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ARTICLE

Model-informed drug development of voxelotor in sickle cell disease: Population pharmacokinetics in whole blood and plasma

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Abstract

Oxbryta (voxelotor) is a small-molecule inhibitor of sickle hemoglobin (Hb) polymerization approved for patients with sickle cell disease (SCD) aged greater than or equal to 12 years at a dose of 1500 mg once daily (q.d.). Voxelotor binds preferentially to Hb, and voxelotor partitioning into red blood cells is an effective predictor of Hb occupancy. The objectives of these analyses were to develop a population pharmacokinetic (PopPK) model for voxelotor in both plasma and whole blood in adults and adolescents to support the dose selection for optimal target engagement and to identify covariates that have a significant effect on voxelotor pharmacokinetics (PK) in plasma and whole blood. An integrated plasma and whole blood PopPK model with two compartments, first-order absorption and elimination, and a site-of-action effect compartment adequately described the concentration-time profiles of voxelotor in plasma and whole blood in patients treated up to 72 weeks. Covariates with significant effects on voxelotor PK included baseline blood volume on apparent volume of the central compartment and time-varying hematocrit and dose on whole blood partitioning, indicating that clinical markers of voxelotor effect can, in turn, influence its PK. Furthermore, the model confirmed that voxelotor PK in plasma and whole blood is linear with dose and time and comparable for adults and adolescents. No clinically important covariate effects on voxelotor PK that warranted dose adjustment were identified in this analysis. Overall, the PopPK analyses contributed significantly to the voxelotor label and support 1500 mg q.d. as the therapeutic dose in adults and adolescents with SCD.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Voxelotor, approved for patients with sickle cell disease (SCD) aged greater than or equal to 12 years at a dose of 1500 mg once daily (q.d.), specifically and

reversibly binds sickle hemoglobin, increasing its oxygen affinity and inhibiting its polymerization.

WHAT QUESTION DID THIS STUDY ADDRESS?

This analysis aimed to support the dose selection for optimal target engagement and identify covariates that significantly affect voxelotor pharmacokinetics (PK) in plasma and whole blood using a single population PK (PopPK) model for voxelotor in both plasma and whole blood in adults and adolescents.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

A joint two-compartment PopPK model with first-order absorption and elimination and a site-of-action effect compartment adequately described the concentration-time profiles of voxelotor in plasma and whole blood. No clinically important covariate effects on voxelotor PK that warranted dose adjustment were identified.

HOW MIGHT THIS CHANGE DRUG DISCOVERY, DEVELOPMENT, AND/OR THERAPEUTICS?

The results of these PopPK analyses support 1500 mg q.d. as the therapeutic dose in adults and adolescents with SCD and provided valuable data for the prescribing information.

INTRODUCTION

Sickle cell disease (SCD) is an autosomal recessive genetic disorder caused by a point mutation in the hemoglobin (Hb) β-globin gene, resulting in the production of sickle hemoglobin (HbS).[1] When deoxygenated, HbS polymerizes and deforms red blood cells (RBCs) into a sickle shape, leading to cell membrane damage and abnormalities.[1–4] These damaged RBCs block capillaries and undergo hemolysis, which can trigger downstream effects, including anemia, fatigue, tissue ischemia, painful vaso-occlusive crisis (VOC), vascular injury, reduced quality of life, significant end-organ damage, and early death.[3,5–9] Approximately one in every 1941 neonates in the United States has SCD, and symptoms develop within the first 2 years of life.[1] Often, the initial sign of disease is a fatal infection, and, if undiagnosed, SCD is associated with significant mortality (25% to 90%, depending on geographic location) within the first 5 years of life. Children with SCD have an up to 300-fold increased risk for stroke and are also at risk for central nervous system injury. Early diagnosis and treatment can help prevent these complications and significantly reduce the risk of death.

Oxbryta (voxelotor) is a first-in-class oral therapy approved for patients with SCD aged greater than or equal to 12 years at a dose of 1500 mg once daily (q.d.).[10] Voxelotor specifically and reversibly binds HbS, increasing Hb-oxygen affinity and inhibiting HbS polymerization, the major driver of SCD pathophysiology.[11–13] Following oral administration, voxelotor is rapidly absorbed into plasma and then more slowly distributed into RBCs due to voxelotor's preferential binding to Hb.[12] Percent Hb occupancy within RBCs can be estimated as the ratio of the voxelotor concentration in RBCs (taking baseline hematocrit [HCT] into account) to the Hb concentration in RBCs. The estimated percent Hb occupancy is a good predictor of voxelotor's pharmacodynamics and correlates with the drug-induced change in Hb-oxygen affinity, Hb change from baseline, and Hb-oxygen saturation.[11] Voxelotor once daily has a linear pharmacokinetic (PK) profile, with dose-dependent increases in Hb-oxygen affinity into a range that is considered therapeutic for patients with SCD.[11] A persistent pancellular fetal Hb level of ~ 30% is observed in adults who are compound heterozygotes for HbS and hereditary persistence of fetal Hb, and these individuals generally have no SCD-related complications.[14] This finding suggests that binding ~ 30% of HbS in all RBCs with voxelotor to stabilize the oxygenated HbS state may be sufficient to inhibit polymerization, RBC sickling, and clinical sequelae of SCD.

For a thorough understanding of voxelotor clinical pharmacology, both whole blood and plasma PK must be considered because whole blood concentrations determine efficacy and both plasma and whole blood concentrations are relevant for safety. Furthermore, the relevant PK information to support the voxelotor label had to be obtained directly in patients with SCD using a population PK (PopPK) approach, as the blood-to-plasma partitioning of voxelotor in healthy subjects is different from patients with SCD, and the PK parameters obtained in healthy subjects are not representative.[11] Initially, two separate PopPK models were developed to describe the concentration-time profiles of voxelotor in whole blood and plasma of patients with SCD independently.[15,16] These two-compartment PopPK models with first-order absorption and first-order elimination

adequately described voxelotor plasma and whole blood PK data. A joint model describing the PK of voxelotor in plasma and whole blood together was considered necessary to allow for inclusion of correlations between plasma and whole blood PK parameters in subsequent simulations and for a single, coherent assessment of covariate effects impacting both plasma and whole blood PK.

