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HEMATOLOGY: RESEARCH ARTICLE

Safety and efficacy of voxelotor in pediatric patients with sickle cell disease aged 4 to 11 years

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Abstract

Background: Sickle cell disease (SCD) is a devastating, multisystemic disorder that affects millions of people worldwide. The earliest clinical manifestations of SCD can affect infants as young as 6 months of age, and pediatric patients are at risk for acute and life-threatening complications. Early intervention with treatments that target the underlying pathophysiological mechanism of SCD, sickle hemoglobin (HbS) polymerization, are expected to slow disease progression and circumvent disease-associated morbidity and mortality.

Procedure: The HOPE-KIDS 1 trial (NCT02850406) is an ongoing four-part, phase 2a, open-label, single- and multiple-dose study to evaluate the pharmacokinetics, efficacy, and safety of voxelotor—a first-in-class HbS polymerization inhibitor—in patients aged 6 months to 17 years with SCD. Initial findings from a cohort of 45 patients aged 4 to 11 years who received voxelotor treatment for up to 48 weeks are reported.

Results: Hemoglobin (Hb) response, defined as a >1.0 g/dl increase from baseline, was achieved at week 24 by 47% (n = 16/34) of patients with Hb measurements at baseline and week 24. At week 24, 35% (n = 12/34) and 21% (n = 7/34) of patients had a >1.5 g/dl increase and a >2.0 g/dl increase from baseline in Hb concentration, respectively. Concurrent improvements in hemolytic markers were observed. Voxelotor was well tolerated in this young cohort, with no newly emerging safety signals.

Abbreviations: Hb, hemoglobin; HbS, sickle hemoglobin; HU, hydroxyurea; LDH, lactate dehydrogenase; PK, pharmacokinetics; SCD, sickle cell disease; TEAE, treatment-emergent adverse event; VOC, vaso-occlusive crisis.

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Conclusions: Based on its mechanism as an HbS polymerization inhibitor, voxelotor improves Hb levels and markers of hemolysis and has the potential to mitigate SCD-related complications; these results support its use in patients aged ≥4 years.

KEYWORDS
clinical data, hemolytic anemia, pediatric, sickle cell disease

1 | INTRODUCTION

Sickle cell disease (SCD) is an inherited hematological disorder caused by mutations in the *HBB* gene that encodes the beta-globin chain of hemoglobin (Hb). SCD is more common among people of sub-Saharan African, Middle Eastern, Indian, and Mediterranean descent.[1–3] Under conditions of deoxygenation, sickle hemoglobin (HbS) undergoes rapid polymerization, causing red blood cell deformation, sickling, and destruction, which in turn triggers a chronic cycle of hemolysis, anemia, and episodic vaso-occlusion.[1] Repetitive ischemic injury and inflammation caused by anemia and hemolysis, beginning as early as 6 months of age in patients with SCD, lead to progressive end-organ damage, substantial morbidity, and early mortality.[2,4] By age 6 years, approximately 25% of children with SCD have evidence of silent cerebral infarct, and 50% have had an episode of acute chest syndrome.[5,6] Furthermore, onset of splenic and renal dysfunction at a young age increases the risk of premature death due to infection and chronic renal failure, respectively.[7–10] Another serious complication, sickle cell retinopathy, which can potentially lead to blindness, is seen in 12.1% of children with SCD.[11] Despite the medical challenges faced by pediatric patients with SCD, current treatment options remain limited, with hydroxyurea (HU) being the sole disease-modifying therapy for many decades. Stem cell transplantation is available as a curative therapy, particularly for those with severe phenotypes and unaffected, human leukocyte antigen-matched siblings; however, stem cell transplantation has its own concurrent risks, including engraftment failure, infertility, infection-related complications, and graft-versus-host disease.[12–14] Transfusion therapy is also an important therapeutic option for management of sickle cell-related anemia, but chronic transfusion poses substantial risks, including alloimmunization, iron overload, hemolysis, and hyperviscosity.[12] Gene therapy and gene editing are currently being investigated as potential curative options, but these remain experimental at this time.[2] However, most patients with SCD can benefit from treatments that target the root cause of SCD pathology, HbS polymerization, which may alter the natural history of the disease.

In 2019, voxelotor, an oral, once-daily HbS polymerization inhibitor, was approved in the United States for the treatment of SCD in adults and adolescents aged ≥12 years under accelerated approval based on increases in Hb.[15] In February 2022, voxelotor was granted marketing authorization in the European Union and United Arab Emirates for the treatment of SCD in adults and children ≥12 years of age.[16] In clinical studies and real-world practice, patients treated with voxelotor have shown improvements in Hb levels and reductions in hemolytic markers.[17–20] Accumulating real-world evidence also indicates that voxelotor may ameliorate complications of SCD, such as leg ulcers and jaundice, as well as reduce transfusion dependence and the occurrence of vaso-occlusive crises (VOCs).[19,21–25] Given the childhood manifestation pattern and progressive nature of SCD, treatment of pediatric patients with disease-modifying agents such as voxelotor may provide clinical benefit if started at a young age.

