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DRUG PROFILE



Voxelotor for the treatment of sickle cell disease in pediatric patients

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ABSTRACT

Introduction: Sickle cell disease (SCD) describes a group of heritable blood disorders caused by the polymerization of sickle hemoglobin (HbS). HbS polymerization leads to anemia and vaso-occlusion, a process that impedes delivery of oxygen to tissues throughout the body, resulting in end-organ damage (EOD). Given the lifelong complications associated with SCD, identification and treatment of early symptoms in childhood is increasingly important. Voxelotor is an oral therapy that inhibits the polymerization of HbS and offers a unique therapeutic mechanism to reduce the causes of EOD. Voxelotor was approved in December 2021 for the treatment of SCD in patients aged ≥ 4 years.

Areas covered: Clinical data on the use of voxelotor in pediatric patients with SCD is reviewed. Ongoing studies examining the clinical efficacy and safety profile of voxelotor in pediatric patients are compared with similar clinical outcomes in adults with SCD. Planned studies of voxelotor in children are also discussed.

Expert opinion: Voxelotor provides a unique therapeutic option to target the root causes of EOD and can potentially be used alongside other SCD therapies. Future studies directly observing the impact of voxelotor on EOD will be important for determining treatment strategies.

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end-organ damage;
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1. Introduction

Sickle cell disease (SCD) describes a group of heritable hematological life-threatening diseases characterized by genetic mutation in the beta-globin gene (*HBB*). Beta-globin is a component (subunit) of hemoglobin (Hb). Abnormal beta-globin subunits can lead to the formation of malformed Hb polymers inside red blood cells (RBCs), substantially reducing RBC health, which leads to hemolysis and vaso-occlusion [1–3].

More than 300,000 infants annually are born with sickle cell anemia (SCA), the most common SCD phenotype; an estimated 500 children with SCA die each day [4–6]. The burden of SCD is greatest among individuals of sub-Saharan African descent. Annually, an estimated 1126 sub-Saharan African infants per 100,000 live births are born with the SCA genotype (HbSS, or homozygous SCD) compared with the global meta-estimate of 112 per 100,000 live births [7]. The rate of childhood mortality due to SCD in this region is approximately 50% in urban areas and as high as 90% in rural areas [8]. In the United States, SCD is the most common heritable hematological disease; approximately 2000 babies with SCD are born each year [9,10], affecting 1/365 Black and 1/16,300 Hispanic/Latinx American infants annually [11]. The disease is also prevalent in India and the Middle East and North Africa (MENA) region, and it is present in Europe, North America, and Latin America through population movement [1]. Because symptoms and complications of SCD begin in childhood and continue throughout adulthood, a greater understanding of the pediatric manifestations of the disease could improve patient care and outcomes over the lifetime course of the disease [9].

End-organ damage (EOD), including damage to the heart, kidney, and lung, is a common complication of SCD. The prevalence of EOD in SCD is linked to insufficient delivery of oxygen to organ tissue due to intravascular hemolytic anemia (ie, fewer RBCs in circulation), a lower affinity of oxygen to HbS, and the blockage of blood vessels by sickled RBCs. Blood vessel blockage is exacerbated by the rupturing of sickled RBCs and the release of free Hb, which leads to inflammation, platelet activation, nitric oxide-induced stress, and increased adhesion by RBCs and platelets [9]. These pathologies thus lead to future occurrences and cycles of inflammation, tissue damage, and anemia.

Pain is the most common reason patients with SCD seek treatment [9]. General pain symptoms occur in 31% to 67% of patients with SCD, and vaso-occlusive crises (VOCs) – acute episodes of severe pain caused by tissue ischemia as a result of adhesion of sickled RBCs to blood vessel endothelium and inflammation of the endothelium due to hemolysis, leading to blockage of blood flow – occur in >60% of patients [12,13]. Acute chest syndrome, which is vaso-occlusion in the pulmonary vasculature with infiltrates identified on a chest X-ray, is experienced by ~70% of patients with SCD before age 10 and is the second most common cause of hospital admission after VOCs; acute chest syndrome is the leading cause of admission to the pediatric intensive care unit [9,12].