The objectives of this analysis were to develop a single PopPK model for voxelotor in both plasma and whole blood in adults and adolescents with SCD to support the dose selection for optimal target engagement, to identify covariates that have a significant effect on voxelotor PK in plasma and whole blood, to derive exposure parameters for subsequent exposure-response analysis, and to provide adequate prescribing information for the voxelotor label.

METHODS

Clinical studies

The dataset comprised three voxelotor clinical studies that were approved by independent ethics committees and conducted in accordance with the Declaration of Helsinki and Good Clinical Practice: voxelotor first-in-human (FIH) study in adults (NCT02285088),[12] HOPE Kids 1 (NCT02850406), and HOPE (NCT03036813).[17] These studies had similar inclusion and exclusion criteria and, thus, had patient populations with similar baseline disease characteristics. All participants provided written informed consent.

The FIH study was a single- and multiple-ascending dose, phase I/II study in which adults with SCD received voxelotor (1000 mg single dose, 500 to 900 mg q.d., or 500 mg twice daily; $n = 52$) or placebo ($n = 17$) up to 90 days. Blood samples were collected intensively, semi-intensively, and sparsely. HOPE Kids 1 is a phase IIa study in which 47 patients with SCD aged 12 to 17 years received a single 600-mg voxelotor dose (part A) or multiple 900- or 1500-mg doses q.d. up to 24 weeks (part B). Blood samples were collected intensively and semi-intensively. HOPE was a multiple-dose, randomized, placebo-controlled phase III study in adolescents and adults with SCD who received voxelotor (900 or 1500 mg, $n = 180$) or placebo ($n = 91$) q.d. up to 72 weeks. Blood samples were collected semi-intensively and sparsely.

Population pharmacokinetic model development, evaluation, and application

Model development

An initial joint PopPK model included all patients from the FIH study and HOPE Kids 1 aged greater than or equal to 12 years who received voxelotor and patients in HOPE who received voxelotor and had up to 24 weeks of evaluable data. This initial model was subsequently updated to include long-term data from patients in HOPE who had evaluable data from weeks 36, 48, 60, and 72. The analyses were performed using a nonlinear mixed-effects modeling approach with NONMEM, version 7.3.0 or higher (ICON Development Solutions, Ellicott City, MD, USA) with Intel Fortran Compiler (version 12.0.4). The PopPK model estimation utilized the first-order conditional estimation with interaction method in NONMEM. Perl-speaks-NONMEM version 4.6.0 (Uppsala University, Sweden) or higher[18,19] was used for NONMEM runs, stepwise covariate modeling (SCM), and model evaluations. The R software version 3.4.0 (R Core Team 2019) or higher was used for post-processing of results.

Model selection was driven by data and based on standard goodness-of-fit plots and changes in the objective function value. Voxelotor concentration-time data were used to estimate PopPK parameters and their associated between-subject variability (BSV). BSV on PK model parameters was modeled assuming multiplicative (proportional) effects. Residual variability included additive and proportional error terms for whole blood and a proportional error term for plasma.

All covariate-parameter relationships evaluated are listed in Table S1. Covariates, including body weight, blood volume, age, hepatic (using baseline direct bilirubin and albumin), and renal (using baseline estimated glomerular filtration rate [eGFR] and cystatin C) impairment, baseline and time-varying HCT or Hb, baseline reticulocytes, and hydroxyurea (HU) use, were selected and tested based on their known or hypothetical effects on voxelotor PK. Cystatin C, evaluated in HOPE, has been identified as a more accurate predictor of renal impairment because patients with SCD hyperfiltrate.[7,20,21] Potential parameter-covariate relationships were identified via a univariate search ($p < 0.05$). Significance levels of $p < 0.01$ and $p < 0.001$ were used in the forward-addition and backward-elimination steps of the SCM process. Covariates that lacked sufficient data for testing in the covariate search or were confounded with other covariates were evaluated graphically by comparing individual post hoc parameter estimates. A full SCM was completed using the week 24 dataset, and a limited covariate search was undertaken with the week 72 PopPK dataset. All significant parameter-covariate relationships were added to the updated PopPK model, and a stepwise backward elimination search was used to identify the final covariate model.

Bootstrap re-sampling (at least 400 bootstrap datasets) was used to estimate nonparametric confidence intervals (CIs) for the model parameters and to assess model stability. Prediction-corrected visual predictive checks were

used to judge the suitability of the final model and greater than or equal to 500 replicates were simulated using the relevant models.

Post hoc estimates of individual PK parameters from the final PopPK model were used to predict the individual steady-state concentration time-course for each patient in the final PopPK analysis dataset. The predicted maximum and minimum voxelotor concentrations at steady-state (C_{max} and C_{min}, respectively) and area under the concentration curve from 0 to 24 h at steady-state (AUC) were calculated for all patients with individual PK parameter estimates. Calculations were based on an average dose, calculated per patient as the average of all doses in the dosing record. In addition, percent Hb occupancy within RBCs was estimated as the ratio of the voxelotor concentration in RBCs to the Hb concentration in RBCs (~ 5000 μM) or $100 \times \left(\frac{\text{Voxelotor RBC concentration}}{5000\ \mu M}\right)$,[11] where Voxelotor RBC concentration = $(\text{Voxelotor}_{\text{whole blood}} - (1 - \text{HCT}) \times \text{Voxelotor}_{\text{plasma}})/\text{HCT}$.

