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A Multicenter, Retrospective Study on Real-World Experience of Patients With Sickle Cell Disease Treated With Voxelotor

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BACKGROUND

- Sickle cell disease (SCD) is characterized by polymerization of sickle hemoglobin (HbS) in the deoxygenated state, causing sickling of red blood cells that leads to hemolysis, anemia, and vaso-occlusion.[1]
- Voxelotor is a first-in-class HbS polymerization inhibitor that reversibly binds to hemoglobin (Hb) and stabilizes the oxygenated state.[2,3]
- Voxelotor is approved by the US Food and Drug Administration for the treatment of SCD in patients aged ≥4 years and received marketing authorization in the European Union and United Arab Emirates for the treatment of patients aged ≥12 years.[4,5]
- The initial approval of voxelotor was based on results from the phase 3 HOPE trial, in which voxelotor-treated adolescents and adults with SCD achieved a significantly increased level of Hb and decreased markers of hemolysis compared with patients given placebo.[3]
- This real-world study expands upon our understanding of the safety and efficacy of voxelotor in clinical practice, complementing results observed in the pivotal HOPE trial.

OBJECTIVE

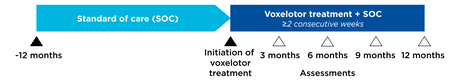
- The Retrospective Study to Evaluate Outcomes in Patients With Sickle Cell Disease Treated With Oxbryta (RETRO) aims to characterize real-world safety and effectiveness of voxelotor in adults and adolescents with SCD treated with voxelotor as part of their usual care.

Presented at the European Hematology Association 2022 Hybrid Congress, June 9-12, 2022; Vienna, Austria, and virtual.

METHODS

- RETRO is a postmarketing study (NCT04930328) that included voxelotor-treated patients from 9 clinical sites in the United States.[6]
- Patients with SCD aged ≥12 years who received voxelotor for ≥2 consecutive weeks were included (**Figure 1**).
- Patients were ineligible if they had participated in a prior investigation (within 1 year), clinical trial, or expanded access program with voxelotor.
- Laboratory and clinical data were collected retrospectively from patients' medical records from 1 year before and up to 1 year after the first voxelotor dose.
- Assessments at 3-, 6-, 9-, and 12-month intervals include hematological outcomes, clinically significant events, healthcare resource utilization, health-related quality of life, and safety.

Figure 1. RETRO Study Design



RESULTS

Patients

- A total of 216 patients aged 12 to 71 years were included.
  - Mean (SD) age was 33.5 (14.2) years, 55.6% were female, 87.5% were Black or African American, and 92.1% had HbSS genotype (**Table 1**).
- Most patients (64.8%) had baseline Hb between 7 and 10.5 g/dL, with a mean (SD) of 7.8 (1.5) g/dL; 68.1% were treated concomitantly with hydroxyurea.
- The mean (SD) duration of voxelotor treatment was 51.1 (25.6) weeks, and most patients (86.6%) initiated treatment with 1500 mg; participant treatment duration was variable (10.2% were treated for <3 months, 7.9% from 3 to <6 months, 10.6% from 6 to <9 months, 13.0% from 9 to <12 months, and 58.3% for ≥12 months).
- The most common reason for voxelotor use was reducing anemia (69.9%).
- A total of 25% of patients (n=54) had a dose change initiated by their physician; reasons for a dose change were adverse event (n=37), pill burden (n=2), lack of efficacy (n=1) or other (n=22).

Table 1. Patient Demographics and Baseline Characteristics

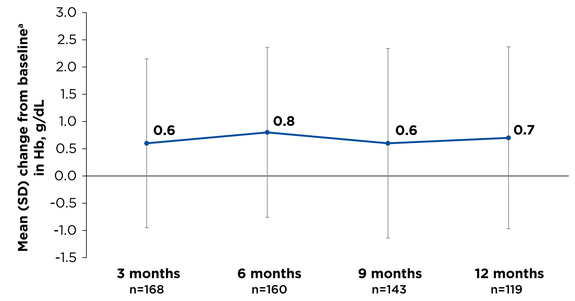
		Patients (N=216)[a]
Age, years	Mean (SD) Range	33.5 (14.2) 12, 71
Patients per age group, n (%)	<18 years 18 to <45 years 45 to <65 years ≥65 years	31 (14.4) 136 (63.0) 43 (19.9) 6 (2.8)
Sex, n (%)	Male Female	96 (44.4) 120 (55.6)
HbS genotype, n (%)	HbSS HbSC HbSβ+ HbSβ0 Other	199 (92.1) 2 (0.9) 3 (1.4) 10 (4.6) 1 (0.5)
Patient insurance, n (%)	Private Medicaid Medicare Medicaid and Medicare Self-insured	94 (43.5) 75 (34.7) 36 (16.7) 7 (3.2) 2 (0.9)
Baseline Hb, g/dL	Mean (SD) Range	7.8 (1.5) 4.3, 13.5
Patient baseline Hb, n (%)	<7 g/dL 7 to 10.5 g/dL >10.5 g/dL	60 (27.8) 140 (64.8) 9 (4.2)
Concomitant HU, n (%)	Yes No	147 (68.1) 68 (31.5)
Reasons for voxelotor use, n (%)	Reducing anemia Reducing pain Reducing frequency of VOC Reducing need for blood transfusion Other	151 (69.9) 51 (23.6) 45 (20.8) 17 (7.9) 44 (20.4)

[a]Missing data: HbS genotype (n=1), baseline Hb (n=7), concomitant HU (n=1).
Hb, hemoglobin; HbS, sickle hemoglobin; HbSβ+, sickle beta plus thalassemia, HbSC, hemoglobin SC disease; HbSS, homozygous for SCD; HU, hydroxyurea; SD, standard deviation; VOC, vaso-occlusive crisis.