Overt symptoms such as pain and VOCs are linked to EOD [14]; however, even in the absence of such symptoms, EOD may still be occurring [15]. Indeed, silent cerebral infarcts (SCIs) are estimated to occur in up to 35% of children with

Article highlights

- Sickle cell disease (SCD) manifests early in life and can lead to overt symptoms and silent end-organ damage; therefore, disease-modifying therapies for pediatric patients are exceedingly important in this lifelong disease.
- Voxelotor is a first-in-class polymerization inhibitor of sickle hemoglobin that has previously been shown to increase hemoglobin levels and reduce erythrocyte hemolysis in patients with SCD.
- Voxelotor efficacy and safety results from the HOPE-KIDS 1 trial in patients with SCD aged 4 to 11 years were similar to results observed in adult patients and patients aged ≥ 12 years with SCD from the pivotal HOPE trial.
- Post-marketing surveillance and real-world evidence have indicated improvements in symptoms of SCD and overall quality of life in patients receiving voxelotor.
- As a result of the HOPE-KIDS 1 trial, voxelotor is approved for use in the United States in patients as young as 4 years of age and in the European Union and United Arab Emirates in patients as young as 12 years of age; voxelotor is available as tablets for oral use and as tablets for oral suspension.
- Although a theoretical decrease in oxygen offloading due to greater hemoglobin-oxygen affinity with voxelotor has been suggested, clinical trial evidence and real-world clinical experience show no evidence of insufficient oxygen delivery.

SCA and in 22% to 59% of all children and adolescents with SCD [9,16–18]. SCIs are associated with cognitive impairment and an increased risk for subsequent overt stroke (occurring in 7%–11% of patients ≤ 20 years old with SCD) [9,17,19]. Transcranial Doppler ultrasonography is recommended as early as 2 years of age to identify children with SCA at risk for stroke [20,21]. Vaso-occlusion can also lead to poor splenic function, another silent and progressive example of EOD. Decreased oxygen tension and high Hb concentrations in the spleen lead to HbS polymerization, and the sickled RBCs readily adhere to blood vessels in the spleen, causing vaso-occlusion. The resulting splenic damage manifests as a compromised immune system and increased susceptibility to infection (including sepsis, which is the primary cause of mortality among pediatric patients) [9,22]. Despite increased disease awareness and advances in patient care, current health outcomes for individuals with SCD are poor. The median life expectancy for individuals with SCD is only 43 years [23].

2. Burden of illness and health inequalities

SCD is a financial burden to both the patient and the health-care system. The overall economic burden of SCD in the United States is estimated to be \$2.98 billion per year, consisting of inpatient, outpatient, and out-of-pocket costs [24]. When comparing patients with SCD to patients without SCD, healthcare expenditures are 6 times higher for patients with Medicaid and 11 times higher for patients with private insurance [25]. A 2012 analysis indicated 47% of pediatric patients with SCD receiving Medicaid were 18 years old or younger [26]. As a disease that predominantly occurs in Black/African American and Latinx American populations, racial and ethnic health disparities within the US healthcare system greatly impact access to care, the type of care received, and the breadth of funding available for research [27]. Additionally,

racial and ethnic disparities in wealth are reflected in the increased vulnerability to social determinants of health facing families of children with SCD, with 66% reporting at least 1 unmet socioeconomic need, such as food insecurity, difficulty paying utilities, and a desire to pursue more education [28].

3. Overview of the market/therapeutic landscape

Only 4 pharmacologic options for the treatment of SCD have been approved by the US Food and Drug Administration (FDA) [29–34].

- Hydroxyurea is approved for ages 2 and older; however, it is frequently prescribed in patients as young as 9 months as a compounded liquid formulation (where available)
- L-glutamine is approved for patients aged 5 years and older
- Crizanlizumab is approved for those aged 16 years and older
- Voxelotor is approved for ages 4 and older

Hydroxyurea, first approved in 1998 for adults with SCD, was the sole disease-modifying therapy for decades. Clinical trials demonstrated that hydroxyurea was well tolerated and increased Hb levels in most trial participants [31]. However, recent analyses of hydroxyurea use among patients with SCD indicate high rates of treatment discontinuation (60%) and low rates of medication possession (a measurement of the ratio of total number of days' supply of hydroxyurea to the total number of days in the follow-up period; only 22% had a medication possession ratio of $\geq 80\%$) [35]. Stem cell transplantation (SCT) and gene therapy are other treatment modalities that represent a potential cure for SCD, but their clinical use thus far has been encumbered by substantial barriers, including engraftment failure in SCT and the need to treat patients with chemotherapy prior to SCT or gene therapy [36–38].