The final PopPK model was also used to simulate exposures in PK-evaluable patients in the final model dataset, assuming steady-state nominal dosing at 1500 mg q.d. for each patient. The resulting individual PK parameter estimates were used in a graphical post hoc analysis to evaluate the influence of intrinsic and extrinsic covariates on voxelotor PK in plasma and whole blood. Covariate effects were evaluated graphically as a function of model-predicted steady-state AUC, C_{max}, and C_{min} dose-normalized to 1500 mg. For categorical covariates, an analysis of variance was conducted to obtain a *p* value estimate for the difference across categories. These covariates included study, dose group, food intake, age, age group (adolescent vs. adult), HU use, SCD genotype, sex, race, region, number of VOCs in the previous 12 months, formulation, baseline Hb, baseline reticulocytes, hepatic and renal impairment, blood volume, baseline weight, and baseline, time-varying, and maximum HCT.

RESULTS

Patient population

The initial PopPK model dataset included 1848 and 1869 plasma and whole blood PK observations, respectively, from 246 patients with SCD who received greater than or equal to 1 voxelotor dose and had greater than or equal to 1 evaluable postdose PK concentration up to week 24 (52 from the FIH study, 47 from HOPE Kids 1, and 147 from HOPE). The dataset was subsequently expanded to include data from weeks 36, 48, 60, and 72, and previously excluded patients from HOPE, for a total of 2884 and 2709 plasma and whole blood PK observations, respectively, from 279 patients with SCD who received greater than or equal to 1 voxelotor dose up to week 72 (52 from the FIH study, 47 from HOPE Kids 1, and 180 from HOPE; Table 1). At baseline, patients were aged 12 to 59 years and weighed 28 to 135 kg; 27% were adolescents; 72% were Black, 12% were Arab or Middle Eastern, and 10% were White; 62% were using HU; and 79% were SCD genotype homozygous Hb S (HbSS), 13% were HbS β0 thalassemia, and 4% were Hb sickle cell. Median baseline Hb was 9 g/dl, blood volume was 4 L, albumin was 43 g/L, and HCT was 27%.

Model development

The original voxelotor plasma PopPK model served as the base for the joint model, with modifications to improve predictions of concentrations around C_{max}. The original model included BSV on apparent clearance (CL/F) and on apparent central volume (V_c/F) and was updated to also include BSV on the absorption rate constant (K_a) and between-occasion variability (BOV) on CL/F, with occasions defined based on sampling visits. Whole blood data were then added, and an effect compartment was incorporated into the model. The final PopPK model is a two-compartment model with first-order absorption and first-order elimination, coupled with a site-of-action effect compartment that describes the transfer of drug from a plasma compartment to a whole blood compartment according to a rate constant (K_{bp}) describing the observed delay for transfer between plasma and whole blood concentrations and a whole blood-to-plasma ratio of voxelotor concentration (R_{bp}) describing the increased voxelotor concentration in whole blood relative to plasma (Figure 1).

The final PopPK dataset included 2155 and 2168 plasma and whole blood PK observations from 264 patients. The resulting model had reasonable estimates of shrinkage on CL/*F* and V_c/F and a low condition number (<100). The results of the full forward addition and backward elimination covariate search using the week-24 data and the backward elimination search using the week-72 data are summarized in Tables S2 and S3, respectively. Ultimately, the final covariate model included relationships for blood volume on V_c/F, time-varying HCT and nominal dose on R_{bp}, and time-varying weak cytochrome P450 3A4 (CYP3A4) inducer on CL/*F*.

Model PK parameter estimates for the final PopPK model are summarized in Table 2. For a typical patient, the estimated CL/*F* was 6.14 L/h, and estimates of V_c/F, apparent peripheral volume (V_p/F), and apparent intercompartmental clearance (Q/F) were 333 L, 72.3 L, and 0.39 L/h, respectively. The typical estimates of K_a, K_{bp}, and R_{bp} were 2.38 h^{-1}, 0.43 h^{-1}, and 16.6, respectively.

TABLE 1 Patient baseline characteristics

Characteristic	PopPK (*N*=279)
Age (years)	22 (12–59)
Age group, *n* (%)	
Adolescent (12 to <18 years old)	76 (27)
Adult (18 to 59 years old)	203 (73)
Body weight (kg)	61 (28–135)
Sex, *n* (%)	
Male	118 (42)
Female	161 (58)
Race, *n* (%)	
Black	202 (72)
White	27 (10)
Arab/Middle Eastern	34 (12)
Other/multiple/missing	16 (6)
Sickle cell disease genotype, *n* (%)	
HbSS	220 (79)
HbSC	11 (4)
HbSβ0	35 (13)
HbSβ+ THAL	8 (3)
Missing/Other	5 (2)
Albumin (g/L)	43 (31–51)
Direct bilirubin (μmol/L)	10 (2–49)
HCT (%)	27.0 (17–40)
Hemoglobin (g/dl)	9 (6–12)
% Reticulocytes	9 (1–26)
Blood volume (L)	4 (2–7)
Maximum HCT (%)	32 (20–53)
HU use, *n* (%)	172 (62)
CYP3A4 inducer use, *n* (%)[a]	
Weak	14 (5)
Moderate	0

Note: All values are median (range) unless otherwise noted. The PopPK dataset comprises patients from the FIH study, HOPE Kids 1, and HOPE. In all studies, patients had to have SCD with Hb between ~ ≥6 and ≤10.5 g/dl, could take concomitant HU, and could not require chronic blood transfusion therapy or have had a transfusion 30 to 60 days prior to screening.

Abbreviations: CYP3A4, cytochrome P450 3A4; FIH, first-in-human; Hb, hemoglobin; HbSS, homozygous hemoglobin S; HbSC, hemoglobin sickle cell; HbSβ0, combination of sickle cell mutation and null beta-thalassemia mutations; HbSβ+ THAL, the combination of sickle cell mutation and beta-thalassemia (β-thal) mutations; HbSβ0 thalassemia, the combination of sickle cell mutation and null beta-thalassemia (β-thal) mutations; HCT, hematocrit; HU, hydroxyurea; *N*, total number of patients; *n*, number of patients in category; PK, pharmacokinetic; PopPK, population pharmacokinetic; SCD, sickle cell disease.

