
Age (y)							
Median	7.00	10.0	13.0	27.5	23.5	23.5	19.0
(Min-Max)	(4.00-16.0)	(5.00-17.0)	(10.0-17.0)	(12.0-64.0)	(12.0-59.0)	(12.0-59.0)	(4.00-64.0)
Baseline Body Weight (kg)							
Median	19.7	31.4	44.7	61.0	61.5	60.1	56.1
(Min-Max)	(12.3-65.3)	(19.2-93.3)	(29.7-72.3)	(25.4-164)	(28.7-135)	(28.0-112)	(12.3-164)
Missing	0 (0%)	0 (0%)	0 (0%)	1 (1.1%)	0 (0%)	0 (0%)	1 (0.3%)
Baseline Hemoglobin (g/dL)							
Median	8.50	8.60	8.80	8.45	8.30	8.75	8.50
(Min-Max)	(6.66-10.4)	(5.80-12.0)	(6.20-10.5)	(6.00-10.7)	(5.60-11.0)	(5.70-10.9)	(5.60-12.0)
Baseline Hematocrit (%)							
Median	24.4	25.3	26.0	28.5	27.0	28.4	27.1
(Min-Max)	(19.7-32.7)	(16.4-36.0)	(18.2-31.6)	(18.2-38.4)	(18.0-39.8)	(17.9-35.9)	(16.4-39.8)
Baseline Indirect Bilirubin (µmol/L)							
Median	34.2	40.2	25.7	33.4	31.6	29.7	33.3
(Min-Max)	(10.6-176)	(8.72-188)	(11.5-123)	(5.4-259)	(7.2-179)	(8.0-234)	(5.4-259)
Missing	5 (22.7%)	21 (34.4%)	8 (29.6%)	6 (6.6%)	3 (3.3%)	3 (3.4%)	46 (12.1%)
Baseline Lactate Dehydrogenase (U/L)							
Median	558	544	499	381	405	350	426
(Min-Max)	(302-1650)	(220-2710)	(274-1050)	(165-1140)	(172-1220)	(164-813)	(164-2710)
Missing	0 (0%)	0 (0%)	1 (3.7%)	4 (4.3%)	2 (2.2%)	0 (0%)	7 (1.8%)
Baseline Reticulocytes (10^9/L)							
Median	NR	NR	NR	300	303	282	292
(Min-Max)	NR	NR	NR	(57.0-671)	(88.0-654)	(24.0-783)	(24.0-783)
Missing	22 (100%)	61 (100%)	27 (100%)	0 (0%)	0 (0%)	0 (0%)	110 (28.8%)
Baseline Percent Reticulocytes (%)							
Median	9.95	9.87	8.50	10.4	11.3	9.40	9.89
(Min-Max)	(3.17-18.5)	(2.10-26.3)	(2.90-20.3)	(1.40-21.8)	(2.40-23.2)	(1.30-22.1)	(1.30-26.3)
Missing	0 (0%)	2 (3.3%)	2 (7.4%)	3 (3.3%)	2 (2.2%)	1 (1.1%)	10 (2.6%)

Note: Values presented as median (minimum - maximum).
NR = not reported
Source: Study Report GBT-CP-018 Table 4

Table 14. Key Baseline Categorical Characteristics

	GBT440-007			GBT440-031			Total
Category	**600 mg (N=22)**	**900 mg (N=61)**	**1500 mg (N=27)**	**Placebo (N=91)**	**900 mg (N=92)**	**1500 mg (N=88)**	**(N=381)**
Age Group							
4 to <6 years	8 (36.4%)	2 (3.3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	10 (2.6%)
6 to <12 years	7 (31.8%)	33 (54.1%)	2 (7.4%)	0 (0%)	0 (0%)	0 (0%)	42 (11.0%)
12 to <18 years	7 (31.8%)	26 (42.6%)	25 (92.6%)	17 (18.5%)	15 (16.3%)	14 (15.9%)	104 (27.2%)
≥18 years	0 (0%)	0 (0%)	0 (0%)	75 (81.5%)	77 (83.7%)	74 (84.1%)	226 (59.2%)
Sex							
Female	14 (63.6%)	27 (44.3%)	15 (55.6%)	49 (53.3%)	51 (55.4%)	57 (64.8%)	213 (55.8%)
Male	8 (36.4%)	34 (55.7%)	12 (44.4%)	43 (46.7%)	41 (44.6%)	31 (35.2%)	169 (44.2%)
Hydroxyurea Use							
No use	6 (27.3%)	7 (11.5%)	3 (11.1%)	35 (38.0%)	29 (31.5%)	31 (35.2%)	111 (29.1%)
Use	16 (72.7%)	54 (88.5%)	24 (88.9%)	57 (62.0%)	63 (68.5%)	57 (64.8%)	271 (70.9%)
Sickle Cell Disease Genotype							
HbSS	21 (95.5%)	58 (95.1%)	24 (88.9%)	74 (80.4%)	71 (77.2%)	60 (68.2%)	308 (80.6%)
HbSC	0 (0%)	0 (0%)	0 (0%)	2 (2.2%)	2 (2.2%)	3 (3.4%)	7 (1.8%)
HbSβ0	1 (4.5%)	3 (4.9%)	3 (11.1%)	11 (12.0%)	13 (14.1%)	18 (20.5%)	49 (12.8%)
HbSβ+ Thal	0 (0%)	0 (0%)	0 (0%)	3 (3.3%)	2 (2.2%)	6 (6.8%)	11 (2.9%)
Missing/Other	0 (0%)	0 (0%)	0 (0%)	2 (2.2%)	4 (4.3%)	1 (1.1%)	7 (1.8%)
Race							
Black or African American	14 (63.6%)	50 (82.0%)	23 (85.2%)	63 (68.5%)	60 (65.2%)	58 (65.9%)	268 (70.2%)
Arab or Middle Eastern	1 (4.5%)	0 (0%)	0 (0%)	18 (19.6%)	19 (20.7%)	15 (17.0%)	53 (13.9%)
White	7 (31.8%)	11 (18.0%)	4 (14.8%)	3 (3.3%)	6 (6.5%)	6 (6.8%)	37 (9.7%)
Asian	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1.1%)	1 (0.3%)
Other	0 (0%)	0 (0%)	0 (0%)	6 (6.5%)	5 (5.4%)	2 (2.3%)	13 (3.4%)
Multiple	0 (0%)	0 (0%)	0 (0%)	2 (2.2%)	2 (2.2%)	5 (5.7%)	9 (2.4%)
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1.1%)	1 (0.3%)

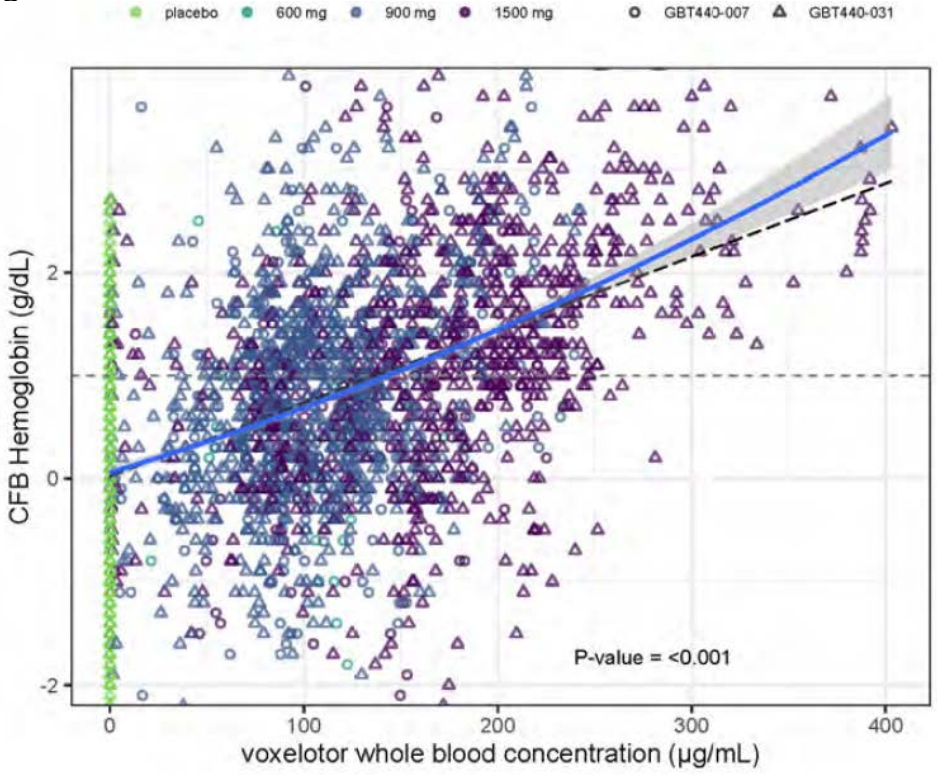
Note: Values presented as N (%).
HbSS = homozygous hemoglobin S, HbSC = hemoglobin sickle cell, HbS β+ thalassemia = the combination of sickle cell mutation and beta-thalassemia (β-thal) mutations, HbS β0 thalassemia = the combination of sickle cell mutation and null beta-thalassemia (β-thal) mutations, NR = not reported

Source: Study Report GBT-CP-018 Table 5

The E-R analysis was conducted for the change from baseline (CFB) Hb (up to week 72 for Study GBT440-031, single dose for Study GBT440-007 Part A, up to week 24 for Study GBT440-007 Part B, up to week 48 for Study GBT440-007 Part C) in placebo and voxelotor treated patients using time-matched model-predicted whole blood voxelotor concentrations (predicted by base PPK model) at all visits post-baseline. Linear regression was performed. Figure 5 shows the relationship between CFB

Hb and time-matched whole blood concentrations. Consistent with the previous analyses (GBT-CP-006 and GBT-CP-014), CFB Hb increases linearly (p<0.001) with increasing whole blood concentration.