In this report, we present initial results from a cohort of 4- to 11-year-old patients with SCD under investigation in part C of the four-part HOPE-KIDS 1 study, which is currently ongoing. These data formed the basis for the FDA-accelerated approval of voxelotor in December 2021 for the treatment of SCD in children aged 4 to 11 years.[26]

2 | METHODS

2.1 | Study design

The GBT440-007 (NCT02850406) phase 2a HOPE-KIDS 1 trial is a multicenter, four-part, open-label, single- and multiple-dose study designed to evaluate the pharmacokinetics (PK), efficacy, and safety of voxelotor administered to pediatric patients with SCD. The four parts of HOPE-KIDS 1, parts A to D, focus on different age groups and treatment regimens. Study parts A (single dose in patients aged 6–17 years)[27] and B (multiple doses in patients aged 12–17 years)[27,28] are complete, and part D (multiple doses in patients aged 6 months to <4 years)[27] is currently enrolling patients. Part C of the study consists of a screening period (day −35 to day −1), a 48-week treatment period, and an end-of-study visit 4 weeks after the last dose of voxelotor for patients who do not enroll into the open-label extension study, GBT440-038 (NCT04188509) (Figure 1A). The PK,

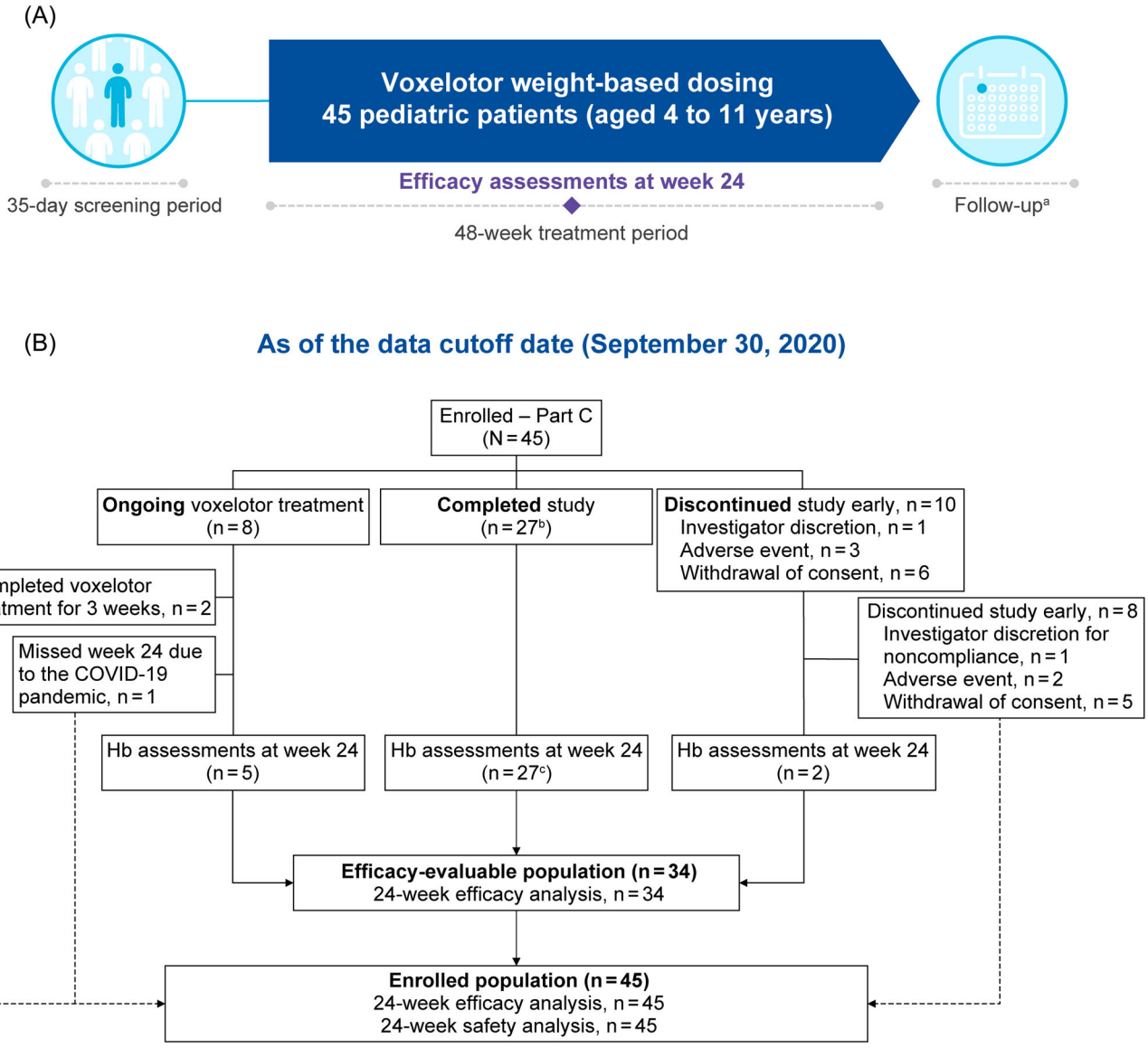

FIGURE 1 Study design and trial profile. (A) Study design for part C of the GBT440-007 (HOPE-KIDS 1) study showing enrollment of study patients as of September 30, 2020. (B) Consort diagram showing disposition of patients as of September 30, 2020. [a]End-of-study visit is 4 weeks after the last dose for patients who will not enroll in the open-label extension study, GBT440-038. [b]One patient discontinued treatment at week 36 due to an adverse event but remained in the study for study assessments. [c]Twenty-one patients entered the open-label extension study

hematological response, and safety data as of September 30, 2020 from 45 patients aged 4 to 11 years, who received at least one dose of voxelotor in part C of the study, were evaluated.

This study was conducted in accordance with Good Clinical Practice guidelines and the ethical principles of the Declaration of Helsinki, and was compliant with all applicable country-specific laws and regulations in the United States, Lebanon, and the United Kingdom. The study protocol and all other appropriate study-related information were reviewed and approved by institutional review boards and independent ethics committees for each of the participating trial sites. Written informed parental/guardian consent and patient assent, when possible, were obtained prior to study.