Voxelotor is the newest treatment in the SCD pharmacological armamentarium that targets the underlying pathophysiology (HbS polymerization) rather than only downstream pathophysiologic effects. Once-daily oral treatment with voxelotor, a first-in-class polymerization inhibitor, is directly associated with a rise in Hb levels and a reduction in hemolysis due to increased durability of RBCs [39–41].

4. Introduction to the drug

Based on results of the phase 3 HOPE trial (ClinicalTrials.gov Identifier: NCT03036813), voxelotor (Oxbryta) was granted accelerated approval by the FDA in 2019 for the treatment of patients with SCD 12 years of age and older [42]. In 2021, voxelotor received FDA approval for the treatment of SCD in adults and pediatric patients aged ≥ 4 years [34]. In February 2022, the European Commission granted marketing authorization for voxelotor in the European Union for the treatment of hemolytic anemia due to SCD in adult and pediatric patients ≥ 12 years of age as monotherapy or in combination with hydroxyurea [43]. Additionally, voxelotor

was granted market authorization by the Ministry of Health and Prevention in the United Arab Emirates for the treatment of SCD in adults and children ≥ 12 years of age [43].

Voxelotor binds directly to Hb molecules within RBCs to increase their affinity for oxygen [44,45]. By stabilizing Hb in the oxygenated state, the cycle of sickling and unsickling of RBCs is disrupted, thus reducing hemolysis and possibly improving RBC membrane integrity [40,46]. Treatment with voxelotor improves anemia, allowing for increased oxygen delivery throughout the body to potentially reduce the incidence of organ damage, stroke, and death [39,47].

Two versions of voxelotor are available: a tablet form for swallowing (500 mg per tablet) and a dispersible tablet form for oral suspension (300 mg per tablet), the latter of which was introduced primarily as a pediatric formulation. For pediatric patients 4 years and older, the appropriate form of voxelotor is selected based on the patient's ability to swallow tablets and the patient's weight (Table 1). The oral suspension can also be used in adult patients and pediatric patients ≥ 12 years old with difficulty swallowing tablets. Pediatric patients with severe hepatic impairment and for those who use concomitant strong or moderate CYP3A4 inducers must adjust their dosage appropriately [34].

5. Voxelotor pediatric clinical trials

Currently, pediatric patients (aged 6 months to < 18 years) are receiving voxelotor as part of the phase 2 HOPE-KIDS 1 trial (NCT02850406), which comprises 4 parts: Part A, a single-dose study in patients aged 6 to 17 years; Part B, a multiple-dose trial in patients aged 12 to 17 years; Part C, a multiple-dose trial in patients aged 4 to 17 years; and Part D, a multiple-dose trial in patients aged 6 months to < 4 years. Results are available for Parts A, B, and C. Parts A and B have concluded, while Parts C and D are ongoing. Enrollment for Part D is planned to conclude by December 2022.

6. Clinical efficacy: the HOPE-KIDS study

Markers of clinical efficacy are being measured or have been measured in the HOPE-KIDS 1 study [42]. **Part A** of the study, which tested a single oral dose of voxelotor 600 mg in children and adolescents, has concluded. In **Part B**, interim results indicated an increase in mean Hb from baseline of 1.1 g/dL at week 16 among adolescents (aged 12–17 years) receiving voxelotor 1500 mg; the Hb response rate (defined as the percentage of patients with a Hb increase of > 1 g/dL from baseline) at week 16 was 55% (6/11) [48]. Additionally, numerical decreases in markers of hemolysis (indirect bilirubin, reticulocyte percentage, lactate dehydrogenase) were evident