Figure 5. CFB Hb Versus Time-Matched Voxelotor Whole Blood Concentration

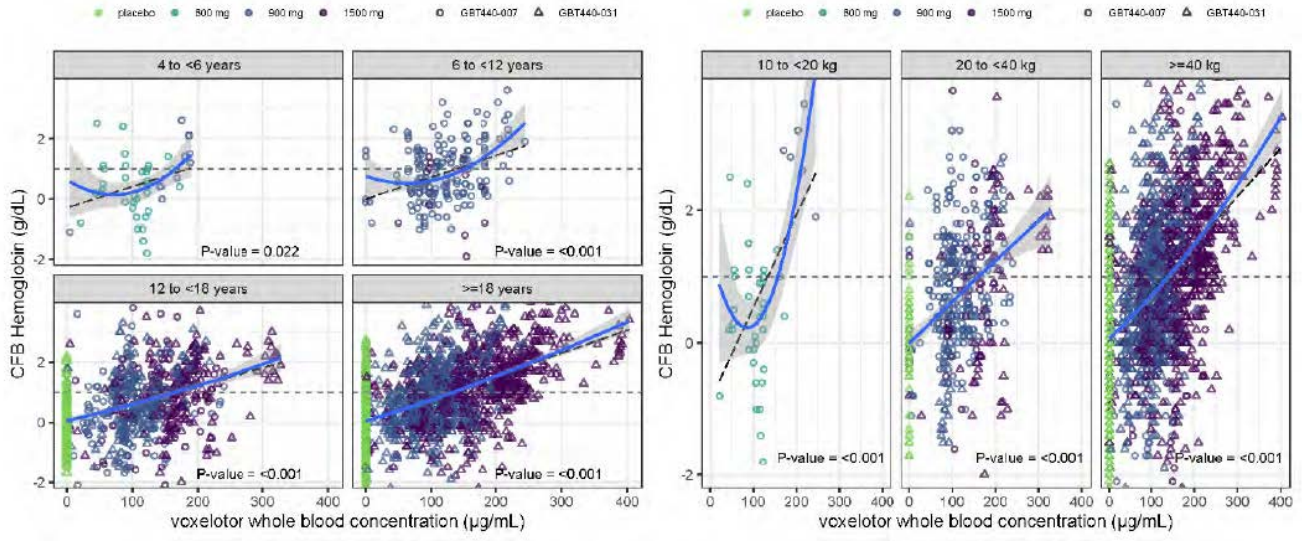


Note: The horizontal gray dashed line indicates the target 1 g/dL increase in Hb. The solid blue line and gray shaded area represent a 2nd degree polynomial regression and 95% confidence interval through the data. The p-value for the polynomial relationship compared to the null model (no relationship) is shown on the plot. The black dashed line is a linear regression line through the data.
CFB = change from baseline, Hb = hemoglobin
Source: pkpd-all-hgb-cp.pdf

Source: Study Report GBT-CP-018 Figure 1

In Figure 6, the data are facetted by patient age group (4 to <6 years, 6 to <12 years, 12 to <18 years, and ≥ 18 years) and by baseline body weight (10 to <20 kg, 20 to <40 kg, and ≥ 40 kg). In each individual plot, the same trends were observed as observed for the data including all subjects and all visits. CFB Hb increases at least linearly (p<0.001) with increasing voxelotor whole blood concentrations. In pediatric patients aged 4 to <6 years, the Applicant claimed that although the slope of the relationship was slightly lower than that in other age groups, the projected CFB Hb still meets the targeted 1 g/dL increase. This may be due to the limited number of patients in this age group (n=9). Relationships with other covariates (not shown) were consistent.

Figure 6. CFB Hb Versus Time-Matched Voxelotor Whole Blood Concentration Facetted by Age and Body Weight



Source: Study Report GBT-CP-018 Figure 12

Reviewer's Comments: The Applicant's E-R analyses for efficacy appear acceptable.

The reviewer performed independent linear regression analysis. The slope of the relationship between CFB Hb and voxelotor concentration using full analysis dataset (beta=0.00738 [95% CI: 0.00687 - 0.00789]) did not change compared to that using dataset removing subjects 4 to <6 years (beta=0.0074 [95% CI: 0.00689 - 0.00791]) and removing both subjects 4 to <6 years and 6 to <12 years (beta=0.00741 [95% CI: 0.00689 - 0.00793]). Also, univariate analysis showed age was not a significant predictor for CFB Hb (p-value=0.98). We confirmed that the slope of the relationship was lower in patients 4 to <6 years than that in other age groups. However, we agree that the difference in slope was minor (4-<6 years: 0.00703 [95% CI: 0.00068 - 0.01337] vs. overall: 0.00738 [95% CI: 0.00687 - 0.00789]) based on our independent analysis.

Based on reviewer's independent analysis and Applicant's analysis, we conclude the E-R relationship for efficacy is comparable between patients aged 4-11 years and ≥12 years.

4.2.3 Summary of Applicant's E-R Analysis for Safety

A total of 358 patients from Studies GBT440-031 and GBT440-007 were included in the E-R analysis for safety. This represents 101 additional patients (or a 39% increase in number of patients) compared to the previous analysis (GBT-CP-014). Due to the small number of patients available for analysis in the 2 pediatric age groups (n=9 for 4 to <6 years and n=35 for 6 to <12 years) and low incidence (<15%) for most endpoints, a subgroup analysis by age group was not performed. The E-R analyses were performed for the most prevalent adverse events in patients aged <12 years, increased ALT [75% incidence] and decreased WBC [27% incidence]. The logistic regression was performed.

Safety endpoints included both SCD-related AEs (e.g., VOCs, acute chest syndrome [ACS], and pneumonia) and non-SCD-related AEs (e.g., pyrexia, headache, and rash). The results for SCD-related

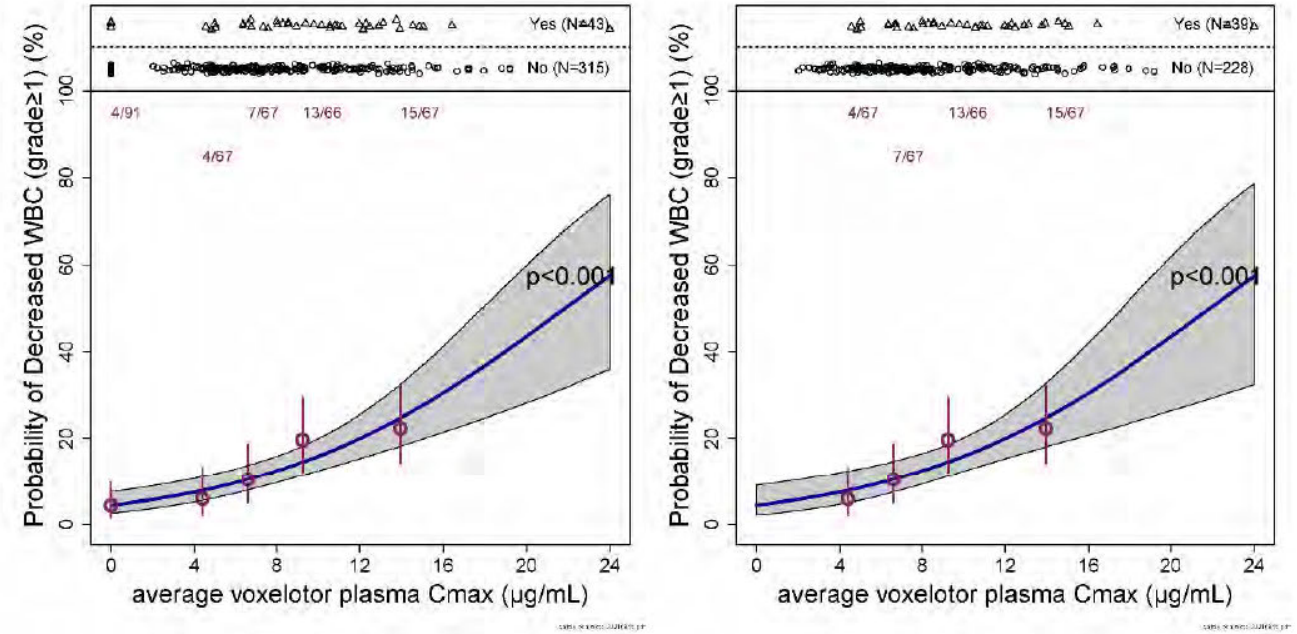
analyses were almost identical to the previous analysis, and no statistically significant relationships were identified with % Hb occupancy at Cmax.

The non-SCD-related safety endpoints included arthralgia, back pain, abdominal pain, headache, diarrhea, nausea, fatigue, pyrexia, rash, increased ALT, and decreased WBC. E-R relationships with voxelotor plasma Cmax were evaluated.

4.2.3.1 Decreased WBC

Figure 7 shows the E-R relationship between the probability of Grade ≥1 decreased WBC and the average voxelotor plasma Cmax for all patients (upper left panel) and for all voxelotor treated patients (upper right panel). The relationship is statistically significant with and without placebo patients. For Grade ≥1 decreased WBC, the treatment effect was also statistically significant compared to the null model (p=0.0118). The observed incidence of Grade ≥1 decreased WBC in 4 to <6 years, 6 to <12 years, 12 to <18 years, and ≥ 18 years age groups was 10% (0.1 to 49%), 32% (17 to 50%), 15% (8.3 to 25%), and 8% (4.5 to 13%), respectively. As in the prior analyses, the total number of Grade ≥2 decreased WBC events (13 events) was small relative to the total number of patients evaluated (358).

Figure 7. Exposure-safety Relationships for Decreased WBC



Note: In the shaded polygon plots, maroon points represent the mean exposure and event incidence in subjects stratified by exposure quartile or for placebo. Vertical maroon bars represent the 90% confidence intervals (CI) on the event incidence. Event numbers in each quartile (subjects with event/total subjects) are displayed above each vertical bar. The solid blue line is the logistic regression model fit. The shaded gray region represents the 5th to 95th CI on the modeled incidence. The p-value for the addition of the slope to the model is indicated on the figure. If p≥0.05, the relationship is not statistically significant. The data points (triangle=event, circle=no event) are shown above the plots. The figure on the left include all subjects including placebo while the figure on the right include only subjects treated with voxelotor.
Source: Study Report GBT-CP-018 Figure 12

No significant E-R relationship was identified for increased ALT, arthralgia, back pain, abdominal pain, headache, diarrhea, nausea, fatigue, pyrexia, or rash.

Reviewer's Comments: The applicant's exposure-response analyses for Grade ≥1 decreased WBC are acceptable. Reviewer's independent analysis showed age was not a significant predictor for Grade ≥ 1 decreased WBC in the studied population. We conclude the E-R for decreased WBC for pediatric patients 4 to <12 years is comparable to that in patients 12 years and older.

4.3. PBPK review

Executive Summary

The objective of this review is to evaluate the adequacy of the Applicant's PBPK report (GBT-CP-012), entitled "Assessment of CYP3A4-mediated DDI liability of voxelotor as a victim in healthy subjects and patients with sickle cell disease" to support the Applicant proposed labeling changes related to the dosing recommendation for voxelotor when co-administrated with CYP modulators.