[a]Denominator is PK evaluable population (*N* = 264).

BSVs on CL/*F*, V_c/F, K_{bp}, and R_{bp} were 34.1%, 21.7%, 43.8%, and 15.2% coefficient of variance, respectively, and BOV on CL/*F* was 56.3%. Shrinkage was low for

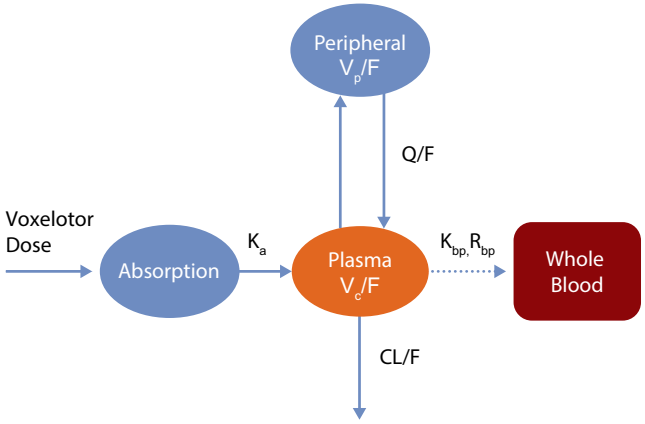

FIGURE 1 Voxelotor PopPK joint model structure. CL/F, apparent clearance; K_a, absorption rate constant; K_{bp}, rate constant for transfer between plasma and whole blood; PopPK, population pharmacokinetics; *Q*/*F*, apparent intercompartmental clearance; R_{bp}, whole blood-to-plasma ratio of voxelotor concentration; V_c/F, apparent central volume; V_p/F, apparent peripheral volume

CL/*F* (10.4%) and R_{bp} (21.3%), moderate for V_c/F (31.5%), and high for K_{bp} (43.4%). Estimates of shrinkage for BOV on CL/*F* were low to moderate, ranging from 6.1% to 40.6%, with a median of 28.5%. Residual shrinkage was low (15.5%).

Statistically significant ($p < 0.001$) covariate effects on the final model were observed on CL/F, V_c/F, and R_{bp}. Plasma PK were affected by concomitant use of a CYP3A4 inducer and by baseline blood volume. With concomitant use of a weak CYP3A4 inducer, CL/*F* increased by 47%, from 6.1 to 9.1 L/h. In addition, the typical V_c/F was 269 L in a patient with blood volume at the 10th percentile (2.9 L) and 413 L in a patient with blood volume at the 90th percentile (5.2 L), 19.5% lower and 23.6% higher, respectively, than the typical V_c/F (334 L) in a patient with median blood volume (3.9 L, which was slightly different than the blood volume reference value of 3.89 L used in the model; Figure 2a).

The predicted R_{bp} increased with increasing time-varying HCT and decreased with increasing dose (Figure 2b,c). R_{bp} was 15.0 at 10th percentile HCT (24.3%), 17.8 at median HCT (30.5%), and 21.0 at 90th percentile HCT (37.7%). At the median time-varying HCT (30.5%), the predicted R_{bp} was 17.2% lower following the 1500-mg dose (14.8) versus the 900-mg dose (17.8). However, at the maximum observed time-varying HCT (geometric mean 32.6% at 900 mg q.d. and 35.1% at 1500 mg q.d.), the covariate-adjusted estimates of R_{bp} were 16.4 at 1500 mg q.d. and 18.8 at 900 mg q.d. (only 12.4% lower vs. 17.2% lower at median time-varying HCT; Table S4). No statistically significant effects of sex, age, age group (adult vs. adolescent), or renal or hepatic impairment were observed in the final PopPK model.

TABLE 2 Final PopPK model parameter estimates

Description	Estimate (RSE [%])[a,b]	Shrinkage
CL/*F* (L/h)	6.14 (2.8)	NA
V_c/F (L)	333 (0.5)	NA
Q/F (L/h)	0.39 (1.9)	NA
V_p/F (L)	72.3 (0.8)	NA
K_{bp} (1/h)	0.43 (6.6)	NA
R_{bp}	16.6 (0.5)	NA
K_a (1/h)	2.38 (FIXED)	NA
Blood volume on V_c/F, $(BLV/3.89^{c})^{TH}$	0.74 (14.1)	NA
Hematocrit on R_{bp}, $(HCT/27.8)^{TH}$	0.77 (8.6)	NA
CYP3A4 inducer on CL/*F*, exp^{TH}	0.39 (4.9)	NA
Nominal dose on R_{bp}, $(dose/900)^{TH}$	−0.37 (10.8)	NA
Between subject or occasion variability		
BSV CL/*F*, % CV	34.1 (5.3)	10.4
CL/*F*-V_c/F BSV correlation	0.1 (123)	NA
BSV V_c/F, % CV	21.7 (7.7)	31.5
BSV K_{bp}, % CV	43.8 (10.4)	43.4
K_{bp}-R_{bp} BSV correlation	−0.102 (124)	NA
BSV R_{bp}, % CV	15.2 (7.6)	21.3
BOV on CL/*F*, % CV	56.3 (3.6)	28.5[d]
Residual variability		
Proportional error, plasma (%)	24.0 (2.1)	NA
Proportional error, whole blood (%)	17.0 (3.2)	NA
Additive error, whole blood (ng/ml)	880 (12.5)	NA

Note: All continuous covariate effects in the model were parameterized as power functions for example, $P = \theta_k \cdot \left(\left(X_i/M(X_i)\right)^{\theta_j}\right)$, where P is the population estimate of a parameter, X_i is the covariate of subject i for the parameter P, $M(X_i)$ is the median of covariate X for the subject population, θ_k is the typical value of the parameter P, and θ_j is a coefficient that reflects the covariate's effect on the parameter.