following treatment with voxelotor 1500 mg [48]. Median (25th, 75th percentile) indirect bilirubin decreased by 36.9% (–58.5%, –5.9%), reticulocyte percentage decreased by 5.8% (–42.1%, 14.7%), and lactate dehydrogenase decreased by 23.1% (–33.2%, 10.9%). Patients in **Part C** received weight-based dosing of voxelotor. Interim results showed a mean increase in Hb from baseline of 1.0 g/dL at week 24 in voxelotor-treated patients 4 to < 12 years old, with increases detected as early as the first measured time point (week 2) [49]. The Hb response rate was 36% (16/45) (95% CI: 21.6%, 49.5%) in all patients who received at least 1 dose of voxelotor [34,49]. Of patients with Hb measurements at both baseline and week 24, the Hb response rate was 47% (16/34) (95% CI: 29.8%, 64.9%) [49]. Numerical decreases in all markers of hemolysis following voxelotor treatment [49]. Mean (minimum, maximum) indirect bilirubin decreased by 38.6% (–76.0%, 40.0%), reticulocyte percentage decreased by 3.3% (–95.0%, 110.3%), and lactate dehydrogenase decreased by 2.6% (–36.6%, 44.2%). In patients aged 4 to 11 years, exposures and percentage of Hb occupancy with voxelotor weight-based dosing was comparable to those in patients aged 12 to 17 years [49]. Despite these promising results, it is important to note that the analysis did not factor in nonresponders and noncompliance, so these data may change as they become more finalized.

7. Safety profile

In HOPE-KIDS 1, the overall safety profile of voxelotor in patients aged 4 to < 12 years was similar to that seen in patients aged 12 years and older [34]. The most common non-SCD-related adverse reactions ($\geq 10\%$) reported in Part C 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%) [34,49]. The most commonly reported drug-related treatment-emergent adverse events (TEAEs; reported in $\geq 10\%$ of patients) were diarrhea (11%), rash (11%), and vomiting (11%); of these, most were grade 1 per the Common Terminology Criteria for Adverse Events; grade 2 rash was reported in 2 patients, and no events of grade 3 or greater severity were observed. A total of 11 patients discontinued voxelotor; 4 of whom discontinued due to adverse events. Of the 4 discontinuations due to an adverse event, 2 were determined to be voxelotor related: 1 patient had pyrexia, SCA with crisis, and allergic edema (facial and pedal); and 1 patient had decreased appetite [49]. A total of 12 patients had dose interruptions due to TEAEs. Of these, 8 patients resumed voxelotor [49].

Despite compelling published efficacy and safety data for voxelotor, a potential risk of reduced oxygen tissue delivery due to a leftward shift of the oxygen dissociation curve has been suggested [50]. This claim was based on allosteric models suggesting that the increase in oxygen delivery resulting from reduced sickling by voxelotor is largely offset by decreased oxygen offloading at the tissue delivery sites due to the increase in Hb-oxygen affinity. It is important to note

Table 1. Recommended dosage of voxelotor for pediatric patients aged 4 to 11 years.

| Body weight | Recommended dose (once daily) |
|--------------------------------|-------------------------------|
| Body weight ≥ 40 kg | 1500 mg |
| Body weight 20 kg to < 40 kg | 900 mg |
| Body weight 10 kg to < 20 kg | 600 mg |

Note: The dispersible tablet for oral suspension is available in a 300 mg dose only.

that the reports of these concerns were based on model simulations rather than in vivo animal models or evidence gathered in clinical studies [50]. Models may not account for all of the physiological variables at play in vivo (for example, the increased oxygen-carrying capacity of RBCs being a larger offset than the Hb occupancy concerns at higher levels of Hb), and clinical and laboratory evidence should be considered when evaluating potential tissue effects. Indeed, empirical evidence supports sufficient offloading of oxygen in the presence of increased oxygen affinity of Hb with voxelotor treatment. Preclinical data showed that GBT1118, a voxelotor analog with the same mechanism of action but improved physicochemical and pharmacokinetic properties in SCD mice, increased oxygen delivery without limiting oxygen extraction by tissues, ultimately improving brain oxygenation and overall survival in the SCD mice [51]. Additionally, in a phase 1/2 study, no significant changes in oxygen uptake from baseline were observed during peak cardiopulmonary exercise testing or in ventilatory thresholds between patients receiving 90 days of voxelotor treatment and those receiving placebo [44].