The Division of Pharmacometrics has reviewed the PBPK report, supporting modeling files, the Applicant's responses to FDA's information requests (IRs) submitted on July 28 and Sep 28, 2021, and the response to labeling information requests submitted on Nov 2 and 16, 2021, and concluded the following:

1. The Applicant's PBPK analysis is adequate to evaluate the effect of a CYP3A inhibitor on the PK of voxelotor. The model predicted ketoconazole (400 mg QD) to increase voxelotor AUC by approximately 10% at steady state.
2. The Applicant's PBPK analysis is inadequate to evaluate the effect of fluconazole (a moderate CYP3A4, CYP2C9 and strong CYP2C19 inhibitor), and fluvoxamine (a moderate CYP3A4, strong CYP2C19 inhibitor and weak CYP2C9 inhibitor) on the PK of voxelotor because contribution of the non-CYP3A pathways to the voxelotor metabolism has not been validated. The DDI potential of voxelotor as a victim of the CYP2C9 or CYP2C19 inhibitors is unknown and cannot be excluded because the fractional contribution of CYP2C9 or CYP2C19 to the elimination of voxelotor has not been determined. Two in vitro studies are recommended to further understand the role and extent of CYP2C9 and CYP2C19 enzymes in the metabolism of voxelotor.
3. The PBPK analysis is adequate to evaluate the effect of a CYP3A inducer on the PK of voxelotor. The model predicted voxelotor AUC ratios in the presence versus in the absence of rifampin (600 mg QD) were between 0.60-0.68, and between 0.72-0.79 in the presence versus in the absence of efavirenz (600 mg QD) at steady state. However, it should be noted that because many CYP3A4 inducers may induce multiple CYP enzymes and the current model analysis only considered the induction effect on CYP3A4, the voxelotor exposure changes with CYP3A4 inducers could be under-predicted given multiple CYP enzymes were identified to be involved in the metabolism of voxelotor. Therefore, the recommended voxelotor doses are 2500 mg with a strong CYP3A4 inducer and 2000 mg with a moderate CYP3A4 inducer, respectively, if unavoidable.

Background

Voxelotor was approved for sickle cell disease (SCD) (b) (4) in 2019. In the original NDA submission, the clinical DDI study was not conducted to evaluate the DDI liability of voxelotor as a victim of CYP modulators. The original PBPK model was developed based on voxelotor ADME (absorption, distribution, metabolism, and excretion) properties, the in vitro chemical

inhibition study, in vitro phenotyping study, human mass balance study, single-dose and multiple-dose PK studies in human. Because the enzymes responsible for about 47% of the total radioactivity administered, which was attributed to a number of minor metabolites, have not been identified, a conservative estimate of DDI risk was conducted by assigning 47% of the total radioactivity as oxidative metabolites after evaluation of the structural characterization of voxelotor and identified metabolites[1]. Based on the predicted exposure changes of voxelotor with CYP modulators along with the safety and efficacy profiles assessment, concomitant use of strong CYP3A4 inhibitors, fluconazole, and strong and moderate CYP3A4 inducers with voxelotor should be avoided. If concomitant use cannot be avoided, voxelotor dosage should be reduced to 1000 mg once daily with strong CYP3A4 inhibitors or fluconazole and increased to 2500 mg once daily with strong or moderate CYP3A4 inducers.

In this submission, the Applicant conducted an in vivo DDI study with itraconazole and based on the DDI study results, the fmCYP3A4 value assigned in the previous PBPK model was refined. The DDI potential of voxelotor with CYP modulators was re-evaluated using the updated PBPK model and based on the model prediction, the Applicant proposed updated dose adjustment when voxelotor is co-administrated with CYP3A4 modulators.

Applicant's PBPK Modeling Effort

PBPK software

Simcyp V17 (Simcyp Ltd, UK) was used to develop PBPK models and predict the effects of ketoconazole, fluconazole, fluvoxamine, rifampin and efavirenz on the PK of voxelotor.

Model development

Healthy subjects

The input parameter values related to the absorption and distribution of voxelotor in healthy subjects are the same as those assigned in the previous PBPK model[1].

The contribution of CYP3A4 to the elimination of voxelotor was assigned to be 0.15 based on a ~11% increase in exposure of voxelotor when co-administrated with itraconazole (2X100 mg, Capsules, Janssen Pharmaceuticals Inc.) in the clinical DDI study (GBT440-0118). The intrinsic clearance values of 15.18 and 16.7 μl/min per mg protein were assigned to UGT1A1 and UGT1A9 (fmUGT = 0.0752), respectively, based on the mass balance study and in vitro metabolism study results. The rest of clearance was lumped into an additional hepatic clearance (additional HML), representing 77.5% of total clearance.

In vitro obtained CYP3A4 Ki value (112.1 μM) of voxelotor using midazolam as a substrate was used in the model to account for the voxelotor-mediated competitive inhibition effect. Voxelotor was also shown to be a time-dependent CYP3A4 inhibitor. The optimized inactivation parameters values (KI = 20 μM and kinact = 3 h^{-1}) were applied in the model to account for the voxelotor-mediated time-

[1] https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/213137Orig1s000Multidiscipline.pdf

dependent inhibitory effect based on the sensitivity analysis and clinically observed DDI study result with midazolam.

Patients with SCD

A lower B:P ratio of 19.3 and a higher fu of 0.003 were used to reflect the reduced hematocrit (0.214) and lower albumin level in the simulations in patients with SCD.

Perpetrator drug models

The default PBPK models of ketoconazole, fluconazole, fluvoxamine, efavirenz, and rifampin, in Simcyp (V17) were used for DDI predictions.

PBPK model application

The developed PBPK model was used to simulate the DDI for voxelotor in the following scenarios:

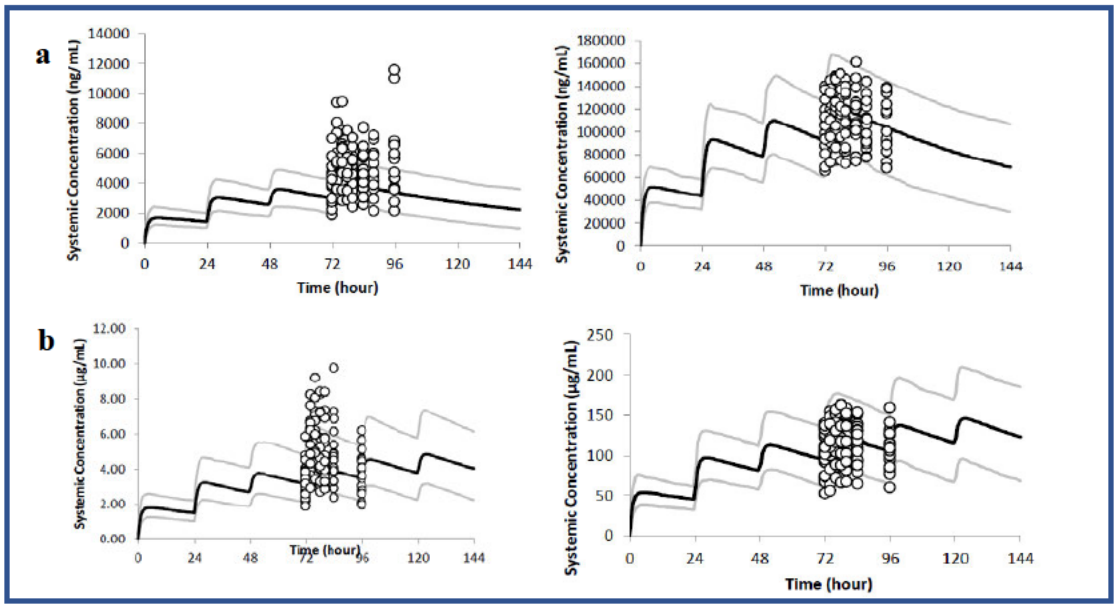
- To predict the effect of ketoconazole (a strong CYP3A inhibitor) on the PK of voxelotor following oral administration in healthy subjects and patients with SCD.
- To predict the effect of fluconazole (a moderate CYP3A4, CYP2C9 and strong CYP2C19 inhibitor) on the PK of voxelotor following oral administration in healthy subjects and patients with SCD.
- To predict the effect of fluvoxamine (a moderate CYP3A4, strong CYP2C19 inhibitor and weak CYP2C9 inhibitor) on the PK of voxelotor following oral administration in healthy subjects and patients with SCD.
- To predict the effect of efavirenz (a moderate CYP3A4, CYP2C19 and CYP2B6 inducer) on the PK of voxelotor following oral administration in healthy subjects and patients with SCD.
- To predict the effect of rifampin (a strong CYP3A4 and CYP2C19 inducer and a moderate CYP2C9 and CYP2B6 inducer) on the PK of voxelotor following oral administration in healthy subjects and patients with SCD.

FDA's assessment

1. Model verification

The Applicant's model reasonably described the voxelotor PK in both plasma and whole blood following a single or multiple oral dose administration. The blood Cmax and AUC were underestimated in some studies in patients with SCD presumably due to the variation of blood to plasma ratios of voxelotor in patients with SCD (Figure 8 and Table 15).