2.2 | Patients and treatment

Patients with SCD were screened at 15 study sites in the United States, Lebanon, and the United Kingdom. Key inclusion criteria included patients with SCD (homozygous SCD [HbSS] or HbSβ^0 genotypes), aged 4 to 11 years, and with Hb concentrations ≤10.5 g/dl at baseline. Concomitant HU was allowed if the dose was stable for ≥3 months at enrollment, with no anticipated need for dose adjustment during the study. There was no eligibility requirement regarding prior VOCs. Patients who were receiving chronic red blood cell transfusion therapy, had received a transfusion in the past 30 days, or had been hospitalized for a VOC, acute chest syndrome, splenic sequestration crisis,

TABLE 1 Voxelotor weight-based dosing for pediatric patients aged 4 to 11 years

Weight	Voxelotor dose
10 to <20 kg	600 mg
20 to <40 kg	900 mg
≥40 kg	1500 mg

or dactylitis within 14 days before providing informed consent were excluded.

All patients received dispersible voxelotor tablets, a pediatric formulation that can be dispersed in clear liquids, such as apple juice, soda, or water, for oral administration. Patients aged 4 to 11 years received weight-based dosing of voxelotor administered once daily (Table 1). The weight-based dosing scheme for patients aged 11 years and younger was developed using population PK and allometric scaling and aimed to achieve comparable voxelotor exposure and similar Hb occupancy as the approved daily dose of 1500 mg voxelotor in patients aged ≥12 years.

Dose modification (reduction or interruption) of study drug was recommended to manage tolerability issues related to voxelotor treatment. Temporary dose modification was permitted for management of suspected drug-related adverse events. The original dose was resumed after resolution of the adverse event, at the discretion of the investigator.

2.3 | Endpoints and assessments

Patients were assessed at the screening visit, day 1, and weeks 2, 4, 8, 12, 16, 20, 24, 36, and 48. Efficacy endpoints evaluated in the current analyses included the percentage of patients who had an Hb response, which was defined as an increase from baseline of >1.0 g/dl at week 24; the change in Hb level from baseline to week 24; and the percentage change in laboratory markers associated with hemolysis, including indirect bilirubin, reticulocytes, and lactate dehydrogenase (LDH), from baseline to week 24. The safety assessment included treatment-emergent adverse events (TEAEs) and adverse events that led to treatment modification or discontinuation.

PK samples were collected post-dose on day 1 (a single sample between 15 minutes and 2 hours post-dose) and pre-dose (up to an hour prior to dosing) at weeks 4, 8, 12, 16, 20, 24, 36, and 48. PK analyses were performed to determine whole-blood and plasma PK parameters using a nonlinear mixed-effects modeling approach with NONMEM, version 7.3.0 or higher (ICON Development Solutions, Elliot City, MD, USA). PK parameters included minimum (C_{min}) and maximum (C_{max}) whole-blood or plasma concentration, area under the concentration–time curve (AUC), terminal elimination half-life ($t_{1/2}$), and percentage Hb occupancy.

2.4 | Statistical analyses

All efficacy and safety assessments were summarized with descriptive statistics.

TABLE 2 Baseline characteristics of patients aged 4 to 11 years

Age group	4–11 years (*N* = 45)
Age at screening, median (range), years	7.0 (4–11)
Female, *n* (%)	23 (51)
Weight at screening, median (range), kg	24 (12–41)
Baseline Hb, g/dl[a]	
Mean (SD)	8.6 (1.0)
Range	6.1–10.5
Baseline reticulocyte count, %[a]	
Mean (SD)	10.4 (4.5)
Range	2.1–19.5
Baseline HbF, %[a]	
Mean (SD)	17.7 (7.9)
Range	2.3–38.4
SCD genotype, *n* (%)	
HbSS	43 (96)
HbSβ^0	2 (4)
Current HU/hydroxycarbamide use, *n* (%)	
Yes	38 (84)
No	7 (16)
No VOCs in the previous 12 months, *n* (%)	21 (47)
≥1 VOC in the previous 12 months, *n* (%)	24 (53)

Abbreviations: Hb, hemoglobin; HbF, fetal hemoglobin; HbSβ^0, sickle beta zero thalassemia; HbSS, homozygous sickle cell disease; HU, hydroxyurea; SCD, sickle cell disease; VOC, vaso-occlusive crisis.

[a]Baseline is defined as the average of all values before the first dose.

3 | RESULTS

3.1 | Patients

As of September 30, 2020, 45 patients aged 4 to 11 years were enrolled in part C of the HOPE-KIDS 1 study. Among these patients, 27 had completed the study, of whom 21 rolled over to the open-label extension study; 10 had discontinued early, and 8 were receiving ongoing treatment. A summary of patient disposition is provided in Figure 1B. Baseline demographics and clinical characteristics are shown in Table 2. At baseline, the mean (SD) Hb was 8.6 g/dl (1.0 g/dl), and the mean (SD) reticulocyte count was 10.4% (4.5%), which closely matches with what was previously reported for the phase 3 HOPE study that comprised mostly adult patients.[18] Baseline mean (SD) fetal Hb percentage was 17.7% (7.9%), consistent with 84% of patients receiving concomitant HU at a stable dose.

