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ARTICLE

Model-informed drug development of voxelotor in sickle cell disease: Exposure-response analysis to support dosing and confirm mechanism of action

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Abstract

Sickle cell disease (SCD) is characterized by the production of sickle hemoglobin (HbS), which when deoxygenated, polymerizes leading to red blood cell damage and hemolytic anemia, a defining feature of SCD. Voxelotor (Oxbryta) is a small molecule inhibitor of HbS polymerization that disrupts the polymerization mechanism by binding HbS to increase HbS oxygen affinity. Voxelotor is approved in the United States for the treatment of SCD in patients greater than or equal to 12 years of age at a 1500 mg once-daily (q.d.) dose. These exposure-response analyses aimed to evaluate the relationships between voxelotor whole blood concentration and change from baseline (CFB) in clinical measures of anemia and hemolysis and between voxelotor whole blood and plasma concentrations and the incidence of selected safety end points to confirm the voxelotor mechanism of action and to support the clinical dose recommendation. In patients treated with voxelotor up to 72 weeks, CFB hemoglobin (Hb) increased linearly ($p < 0.001$) with increasing voxelotor concentration and percent Hb occupancy and increases in CFB Hb corresponded to improvements in measures of hemolysis. The target 1 g/dl increase in CFB Hb was achieved with 1500 mg voxelotor q.d. Significant relationships were observed between voxelotor exposures and grade greater than or equal to 1 increased alanine aminotransferase and decreased white blood cell count; however, most events were grade 1. No clinically important covariate effects on voxelotor efficacy or safety were observed. Overall, these analyses support 1500 mg q.d. as the therapeutic dose for voxelotor in adults and adolescents.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Voxelotor is a small molecule inhibitor of sickle hemoglobin (HbS) polymerization that increases HbS oxygen affinity to reduce anemia and hemolysis, hallmarks of sickle cell disease pathogenesis.

WHAT QUESTION DID THIS STUDY ADDRESS?

The voxelotor therapeutic dose of 1500 mg q.d. was evaluated through an exposure-response (E-R) analysis of efficacy and safety between voxelotor concentration, clinical measures of anemia and hemolysis, and treatment-emergent adverse events (TEAEs) in adult and adolescent patients up to 72 weeks of treatment.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

Significant relationships between voxelotor concentration and clinical measures of anemia and hemolysis confirm the 1500 mg q.d. dose compared to 900 mg. The significant relationship between change in hemoglobin with hemolysis improvements supports the voxelotor mechanism of action. No statistically significant E-R safety relationships with grade greater than or equal to 2 TEAEs suggest minimal clinical impact for grade greater than or equal to 1 relationships for alanine aminotransferase and white blood cell counts.

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

The study was part of the registration package and supported approval of 1500 mg q.d. as the recommended voxelotor dose. It also supports expansion to younger patients.

INTRODUCTION

Sickle cell disease (SCD) is an autosomal recessive disorder characterized by the production of sickle hemoglobin (HbS) caused by a point mutation in the hemoglobin (Hb) β-globin gene.[1] When HbS is deoxygenated, HbS polymerizes resulting in red blood cell (RBC) sickling and membrane damage, leading to hemolysis, chronic hemolytic anemia, inflammation, and vaso-occlusion.[1,2] The polymerization of HbS drives SCD pathogenesis and patients with SCD experience chronic hemolysis and hemolytic anemia, resulting in vascular damage and tissue hypoxia, which contribute to multi-organ damage and an increased risk of death.[3–6] The rate of HbS polymerization, which is sensitive to deoxygenated HbS concentration, is inhibited by oxygenated Hb and fetal hemoglobin (HbF) production and provides a therapeutic target.[7,8]

Voxelotor (Oxbryta), an orally administered inhibitor of HbS polymerization, is approved for the treatment of SCD in adult and pediatric patients 12 years of age and older at a dose of 1500 mg once daily (q.d.) in the United States.[9] Voxelotor targets the HbS polymerization mechanism by binding to HbS through a reversible covalent bond with the N-terminal valine of one of the Hb alpha chains. The corresponding increase in HbS oxygen affinity through an allosteric modification stabilizes the oxygenated Hb state and inhibits polymerization.[7] Compound heterozygote individuals with hereditary persistence of HbF maintain ~ 30% circulating HbF without a severe SCD clinical course.[10] Based on this clinical data, voxelotor treatment aims for 20–30% HbS occupancy to inhibit HbS polymerization.

After oral administration, voxelotor is rapidly absorbed into plasma and distributed into RBCs, due to voxelotor's preferential binding to Hb.[11,12] Voxelotor RBC partitioning plays an essential role in its pharmacokinetics (PKs) in plasma and whole blood and represents at the same time the target compartment for the voxelotor pharmacodynamic (PD) effect. This feature makes voxelotor a very unique case for model-informed drug development (MIDD). We developed a population PK (PopPK) model to describe the voxelotor concentration versus time profiles in plasma and whole blood and approximated the increase of Hb oxygen affinity by calculating the RBC voxelotor concentration (percent Hb [%Hb] occupancy) from whole blood and plasma concentrations.[13] Because increases in Hb decrease the rate of multi-organ failure and death, a targeted increase in Hb levels of 1 g/dl has been used to determine the efficacious dose for voxelotor in a broad patient population (adults and adolescents).[8]

Chronic hemolysis and anemia are defining features of SCD due to RBC sickling and membrane damage. Anemia in SCD has consistently been shown to predict end-organ damage and is directly related to Hb levels. Reduced HbS polymerization decreases RBC damage. Model-based techniques were used to explore the effects of voxelotor by linking the increases in Hb to clinical measures of anemia (change from baseline [CFB] Hb) and hemolysis (percent CFB [%CFB] indirect bilirubin, %CFB reticulocytes [absolute and percent], and %CFB lactate dehydrogenase [LDH]).

The pivotal voxelotor phase III HOPE clinical trial (NCT03036813) included a higher dose than previously evaluated[11] as a result of the prediction from the PopPK

model that a 1500 mg dose could achieve the targeted 1 g/dl increase in Hb.[13] In the HOPE study, voxelotor demonstrated a clinically meaningful and statistically significant increase in Hb, decreased clinical measures of hemolysis, and had a favorable safety profile in a comparison of 1500 mg and 900 mg q.d. doses.[8,14] This study was the basis for the marketing authorization submissions of voxelotor for SCD in patients 12 years and older in the United States and Europe. This paper describes the exposure-response (E-R) analysis of efficacy and safety results that were part of the marketing authorization submissions to the US Food and Drug Administration and the European Medicines Agency to support the evaluation of the benefit/risk of 1500 mg versus 900 mg voxelotor q.d. for 24 or 72 weeks of treatment based on the phase III voxelotor HOPE trial.[8,14] Three E-R analyses for efficacy were completed. The first PK/PD analysis at 24 weeks examined CFB Hb (primary efficacy end point) as a function of PK parameters and %Hb occupancy as an indicator of Hb modification to support dose selection. The second PK/PD analysis evaluated clinical measures of hemolysis and anemia as a function of time-matched voxelotor concentrations to evaluate the persistence of the relationship up to 72 weeks. The third PD/PD analysis evaluated the relationship between CFB Hb with clinical measures of hemolysis. This evaluation of the relationship between the primary clinical end point and further downstream efficacy markers provided further evidence for the voxelotor mechanism of action (MOA). These analyses aimed to assess the benefit/risk of the subsequently approved dose of 1500 mg voxelotor q.d. up to 72 weeks while also confirming the MOA.