A



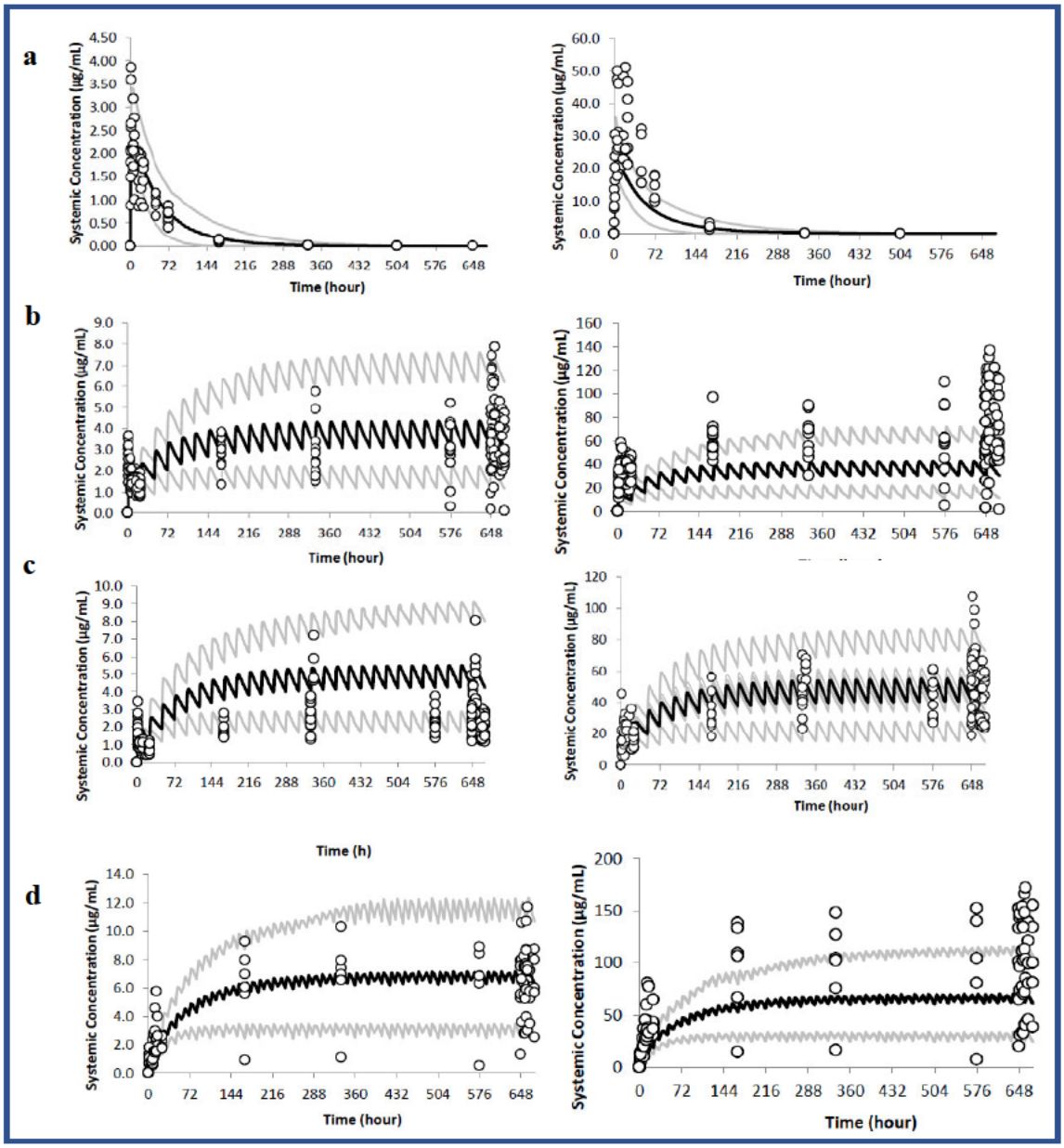


Figure 8. Observed (dots) and simulated (lines) voxelotor plasma (left panel) and blood (right panel) concentration-time profiles following a single or multiple oral dose administration of voxelotor in healthy subjects (A) and patients with SCD (B).

A: a, a loading dose of 900 mg QD on day 1 and day 2 and 600 mg QD on day 3 and day 4; b, a loading dose of 900 mg QD on day 1 and day 2 and 600 mg QD on day 3 through day 6.

B: a, single dose 1000 mg; b, 500 mg QD for 28 days; c, 700 mg QD for 28 days; d, 500 mg BID for 28 days

Sources: Simulated data were from Applicant's PBPK report (GBT-CP-012). Observed data in healthy subjects were from study GBT440-008 (a) and GBT440-0017 (b). Observed data in patients with SCD were from study GBT440-001-Cohort 7 (a), GBT440-001-Cohort 12 (b), GBT440-001-Cohort 11 (c), and GBT440-001-Cohort 14 (d).

Table 15. 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 healthy subjects (A) and patients with SCD (B).

(A) Healthy Subjects		Cmax (μg/mL)			AUC (μg*h/mL)			Sources for observed data
		Obs.	Pred.	$R_{Pred/Obs}$	Obs.	Pred.	$R_{Pred/Obs}$	
900 mg on day 1 & 2, and 600 mg QD on day 4 and day 5, **day 4 data**	**Whole Blood**	117	121	1.04	2547	2678	1.05	Study GBT440-008
	Plasma	5.79	3.92	0.68	115	86.7	0.75	
900 mg on day 1 & 2, and 600 mg QD on day 3 through day 6, **day 4 data**	**Whole Blood**	122	124	1.02	2666	2730	1.02	Study GBT440-017
	Plasma	5.40	4.07	0.75	102	89.7	0.88	

(B) SCD Patients		Cmax (μg/mL)			AUC (μg*h/mL)			Sources for observed data
		Obs.	Pred.	$R_{Pred/Obs}$	Obs.	Pred.	$R_{Pred/Obs}$	
Single dose, 1000 mg	**Whole Blood**	34.4	23.3	0.67	2390	1363	0.57	Study GBT440-001, Cohort 7
	Plasma	2.87	2.40	0.84	131	140	1.07	
700 mg QD, **day 1**	**Whole Blood**	43.1	26.3	0.61	805	539	0.67	Study GBT440-001, Cohort 11
	Plasma	2.48	1.47	0.59	35.0	30.1	0.86	
700 mg QD, **day 28**	**Whole Blood**	77.1	92.7	1.20	1850	1951	1.05	
	Plasma	4.86	5.17	1.06	92.3	108.9	1.18	
500 mg QD, **day 1**	**Whole Blood**	19.6	21.5	1.10	352	431	1.22	Study GBT440-001, Cohort 12
	Plasma	1.59	1.27	0.80	20.1	25.5	1.27	
500 mg QD, **day 28**	**Whole Blood**	61.4	67.4	1.10	1180	1385	1.17	
	Plasma	3.48	3.98	1.14	58.7	81.8	1.39	
500 mg BID, **day 1**	**Whole Blood**	44.1	21.3	0.48	687	359	0.52	Study GBT440-001, Cohort 14
	Plasma	3.07	2.19	0.71	41	36.9	0.90	
500 mg BID, **day 28**	**Whole Blood**	104	66.5	0.64	2180	1498	0.69	
	Plasma	7.60	6.84	0.90	143	154	1.08	

Source: Simulated data were from Applicant's PBPK report (GBT-CP-012).

2. The effect of strong CYP3A4 inhibitors

The Applicant's PBPK analysis is adequate to evaluate the effect of a CYP3A inhibitor on the PK of voxelotor. The model predicted voxelotor AUC ratio was about 1.1 with versus without ketoconazole (400 mg QD) at steady state (Table 21).

3. The effect of strong or moderate CYP2C9 or CYP2C19 inhibitors

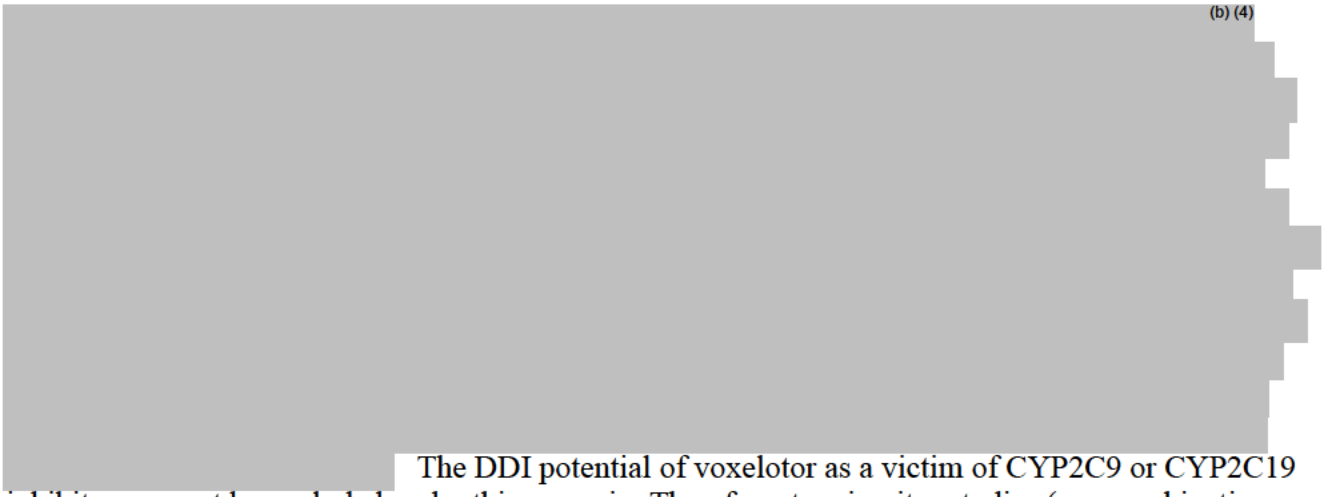
CYP2C9, CYP2C19, CYP2B6 and CYP3A5 have been identified as the enzymes involved in the metabolism of voxelotor but were not incorporated in the model in the original submission. The DDI potential of voxelotor with fluconazole (a moderate CYP3A4, CYP2C9 and strong CYP2C19 inhibitor), or other CYP2C9 or CYP2C19 inhibitors was unable to be estimated using the originally submitted model. The DDI potential of voxelotor as a victim of CYP2C9 or CYP2C19 inhibitors is

unknown and cannot be excluded because the fractional contributions of CYP2C9 or CYP2C19 to the elimination of voxelotor have not been determined.

During the labeling negotiation, the Applicant submitted a new PBPK analysis to address the concern with respect to the DDI potential with CYP2C9 and CYP2C19 inhibitors. Two scenarios were discussed.

Scenario 1

Scenario 2



The DDI potential of voxelotor as a victim of CYP2C9 or CYP2C19 inhibitors cannot be excluded under this scenario. Therefore, two in vitro studies (enzyme kinetics study and chemical inhibition study) are recommended to further understand the role and extent of CYP2C9 and CYP2C19 enzymes in the metabolism of voxelotor.

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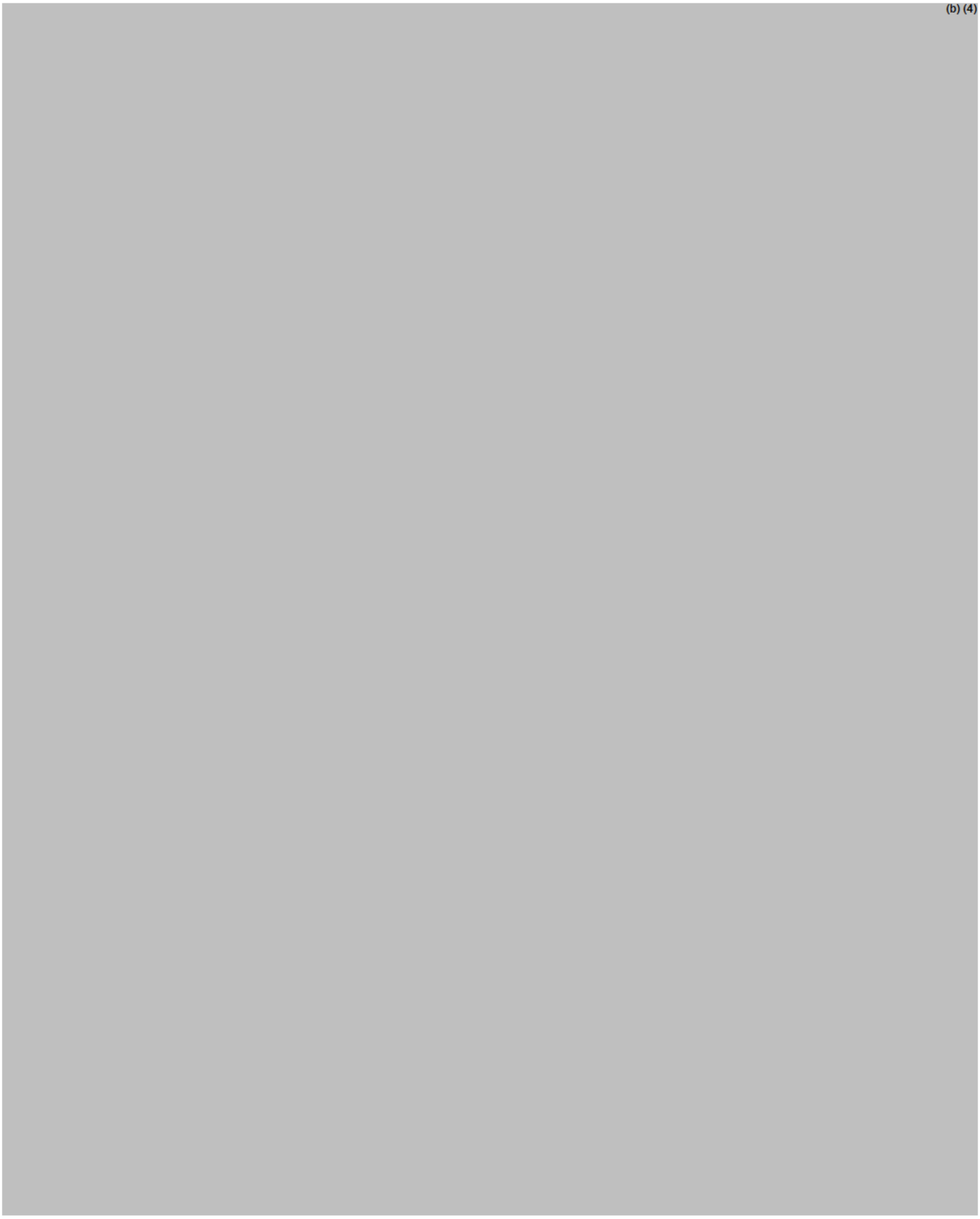