Abbreviations: % CV, percentage of coefficient of variance; BLV, blood volume; BOV, between occasion variability; BSV, between subject variability; CI, confidence interval; CL/F, apparent clearance; exp, exponential; CYP3A4, cytochrome P450 3A4; FIH, first-in-human; HCT, hematocrit; K_a, absorption rate constant; K_{bp}, rate constant from plasma to whole blood; NA, not applicable; PopPK, population pharmacokinetics; Q/F, apparent intercompartmental clearance; R_{bp}, whole blood-to-plasma ratio of voxelotor concentration; RSE, relative standard error; sqrt, square root; SE, standard error; TH, fixed-effect parameter estimate; V_c/F, apparent central volume; V_p/F, apparent peripheral volume.

[a]Estimates for CL/*F*, V_c/F, Q/F, V_p/F, K_{bp}, R_{bp}, and K_a are reported as exp(TH). Parameters were estimated as MU-referenced variables.[19] The RSEs are reported on the theta estimate. The % CV for omega is calculated as $100 \times \sqrt{(\text{omega})}$.

[b]The RSEs for omega (BSV and BOV) are reported on the approximate standard deviation scale (SE/variance estimate)/2.

[c]The blood volume reference value used in the model was 3.89 L.

[d]The shrinkage is the median of the 13 defined occasions. The individual estimates ranged from 6.1% at week 72 to 40.6% on day 25. The day 25 occasion was limited to 29 plasma and 29 whole blood observations in the FIH study patients.

Final model assessment

The parametric and bootstrap median estimates were similar, with the largest differences observed for estimates of BSV on K_{bp} (27.4%), BOV on CL/*F* (−18.6%), and blood volume on V_c/F (11.8%). All remaining differences were less than ±7%, and CIs were mostly similar. The median observed data in the studies with intensive data (the FIH study and HOPE Kids 1) were very well-described by the model. For HOPE, the data as a function of time after dose were mostly well-described; however, as shown in Figure 3, the solid line (median of the observed data) falls outside the darker shaded area at some time points, particularly for plasma data. The slight underprediction in plasma is not observed around the trough observations for the other studies, suggesting that it may be study related (e.g., due to potential errors in sample time records or unreported noncompliance).

Final model simulation

The final PopPK model was used to predict exposure metrics following a single nominal dose at steady-state. Exposures were predicted at the nominal dose received by each patient. PK in plasma and whole blood were linear from 500 to 1500 mg voxelotor q.d. Mean plasma and whole blood exposures and percent Hb occupancy at C_{min} and C_{max} were similar between adults and adolescents at 900 and 1500 mg voxelotor q.d. (Table 3). In addition, mean exposures and percent Hb occupancy in both age groups were greater at 1500 versus 900 mg q.d. At C_{min}, mean percent Hb occupancy in adults and adolescents was 16.2% and 16.1%, respectively, at 900 mg q.d. and 26.5% and 25.3%, respectively, at 1500 mg q.d.

The final PopPK model was also used to predict exposure metrics following a single 1500-mg nominal dose at steady-state, which were analyzed as a function of relevant covariates. Consistent with the final PopPK model, relationships between voxelotor plasma and/or whole blood exposures were observed for dose, baseline blood volume, and maximum HCT (included as a measure of time-varying HCT). Significant relationships were also observed between voxelotor whole blood and plasma exposures and baseline Hb, percent reticulocytes, baseline body weight, and sex. However, with effects of blood volume (calculated based on body weight and sex) on V_c/F included in the model, the effects of weight and sex were not statistically significant in the covariate search.

Although blood volume has a significant effect on voxelotor exposure and age and blood volume are correlated (blood volume was lower in adolescents), whole blood (Figure 4a) and plasma (Figure 4b) exposures and percent Hb occupancy in adolescents and adults were comparable in whole blood