METHODS

Clinical studies and design

Data from two voxelotor clinical studies were included in the E-R analyses: HOPE Kids 1 (phase IIa, NCT02850406) and HOPE.[8,14] Both studies were approved by independent ethics committees and conducted in accordance with the Declaration of Helsinki and Good Clinical Practice. All participants provided written, informed consent for participation.

HOPE Kids 1 is a phase IIa study with multiple parts in pediatric patients with SCD. Adolescent patients aged 12–17 years from part B (multiple-dose, 900 or 1500 mg, up to 24 weeks), that has been completed, were included. Semi-intensive whole blood and plasma PK samples were collected. HOPE was a multiple-dose, randomized, placebo-controlled phase III study in adolescents and adults with SCD who received voxelotor 900 or 1500 mg or placebo up to 72 weeks. Semi-intensive and sparse whole blood and plasma PK samples were collected. Further study design details and results have been reported previously.[8,14]

E-R efficacy analyses at 24 weeks included data from HOPE Kids 1 ($n = 34$ adolescents from part B) and HOPE ($n = 169$ adults, $n = 35$ adolescents). E-R efficacy analyses at 72 weeks included data from HOPE Kids 1 ($n = 39$ adolescents from part B) and HOPE ($n = 212$ adults, $n = 45$ adolescents). E-R safety analyses included data from 257 adults and adolescents in HOPE at 72 weeks.

PK parameter estimates

For the E-R analysis, PK parameters were calculated from individual post hoc parameters from the PopPK analysis.[13] PK parameters (area under the concentration-time curve at steady-state over 24 h [AUC] and the maximum concentration and minimum concentration at steady-state [C_{max} and C_{min}]) were predicted following steady-state voxelotor dosing. In addition, the %Hb occupancy within RBCs at C_{max} and C_{min} were calculated for each subject. Further details are provided in the Supplementary Methods.

Exposure-Efficacy analysis

Three separate analyses evaluated the impact of voxelotor exposure on efficacy end points. The first was an E-R analysis using steady-state PK parameters where clinical measures of anemia (CFB Hb at week 24, the primary end point) and hemolysis (%CFB reticulocytes [absolute and percent], indirect bilirubin, and LDH at week 24) were explored as a function of whole blood AUC, C_{max}, C_{min}, and %Hb occupancy at C_{min} to support dose selection. Null, linear, and polynomial functions of exposure were compared. The Akaike Information Criterion was used for model discrimination.

The second analysis evaluated the persistence of the concentration-effect relationships over time. Relationships between time-matched voxelotor whole blood concentrations and CFB Hb or %CFB reticulocytes (absolute and percent), indirect bilirubin, and LDH, including data from all visits until week 72 were analyzed graphically by linear regression. This analysis is described as a "PK/PD" evaluation to distinguish it from the "PD/PD" evaluation described below. The use of time-matched data facilitated evaluation of the effect's persistence over the course of treatment because previous exploratory studies suggested maximal responses were achieved within 2 weeks of treatment initiation[8,11] and turnover half-life estimates were 1 to 4 days (data not shown).

The third analysis evaluated the PD/PD relationships between clinical measures of hemolysis and CFB Hb. Graphical linear regression analyses aimed to identify correlations between improvements in CFB Hb with improvements in clinical measures of hemolysis, including data from all visits until week 72.

For the three analyses, linear and second-degree polynomial relationships were evaluated graphically. Covariates were examined graphically and included study, age group (adult vs. adolescent), hydroxyurea (HU) use, sex, SCD genotype, and baseline body weight quantile. PK/PD and PD/PD relationships were also evaluated across bins of nominal visit time (i.e., ≤12 weeks, 12 to 24 weeks, and 24–72 weeks). Linear regression of the E-R relationship between CFB Hb at week 24 and %Hb occupancy provided an estimated dose required to achieve a 1 or 2 g/dl increase in Hb at week 24. Final model parameters are provided in Tables S1–S4.

Exposure-safety analysis

The exposure-safety analysis of week 72 data tested non-SCD-related treatment-emergent adverse events (TEAEs) grade greater than or equal to 1 and SCD-related TEAEs grade greater than or equal to 2. Non-SCD-related TEAEs included the laboratory variables increased alanine aminotransferase (ALT) and decreased white blood cell (WBC) count. SCD-related TEAEs included sickle cell anemia with crisis, acute chest syndrome, pneumonia, and vaso-occlusive crisis, among others. Exposure metrics included AUC, C_{min}, and C_{max}, and %Hb occupancy. Further details are provided in the Supplementary Methods.

Safety end points were analyzed by logistic regression with a linear drug effect model, where each variable was represented as a binary end point, with a single record for each patient. Patients not experiencing an event were assigned "0" and patients who experienced a transition from a null baseline status to a recorded event (e.g., an increase in grade from baseline and a grade ≥1 or grade ≥2 observation, as appropriate) were assigned "1." Covariate effects were tested on the intercept and as an interaction with voxelotor exposure, using a two-stage approach where all covariates found to be statistically significant in a univariate search were tested in a stepwise forward ($p < 0.05$) and backward ($p < 0.01$) search. Safety end points and covariate evaluations with either no or very few patients with or without events and no or few patients within subgroups, respectively, were excluded from the analysis.[15,16] Covariates included age group (adolescent vs. adult), race, body weight, sex, and HU use; voxelotor exposure was added to the model regardless of statistical significance. Given the increased whole blood exposures observed for patients of Arab or Middle Eastern race in the PopPK analysis,[13] effects of race were evaluated in the safety analysis to account for confounded effects that might mask E-R relationships in the larger population. Final models for end points with statistically significant relationships are provided in Tables S5 and S6.

RESULTS

Patient populations

At week 24, the E-R efficacy analysis dataset included 238 placebo or PK-evaluable patients, comprising 34 patients from HOPE Kids 1 (22 in 900 mg and 12 in 1500 mg voxelotor dose groups), and 204 patients from HOPE (76 in placebo, 66 in 900 mg, and 62 in 1500 mg voxelotor dose groups). The PK/PD analysis dataset at 72 weeks for time-matched concentrations included up to 296 placebo or PK-evaluable patients, 39 patients from HOPE Kids 1 (24 in 900 mg and 15 in 1500 mg voxelotor dose groups), and 257 patients from HOPE (91 in placebo, 84 in 900 mg, and 82 in 1500 mg voxelotor dose groups; Table 1). The PD/PD dataset included up to 311 placebo or treated patients depending on the end point. The E-R safety analysis dataset included only the 257 placebo or PK-evaluable patients from HOPE. Baseline covariates were relatively well-matched between dose and treatment groups in both HOPE Kids 1 and HOPE at 24 weeks (data not shown) and 72 weeks (Table 1). For HOPE Kids 1 and HOPE combined, the median age was 22 years, median body weight was 59.2 kg, the majority of patients were SCD homozygous hemoglobin S genotype (77%), and the median Hb was 8.5 g/dl.