3.2 | Efficacy

An increase in mean Hb levels was observed as early as 2 weeks after voxelotor initiation and was maintained through week 24 (Figure 2A). The mean (SD) change in Hb from baseline at week 24 (n = 34) was 1.0 g/dl (1.2 g/dl). Of patients with Hb measurements at both

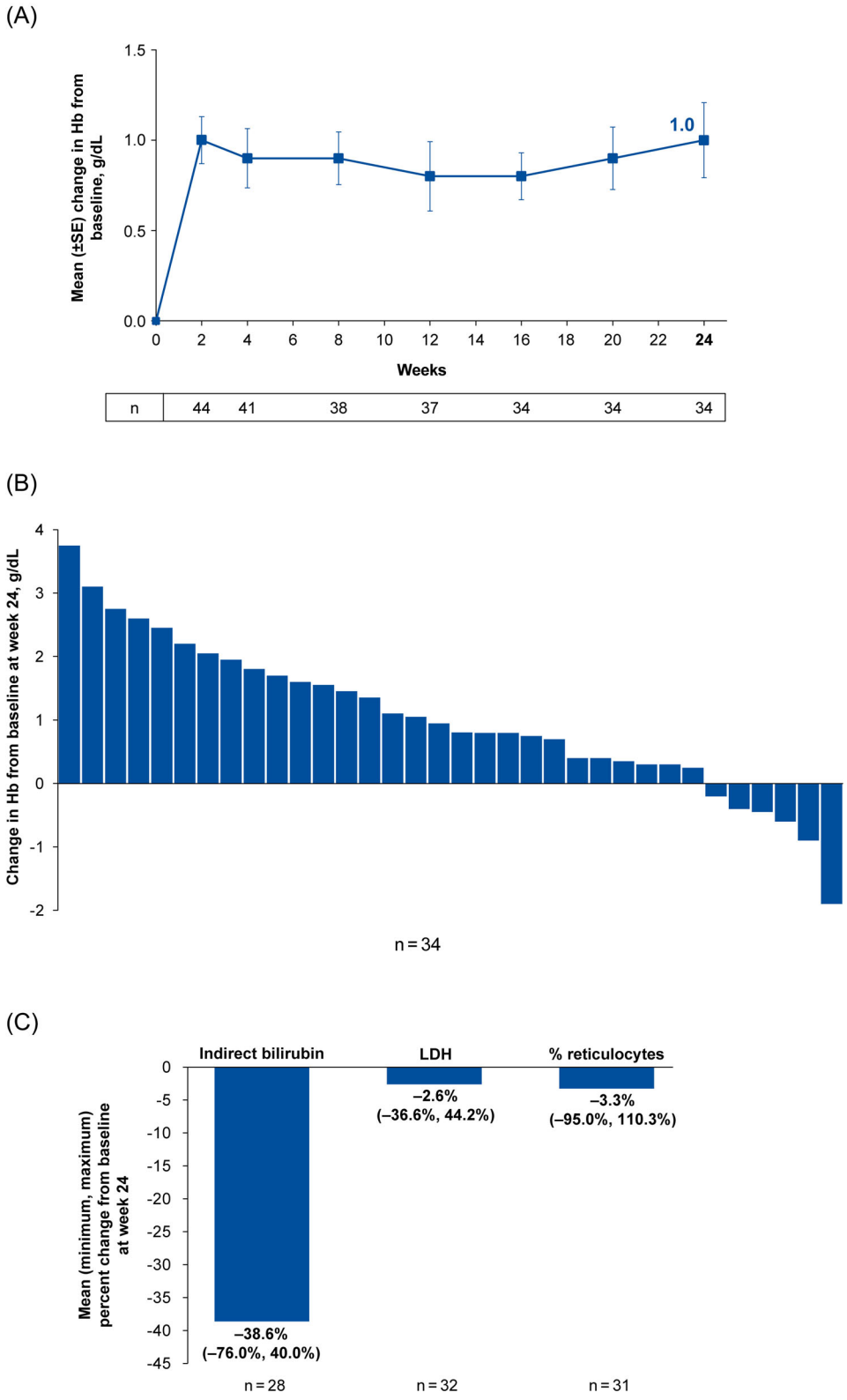

FIGURE 2 Changes in blood parameters from baseline. (A) Mean change in Hb from baseline at week 24. (B) Per patient change in Hb from baseline at week 24. Each bar represents an individual patient. (C) Mean percentage change in hemolysis markers from baseline at week 24. Hb, hemoglobin; LDH, lactate dehydrogenase

TABLE 3 PK parameters of voxelotor in patients aged 4 to 11 years in part C of the HOPE-KIDS 1 study[a]

	4–11 years Voxelotor 600/900/1500 mg[b] ($n = 38$)	
PK parameter	**Whole blood**	**Plasma**
$AUC_{0\text{-}24h}$ (μg·h/mL)[c]	3257 (31.2)	221.8 (34.4)
C_{min} (μg/mL)[c]	117.8 (35)	7.7 (40)
C_{max} (μg/mL)[c]	148.3 (30.2)	10.3 (32.9)
$t_{1/2}$ (h)[c]	27.2 (28.3)	
% Hb occupancy[c]	26.2 (32.2)	
% of patients with ≥20% Hb occupancy[d]	76.3 (59.8–88.6)	

Abbreviations: $AUC_{0\text{-}24h}$, area under the concentration–time curve from 0 to 24 hours; BLQ, below the limit of quantification; C_{max}, maximum whole-blood or plasma concentration; C_{min}, minimum whole-blood or plasma concentration; CI, confidence interval; CV, coefficient of variation; Hb, hemoglobin; PK, pharmacokinetics; $t_{1/2}$, terminal elimination half-life.

[a]Estimates are based on 158 plasma observations and 173 whole-blood observations from day 1 to week 48; measurements that were BLQ or collected outside of the prespecified post-dose timeframe were not included in the analysis.

[b]Weight-based dosing for pediatric patients aged 4 to 11 years.

[c]Geometric mean (%CV).