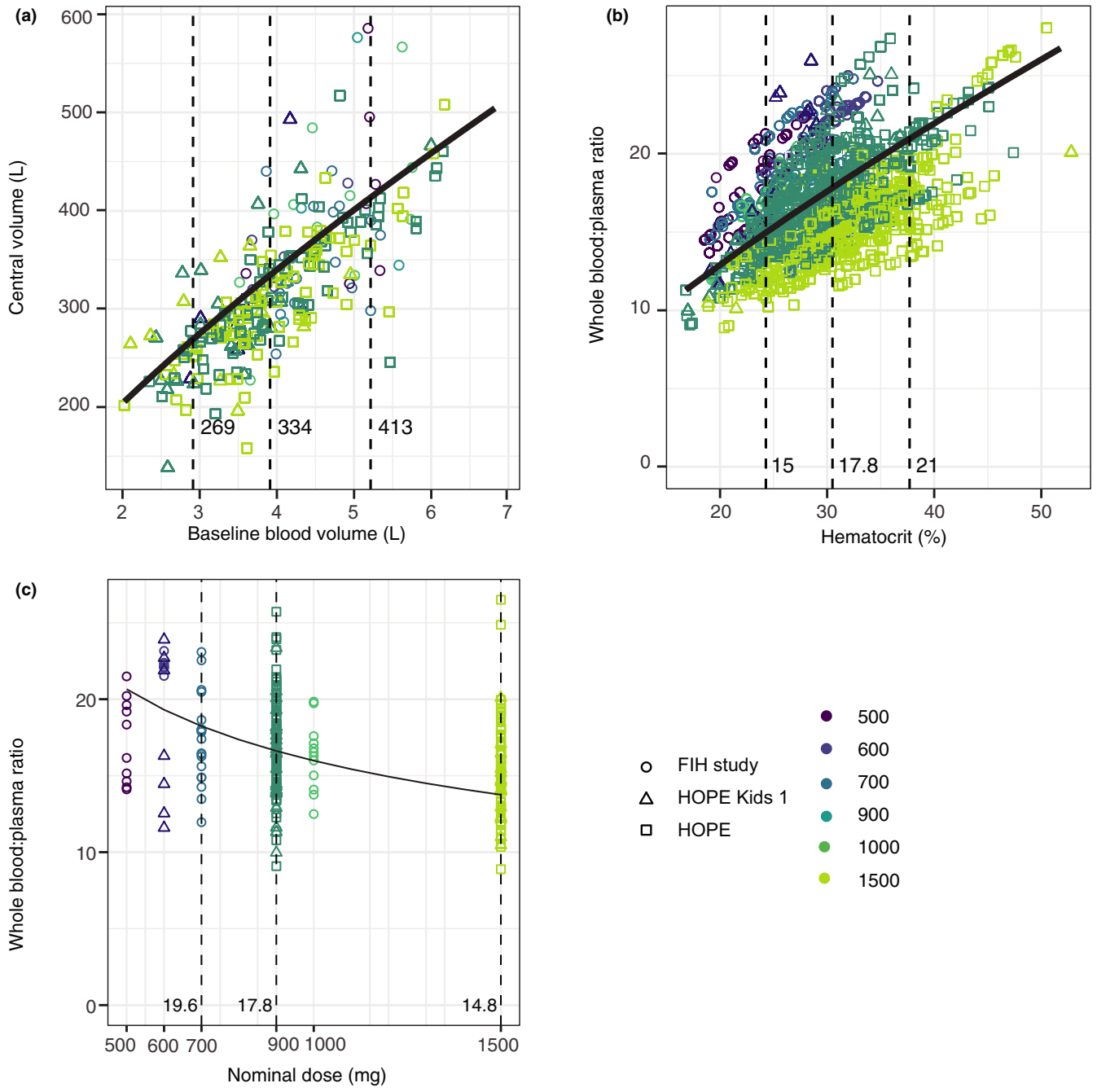

FIGURE 2 Effects of baseline blood volume on V_c/F, baseline hematocrit on R_{bp}, and dose on R_{bp} in the week-72 final PopPK model. Symbol colors correspond to the nominal dose in milligrams. Symbol shapes indicate the study number. The solid lines indicate the relationship described by each covariate-parameter effect in the PopPK model. FIH, first-in-human; PopPK, population pharmacokinetics; R_{bp}, whole blood-to-plasma ratio of voxelotor concentration; V_c/F, apparent central volume

and plasma, with no statistically significant differences observed. Similarly, no clinically relevant relationships (<20% difference) were observed between model-predicted voxelotor whole blood and plasma exposures and food, baseline direct bilirubin, HU use, number of prior VOCs, renal or hepatic impairment, or geographic region. Whole blood and plasma voxelotor exposures were slightly elevated in patients with unrestricted food status compared with patients who fasted or avoided high-fat meals prior to PK sample collection; however, they were less than 20% for all parameters and not likely to be clinically significant. There was a trend toward higher voxelotor exposures with lower cystatin C levels (17% to 35% higher at 0.5 to 0.7 vs. 1.0 to 2.6 mg/L), indicating that renal impairment did not impact voxelotor elimination or that there were too few patients with values outside the normal range (0.6 to 1 mg/L)[22] to detect any impact (cystatin C data were only available for 161 patients in HOPE, and only 34 of these patients had a value above 1 mg/L).

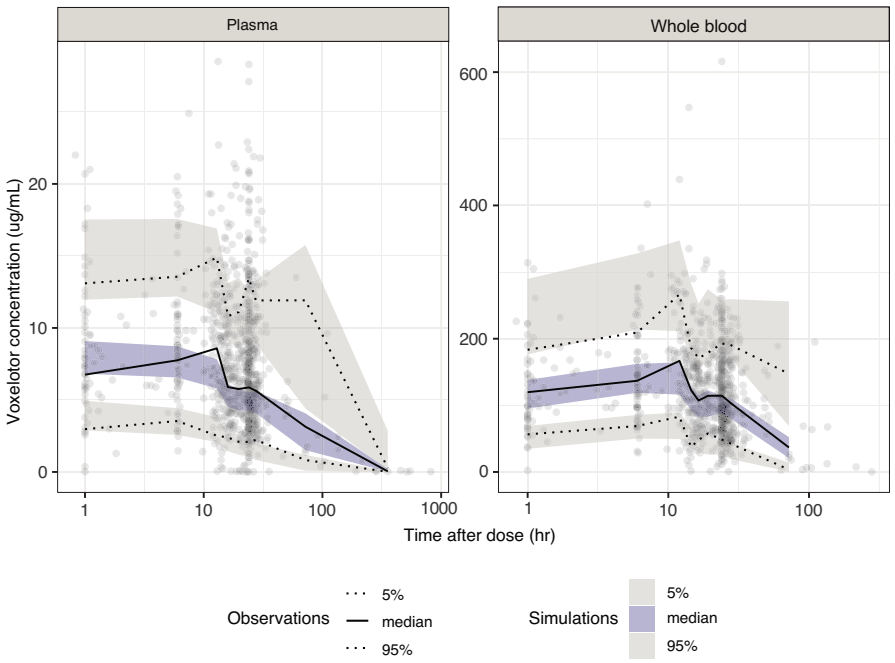

FIGURE 3 Prediction-corrected visual predictive check for HOPE by time after dose. The solid and dashed lines represent the median and the 5th and 95th percentiles of the observed data, respectively. The dark and light shaded regions represent the 90% confidence intervals around the median and the 5th and 95th percentiles of the simulated values ($N = 500$), respectively. The individual points are prediction-corrected observed pharmacokinetic data. *N*, number of values

TABLE 3 Voxelotor exposure and percent Hb occupancy estimates in adults and adolescents with SCD