Exposure-response analyses for efficacy

Efficacy E-R analysis with PK parameters

The E-R analysis showed at week 24 with a voxelotor dose of 1500 mg q.d., CFB Hb increases were significantly ($p < 0.001$) correlated with increases in voxelotor steady-state PK parameters (AUC, C_{min}, and C_{max}). Similarly, increases in %Hb occupancy at C_{min} were significantly ($p < 0.001$) correlated with increased CFB Hb. The predicted mean CFB Hb following 24 weeks of treatment at 1500 mg voxelotor q.d. met or exceeded the 1 g/dl target increase for all PK parameters, including %Hb occupancy, whereas treatment with 900 mg voxelotor q.d. did not meet the 1 g/dl targeted Hb increase across the four parameters (Figure 1).

Percent CFB for clinical measures of hemolysis (absolute and percent reticulocytes, indirect bilirubin, and

TABLE 1 Patient baseline characteristics at 72 weeks

	E-R efficacy analyses				
			E-R safety analyses		
Characteristic	HOPE Kids 1 900 mg, *n* = 24	HOPE Kids 1 1500 mg, *n* = 15	HOPE placebo, *n* = 91	HOPE 900 mg, *n* = 84	HOPE 1500 mg, *n* = 82
Age, years	14.0 (12–17)	14.0 (12–17)	27.0 (12–64)	23.5 (12–59)	23.0 (12–59)
Age group, *n* (%)					
Adolescent	24 (100)	15 (100)	17 (19)	14 (17)	14 (17)
Adult	0	0	74 (81)	70 (83)	68 (83)
Body weight, kg	49.0 (30.2–93.3)	48.0 (31.0–72.3)	61.0 (25.4–164.0)	60.9 (28.7–135.0)	59.9 (28.0–112.0)
Sex, *n* (%)					
Male	13 (54)	5 (33)	42 (46)	38 (45)	30 (37)
Female	11 (46)	10 (67)	49 (54)	46 (55)	52 (63)
Race, *n* (%)					
Black/African American	17 (71)	11 (73)	62 (68)	53 (63)	53 (65)
White	7 (29)	4 (27)	3 (3)	6 (7)	6 (7)
Arab/Middle Eastern	0	0	18 (20)	18 (21)	14 (17)
Other/multiple/missing	0	0	8 (9)	7 (8)	9 (11)
Region, *n* (%)					
North America	17 (71)	12 (80)	34 (37)	31 (37)	31 (38)
Mid-southern Africa			18 (20)	17 (20)	14 (17)
Middle East	7 (29)	3 (20)	21 (23)	24 (29)	24 (29)
Europe			16 (18)	12 (14)	13 (16)
Caribbean			2 (2)	0	0
Sickle cell disease genotype, *n* (%)					
HbSS	24 (100)	12 (80)	73 (80)	64 (76)	55 (67)
HbSC	0	0	2 (2)	2 (2)	3 (4)
HbSβ0	0	3 (20)	11 (12)	12 (14)	17 (21)
HbSβ+ THAL	0	0	3 (3)	2 (2)	6 (7)
Missing/other	0	0	2 (2)	4 (5)	1 (1)
Albumin (g/L)	NR	NR	43 (33–50)	43 (33–49)	43 (35–50)
Indirect bilirubin, μmol/L	51.3 (8.7–188.0)	25.7 (11.5–123.0)	33.4 (5.4–259.0)	30.6 (7.2–179.0)	29.6 (8.0–160.0)
HCT (%)	25.7 (17.0–36.0)	26.0 (18.2–31.6)	28.5 (18.2–38.4)	27.1 (18.0–39.8)	28.5 (17.9–35.2)
Hemoglobin, g/dl	8.8 (6.4–12.0)	8.8 (6.2–10.5)	8.5 (6.0–10.7)	8.4 (5.9–11.0)	8.8 (5.7–10.9)
LDH (U/L)	536.5 (220.0–1280.0)	446.0 (274.0–1050.0)	377.0 (165.0–1140.0)	409.0 (172.0–1220.0)	340.5 (164.0–813.0)
Reticulocytes (10^9/L)	NR	NR	294.0 (57.0–671.0)	329.0 (88.0–654.0)	278.5 (24.0–783.0)
% Reticulocytes	9.7 (3.2–26.3)	8.8 (3.8–20.3)	10.2 (1.4–21.8)	11.6 (2.4–23.2)	9.2 (1.3–22.1)
Blood volume (L)	NR	NR	4.0 (2.3–8.2)	3.9 (2.4–6.9)	3.9 (2.0–6.2)
Maximum HCT (%)	30.6 (21.0–36.8)	32.0 (29.0–52.8)	31.0 (20.6–42.3)	33.5 (21.6–47.4)	36.9 (24.7–50.5)
HU use, *n* (%)	21 (88)	15 (100)	57 (63)	56 (67)	55 (67)

Data include patients in the week 24 E-R analyses.

All values are median (range) unless otherwise noted.

Placebo patients from HOPE were included in both the week 72 analysis and the analysis of data at all timepoints.

Abbreviations: E-R, exposure-response; HbSC, hemoglobin sickle cell; HbSS, homozygous hemoglobin S; HbSβ+ THAL, the combination of sickle cell mutation and beta-thalassemia mutations; HbSβ0, the combination of sickle cell mutation and null beta-thalassemia mutations; HCT, hematocrit; HU, hydroxyurea; LDH, lactate dehydrogenase; *n*, number of patients; NR, not reported.