In the phase 3 HOPE trial, several metrics were used to examine potential effects of voxelotor on oxygen delivery. Serum erythropoietin levels were also evaluated throughout the treatment phase as a proxy for tissue oxygenation (because erythropoietin levels increase in response to tissue hypoxia); by week 24, no correlation between percent voxelotor Hb occupancy and percent change from baseline in erythropoietin level was observed [39]. Furthermore, the safety profile of voxelotor in clinical trials suggests that insufficient oxygen offloading was not observed clinically, as no indicators of reduced oxygen offloading, such as tachycardia and reduced exercise capacity, were observed in over 2% of participants. No new safety signals were identified during the 72-week safety evaluation phase of the phase 3 HOPE trial, and most adverse events reported were unrelated to voxelotor treatment [40]. Notably, there were no reports of stroke or transient ischemic attack in the voxelotor 1500 mg treatment arm, no increase of VOCs associated with voxelotor treatment, and no reports of kidney damage, all of which would have been indicators of decreased oxygen tissue delivery. Although the HOPE trial was not powered to detect the effect of voxelotor on VOCs, subsequent real-world evidence indicated that VOC incidence significantly decreased following voxelotor treatment among patients who have experienced at least 1 VOC in the prior 3 months [52]. In the same study, the need for other SCD treatments, such as transfusions, VOC-related hospitalizations, and all-cause hospitalizations (indicated by both the total number of hospitalizations and the length of stay of hospitalizations) was also reduced in the 3-month follow-up period. Another study has shown reductions in albuminuria, a marker of SCD-related nephropathy, in patients receiving voxelotor [53].

If a risk of oxygen offloading as a result of voxelotor treatment did exist, it would have revealed itself clinically among the more than 8300 new prescriptions that have been recorded for voxelotor from its approval in November 2019 to December 2021.

8. Post-approval clinical trials in children

HOPE-KIDS 2 is a phase 3, randomized, double-blind, placebo-controlled, multicenter trial that is currently recruiting participants. It is designed to evaluate the effect of voxelotor on transcranial Doppler measurements (the change in time-averaged maximum of the mean velocity arterial cerebral blood flow) in pediatric patients ≥ 2 to 14 years old (ClinicalTrials.gov Identifier: NCT04218084) [54].

Other studies include an open-label, expanded-access trial (ClinicalTrials.gov Identifier: NCT04724421) that provided early access to pediatric patients with SCD (aged 4–11 years) who had no alternative treatment options before the commercial availability of voxelotor in these younger patients [55]; an ongoing multicenter, post-marketing, retrospective chart review characterizing real-world clinical outcomes in patients with SCD who have been treated with voxelotor (ClinicalTrials.gov Identifier: NCT04930328) [56]; and a randomized, double-blind, placebo-controlled trial to evaluate the effect of voxelotor on neurocognitive function in patients 8 to 17 years old that is currently recruiting (ClinicalTrials.gov Identifier: NCT05228834) [57]. A summary of these clinical trials, along with clinical trials that have concluded, is available in Table 2.

9. Post-marketing studies

A qualitative study involving one-time interviews was conducted with 10 patient-caregiver dyads to elicit the perspectives of both the children and their primary caregivers [58]. All patients (aged 4–11 years) were receiving voxelotor and had participated in a voxelotor clinical trial at a single academic site in the United States. Current SCD severity was rated by physicians as ‘mild’ for all patients. Physicians also reported improvement in 8 patients (80%) using the Clinical Global Impression of Change scale. Based on the most recent steady-state Hb measurements at the time of study screening, Hb levels improved in 90% of patients (9/10), from a mean of 9.0 g/dL (range: 7.6–11.1 g/dL) before voxelotor initiation to 9.6 g/dL (8.2–12.2 g/dL) after treatment [58]. This significant rise in Hb levels occurred in a cohort that was receiving hydroxyurea at a stable optimal dose. Most respondents reported improvement in the severity and/or frequency of pain crises (63% [5/8]), fatigue (80% [4/5]), and jaundice (80% [4/5]). Caregivers and patients also reported positive changes with respect to chronic and breakthrough pain other than pain crises ($n = 2$), ability to focus ($n = 1$), nail strength ($n = 1$), and appetite ($n = 1$) [58]. Most responders (80% [8/10]) reported improvement in their perceived quality of life, specifically citing a general feeling of improved quality of life after starting voxelotor treatment. Half of the caregiver-patient dyads (5/10) reported improvements in the patient’s ability to engage in activities such as swimming and other play. Overall, 30% of caregivers (3/10) reported improvements in the school/academic environment for their child, which was attributed to increased focus, reduced absences from school, and increased participation in the classroom and other school-related activities. It is important to note that these results represent data gathered from a small sample of patients and caregivers who participated in semi-structured interviews