[d]Percentage (95% exact CI).

baseline and week 24, 47% ($n = 16/34$; 95% CI: 30%–65%) achieved an Hb response, defined for this study as an increase in Hb of >1.0 g/dl from baseline to week 24 (Figure 2A). The Hb response for voxelotor was 36% ($n = 16/45$) in patients who received at least one dose of voxelotor, regardless of whether they had an Hb measurement at week 24. At week 24, 35% ($n = 12/34$) and 21% ($n = 7/34$) of patients had a >1.5 g/dl increase and a >2.0 g/dl increase in Hb from baseline, respectively. Overall, 82% ($n = 28/34$) of patients had an increase in Hb of any magnitude from baseline at week 24 (Figure 2B). Additionally, concurrent reductions in hemolytic markers were observed with voxelotor therapy. The mean (range) percentage change from baseline at week 24 was −38.6% (−76.0% to 40.0%; $n = 28$) for indirect bilirubin, −3.3% (−95.0% to 110.3%; $n = 31$) for reticulocyte count, and −2.6% (−36.6% to 44.2%; $n = 32$) for LDH (Figure 2C).

3.3 | Pharmacokinetics

Voxelotor PK parameter estimates for whole blood and plasma are summarized in Table 3. The half-life of voxelotor in children aged 4 to 11 years was 27.2 hours. The estimated mean Hb occupancy based on C_{min} was 26.2% in this population, with approximately 76% of patients achieving an Hb occupancy >20%.

3.4 | Safety

Safety analyses included all patients who received at least one dose of the study drug (Table 4). As of the data cutoff date, the median exposure was 43.3 weeks. Weight-based dosing of voxelotor was well tolerated in this patient population. Per the study protocol, a TEAE was defined as an adverse event occurring between the first dose and 28 days after the last dose (inclusive) regardless of relationship to the study drug. A drug-related TEAE was defined as an adverse event assessed by the investigator as related to voxelotor. The most common non-SCD-related TEAEs (reported in ≥10% of patients) were pyrexia (36%), vomiting (33%), rash (20%), abdominal pain (18%), diarrhea (18%), headache (18%), viral infection (18%), pain in extremity (16%), and upper respiratory tract infection (16%). The most commonly reported drug-related TEAEs (reported in ≥10% of patients) were

TABLE 4 Safety assessments at time of data cutoff date (September 30, 2020)

Drug-related TEAEs (preferred term) reported for ≥2 patients	
Adverse events,[a] *n* (%)	**4–11 years ($n = 45$)**
Any drug-related TEAE	22 (49)
Diarrhea	5 (11)
Rash[b]	5 (11)
Vomiting	5 (11)
Abdominal pain[c]	4 (9)
Transaminases increased[d]	4 (9)
Headache	2 (4)
Hypersplenism	2 (4)
Pyrexia	2 (4)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CTCAE, Common Terminology Criteria for Adverse Events; MedDRA, Medical Dictionary for Regulatory Activities; NCI, National Cancer Institute; SCD, sickle cell disease; TEAE, treatment-emergent adverse event.

[a]TEAEs were coded using MedDRA version 23.0. NCI-CTCAE version 4.03 was used to determine grade. Patients may be counted in more than one row.

[b]Includes the following preferred terms: rash, rash maculopapular, and rash papular.

[c]Includes the following preferred terms: abdominal pain and abdominal pain upper.

[d]Includes the following preferred terms: ALT increased, AST increased, and transaminases increased.

diarrhea (11%), rash (11%), and vomiting (11%); of these, most were grade 1; grade 2 rash was reported in two instances, and no events of grade 3 or higher severity were observed. Only one temporary dose reduction occurred in one patient who had a drug-related TEAE of grade 2 rash that led to an initial dose interruption for 5 days, followed by a dose reduction for eight doses, and ultimately restoration of the original dose, with no further incidence of rash and subsequent patient enrollment into the open-label extension study. Three additional patients had temporary dose interruptions due to drug-related TEAEs: one patient with a grade 2 hypersensitivity, one patient with a grade 2 alanine aminotransferase increase and a grade 2 aspartate aminotransferase increase, and one patient with a grade 3 bilirubin increase and a grade 3 liver transaminase increase. In both patients with elevated liver enzyme TEAEs, the events resolved after the temporary dose interruption with no further incidence, and both patients enrolled into the open-label extension study for continued voxelotor dosing. The patient with a temporary dose interruption due to a grade 2 hypersensitivity initially recovered but then discontinued voxelotor due to multiple drug-related adverse events of grade 2 allergic edema, grade 2 pyrexia, and grade 2 sickle cell anemia with crisis. Nonetheless, overall drug discontinuation due to TEAEs was low. A total of 11 patients discontinued voxelotor early, and a breakdown of these discontinuations are listed in Figure 1B. There were no deaths reported.

4 | DISCUSSION

The HOPE-KIDS 1 study is the first trial investigating the PK, efficacy, and safety of voxelotor treatment in patients aged 4 to 11 years with SCD. These initial results from part C of the trial show that the efficacy of voxelotor in patients with SCD aged 4 to 11 years is consistent with that observed in adult and adolescent (aged ≥12 years) patients in the phase 3 HOPE trial.[18] Hb response (defined in this study as >1.0 g/dl increase from baseline) was achieved by 55% (n = 24/44) of patients as early as week 2 and maintained through week 24 in 47% (n = 16/34) of patients who had Hb measurements at baseline and week 24. In addition, 35% and 21% of patients achieved Hb increases >1.5 g/dl and >2.0 g/dl, respectively. Overall, 82% patients had an increase in Hb from baseline at week 24. The mean increase in Hb from baseline at week 24 was 1.0 g/dl. Furthermore, at week 24, concurrent improvements in hemolytic markers were also observed. These results are comparable to findings from the phase 3 HOPE trial and emerging evidence from real-word analyses.[18,20,25,29] In the HOPE study, 51% of adult and adolescent (aged ≥12 years) patients treated with voxelotor 1500 mg demonstrated a Hb response, and the mean change in Hb from baseline at week 24 was 1.1 g/dl.[18] Additionally, the percentage changes in indirect bilirubin and LDH at week 24 in the HOPE study (−29.1%, n = 67, and −4.5%, n = 72, respectively) were similar to changes observed in this analysis (−38.6%, n = 28, and −2.6%, n = 32, respectively). The percentage change in reticulocyte count at week 24 was greater in the HOPE study (−19.9%, range: −29.0% to −10.9%; n = 71) compared with that in this analysis (−3.3%, range: −95.0% to 110.3%; n = 31).[18] This variation could be reflective of the smaller study population and the wide range of response observed among 4- to 11-year-old patients in the current analysis.