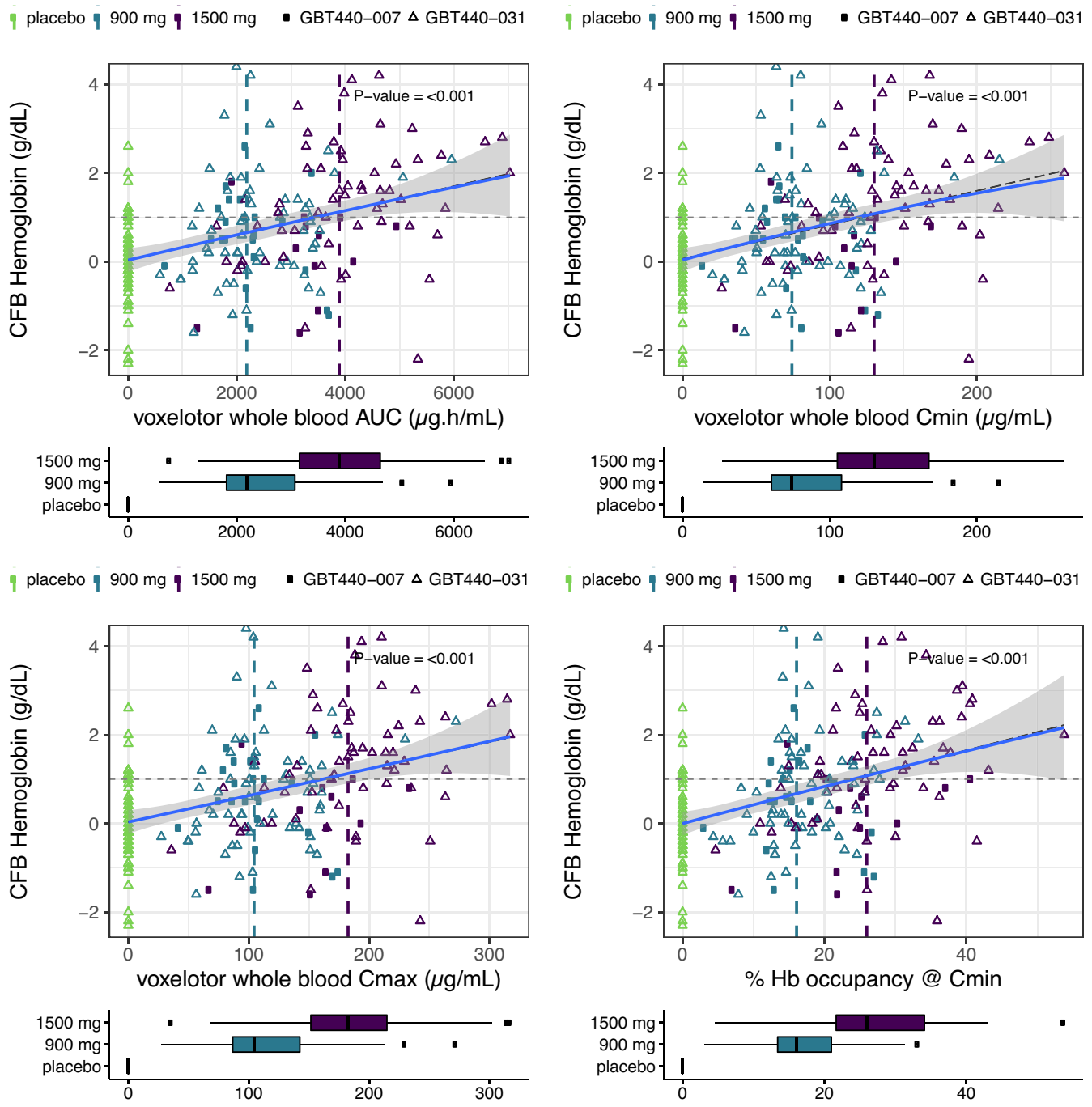

FIGURE 1 Relationship between CFB Hb at week 24 and voxelotor whole blood PK parameters or %Hb occupancy. AUC, C_{max}, and C_{min} are steady-state PK parameters based on the average dose over 24 weeks of treatment for each subject. The vertical dashed lines indicate the median of the PK parameter for each dose group. The boxplots describe the distribution in each dose group. The left and right edges of the box correspond to the 25th and 75th percentiles, and the vertical line inside the box indicates the median. The solid blue line and gray shaded area represent a second-degree polynomial regression and 95% CI 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. AUC, area under the concentration-time curve at steady-state over 24 h; CI, confidence interval; C_{max}, the maximum concentration at steady-state; C_{min}, the minimum concentration at steady-state; CFB, change from baseline; Hb, hemoglobin; PK, pharmacokinetic

LDH) as a function of %Hb occupancy at C_{min} showed correlations between increases in Hb occupancy and improved response. With increasing %Hb occupancy, significant improvements in indirect bilirubin ($p < 0.001$) and percent reticulocytes ($p = 0.0013$) were observed, and a larger %CFB was projected following steady-state 1500 mg than 900 mg dosing. Absolute reticulocytes ($p = 0.4$) and LDH ($p = 0.018$) trended toward larger improvements

with increasing %Hb occupancy. Similar relationships for each clinical measure of hemolysis were observed across PK parameters (not shown).

PK/PD evaluation with time-matched concentrations

PK/PD analyses with time-matched concentrations demonstrated increased voxelotor whole blood concentrations and were significantly ($p < 0.001$) correlated with improvements in clinical measures of anemia (CFB Hb) and hemolysis. CFB Hb increased linearly with time-matched model-predicted voxelotor whole blood concentrations consistently over 72 weeks. Trends were similar across age group (adolescent vs. adult) and by nominal time of visit (≤12 weeks, 12–24 weeks, and 24–72 weeks; Figure 2). The consistent relationship over time suggests the voxelotor impact on CFB Hb is similar after 24 and 72 weeks of treatment. No clinically impactful differences in the relationship between CFB Hb and covariates were observed (not shown).

PD/PD evaluation of hemolysis as a function of CFB Hb

PD/PD analyses showed improvements in anemia (measured by CFB Hb) were significantly ($p < 0.001$) correlated with improvements in clinical measures of hemolysis at 72 weeks. The %CFB in assessed clinical measures of hemolysis increased as CFB Hb increased (Figure 3). Similar relationship trends for age group and nominal time were observed compared to the full dataset. Although the relationship correlation holds over time, the %CFB percent reticulocytes compared to time-matched CFB Hb flattened slightly. However, the confidence intervals (CIs) around the local regression show some overlap between subcategories, suggesting that the change in slope may not be significant. No clinically important covariate effects were observed (data not shown).

Exposure-response analyses for safety

Exposure-safety relationships were evaluated using week 72 data. For non-SCD-related TEAEs, the E-R safety analyses identified statistically significant ($p < 0.001$) relationships between voxelotor exposure and grade greater than or equal to 1 increased ALT and decreased WBC count.

The observed incidence (95% exact CI) of grade greater than or equal to 1 increased ALT in the placebo, 900 mg, and 1500 mg dose groups was 19% (11–28%), 29% (19–39%), and 48% (36–59%), respectively (Figure 4). The E-R relationship between the probability of grade greater than or equal to 1 increased ALT and the average voxelotor plasma C_{max} was significant ($p \leq 0.002$) for all patients and all voxelotor-treated patients. The observed incidence (95% exact CI) of grade greater than or equal to 2 increased ALT was 6.6% (2.5–14%), 3.6% (0.74–10%), and 8.5% (3.5–17%) in the placebo, 900 mg, and 1500 mg dose groups, respectively. The E-R relationship between grade greater than or equal to 2 increased ALT and voxelotor plasma C_{max} was not significant ($p \geq 0.338$).