Table 2. Completed and ongoing clinical trials involving voxelotor treatment in pediatric patients.

| Clinical study | Status | Objective | Patient population | Study arms | Key endpoints |
|--|------------|---|---|---|---|
| Observational studies | | | | | |
| RETRO (NCT04930328) Location: United States Primary completion: Dec 2021 N = 216 | Completed | To retrospectively evaluate the effect of voxelotor in real-world settings | All patients of all ages with a documented SCD diagnosis (all genotypes) treated with voxelotor for ≥ 2 weeks | Voxelotor prescribed according to the USPI | <ul style="list-style-type: none"> Hb level Hemolysis measures Significant SCD-related clinical events HRU HRQOL Adverse events |
| Interventional studies | | | | | |
| HOPE-KIDS 1: Part D (NCT02850406) Location: United States, United Kingdom, and Lebanon Est. primary completion: Dec 2022 N = 30 | Ongoing | To evaluate the safety, tolerability, and PK of voxelotor in pediatric patients with SCD | <ul style="list-style-type: none"> Aged 6 months to 4 years Background HU allowed if dose has been stable for ≥ 1 month, titration to maximum tolerated dose allowed Hb ≤ 10.5 g/dL at screening No transfusions in past 30 days Body weight ≥ 5 kg for 1 month prior to screening | Voxelotor 1500 mg (or weight-adjusted equivalent) | <p>Primary</p> <ul style="list-style-type: none"> Treatment-emergent adverse events and serious adverse events <p>Secondary</p> <ul style="list-style-type: none"> Hb level Hemolysis measures PK profile |
| HOPE-KIDS 2 (NCT04218084) Location: International Est. primary completion: Mar 2026 N = 224 | Recruiting | To evaluate the effect of voxelotor on transcranial Doppler flow velocity in pediatric patients with SCD | <ul style="list-style-type: none"> Aged 2–14 years Confirmed SCD (HbSS, HbSβ^0) TCD TAMMV arterial cerebral blood flow ≥ 170 to < 200 cm/s during screening | <ul style="list-style-type: none"> Voxelotor 1500 mg or weight-adjusted equivalent dose for patients aged < 12 years Matching placebo | <p>Primary</p> <ul style="list-style-type: none"> Change in TCD FV (24 weeks) <p>Secondary</p> <ul style="list-style-type: none"> Change in TCD FV (48 and 96 weeks) Conversion to abnormal TCD FV Reversion to normal TCD FV TCD FV reduction ≥ 15 cm/s Hb level Hemolysis measures |
| EAP (NCT04724421) Location: United States Primary completion: Nov 2021 N = 66 | Completed | To provide early access to treatment with voxelotor prior to market authorization for pediatric patients with SCD who have no alternative treatment options and are ineligible to participate in clinical trials of voxelotor | <ul style="list-style-type: none"> Aged 4–11 years Confirmed SCD (any genotype) | Voxelotor (weight-adjusted equivalent dose) + SOC | <ul style="list-style-type: none"> PGI-C CGI-C Hb levels Adverse events |
| Neurocognitive Function (NCT05228834) Location: United States Est. primary completion: Oct 2023 N = 80 | Recruiting | To assess the treatment effects of voxelotor on neurocognitive function as measured by the NIH Toolbox Cognition Model of executive abilities in children and adolescents with SCD | <ul style="list-style-type: none"> Aged 8–17 years Confirmed SCD (all genotypes) | <ul style="list-style-type: none"> Voxelotor 1500 mg or weight-adjusted equivalent dose for patients aged < 12 years + SOC Matching placebo + SOC | <p>Primary</p> <ul style="list-style-type: none"> Executive abilities composite score <p>Secondary</p> <ul style="list-style-type: none"> Processing speed Nonexecutive cognitive abilities Hb level Hemolysis measures |

CGI-C, Clinical Global Impression of Change; EAP, expanded access program; FV, flow velocity; Hb, hemoglobin; HbS β^0 , sickle cell beta zero thalassemia; HbSS, homozygous for SCD; HRQOL, health-related quality of life; HRU, healthcare resource utilization; HU, hydroxyurea; NIH, National Institutes of Health; PGI-C, Patient Global Impression of Change; PK, pharmacokinetics; SCD, sickle cell disease; SOC, standard of care; TAMMV, time-averaged maximum of the mean velocity; TCD, transcranial Doppler ultrasound; USPI, United States prescribing information.

conducted by interviewers trained in qualitative research methodology; some questions required quantitative responses, and others required qualitative or descriptive responses. While improvements in both Patient Global Impression of Change (PGI-C) and Clinical Global Impression of Change (CGI-C) scores have been reported in voxelotor-treated patients with SCD aged 12 to 70 years and 20 to 66 years in 2 single-center retrospective studies [59,60], such real-world PGI-C and CGI-C analyses in patients aged < 12 years

are anticipated now that voxelotor is approved in the younger age group.