The half-life of voxelotor in patients aged 4 to 11 years was 27.2 hours, supporting once-daily dosing. The mean Hb occupancy achieved with voxelotor weight-based dosing with dispersible tablets was 26%, which is within the target therapeutic range of 20% to 30% Hb occupancy. This target is based on the observation that individuals who are compound heterozygous for HbS and a deletional form of hereditary persistence of fetal Hb and who maintain a pancellular fetal Hb distribution of 20% to 30%, generally exhibit a very mild clinical phenotype of SCD.[30]

The safety profile of voxelotor in patients 4 to 11 years of age was consistent with the existing safety profile in adult and adolescent (aged ≥12 years) patients. The most common non-SCD-related TEAEs (reported in ≥10% of patients) were pyrexia, vomiting, rash, abdominal pain, diarrhea, headache, viral infection, pain in extremity, and upper respiratory tract infection. Temporary dose modifications were infrequent and were used to manage TEAEs. This likely contributed to the low rate of drug discontinuation due to TEAEs observed in this study. No new safety signals were identified.

Patients in the study received weight-based dosing of voxelotor in a dispersible tablet-based pediatric formulation. This requires dispersion of 300-mg tablets, of a variable number depending on the patient's weight, in room temperature water or some other clear drink, such as apple juice or soda, immediately before administration. Contents are swirled to mix thoroughly prior to oral consumption. Tablets are expected to disperse but not fully dissolve, and any leftover residue should be resuspended in additional liquid and administered. Given the novel texture and taste of this suspension, patients were encouraged to dissolve tablets in their favorite clear beverage and/or to keep a favorite beverage available for consumption immediately after drug administration.

Despite the risk of serious and potentially life-threatening complications in young children with SCD, current treatment options for pediatric patients are lacking. While transfusion therapy represents an effective way to manage both acute and chronic comorbid complications of SCD (such as stroke, acute chest syndrome, and multisystem organ failure), the safe implementation of chronic transfusion therapy requires careful monitoring for potentially severe side effects, including alloimmunization, iron overload, hemolysis, and hyperviscosity.[12] In infants older than 9 months of age, children, and adolescents with sickle cell anemia, the 2014 National Institutes of Health guidelines recommend treatment with HU regardless of clinical severity to reduce SCD-related complications such as pain, dactylitis, acute chest syndrome, and anemia.[12] For children aged 2 to 16 years with SCD, the 2020 American Society of Hematology guidelines suggest HU treatment for patients with abnormal transcranial Doppler results (≥200 cm/s time-averaged mean of maximum velocity) who have been receiving transfusion therapy for primary stroke prevention for ≥1 year, have magnetic resonance imaging/magnetic resonance angiography findings that exclude silent cerebral infarcts and cerebral vasculopathy, and are interested in stopping transfusion therapy.[31] However, despite the use of HU in the majority of pediatric patients (84%) and a mean fetal Hb

level of 17.7% at baseline in this analysis, there was substantial evidence of elevated hemolysis and low Hb levels at baseline, which are risk factors associated with adverse outcomes such as an increased risk of stroke in children with SCD.[32–34] With the advent of stem cell transplantation and investigation of gene therapy as SCD modalities, there may be potential to cure SCD; however, substantial barriers to use of such therapies currently exist.[12,35] Therefore, evaluating the clinical benefit of treatment with other disease-modifying agents in pediatric patients with SCD should be a research priority.

Voxelotor is the only approved therapy for the treatment of SCD in adult and pediatric patients aged ≥4 years that targets the primary trigger of SCD pathology: HbS polymerization.[15] HbS polymerization and red blood cell sickling underlie the serious and life-threatening clinical complications of SCD.[2,36] Voxelotor has been shown to disrupt the relentless cycle of sickling and to improve key measures of red blood cell health (improved RBC deformability), which can translate to reduced hemolysis, improvements in anemia, and increased ability of blood to deliver oxygen to tissues.[1,17,37–40] Furthermore, mounting real-world evidence suggests that voxelotor may ameliorate SCD complications (e.g., leg ulcers and jaundice) and reduce transfusion dependence and the occurrence of VOCs.[19,21–25] Due to its mechanism of action, voxelotor has the potential to alter disease pathogenesis and mitigate disease-associated morbidity and mortality, especially when used as an early intervention for pediatric patients.

The analysis presented here has some limitations. It is subject to the biases associated with an open-label study design, and the data are in a limited number of patients. Nonetheless, these findings provide evidence that the efficacy and safety profile of voxelotor in patients aged 4 to 11 years are consistent with the existing profiles in adult and adolescent (aged ≥12 years) patients. These data also support the therapeutic efficacy of weight-based dosing in children aged 4 to 11 years. Overall, these data support the use of voxelotor in pediatric patients aged 4 years and older with SCD as a strategy to target the disease at an early stage and impede or prevent disease sequelae. The effect of voxelotor on cerebral hemodynamics in pediatric patients with SCD is currently being investigated in the HOPE-KIDS 2 (NCT04218084) trial.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