The observed incidence (95% exact CI) of grade greater than or equal to 1 decreased WBC count was 4.4% (1.28–11%), 11% (5–19%), and 17% (9.7–27%) in the placebo, 900 mg, and 1500 mg dose groups, respectively (Figure 5). The E-R relationship between the probability of grade greater than or equal to 1 decreased WBC count and the average voxelotor plasma C_{max} was significant ($p \leq 0.001$) for all patients and all voxelotor-treated patients. The observed incidence (95% exact CI) of grade greater than or equal to 2 decreased WBC count events was 1.1% (0.028–6.0%), 3.6% (0.74–10%), and 4.9% (1.3–12%), respectively, in the placebo, 900 mg, and 1500 mg dose groups. The total number of grade greater than or equal to 2 decreased WBC count events was insufficient for analysis.

For SCD-related and other non-SCD-related TEAEs, no statistically significant E-R relationships were observed, and laboratory variables were not significant at grade greater than or equal to 2. No statistically significant covariate effects were identified on the slope of any relationship, including race, for any SCD or non-SCD-related TEAEs (not shown).

Expected efficacy and safety responses

Summary exposure estimates were calculated at week 24 where exposures were based on the average dose for each patient over the course of treatment, and expected responses for efficacy and safety end points were calculated from the analysis of clinical measures of anemia and hemolysis (Table 2). The estimated expected efficacy responses were greater for the 1500 mg versus 900 mg voxelotor dose and correlated with estimates of voxelotor whole blood exposures and %Hb occupancy. The whole blood C_{max} and plasma C_{max} were 104 and 6.7 μg/ml, respectively, with the 900 mg dose and 180 and 13 μg/ml, respectively, with the 1500 mg dose. Percent Hb occupancy increased (16.1–26%) and CFB Hb increased (0.666–1.07 g/dl) with an increase in voxelotor dose (900–1500 mg).

The incidences of grade greater than or equal to 1 increased ALT (30.5–44.8%) and decreased WBC count

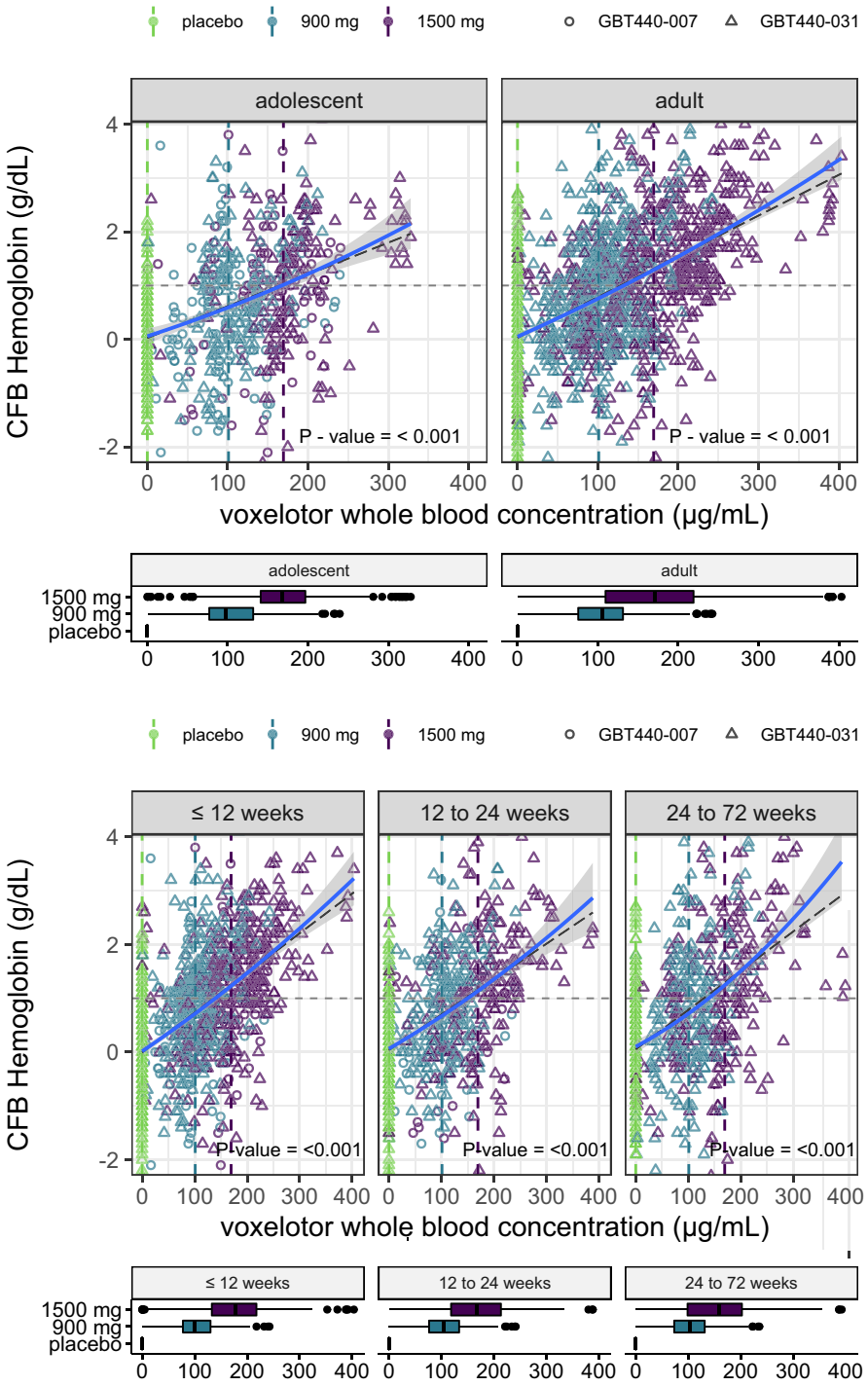

FIGURE 2 Relationships between CFB in Hb and time-matched voxelotor whole blood concentration, facetted by age group and stratified by nominal time of visit. The vertical dashed lines in each plot correspond to the overall median of the whole blood concentrations in each dose group in the full dataset, not the subcategory shown in each panel. The boxplots at the bottom of each plot are based on the exposures in the subcategory of the panel above. The boxplots describe the distribution of predose whole blood concentrations in each dose group. The left and right edges of the box correspond to the 25th and 75th percentiles, and the vertical line inside the box indicates the median. The horizontal gray dashed line indicates the target 1 g/dl increase in Hb. The solid blue line and gray shaded area represent a second-degree polynomial regression and 95% CI through the data. The *p* value for the second-degree 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. Adolescent patients are all 12–17 years of age in HOPE Kids 1 or HOPE. CFB, change from baseline; CI, confidence interval; Hb, hemoglobin

(7.0% to 13.5%) increased with increasing dose of voxelotor (900–1500 mg); however, the increased incidences may not be clinically impactful given the low observed incidence of grade greater than or equal to 2 events for increased ALT and decreased WBC count.