10. Regulatory affairs

In 2019, voxelotor was granted FDA approval for patients 12 years and older in the United States [34,39]. In December 2021, the FDA expanded the approval of voxelotor for patients 4 years and older [34]. The HOPE-KIDS 1 trial

(ClinicalTrials.gov Identifier: NCT02850406) is currently ongoing [61]. In February 2022, the European Medicines Agency granted marketing authorization for voxelotor as a monotherapy or in combination with hydroxycarbamide for the treatment of hemolytic anemia due to SCD in adults and pediatric patients 12 years of age and older [43]. Voxelotor has also been granted marketing authorization by the Ministry of Health and Prevention in the United Arab Emirates for patients with SCD 12 years of age and older [43].

11. Conclusion

The signs and symptoms of SCD are evident in early childhood and persist through the patient's life. A greater understanding of available treatments for pediatric use is increasingly necessary to mitigate the long-term consequences of this lifelong disease. Voxelotor targets the underlying cause of SCD – HbS polymerization – and has clinical implications for downstream effects. These effects, such as increased Hb and decreased markers of hemolysis, may improve EOD outcomes associated with SCD due to greater oxygen affinity and an overall improvement in RBC health. The safety profile of voxelotor in pediatric clinical trials is similar to the safety profile in adult patients in the pivotal HOPE trial. The amendment to the voxelotor prescribing information in 2021 to include children as young as 4 years of age widens the treatment landscape for patients with SCD and will likely lead to better long-term patient outcomes.

12. Patient/HCP resources

Several resources are available to pediatric patients with SCD in the United States:

- Oxbryta.com has educational resources for patients, parents, and caregivers on the use of voxelotor.
- A patient medication education sheet is included with each pediatric prescription dispensed from a specialty pharmacy. The pharmacist reviews the information with the patient, parent, and caregiver to help patients, parents, and caregivers understand the procedure for daily dose preparation and administration.
- High-touch services from specialty pharmacies and nursing staff ensure the availability of pharmacists and nurses for counseling and questions regarding appropriate dosing and therapy initiation, as well as providing support for treatment adherence.

13. Expert opinion

The primary strength of voxelotor lies in its ability to target the underlying pathophysiological cause of SCD, polymerization of HbS. Inhibiting the polymerization of HbS and directly increasing oxygen-carrying Hb levels has important implications for pain-related HbS effects, oxygen delivery to organs, and the potential reduction in EOD. Greater RBC oxygen affinity ensures higher oxygen delivery throughout the body. Although concerns have been raised about a theoretical risk

of hypoxic damage to organs as a result of increased oxygen affinity, mice treated with a voxelotor analog did not demonstrate increased hypoxia [46], and measures of cardiopulmonary health among trial participants receiving voxelotor did not differ from those seen in participants given placebo [62].

The availability of 2 different tablet formulations of voxelotor, 1 that can be directly swallowed and 1 that can be dispersed in a liquid, overcomes limitations for young children and patients with issues swallowing pills, potentially increasing patient adherence to the once-daily dosing regimen.

It is important to note that voxelotor can also be used in combination with other available SCD therapies. In a study by Ware et al, voxelotor administered with or without hydroxyurea led to significant dose-dependent Hb increases [63]. The generally favorable safety profile of voxelotor combined with its clinical effectiveness represents an important treatment option for the many children for whom their current treatment has been unsatisfactory, as well as for children needing a preventive intervention or an alternative to currently available therapies.

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Declaration of Interest

C Brown declares consultancy work for Global Blood Therapeutics, Inc. M Tonda is an employee and equity owner of Global Blood Therapeutics, Inc. MR Abboud is a consultant for Novartis and Novo Nordisk and receives additional research funding from Eli Lilly and Modus Pharmaceuticals. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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