4. The effect of strong or moderate CYP3A4 inducers

a. Model analysis only considered the CYP3A4 inducer mediated induction effect on CYP3A4

In general, FDA agrees with the Applicant's model analysis regarding the predicted effect of strong or moderate CYP3A4 inducers on the PK of voxelotor if only considered the CYP3A4 inducer mediated induction effect on CYP3A4. The fmCYP3A4 was verified against the itraconazole DDI study results. The Applicant's model predicted rifampin (600 mg QD) and efavirenz (600 mg QD) decreased voxelotor AUC by 32% and 20%, respectively, at steady state.

One additional scenario was explored by the FDA reviewer. It was noticed that the voxelotor mediated time dependent inhibition of CYP3A4 was incorporated in the current model and considered as the main factor driving the voxelotor mediated CYP3A4 inhibition effect. The in vitro study showed that voxelotor was a time dependent CYP3A4 inhibitor (KI = 4.0 μM and Kinact = 0.5 S^{-1} using midazolam as a substrate; Ki = 2.8 μM and Kinact = 0.068 S^{-1} using testosterone as a substrate, Study PRC-18-040) and a competitive CYP3A4 inhibitor (Ki=1.3 μM using testosterone as a substrate; Ki=112 μM using midazolam as a substrate, Study PRC-15-015).

The incorporation of voxelotor mediated time dependent inhibition of CYP3A4 in the model would potentially reduce the DDI liability between voxelotor and CYP3A4 inducers as compared to the scenario where voxelotor mediated competitive inhibition is considered as the main factor driving the voxelotor mediated CYP3A4 inhibition effect. We explored the DDI potential between voxelotor and CYP3A4 inducers by considering the voxelotor mediated CYP3A4 competitive inhibition to be the main factor driving the voxelotor mediated CYP3A4 inhibitory effect. The CYP3A4 Ki value for voxelotor was optimized to allow accurate recovery of the observed midazolam AUC ratio with voxelotor. The optimized CYP3A4 Ki value of 0.15 μM was applied in the model to simulate the DDI with rifampin or efavirenz when only considering CYP3A4 being the only enzyme involved in the DDI. The predicted voxelotor exposures (1500, 2000, or 2500 mg QD) with concomitant rifampin or efavirenz compared to voxelotor exposure (1500 mg QD alone) are shown in Table 21.

b. Model analysis considered the CYP3A inducer mediated induction effect on CYP3A4, 2C9, 2C19 and 2B6, given multiple CYP enzymes were identified to be involved in the metabolism of voxelotor.

Since the definitive fm values were unable to be determined for CYP2C19, CYP2C9 and CYP2B6 based on currently available data, a conservative analysis was conducted by the reviewer. In this analysis, the following model settings were considered.

1. The contributions of each CYP enzyme to the total clearance of voxelotor were assigned in the model according to the fm values in Table 18C. It should be noted that the fm values in Table 18C were the possible lowest values for CYP2C9, CYP2C19 and CYP2B6 based on the analysis of currently available data. Please refer to "The effect of strong or moderate CYP2C9 or CYP2C19 inhibitors" for details.
2. (b) (4) % of oxidation was not assigned to any CYP enzyme mediated metabolic pathway.
3. CYP enzymes were assumed to be not involved in the formation of the unidentified metabolites which accounted for (b) (4) % of total clearance of voxelotor.
4. Voxelotor mediated CYP3A4 competitive inhibition was not considered in the simulations.
5. CYP2C19 induction effect was not incorporated in the efavirenz model.

The model predicted voxelotor Cmax and AUC ratios with rifampin or efavirenz under steady state are shown in Table 22. The predicted ratios in Table 18C represented a conservative estimate of voxelotor Cmax and AUC ratios with CYP3A4 inducers. These predicted ratios would be expected to be lower if any of the situations listed above was considered in the model. Therefore, adjustment of voxelotor dose to 2500 mg and 2000 mg when co-administered with strong and moderate CYP3A inducers, respectively, appears reasonable.

Table 21. Predicted Voxelotor Plasma and Blood Cmax and AUC ratios (CmaxR and AUCR) when Voxelotor is Co-administered with Ketoconazole, Rifampin or Efavirenz in Healthy Subjects (A: plasma; B: blood) and Patients with SCD (C: plasma; D: blood). (The CmaxR and AUCR were calculated comparing the Cmax and AUC of voxelotor when voxelotor is co-administered with a modulator to when it is administered alone [1500 mg]).

A Healthy subjects Plasma	Ketoconazole, 400 mg QD CmaxR/AUCR	Rifampin, 600 mg QD CmaxR/AUCR			Efavirenz, 600 mg QD CmaxR/AUCR		
	1500 mg QD	1500 mg QD	2000 mg QD	2500 mg QD	1500 mg QD	2000 mg QD	2500 mg QD
CYP3A4 TDI[a]	1.07/1.08	0.71/0.68	0.98/0.95	1.27/1.23	0.81/0.79	1.12/1.10	1.43/1.41
CYP3A4 competitive inhibition[b]	1.13/1.15	0.64/0.60	0.85/0.80	1.06/1.00	0.75/0.72	1.00/0.97	1.25/1.21

B Healthy subjects Blood	Ketoconazole 400 mg QD CmaxR/AUCR	Rifampin, 600 mg QD CmaxR/AUCR			Efavirenz, 600 mg QD CmaxR/AUCR		
	1500 mg QD	1500 mg QD	2000 mg QD	2500 mg QD	1500 mg QD	2000 mg QD	2500 mg QD
CYP3A4 TDI[a]	1.07/1.08	0.71/0.68	0.98/0.95	1.27/1.23	0.82/0.80	1.13/1.11	1.44/1.42
CYP3A4 competitive inhibition[b]	1.13/1.15	0.63/0.60	0.85/0.80	1.06/1.00	0.75/0.73	1.00/0.98	1.25/1.21

C Patients with SCD Plasma	Ketoconazole, 400 mg QD CmaxR/AUCR	Rifampin, 600 mg QD CmaxR/AUCR			Efavirenz, 600 mg QD CmaxR/AUCR		
	1500 mg QD	1500 mg QD	2000 mg QD	2500 mg QD	1500 mg QD	2000 mg QD	2500 mg QD
CYP3A4 TDI[a]	1.07/1.09	0.73/0.68	1.01/0.94	1.29/1.22	0.82/0.79	1.13/1.09	1.44/1.40
CYP3A4 competitive inhibition[b]	1.14/1.16	0.67/0.60	0.89/0.80	1.11/1.00	0.76/0.72	1.02/0.96	1.27/1.19

D Patients with SCD Blood	Ketoconazole, 400 mg QD CmaxR/AUCR	Rifampin, 600 mg QD CmaxR/AUCR			Efavirenz, 600 mg QD CmaxR/AUCR		
	1500 mg QD	1500 mg QD	2000 mg QD	2500 mg QD	1500 mg QD	2000 mg QD	2500 mg QD
CYP3A4 TDI[a]	1.07/1.09	0.73/0.68	1.01/0.94	1.29/1.22	0.83/0.79	1.13/1.09	1.44/1.40
CYP3A4 competitive inhibition[b]	1.14/1.16	0.67/0.60	0.89/0.80	1.11/1.00	0.77/0.72	1.02/0.96	1.27/1.19

Sources: a) data were from Applicant's PBPK report (GBT-CP-012). b) data were from FDA reviewer's simulations using the PBPK model considering the voxelotor mediated CYP3A4 competitive inhibition is the main factor driving the voxelotor mediated CYP3A4 inhibitory effect.

Table 22. Predicted Voxelotor Plasma Cmax and AUC Ratios (CmaxR and AUCR) when Voxelotor is Co-administered with Rifampin or Efavirenz in Healthy Subjects based on the fm Values in Table 18C. (The CmaxR and AUCR were calculated comparing the Cmax and AUC of voxelotor when voxelotor is co-administered with a modulator to when it is administered alone [1500 mg]).

	Rifampin, 600 mg QD CmaxR/AUCR	Efavirenz, 600 mg QD CmaxR/AUCR[a]	Efavirenz, 600 mg QD CmaxR/AUCR[b]
1500 mg QD	0.64/0.60	0.79/0.77	0.72/0.69
2000 mg QD	0.87/0.83	1.08/1.05	0.98/0.95/
2500 mg QD	1.12/1.07	1.38/1.35	1.25/1.22

Note: The predicted voxelotor Cmax and AUC ratios in blood and in patients with SCD were expected to be similar to those in plasma in heathy subjects and were not shown.

a: CYP2C19 induction effect was not incorporated in the efavirenz model.
b: CYP2C19 induction effect was incorporated in the efavirenz model. CYP2B6 induction parameter values in efavirenz model in Simcyp were used to simulate the efavirenz mediated CYP2C19 induction effect.