Results from the week 24 analysis of clinical measures of anemia and hemolysis were used to estimate the voxelotor dose required to achieve a 2 g/dl increase in Hb. Assuming the linear relationship between CFB Hb and %Hb occupancy is maintained at higher %Hb occupancy, a voxelotor dose of 2800 mg was projected to achieve a 2 g/dl increase in Hb (Table 2). At this dose, voxelotor whole blood and plasma C_{max} were estimated to be 337 and 24.3 µg/ml, respectively. The estimated %Hb occupancy was 48.4%. The higher dose may increase the occurrence of safety events.

DISCUSSION

Voxelotor is rapidly absorbed into plasma and distributed to RBCs due to preferential binding to Hb. This close

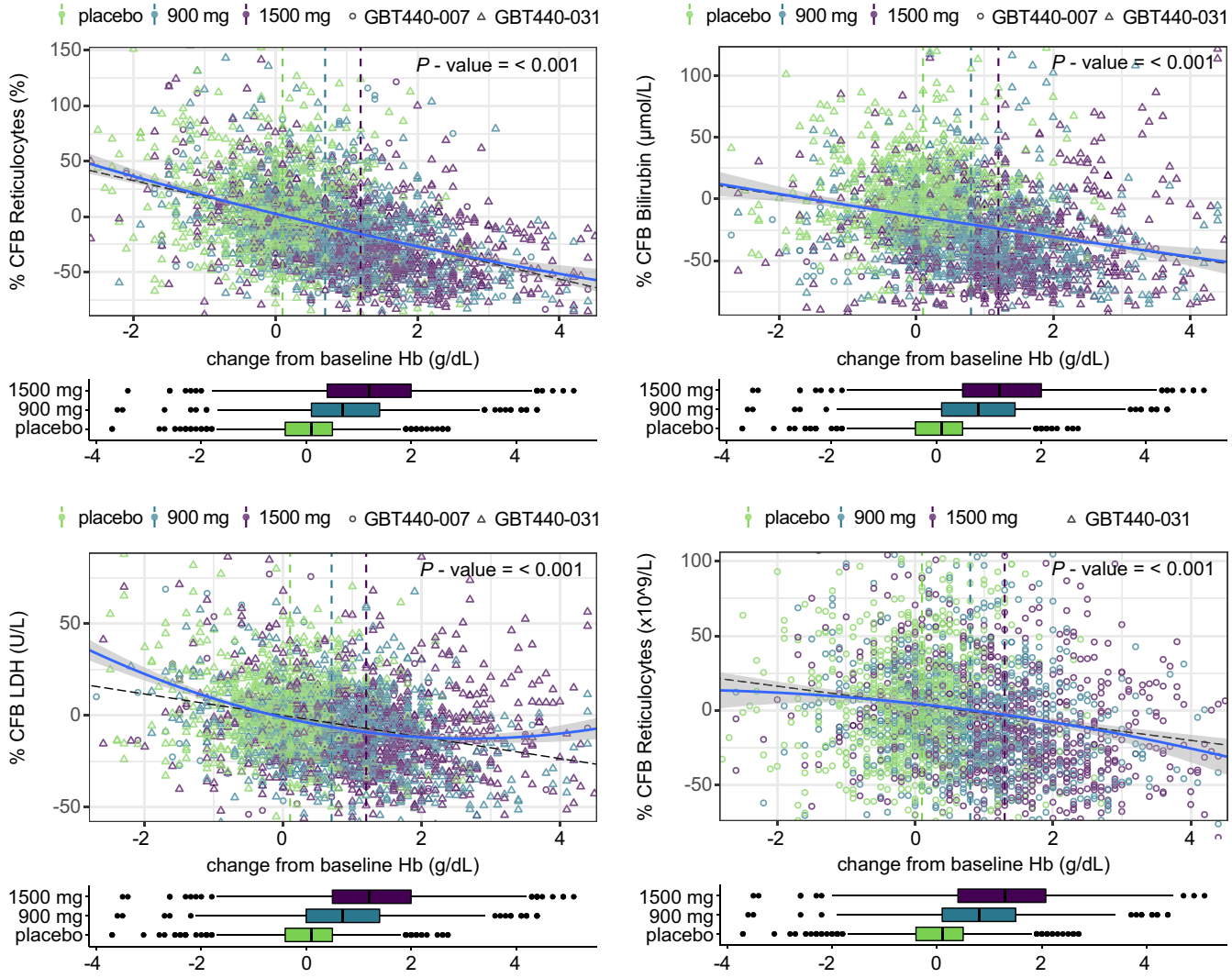

FIGURE 3 Relationships between CFB in clinical measures of hemolysis and observed change from baseline in Hb at all visits. The vertical dashed lines indicate the median of the CFB Hb for each dose group. The boxplots describe the distribution of CFB Hb in each dose group. The left and right edges of the box correspond to the 25th and 75th percentiles, and the vertical line inside the box indicates the median. The solid blue line and gray shaded area represent a second-degree polynomial regression and 95% CI through the data. The *p* value for the second-degree 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. The highest and lowest 0.5% of CFB Hb values are excluded from the scatterplots to improve visibility. All data were used for calculation of *p* values and linear and polynomial regressions. CFB, change from baseline; CI, confidence interval; Hb, hemoglobin; LDH, lactate dehydrogenase

association between PK and PD (represented by CFB Hb) provided a unique opportunity to apply MIDD to our understanding of voxelotor efficacy and safety in patients and to support the marketing authorization submissions in the United States and Europe. In this study, MIDD was used to support dose selection for adults and adolescents, to evaluate the persistence of relationships between concentration and clinical measures of anemia and hemolysis, and to confirm the MOA.

The analyses demonstrated CFB Hb increased linearly with increasing voxelotor exposure (PK parameters) and %Hb occupancy at week 24 and with voxelotor time-matched whole blood concentration up to week 72. The linear relationship was maintained in adult and adolescent patients and was similarly consistent across time in both populations, supporting the approval of voxelotor in patients 12 years and older in the United States. Combined, E-R analyses of anemia and hemolysis as a function of PK parameters, %Hb occupancy, and time-matched voxelotor concentration at 24 and 72 weeks showed greater improvement with the 1500 mg dose and suggests the 900 mg dose risks underexposing a majority of patients.