Clark Brown, Margaret Tonda, Carla Washington, and Sandra Dixon conceptualized and designed the study. Carla Washington conducted the PK analyses. Sandra Dixon statistically analyzed the data. All authors were involved in analysis and interpretation of the data. Clark Brown, Margaret Tonda, Noelle M. Griffin, and Sandra Dixon contributed to drafting the manuscript. All authors contributed to critically reviewing and revising the manuscript prior to approval for submission.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

LINKED ARTICLE

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REFERENCES

1. Kato GJ, Piel FB, Reid CD, et al. Sickle cell disease. *Nat Rev Dis Primers*. 2018;4:18010. https://doi.org/10.1038/nrdp.2018.10
2. Ware RE, de Montalembert M, Tshilolo L, Abboud MR. Sickle cell disease. *Lancet*. 2017;390(10091):311-323. https://doi.org/10.1016/S0140-6736(17)30193-9
3. Piel FB, Steinberg MH, Rees DC. Sickle cell disease. *N Engl J Med*. 2017;376(16):1561-1573. https://doi.org/10.1056/NEJMra1510865

4. Claster S, Vichinsky EP. Managing sickle cell disease. *BMJ*. 2003;327(7424):1151-1155. https://doi.org/10.1136/bmj.327.7424.1151
5. Kwiatkowski JL, Zimmerman RA, Pollock AN, et al. Silent infarcts in young children with sickle cell disease. *Br J Haematol*. 2009;146(3):300-305. https://doi.org/10.1111/j.1365-2141.2009.07753.x
6. Gill FM, Sleeper LA, Weiner SJ, et al. Clinical events in the first decade in a cohort of infants with sickle cell disease. Cooperative Study of Sickle Cell Disease. *Blood*. 1995;86(2):776-783.
7. Topley JM, Rogers DW, Stevens MC, Serjeant GR. Acute splenic sequestration and hypersplenism in the first five years in homozygous sickle cell disease. *Arch Dis Child*. 1981;56(10):765-769. https://doi.org/10.1136/adc.56.10.765
8. Meier ER, Miller JL. Sickle cell disease in children. *Drugs*. 2012;72(7):895-906. https://doi.org/10.2165/11632890-000000000-00000
9. Brousse V, Buffet P, Rees D. The spleen and sickle cell disease: the sick(led) spleen. *Br J Haematol*. 2014;166(2):165-176. https://doi.org/10.1111/bjh.12950
10. McPherson Yee M, Jabbar SF, Osunkwo I, et al. Chronic kidney disease and albuminuria in children with sickle cell disease. *Clin J Am Soc Nephrol*. 2011;6(11):2628-2633. https://doi.org/10.2215/CJN.01600211
11. Li J, Bender L, Shaffer J, Cohen D, Ying GS, Binenbaum G. Prevalence and onset of pediatric sickle cell retinopathy. *Ophthalmology*. 2019;126(7):1000-1006. https://doi.org/10.1016/j.ophtha.2019.02.023
12. National Heart Lung and Blood Institute. *Evidence-Based Management of Sickle Cell Disease. Expert Panel Report, 2014*. Bethesda, MD: National Institutes of Health; 2014. Accessed September 10, 2021. https://www.nhlbi.nih.gov/sites/default/files/media/docs/sickle-cell-disease-report%20020816_0.pdf
13. Furstenau DK, Tisdale JF. Allogenic hematopoietic stem cell transplantation in sickle cell disease. *Transfus Apher Sci*. 2021;60(1):103057. https://doi.org/10.1016/j.transci.2021.103057
14. Arnold SD, Brazauskas R, He N, et al. Clinical risks and healthcare utilization of hematopoietic cell transplantation for sickle cell disease in the USA using merged databases. *Haematologica*. 2017;102(11):1823-1832. https://doi.org/10.3324/haematol.2017.169581
15. Oxbryta. Prescribing information. Global Blood Therapeutics, Inc.; December 2021.
16. European Commission approves Oxbryta® (voxelotor) for the treatment of hemolytic anemia in patients with sickle cell disease age 12 years and older. Global Blood Therapeutics, Inc.; 2022. Accessed Feb 17, 2022. https://ir.gbt.com/news-releases/news-release-details/european-commission-approves-oxbrytar-voxelotor-treatment.
17. Howard J, Hemmaway CJ, Telfer P, et al. A phase 1/2 ascending dose study and open-label extension study of voxelotor in patients with sickle cell disease. *Blood*. 2019;133(17):1865-1875. https://doi.org/10.1182/blood-2018-08-868893
18. Vichinsky E, Hoppe CC, Ataga KI, et al. A phase 3 randomized trial of voxelotor in sickle cell disease. *N Engl J Med*. 2019;381(6):509-519. https://doi.org/10.1056/NEJMoa1903212
19. Howard J, Ataga K, Brown R, et al. Voxelotor in adolescents and adults with sickle cell disease (HOPE): long-term follow-up results of an international, randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Haematol*. 2021;8(5):e323-e333. https://doi.org/10.1016/S2352-3026(21)00059-4
20. Muschick K, Fuqua T, Stoker-Postier C & Andreson AR Real-world experience of voxelotor for the treatment of patients with sickle cell disease: a single-center study. Presented at: European Hematology Association 2021 Virtual Congress. Accessed September 10, 2021. https://www.gbt.com/wp-content/uploads/2021/06/21-05-28-EHA-RWE-Single-Site-Poster_EP1209_FINAL.pdf
21. Minniti CP, Knight-Madden J, Tonda M, Gray S, Lehrer-Graiwer J, Biemond BJ. The impact of voxelotor treatment on leg ulcers in patients with sickle cell disease. *Am J Hematol*. 2021;96(4):E126-E128. https://doi.org/10.1002/ajh.26101
22. Brown C, Achebe MM, Colombatti R, et al. Effect of voxelotor on hyperbilirubinemia in patients with SCD: results from the phase 3 HOPE study. *JSCDH*. 2021;7;22. Accessed September 10, 2021. https://www.gbt.com/wp-content/uploads/2021/06/21-05-28-EHA-RWE-Single-Site-Poster_EP1209_FINAL.pdf
23. Telfer P, Agodoa I, Fox KM, et al. Impact of voxelotor (GBT440) on unconjugated bilirubin and jaundice in sickle cell disease. *Hematol Rep*. 2018;10(2):7643. https://doi.org/10.4081/hr.2018.7643
24. Ershler WB, Holbrook ME. Sickle cell anemia and COVID-19: Use of voxelotor to avoid transfusion. *Transfusion*. 2020;60(12):3066-3067. https://doi.org/10.1111/trf.16068
25. Zaidi A, Lipato T, Alvarez O, et al. Real-world effectiveness of voxelotor for treating sickle cell disease in the US. Presented at: 62nd Annual Meeting of the American Society of Hematology; Virtual Meeting. December 5–8, 2020. #2627. Accessed September 10, 2021. https://www.gbt.com/wp-content/uploads/2020/12/201207-ASH-RWE-Poster.pdf
26. Global Blood Therapeutics. U.S. FDA approves supplemental new drug application for expanded indication of Oxbryta (voxelotor) for children as young as 4 years of age with sickle cell disease. Globe Newswire; December 17, 2021. Accessed January 27, 2022. https://ir.gbt.com/news-releases/news-release-details/us-fda-approves-supplemental-new-drug-application-expanded
27. Study to evaluate the effect of GBT440 in pediatrics with sickle cell disease (HOPE Kids). ClinicalTrials.gov identifier: NCT02850406. ClinicalTrials.gov. Accessed August 11, 2021. https://clinicaltrials.gov/ct2/show/NCT02850406
28. Brown C, Hoppe C, Inati A, et al. Efficacy and safety of 1500 mg voxelotor in a phase 2a study (GBT440-007) in adolescents with sickle cell disease. *Blood*. 2018;132(suppl 1):509-509. https://doi.org/10.1182/blood-2018-99-117510
29. Andemariam B, Achebe M & Clay ELJ et al. Real-world experience of patients with sickle cell disease treated with voxelotor: a multicenter, retrospective study. Presented at: European Hematology Association Virtual Congress; June 9–17, 2021; Virtual. Session poster presentation EP1206. Accessed November 19, 2021. https://library.ehaweb.org/eha/2021/eha2021-virtual-congress/324927/biree.andemariam.real-world.experience.of.patients.with.sickle.cell.disease.html?f=listing%3D0%2Abrowseby%3D8%2Asortby%3D1%2Asearch%3Dep1206
30. Ngo DA, Aygun B, Akinsheye I, et al. Fetal haemoglobin levels and haematological characteristics of compound heterozygotes for haemoglobin S and deletional hereditary persistence of fetal haemoglobin. *Br J Haematol*. 2012;156(2):259-264. https://doi.org/10.1111/j.1365-2141.2011.08916.x
31. DeBaun M, Jordan L, King A, et al. American Society of Hematology 2020 guidelines for sickle cell disease: prevention, diagnosis, and treatment of cerebrovascular disease in children and adults. *Blood Adv*. 2020;4(8):1554-1588. https://doi.org/10.1182/bloodadvances.2019001142
32. DeBaun MR, Sarnaik SA, Rodeghier MJ, et al. Associated risk factors for silent cerebral infarcts in sickle cell anemia: low baseline hemoglobin, sex, and relative high systolic blood pressure. *Blood*. 2012;119(16):3684-3690. https://doi.org/10.1182/blood-2011-05-349621
33. DeBaun MR, Armstrong FD, McKinstry RC, Ware RE, Vichinsky E, Kirkham FJ. Silent cerebral infarcts: a review on a prevalent and progressive cause of neurologic injury in sickle cell anemia. *Blood*. 2012;119(20):4587-4596. https://doi.org/10.1182/blood-2011-02-272682
34. Guilliams KP, Fields ME, Dowling MM. Advances in understanding ischemic stroke physiology and the impact of vasculopa-