	Voxelotor			
	900 mg		1500 mg	
	Adolescents	Adults	Adolescents	Adults
	N = 38	*N* = 70	*N* = 29	*N* = 68
Half-life, h (plasma)	30.3 (43)	35.6 (33)	32.7 (27)	39.4 (31)
AUC, h×μg/ml				
Plasma	143 (41)	142 (32)	265 (32)	274 (28)
Whole blood	2280 (44)	2250 (36)	3610 (33)	3780 (35)
C_{min}, μg/ml				
Plasma	4.37 (61)	4.61 (40)	8.47 (39)	9.14 (34)
Whole blood	74.9 (57)	76.8 (43)	122 (38)	132 (40)
C_{max}, μg/ml				
Plasma	7.59 (31)	7.24 (26)	13.7 (27)	13.7 (24)
Whole blood	110 (38)	107 (33)	172 (30)	177 (32)
% Hb occupancy				
At C_{min}	16.1 (55)	16.2 (37)	25.3 (36)	26.5 (33)
At C_{max}	23.4 (38)	22.4 (27)	35.4 (28)	35.4 (26)

Note: All values are geometric mean (% CV).

Abbreviations: % CV, percentage of coefficient of variance; AUC, area under the curve from 0 to 24 h at steady-state; C_{max}, maximum drug concentration at steady-state; C_{min}, minimum drug concentration at steady-state; Hb, hemoglobin; SCD, sickle cell disease.

DISCUSSION

This PopPK analysis demonstrated that a joint two-compartment PK model with first-order absorption and elimination and a site-of-action effect compartment adequately described the concentration-time profiles of voxelotor in plasma and whole blood of patients with SCD. For a typical patient, the estimated CL/*F* was 6.14 L/h, and estimates of V_c/F, V_p/F, and Q/F were 333 L, 72.3 L, and 0.39 L/h, respectively. The partitioning into blood was slow (K_{bp} 0.43 h^{-1}), and the estimated R_{bp} of 16.6 confirmed the strong partitioning into RBCs. The estimated R_{bp} of 16.6 implies an RBC/plasma ratio of 58.8, which is in the expected range for patients with SCD.[11]

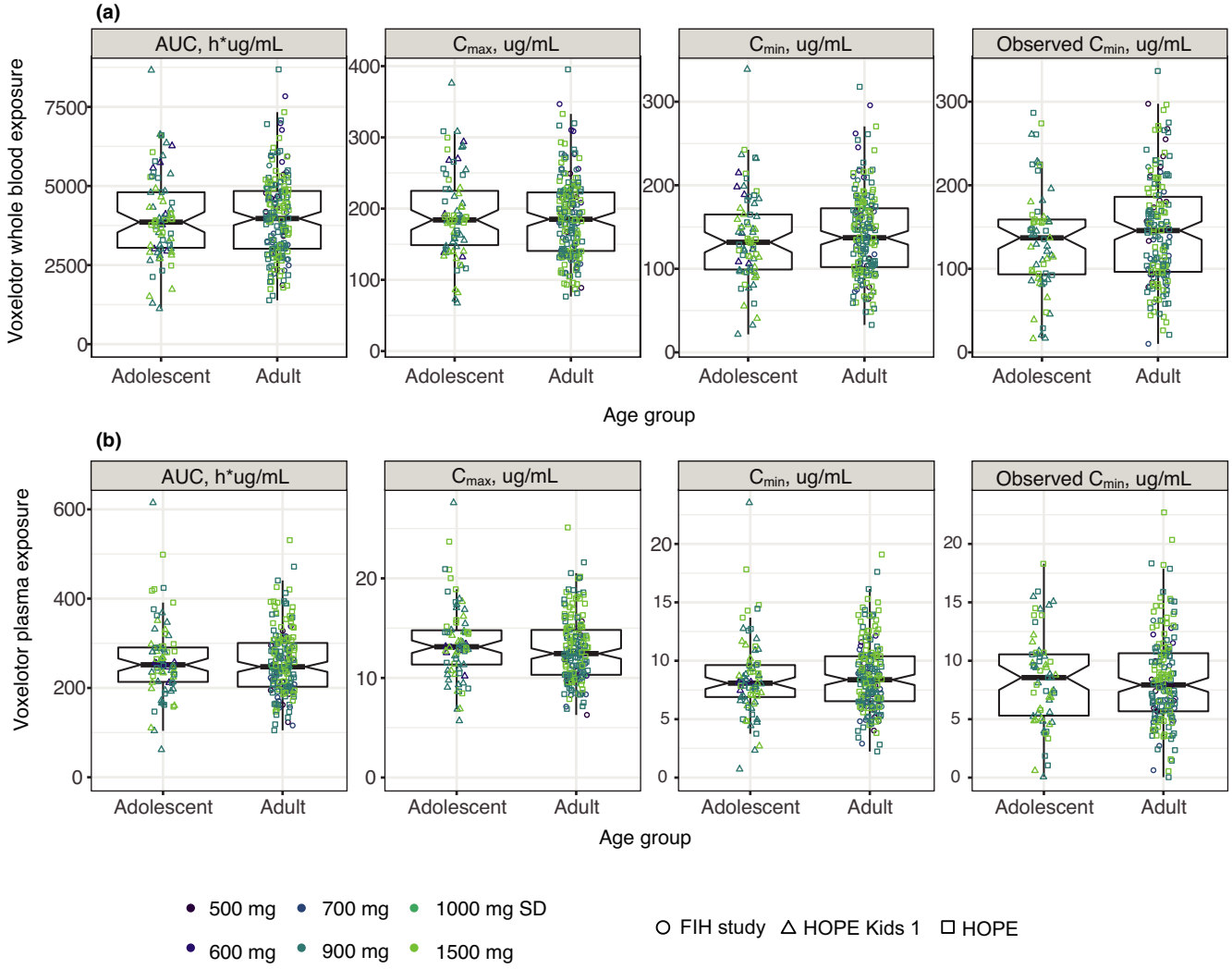

FIGURE 4 Model-predicted and observed steady-state and dose-normalized plasma and whole blood exposures in adolescents and adults. Observed C_{min} is the median observed dose-normalized trough concentration. AUC, area under the curve from 0 to 24 h at steady-state; C_{max}, maximum drug concentration at steady-state; C_{min}, minimum drug concentration at steady-state; FIH, first-in-human; SD, single dose