In the week 72 analysis, no new or clinically relevant safety risks for the 900 to 1500 mg voxelotor dose range were identified, and no clinically significant increase in risk was observed. No statistically significant E-R

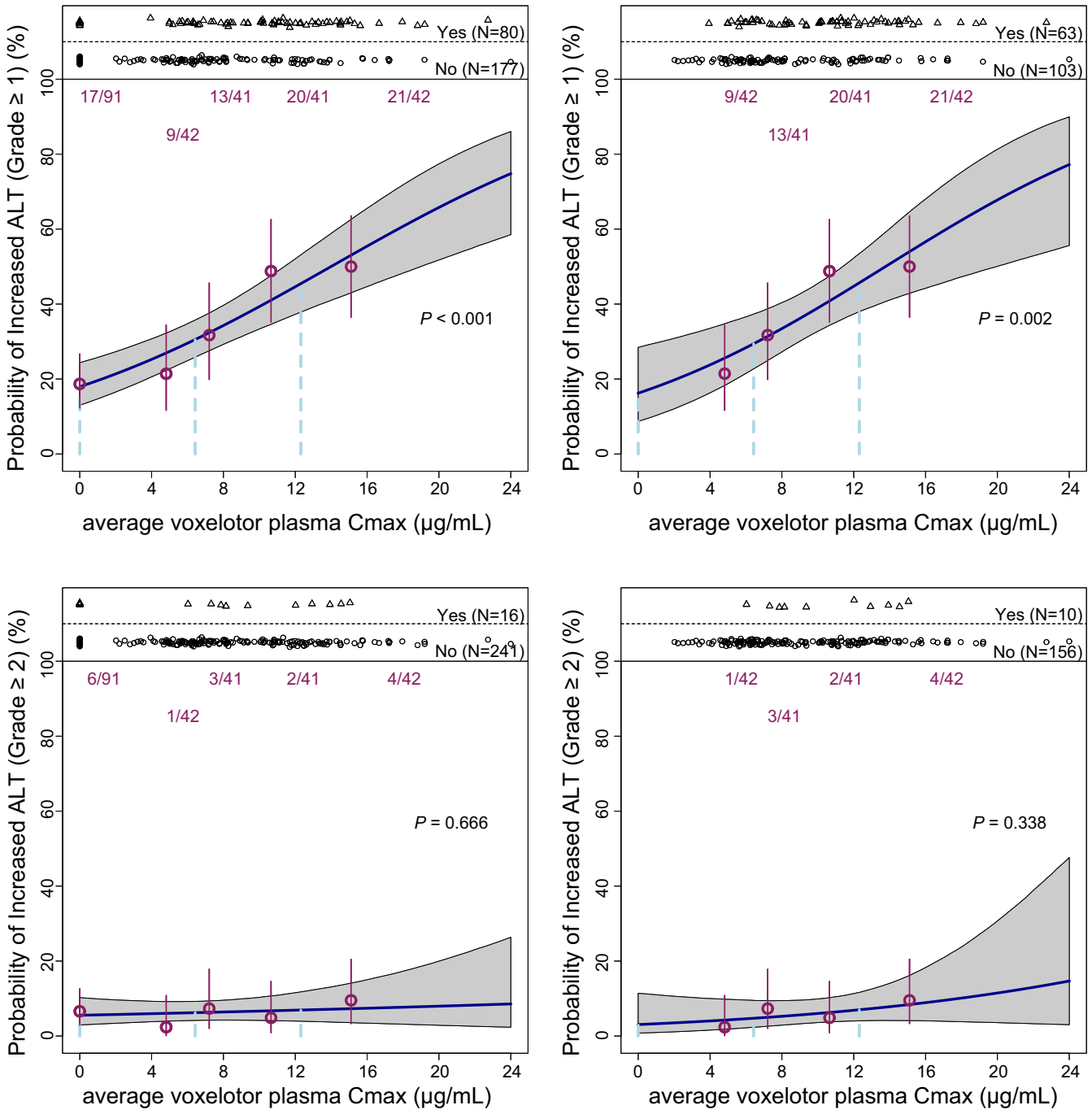

FIGURE 4 Exposure-safety relationships for increased ALT. All patients, including patients who received placebo, are shown in the left panels and only voxelotor-treated patients are shown in the right panels. In the shaded polygon plots, maroon points represent the mean exposure and event incidence in patients stratified by exposure quartile or for placebo. Vertical maroon bars represent the 90% CI on the event incidence. Event numbers in each quartile (patients with event/total patients) 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 $p \geq 0.05$, the relationship is not statistically significant. The dashed vertical blue lines represent placebo, and the median and 5th and 95th percentiles of exposure for the 900 and 1500 mg dose levels. The data points (triangle = event, circle = no event) are shown above the plots. ALT, alanine aminotransferase; CI, confidence interval; C_{max}, the maximum concentration at steady-state

relationships were observed for other non-SCD-related TEAEs or any SCD-related TEAEs. Despite higher whole blood exposures observed in patients of Arab or Middle Eastern race, the probability of safety events was lower in these patients for all safety end points. No clinically important covariate effects were observed for efficacy or safety evaluations. Improvements in clinical measures of anemia and hemolysis at week 72 with the 1500 mg dose without significant increase in TEAEs compared to the 900 mg dose, as shown by the