thy in children with sickle cell disease. *Stroke*. 2019;50(2):266-273.
35. Robinson TM, Fuchs EJ. Allogeneic stem cell transplantation for sickle cell disease. *Curr Opin Hematol*. 2016;23(6):524-529. https://doi.org/10.1097/MOH.0000000000000282
36. Steinberg MH. Sickle cell anemia, the first molecular disease: overview of molecular etiology, pathophysiology, and therapeutic approaches. *ScientificWorldJournal*. 2008;8:1295-1324. https://doi.org/10.1100/tsw.2008.157
37. Oksenberg D, Dufu K, Patel MP, et al. GBT 440 increases haemoglobin oxygen affinity, reduces sickling and prolongs RBC half-life in a murine model of sickle cell disease. *Br J Haematol*. 2016;175(1):141-153. https://doi.org/10.1111/bjh.14214
38. Chonat S, Fields E, Baratz H, et al. Improvement in red blood cell physiology in children with sickle cell anemia receiving voxelotor. *Blood*. 2019;134(suppl 1):2281-2281. https://doi.org/10.1182/blood-2019-129351
39. Dufu K, Patel M, Oksenberg D, Cabrales P. GBT440 improves red blood cell deformability and reduces viscosity of sickle cell blood under deoxygenated conditions. *Clin Hemorheol Microcirc*. 2018;70(1):95-105. https://doi.org/10.3233/CH-170340
40. Connes P, Alexy T, Detterich J, Romana M, Hardy-Dessources M-D, Ballas SK. The role of blood rheology in sickle cell disease. *Blood Rev*. 2016;30(2):111-118. https://doi.org/10.1016/j.blre.2015.08.005

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