The joint model describing the PK of voxelotor in plasma and whole blood together allowed a coherent assessment of covariate effects impacting both plasma and whole blood PK and gave some interesting insights into the effects of patient and disease characteristics on the compound's behavior. Covariates with significant effects on voxelotor PK in the final PopPK model included baseline blood volume on V_c/F and time-varying HCT and voxelotor dose on whole blood partitioning, indicating that clinical markers of voxelotor effect can, in turn, influence its PK. This is most likely because as dose increases, voxelotor partitioning decreases, but HCT increases, partially offsetting the difference in partitioning. In addition, exposure-response analyses have demonstrated a concentration-dependent voxelotor effect on measures of hemolysis, including Hb, reticulocytes, lactate dehydrogenase, and indirect bilirubin (unpublished data). Indeed, the covariate-adjusted estimate of R_{bp} was 17.2% lower with the 1500-mg versus 900-mg voxelotor dose at median time-varying HCT but only 12.4% lower at maximum observed time-varying HCT.

Concomitant CYP3A4 inducer use had a significant effect on CL/F; however, the use of strong CYP3A4 inducers was prohibited in the studies, and there were only nine patients in the dataset who were using weak CYP3A4 inducers concomitantly. Furthermore, results from a separate drug-interaction study and a physiologically based PK model suggest that strong CYP3A4 inducers will significantly reduce voxelotor exposures but that weak CYP3A4 inducers will not. No statistically significant effects of sex, age, age group, or renal or hepatic impairment on the final model were observed in this PopPK analysis.

Model-predicted exposure metrics following a single nominal dose at steady-state at the nominal dose received by each patient demonstrated that voxelotor PK is linear and dose proportional, with comparable exposure

and percent Hb occupancy in adults and adolescents. In both groups, mean exposures and percent Hb occupancy were greater with the 1500-mg q.d. voxelotor dose versus the 900-mg q.d. dose. Mean percent Hb occupancy at C_{min} was 25% to 27% at the 1500-mg dose and ~ 16% at the 900-mg dose in adults and adolescents, supporting the approval of 1500 mg q.d. as the effective dose based on the fact that individuals with HbS and hereditary persistence of fetal Hb who typically have ~ 30% circulating fetal Hb generally do not experience a severe SCD clinical course.[14]

Post hoc analysis of model-predicted exposures in plasma and whole blood as a function of relevant covariates revealed relationships between voxelotor plasma and whole blood exposures for dose, baseline blood volume, maximum HCT, baseline Hb, and percent reticulocytes. These results suggest that Hb and HCT, which are both measures of anemia, are also important cofactors for the PK of voxelotor in patients with SCD. The low levels of Hb and HCT at baseline in patients with SCD increase in response to treatment, more so with 1500 versus 900 mg q.d., thus, increasing the HbS available for binding of voxelotor. As Hb and HCT increase due to the drug effect, voxelotor whole blood exposures at a given dose continue to increase.

Voxelotor PK in plasma and whole blood were not significantly impacted by age, sex, food intake, renal function, or concomitant use of HU; thus, as is noted in the prescribing information, there is no cause for dose adjustment in these populations. In addition, voxelotor PK in plasma and whole blood were comparable between adolescents and adults. There was a slight increase in exposure in adolescents, most likely because age is related to blood volume, but this difference was not statistically or clinically significant, and no dose adjustment is warranted for adolescents. These data are important because early, effective treatment can prevent mortality and complications in children. In addition, as noted in the prescribing information,[10] we found that exposures were slightly elevated in patients with unrestricted food status compared with patients who fasted or avoided high-fat meals prior to PK sample collection. However, increases were less than 20% for all parameters and not likely to be clinically significant; thus, in the prescribing information, it is noted that voxelotor can be taken with or without food.

Voxelotor PK in plasma and whole blood were not significantly impacted by renal impairment in this analysis, which is consistent with the results of a previously published study[22] in which only minor effects of severe renal impairment (eGFR <30 ml/min/1.73 m^2) on voxelotor exposure were observed compared with controls, suggesting that dose adjustment is not warranted in this patient population. In contrast, voxelotor exposure was ~ 90% higher in patients with severe hepatic impairment (Child-Pugh C) compared with controls, and a lower voxelotor dose (1000 mg) is recommended in this patient population in the approved prescribing information.[22]

In conclusion, these analyses demonstrated that voxelotor PK in both plasma and whole blood can be adequately described using a joint model. Mean exposures and percent Hb occupancy were greater with voxelotor 1500 versus 900 mg q.d. and similar in adults and adolescents. Simulations confirmed that effects of the intrinsic and extrinsic covariates tested on voxelotor PK in plasma and whole blood were not clinically significant, and no dose adjustments are warranted except in patients with severe hepatic impairment, which is based on results from a separate study. Overall, the PopPK analyses contributed significantly to the voxelotor label and support 1500 mg q.d. as the therapeutic dose in adults and adolescents with SCD.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

R.M.S., M.G., K.J., M.Z., and C.B.W. wrote the manuscript. R.M.S., K.J., and C.B.W. designed the research. K.J. and C.B.W. performed research. R.M.S., M.G., and M.Z. analyzed the data.

DATA AVAILABILITY STATEMENT

The datasets and model code generated and/or analyzed during the current study are not publicly available because they contain human subject data but are available from the corresponding author on reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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