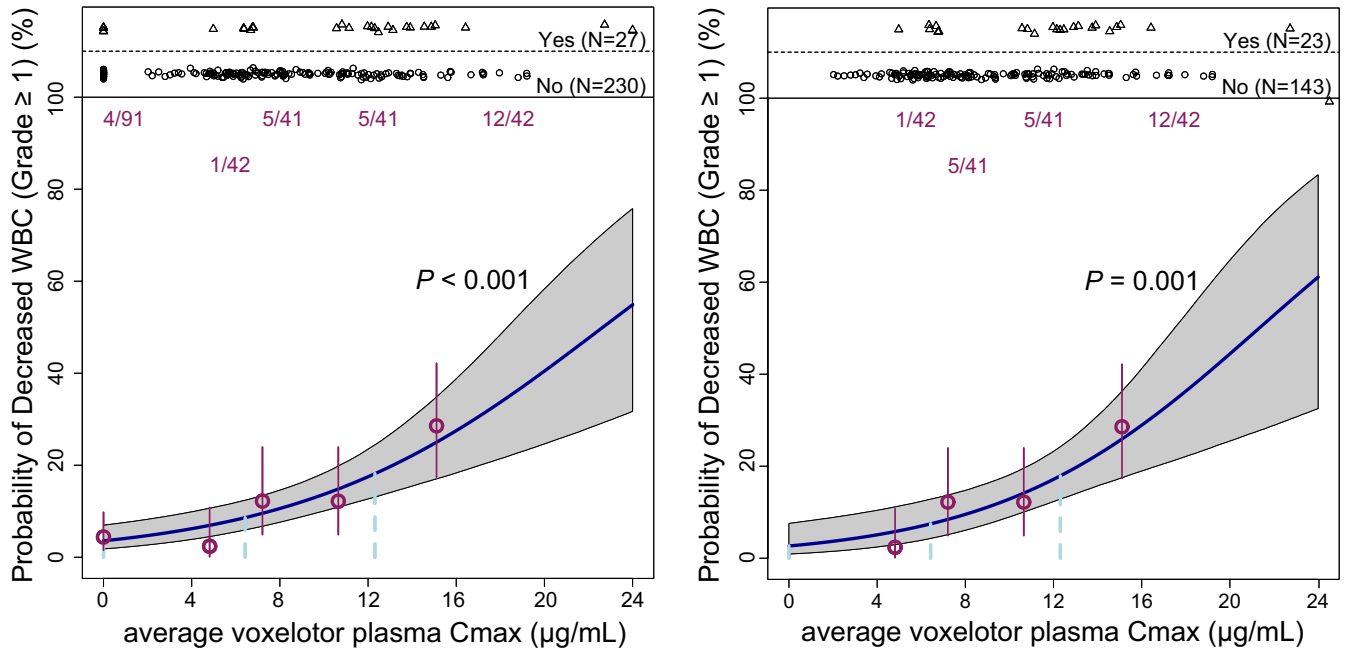

FIGURE 5 Exposure-safety relationships for decreased WBC. All patients, including patients who received placebo, are shown in the left panel and only voxelotor-treated patients are shown in the right panel. In the shaded polygon plots, maroon points represent the mean exposure and event incidence in patients stratified by exposure quartile or for placebo. Vertical maroon bars represent the 90% CI on the event incidence. Event numbers in each quartile (patients with event/total patients) 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 $p \geq 0.05$, the relationship is not statistically significant. The dashed vertical blue lines represent placebo, and the median and 5th and 95th percentiles of exposure for the 900 and 1500 mg dose levels. The data points (triangle = event, circle = no event) are shown above the plots. CI, confidence interval; C_{max}, the maximum concentration at steady-state; WBC, white blood cells

E-R safety analysis, supports 1500 mg q.d. as the therapeutic dose.

Based on the linear relationship between CFB Hb and %Hb occupancy, the estimated voxelotor doses required to achieve a 1 and 2 g/dl increase in Hb at 24 weeks were 1500 and 2800 mg, respectively. A corresponding increase in most measures of hemolysis is predicted at a higher voxelotor dose. Higher doses (above 1500 mg) may also increase the incidence of safety events. Although extrapolation of efficacy and safety from a linear model may have limitations, for the %Hb occupancy extrapolation, both the observed data and the expected response from the regression model included 2 g/dl increases in Hb (Figure 1). The broader CI reflects the limited data at higher exposures. Evaluation of the relationship at all visits (Figure 2) suggests a 2 g/dl increase in Hb, which is achieved at whole blood trough concentrations between 250 and 300 µg/ml, close to the 242 µg/ml prediction from the week 24 model (Table 2). For the extrapolation of safety events, plasma exposures associated with a 2 g/dl increase in Hb are slightly higher than those observed in the analysis; thus, the predicted safety responses should be considered with caution given that the incidence of events may increase at a higher dose.

Voxelotor approval in SCD is based on CFB Hb as an indicator for decreased HbS polymerization to reduce RBC damage and sickling. Our PD/PD analyses provided clinical pharmacology evidence for the voxelotor MOA as clinical measures of hemolysis improved with improvements in CFB Hb, higher %Hb occupancy, and higher whole blood voxelotor exposures. Voxelotor, through allosteric modification of Hb, increases Hb oxygen affinity and decreases HbS polymerization to reduce RBC damage and sickling. In previous clinical studies, increased oxygen affinity caused by voxelotor has not led to safety concerns related to tissue hypoxia, increased erythropoietin levels, or other significant safety concerns.[8,11,12] In this study, with the recommended 1500 mg voxelotor dose up to 72 weeks, a similar lack of safety issues relating to the voxelotor MOA, including the lack of tissue hypoxia and reduced RBC damage was observed. The decrease in reticulocytes with increasing voxelotor is suggestive of reduced tissue hypoxia and improved RBC survival.

In conclusion, voxelotor has a favorable benefit/risk profile in adults and adolescents. By inhibiting HbS polymerization, voxelotor has the potential to alter the clinical course of SCD through durable improvements in anemia and hemolysis. The E-R analysis of clinical measures of anemia and hemolysis and

TABLE 2 Exposure estimates and estimated responses for placebo, 900, and 1500 mg voxelotor at 24 weeks

		Voxelotor		CFB Hb	
	Placebo	900 mg	1500 mg	1 g/dl	2 g/dl
Required dose, mg[a]	–	900	1500	1400	2800
Whole blood AUC, μg h/ml	–	2180	3840	3580	7170
Whole blood C_{min}, μg/ml	–	74.1	130	121	242
Whole blood C_{max}, μg/ml	–	104	180	168	337
Plasma C_{max}, μg/ml	–	6.7	13.0	12.1	24.3
% Hb occupancy	–	16.1	26.0	24.2	48.4
CFB Hb, g/dl	0.00375	0.666	1.07	1	2
% CFB reticulocytes (%)	8.1	−5.6	−14.0	−12.5	−33.2
% CFB bilirubin, μmol/L	−1.8	−22.0	−34.5	−32.2	−62.7
% CFB LDH, U/L	0.26	−2.30	−3.87	−3.58	−7.44
Grade ≥1 increased ALT (%)	18.6	30.5	44.8	42.7	70.9
Grade ≥1 decreased WBC (%)	3.4	7.0	13.5	12.4	36.3

Abbreviations: ALT, alanine aminotransferase; AUC, area under the concentration-time curve at steady-state over 24 h; CFB, change from baseline; C_{max}, maximum concentration at steady-state; C_{min}, minimum concentration at steady-state; Hb, hemoglobin; LDH, lactate dehydrogenase; WBC, white blood cells.

[a]Required dose was estimated (by dose normalization) based on the %Hb occupancy required to achieve a 1 or 2 g/dl increase in Hb.

safety support the selection of 1500 mg as the therapeutic dose of voxelotor and demonstrated persistent concentration-effect relationships up to 72 weeks. As projected from the MIDD, the 1500 mg q.d. dose of voxelotor achieved the target 1 g/dl increase in Hb. The linear relationship suggests a higher dose may have an increased benefit, but potentially also a higher risk. The voxelotor MOA was confirmed and covariate analysis confirmed E-R relationships were comparable between adult and adolescent populations. The safety analysis demonstrated no clinically significant risk at 72 weeks. Overall, the MIDD approach applied for voxelotor provided additional understanding of voxelotor efficacy and safety in adults and adolescents with SCD and supported the marketing authorization submissions in the United States and Europe.

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CONFLICT OF INTEREST

M.L.G. was an employee of Certara who was paid by Global Blood Therapeutics to conduct the analysis described herein. R.M.S. is an employee of the University of California, San Francisco, who received consultancy fees from Global Blood Therapeutics to contribute to the analysis described herein. M.T. is an employee and stockholder of Global Blood Therapeutics. K.J. is a clinical pharmacology consultant who was paid by Global Blood Therapeutics to support the analysis described herein. C.W. was an employee and stockholder of Global Blood Therapeutics at the time the work was conducted.

AUTHOR CONTRIBUTIONS

M.G., R.S., M.T., K.J., and C.W wrote the manuscript. K.J., C.W., M.G., and M.T. designed the research. M.G. and R.S. performed the research. M.G. 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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