4.4. Individual Study Review for Study 0114 and 018

4.4.1 Relative BA study: Dispersible tablets vs. 300 mg F1 tablets (Protocol# GBT440-0113)

Title: A Phase 1, Single-Dose, Open-Label, Randomized, Two-Period Crossover Study to Evaluate the Relative Bioavailability of GBT440 Dispersible Tablets in Healthy Subjects

Study Design:
This was a Phase 1, randomized, open-label, 2-period, crossover study to evaluate the relative bioavailability of GBT440 administered as a dispersible 900-mg tablet (new formulation) versus 3 × 300-mg tablets of the current formulation. Twenty subjects (with at least 25% African Americans) were planned to be enrolled in this study. Screening occurred within a 28-day screening window. Subjects were admitted to the clinical research unit (CRU) on Day -1 of each treatment period. Subjects were dosed on Day 1 of each treatment period. Eligible subjects received the following treatments according to the randomization schedule and crossover design:

- Treatment A: 900-mg dispersible tablet of GBT440 administered in a fasted state (test)
- Treatment B: 900-mg (3 × 300-mg tablets) of GBT440 administered in a fasted state (reference [Ref])

Subjects remained resident in the CRU until discharge on Day 5 of each treatment period. Subjects returned to the CRU on Days 12 (± 1 day) and 20 (± 1 day) of each treatment period for safety and PK assessments. A follow-up visit with PK and safety assessments was performed on Day 29 (± 1 day) of Period 2. The 2 doses were separated by a 28-day washout period.

Whole blood concentrations of voxelotor were analyzed using a validated LC/MS/MS assays with LLOQ of 120 pg/mL.

Dose for Each Subject:
Treatment A: The 900-mg dispersible tablet was dispersed in 15 mL of water prior to administration. Following an overnight fast of at least 10 hours, subjects receiving Treatment A consumed an additional 225 mL of water following the dose.

Treatment B: Following an overnight fast of at least 10 hours, subjects receiving Treatment B were administered study drug with 240 mL of water.

Subject Disposition:
Nineteen of 20 enrolled subjects completed the study, one subject (Subject (b) (6), Treatment Sequence BA) withdrew consent for the study prior to Period 2 dose administration. Summary of subject disposition was summarized in Table 17.

Table 23.*Summary of Subject Disposition (All Subjects Randomized)*

Disposition	Sequence AB (N = 10)	Sequence BA (N = 10)	Overall (N = 20)
Subjects randomized	10	10	20
Subjects who were dosed (Safety Population), n (%) [a]	10 (100.0)	10 (100.0)	20 (100.0)
Dosed with Treatment A, n (%) [a]	10 (100.0)	9 (90.0)	19 (95.0)
Dosed with Treatment B, n (%) [a]	10 (100.0)	10 (100.0)	20 (100.0)
Subjects who completed study, n (%) [a]	10 (100.0)	9 (90.0)	19 (95.0)
Subjects who discontinued early, n (%) [a]	0	1 (10.0)	1 (5.0)
Reason for early termination:			
Withdrawal by subject, n (%) [a]	0	1 (10.0)	1 (5.0)

a. Percentages are based on the number of subjects randomized.
Treatment A: 900-mg dispersible tablet of GBT440 administered in a fasted state (Test)
Treatment B: 900-mg (3 × 300-mg tablets) of GBT440 administered in a fasted state (Ref)

Source: Table 10.1 of CSR

A minimum of 25% African American subjects were enrolled. Demographic data are presented in Table 18.

Table 24. Summary of Demographic Data (Safety population)

Parameter	Sequence AB (N = 10)	Sequence BA (N = 10)	Overall (N = 20)
Age, years			
n	10	10	20
Mean	34.2	44.1	39.2
SD	12.34	12.58	13.15
Median	30.0	45.5	35.5
Minimum	23	27	23
Maximum	60	60	60
Sex, n (%) [a]			
Male	8 (80.0)	9 (90.0)	17 (85.0)
Female	2 (20.0)	1 (10.0)	3 (15.0)
Ethnicity, n (%) [a]			
Hispanic or Latino	3 (30.0)	4 (40.0)	7 (35.0)
Not Hispanic or Latino	7 (70.0)	6 (60.0)	13 (65.0)
Race, n (%) [a]			
Asian	0	1 (10.0)	1 (5.0)
Black or African American	5 (50.0)	3 (30.0)	8 (40.0)
White	5 (50.0)	6 (60.0)	11 (55.0)

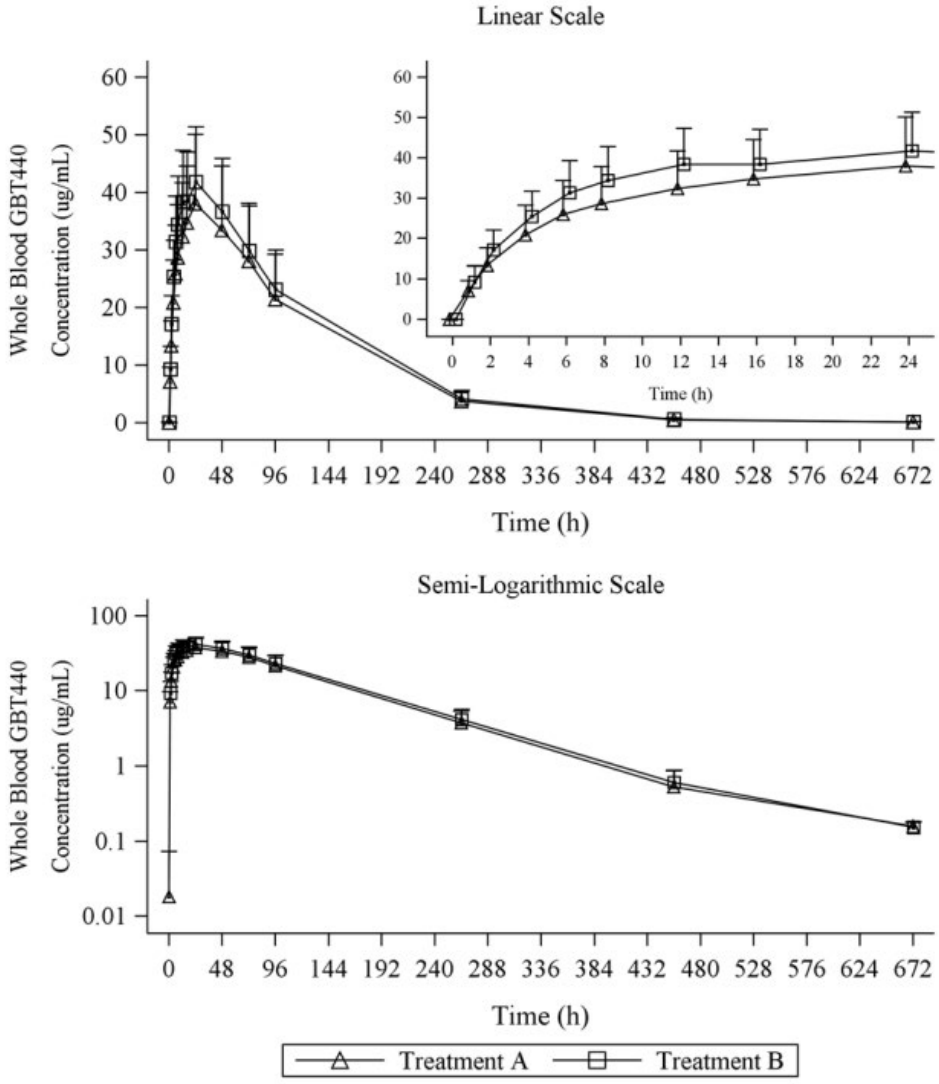
a. Percentages are based on the number of subjects included in the Safety Population.
Treatment A: 900-mg dispersible tablet of GBT440 administered in a fasted state (Test)
Treatment B: 900-mg (3 × 300-mg tablets) of GBT440 administered in a fasted state (Ref)

Source: Table 10.2 of CSR

Pharmacokinetic Results:

Mean (+SD) whole blood GBT440 concentration-time profiles is presented in Figure 9. Summary statistics were calculated for the whole blood GBT440 PK parameters Cmax, AUCt, and AUCinf for each treatment and presented in *Table 19*.

Figure 9. Mean (+ SD) Whole Blood GBT440 Concentration-time Profiles (Pharmacokinetic Evaluable Population)



Treatment A: 900-mg dispersible tablet of GBT440 administered in a fasted state (Test)
Treatment B: 900-mg (3 × 300-mg tablets) of GBT440 administered in a fasted state (Ref)

Source: Figure 11.1 of CSR

Table 25. Statistical Analysis of Whole Blood Pharmacokinetic Data (PK evaluable population)

PK Parameter	Comparison	Number of Subjects		Geometric LS Mean		Ratio of Geometric LS Means (Test to Ref)	90% CI for Geometric LS Mean Ratio (Test to Ref)
		Test	Ref	Test	Ref		
C_{max} (µg/mL)	A (Test) vs B (Ref)	19	20	37.0	40.8	0.909	(0.821, 1.005)
AUC_t (h*µg/mL)	A (Test) vs B (Ref)	19	20	4632	5179	0.894	(0.795, 1.006)
AUC_{inf} (h*µg/mL)	A (Test) vs B (Ref)	19	20	4694	5221	0.899	(0.798, 1.012)

Note: The log-transformed PK parameters (C_{max}, AUC_t, and AUC_{inf}) were analyzed using a linear mixed model, with fixed effects for sequence, treatment, period, and subject nested within sequence as random effect.
Treatment A: 900-mg dispersible tablet of GBT440 administered in a fasted state (Test)
Treatment B: 900-mg (3 × 300-mg tablets) of GBT440 administered in a fasted state (Ref)

Source: Table 11.2 of CSR

Reviewer's comments:
The Cmax, AUCt, and AUCinf were all approximately 10% lower for GBT440 when administered as a single 900-mg dispersible tablet compared to 3 × 300-mg tablets. The 10% lower overall exposure following administration of the GBT440 dispersible tablet is not expected to have any clinical relevance.

For whole blood GBT440 AUCt and AUCinf, the lower bounds of the 90% CIs for the ratio of geometric least squares (LS) means for the comparison of the 900-mg dispersible tablet and 3 × 300-mg tablet formulations fell below the prespecified bioequivalence lower limit of 0.80 (0.795 and 0.798, respectively). For whole blood GBT440 Cmax, the 90% CI for the ratio of geometric LS mean for the comparison of the 900-mg dispersible tablet and 3 × 300-mg tablet formulations (0.821, 1.005) were contained within the prespecified bioequivalence range of 0.80 to 1.25. The median tmax was the same for both formulations.

The sponsor's bioequivalence analysis was verified by the reviewer's analysis.

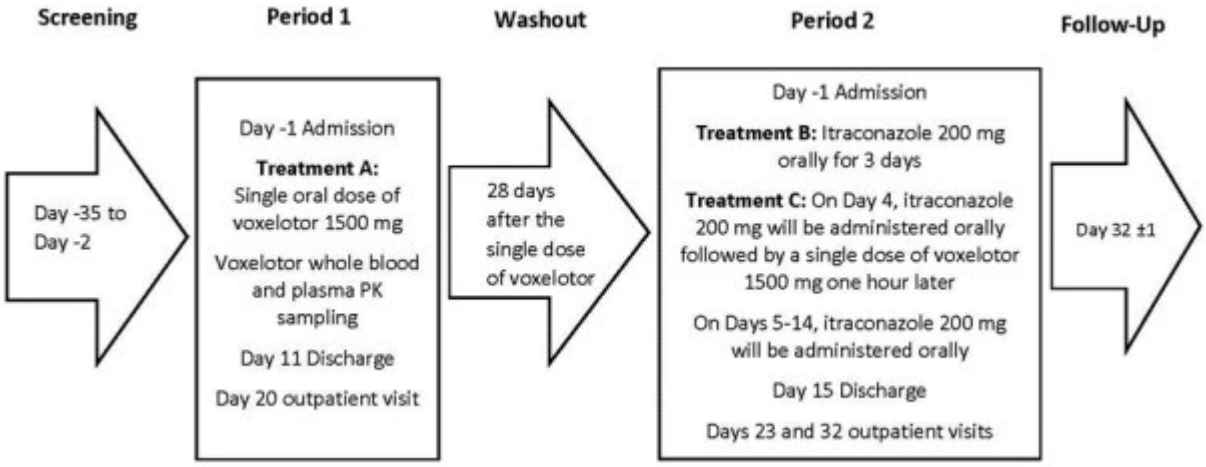
In addition, for this efficacy supplement, the sponsor is seeking approval of the 300-mg dispersible tablets because only the 300-mg dispersible tablets were tested in Study 007 (Part C), the pivotal study in pediatric patients with sickle cell disease. Although Study 0113 tested the 900-mg dispersible tablet strength, not the 300-mg, the 300-mg dispersible tablet and the 900-mg dispersible tablet strengths are adequately bridged because they are compositionally proportional and have comparable dissolution profiles.

4.4.2 DDI study: Effect of itraconazole on PK of voxelotor (Protocol #GBT440-0118)

Title: A Phase 1, Open-Label, Fixed-Sequence, Two-Period, Drug Interaction Study to Evaluate the Effect of Itraconazole, a Strong CYP3A4 Inhibitor, on the Pharmacokinetics of Voxelotor

Study Design:
This was a Phase 1, open-label, fixed-sequence, two-period study to evaluate the effect of concomitant administration of itraconazole (a strong CYP3A4 inhibitor) on voxelotor exposures. Approximately 25

subjects were enrolled to complete at least 20 subjects. A minimum of 30% African American subjects were enrolled. A study schematic is presented below.



Screening:
The screening window was 34 days in duration (Days -35 to Day -2). Subjects were admitted to the CRU on Day -1 of each study period and received the following treatments:

Period 1:

- Treatment A: Single oral dose of voxelotor 1500 mg (3 x 500 mg tablets) on Day 1

Subjects remained resident in the CRU until discharge on Day 11 of Period 1. Subjects returned to the CRU for PK blood sampling on Day 20.

Washout:
There was at least a 28-day washout between dosing Day 1 of Period 1 and dosing Day 1 of Period 2.

Period 2:

- Treatment B: Itraconazole 200 mg orally (2x 100 mg capsules) for 3 days (Day 1 to Day 3) of Period 2
- Treatment C: On Day 4, itraconazole 200 mg was administered orally followed by a single oral dose of voxelotor 1500 mg (3 x 500 mg tablets) 1 hour later. Itraconazole 200 mg was administered orally on Days 5 through 14 of Period 2.

Subjects remained resident in the CRU until discharge on Day 15 of Period 2. Subjects returned to the CRU for PK blood sampling on Days 23 and 32. Follow-up procedures were performed on Day 32 ±1.

Whole blood concentrations of voxelotor were analyzed using a validated LC/MS/MS assays with LLOQ of 120 pg/mL. Plasma concentrations of voxelotor were analyzed using a validated LC/MS/MS assays with LLOQ of 6 ng/mL. Plasma concentrations of itraconazole were analyzed using a validated LC/MS/MS assays with LLOQ of 2 ng/mL.

Dose of Each Subject:
Subjects were fasted at least 8 hours prior to study drug administration on Period 1 Day 1 and Period 2 Day 4. Subjects were fed a low-fat meal 30 minutes prior to study drug administration for all other days. Study drug was administered with 240 mL (8 fluid ounces) of noncarbonated room temperature water.

Subject Disposition:
Subject disposition is presented in Table 20. Overall, 25 subjects were enrolled into this fixed-sequence study and 20 subjects (80%) completed the study. For the 5 subjects (20%) that discontinued early, 2 subjects (8%) were terminated early due to physician decision, 2 subjects (8%) due to protocol deviations (positive urine drug screens), and 1 subject (4%) withdrew consent.

Table 26. Summary of Subject Disposition (All Enrolled Subjects)

Disposition (Number [%] of Subjects)	Overall (N = 25)
Number of subjects who were enrolled	25
Number of subjects who were dosed with Treatment A	25 (100)
Number of subjects who were dosed with Treatment B	21 (84)
Number of subjects who were dosed with Treatment C	21 (84)
Number of subjects who completed Study	20 (80)
Number of subjects in Safety Population	25 (100)
Number of subjects in PK Full Population	25 (100)
Number of subjects in PK Evaluable Population	25 (100)
Subjects who discontinued early	5 (20)
Reason for early termination:	
Physician decision	2 (8)
Protocol deviation	2 (8)
Withdrawal by subject	1 (4)

Abbreviation: PK = pharmacokinetic
Treatment A: Single oral dose of voxelotor 1500 mg (3 x 500 mg tablets) on Day 1 of Period 1
Treatment B: Itraconazole 200 mg orally for 3 days (Day 1 to Day 3) of Period 2
Treatment C: On Day 4, itraconazole 200 mg followed by a single oral dose of voxelotor 1500 mg (3 x 500 mg tablets) 1 hour later. Itraconazole 200 mg orally on Days 5 through 14 of Period 2.
Source: Table 10.1 of CSR

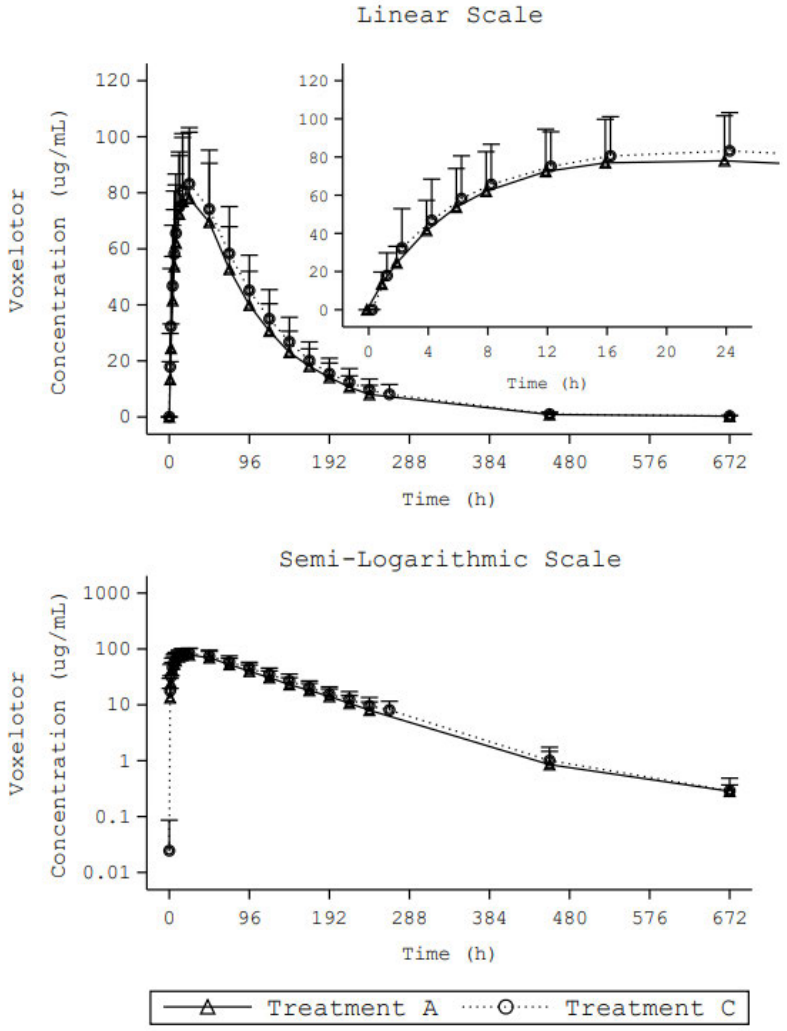
In addition, among the 25 enrolled subjects, 1 (4%) subject was Asian, 9 (36%) subjects were Black or African American, and 15 (60%) were White.

Pharmacokinetic Results:

- Whole blood voxelotor concentrations

Mean (+SD) whole blood voxelotor concentration-time profiles is presented in Figure 10. Individual voxelotor whole blood PK parameters were summarized in Table 21. Statistical analyses of the whole blood PK parameters are presented in Table 22.

Figure 10. Mean (+SD) Voxelotor Whole Blood Concentration-Time Profiles (PK Evaluable Population)



Treatment A: Single oral dose of voxelotor 1500 mg (3 x 500 mg tablets) on Day 1

Treatment C: On Day 4, itraconazole 200 mg followed by a single oral dose of voxelotor 1500 mg (3 x 500 mg tablets) 1 hour later. Itraconazole 200 mg orally on Days 5 through 14 of Period 2.

Source: Figure 11.1 of CSR

Table 27. Summary of Voxelotor Whole Blood PK Parameters (PK Evaluable Population)

Parameter (unit)	Statistic	Treatment A	Treatment C
C_{max} (µg/mL)	n	25	21
	GM (CV%)	79.2 (32.7)	83.7 (26.2)
AUC_t (h*µg/mL)	n	25	20
	GM (CV%)	9028 (30.0)	10181 (30.0)
AUC_{inf} (h*µg/mL)	n	25	20
	GM (CV%)	9083 (29.5)	10230 (30.0)
AUC_{0-24} (h*µg/mL)	n	25	21
	GM (CV%)	1418 (35.0)	1536 (27.1)
t_{max} (h)	n	25	21
	Median (min, max)	16.0 (6.0, 48.0)	24.0 (8.0, 48.0)
$t_{1/2}$ (h)	n	25	20
	Mean (SD)	63.5 (11.7)	62.7 (10.2)
CL/F (L/h)	n	25	20
	GM (CV%)	0.165 (29.5)	0.147 (30.0)
V_z/F (L)	n	25	20
	GM (CV%)	14.9 (36.9)	13.1 (30.0)

Abbreviations: AUC = area under the plasma concentration-time curve; AUC_{0-24} = AUC from time 0 to 24 hours; AUC_{inf} = AUC from time 0 extrapolated to infinity; AUC_t = AUC from time 0 to the time of the last quantifiable concentration; CL/F = oral clearance; C_{max} = maximum observed concentration; CV% = percent coefficient of variation; GM = geometric mean; max = maximum; min = minimum; n = number; PK = pharmacokinetic; $t_{1/2}$ = terminal elimination half-life; t_{max} = time that C_{max} was observed; V_z/F = apparent volume of distribution (oral)

Period 1/Treatment A: Single oral dose of voxelotor 1500 mg (3 x 500 mg tablets) on Day 1

Period 2/Treatment C: On Day 4, itraconazole 200 mg followed by a single oral dose of voxelotor 1500 mg (3 x 500 mg tablets) 1 hour later. Itraconazole 200 mg orally on Days 5 through 14 of Period 2

Subject (b) (6) was only included in the summaries for C_{max} and t_{max} for Treatment C as the subject withdrew from the study on Day 7 of Period 2.

Source: Table 11.1 of CSR

Table 28. Statistical Analysis of the Effect of Itraconazole on Voxelotor Whole Blood PK Data (PK Evaluable Population)

Comparison		PK Parameter	Geometric LS Mean		Ratio of Geometric LS Mean (Test/Reference)	90% Confidence Interval
Test	Reference		Test	Reference		
TRT C	TRT A	C_{max} (µg/mL)	80.6	79.2	1.018	(0.912, 1.136)
		AUC_t (h*µg/mL)	9870	9028	1.093	(0.9786, 1.222)
		AUC_{inf} (h*µg/mL)	9925	9083	1.093	(0.9783, 1.220)

Abbreviations: AUC = area under the plasma concentration-time curve; AUC_{inf} = from time 0 extrapolated to infinity; AUC_t = AUC from time 0 to the time of the last quantifiable concentration; C_{max} = maximum observed concentration; LS = least squares; PK = pharmacokinetic; TRT = treatment

Period 1/Treatment A: Single oral dose of voxelotor 1500 mg (3 x 500 mg tablets) on Day 1

Period 2/Treatment C: On Day 4, itraconazole 200 mg followed by a single oral dose of voxelotor 1500 mg (3 x 500 mg tablets) 1 hour later. Itraconazole 200 mg orally on Days 5 through 14 of Period 2

Source: Table 11.2 of CSR

Reviewer's comment:
Based on ratio of geometric LS mean, voxelotor whole blood Cmax, AUCt, and AUCinf were 2%, 9%, and 9% higher, respectively, in the presence of itraconazole.

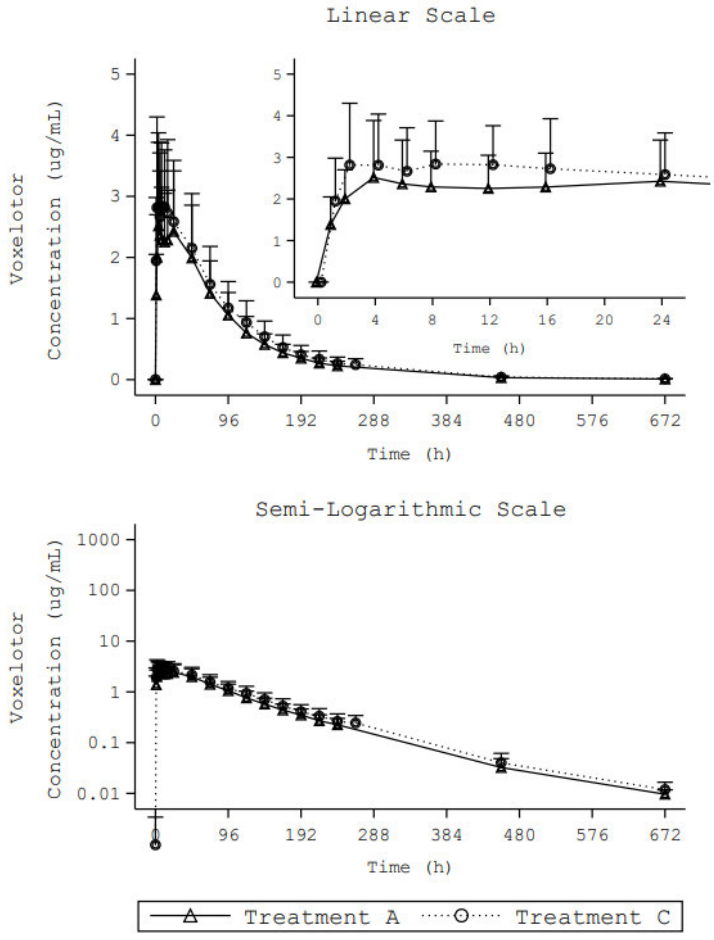
The median whole blood tmax (16 to 24 hours) was similar when voxelotor was administered alone or when co-administered with itraconazole. The mean whole blood t1/2 (approximately 63 hours), geometric mean CL/F (0.147 to 0.165 L/h) and Vz/F (13.1 to 14.9 L) were also similar when voxelotor was administered alone or when co-administered with itraconazole.

The sponsor's PK results were verified by the reviewer's analysis.

- Plasma voxelotor concentrations

Mean (+SD) plasma voxelotor concentration-time profiles is presented in Figure 11. Individual voxelotor plasma PK parameters were summarized in Table 23. Statistical analyses of the plasma PK parameters are presented in Table 24.

Figure 11. Mean (+SD) Voxelotor Plasma Concentration-Time Profiles (PK Evaluable Population)



Treatment A: Single oral dose of voxelotor 1500 mg (3 x 500 mg tablets) on Day 1
Treatment C: On Day 4, itraconazole 200 mg followed by a single oral dose of voxelotor 1500 mg (3 x 500 mg tablets) 1 hour later. Itraconazole 200 mg orally on Days 5 through 14 of Period 2.

Source: Figure 11.2 of CSR

Table 29. Summary of Voxelotor Plasma PK parameters (PK Evaluable Population)

Parameter (unit)	Statistic	Treatment A	Treatment C
C_{max} (µg/mL)	n	25	21
	GM (CV%)	2.81 (42.2)	3.24 (39.2)
AUC_t (h*µg/mL)	n	25	20
	GM (CV%)	259 (32.9)	297 (39.7)
AUC_{inf} (h*µg/mL)	n	25	20
	GM (CV%)	261 (32.5)	299 (39.3)
AUC_{0-24} (h*µg/mL)	n	25	21
	GM (CV%)	50.0 (40.6)	60.0 (35.4)
t_{max} (h)	n	25	21
	Median (min, max)	6.00 (2.00, 48.0)	4.00 (2.00, 24.0)
$t_{1/2}$ (h)	n	25	20
	Mean (SD)	78.9 (10.5)	78.9 (10.4)
CL/F (L/h)	n	25	20
	GM (CV%)	5.75 (32.6)	5.01 (39.3)
V_z/F (L)	n	25	20
	GM (CV%)	649 (34.5)	566 (41.4)

Abbreviations: AUC = area under the plasma concentration-time curve; AUC_{0-24} = AUC from time 0 to 24 hours; AUC_{inf} = AUC from time 0 extrapolated to infinity; AUC_t = AUC from time 0 to the time of the last quantifiable concentration; CL/F = oral clearance; C_{max} = maximum observed concentration; CV% = percent coefficient of variation; GM = geometric mean; max = maximum; min = minimum; n = number; PK = pharmacokinetic; $t_{1/2}$ = terminal elimination half-life; t_{max} = time that C_{max} was observed; V_z/F = apparent volume of distribution (oral)

Period 1/Treatment A: Single oral dose of voxelotor 1500 mg (3 x 500 mg tablets) on Day 1

Period 2/Treatment C: On Day 4, itraconazole 200 mg followed by a single oral dose of voxelotor 1500 mg (3 x 500 mg tablets) 1 hour later. Itraconazole 200 mg orally on Days 5 through 14 of Period 2

Subject (b) (6) was only included in the summaries for C_{max} and t_{max} for Treatment C as the subject withdrew from the study on Day 7 of Period 2.

Source: Figure 11.3 of CSR

Table 30. Statistical Analysis of the Effect of Itraconazole on Voxelotor Plasma PK Data (PK Evaluable Population)

Comparison		PK Parameter	Geometric LS Mean		Ratio of Geometric LS Mean (Test/Reference)	90% Confidence Interval
Test	Reference		Test	Reference		
TRT C	TRT A	C_{max} (µg/mL)	3.12	2.81	1.111	(0.972, 1.271)
		AUC_t (h*µg/mL)	288	259	1.113	(0.982, 1.260)
		AUC_{inf} (h*µg/mL)	291	261	1.114	0.985, 1.260)

Abbreviations: AUC = area under the plasma concentration-time curve; AUC_{inf} = from time 0 extrapolated to infinity; AUC_t = AUC from time 0 to the time of the last quantifiable concentration; C_{max} = maximum observed concentration; LS = least squares; PK = pharmacokinetic; TRT = treatment

Period 1/Treatment A: Single oral dose of voxelotor 1500 mg (3 x 500 mg tablets) on Day 1

Period 2/Treatment C: On Day 4, itraconazole 200 mg followed by a single oral dose of voxelotor 1500 mg (3 x 500 mg tablets) 1 hour later. Itraconazole 200 mg orally on Days 5 through 14 of Period 2

Source: Table 11.4 of CSR

Reviewer's comment:
Design of this DDI study is consistent with what is commonly adopted[1].

Based on ratio of geometric LS mean, voxelotor plasma Cmax, AUCt, and AUCinf were 11% higher in the presence of itraconazole.

The median plasma tmax (4 to 6 hours) was similar when voxelotor was administered alone or when co-administered with itraconazole. The mean plasma t1/2 (approximately 79 hours), geometric mean CL/F (5.01 to 5.75 L/h) and Vz/F (566 to 649 L) were also similar when voxelotor was administered alone or when co-administered with itraconazole.

The sponsor's PK results were verified by the reviewer's analysis.

- Plasma itraconazole concentrations

The itraconazole arithmetic mean ± SD concentrations at predose on Day 4 were 138 ± 60.5 ng/mL and 24 hours post Day 15 dose were 442 ± 195 ng/mL. The itraconazole concentrations are in the range of those expected (USPI of itraconazole).

REFERENCES

1. Liu L, Bello A, Dresser MJ, Heald D, Komjathy SF, O'Mara E, et al. Best practices for the use of itraconazole as a replacement for ketoconazole in drug-drug interaction studies. J Clin Pharmacol. 2016. 56(2) 143-151.

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