Hb Levels and Markers of Hemolysis

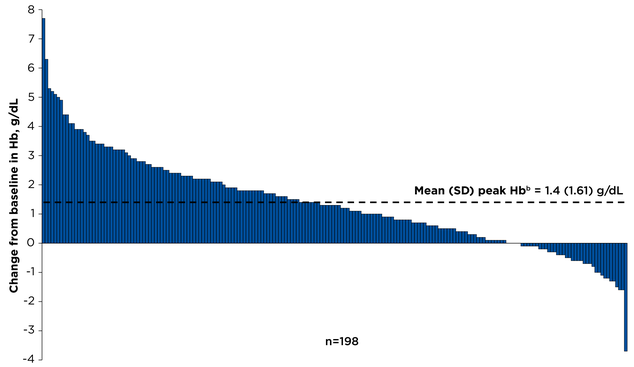
- Mean Hb levels remained elevated over the 12-month treatment period (**Figure 2**).
- Mean (SD) peak Hb increased from baseline by 1.4 (1.61) g/dL with voxelotor treatment (**Figure 3**).

Figure 2. Hb Levels Increased and Were Maintained Over 12 Months of Voxelotor Use



[a]Baseline was defined as the mean of available measurements up to 1 year prior to initiation of voxelotor treatment.
Hb, hemoglobin; SD, standard deviation.

Figure 3. Per-Patient Peak Hb Change From Baseline[a] During the Study Period

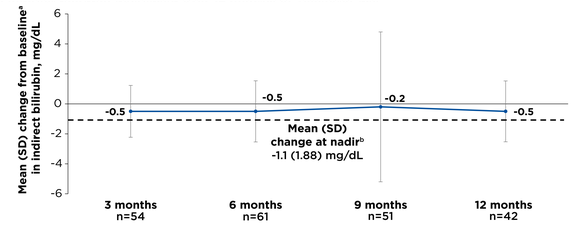


[a]Baseline was defined as the mean of available measurements up to 1 year prior to initiation of voxelotor treatment.
[b]Peak Hb was defined as the highest post-baseline Hb value while on voxelotor treatment.
Hb, hemoglobin; SD, standard deviation.

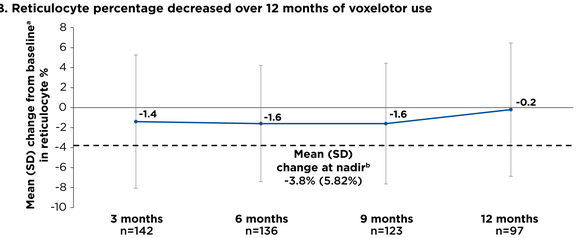
- Mean indirect bilirubin and mean reticulocyte percentage remained decreased over the 12 months after voxelotor initiation (**Figure 4**).

Figure 4. 12 Months of Voxelotor Treatment Improved Markers of Hemolysis

A. Indirect bilirubin decreased over 12 months of voxelotor use



B. Reticulocyte percentage decreased over 12 months of voxelotor use



[a]Baseline was defined as the mean of available measurements up to 1 year prior to initiation of voxelotor treatment.
[b]Nadir indirect bilirubin and reticulocyte percentage were defined as the lowest post-baseline values while on voxelotor treatment. Dotted line indicates mean (SD) change at nadir. SD, standard deviation.

Safety

- Of the 216 patients in this study, 25.5% (n=55) experienced an adverse event deemed related to treatment; the most common (≥3%) were diarrhea (13.0%), headache (7.4%), abdominal pain (3.2%), and rash (5.6%).
- Treatment-emergent adverse events (TEAEs) unrelated to SCD were mild in 14.8% of the participants, moderate in 10.2%, and severe in 11.6% (**Table 2**).
- Overall, the most common TEAEs (≥5%) included diarrhea (17.1%), headache (12.5%), and rash (6.5%) (**Table 2**).

Table 2. Safety and Tolerability of Voxelotor in Study Patients

TEAEs not related to SCD, n (%)	Patients (N=216)
Patients with any adverse event	80 (37.0)
Severity of TEAEs, n (%)[a]	
Mild	32 (14.8)
Moderate	22 (10.2)
Severe	25 (11.6)
TEAEs leading to voxelotor dose modification or discontinuation, n (%)	
Patients with any adverse event	67 (31.0)
TEAEs with ≥5% incidence	
Diarrhea	37 (17.1)
Headache	27 (12.5)
Rash	14 (6.5)

[a]Missing data on TEAE severity in 1 (0.5%) patient. TEAE, treatment-emergent adverse event; SCD, sickle cell disease.

LIMITATIONS

- As with all retrospective studies, data were limited to those captured in medical records.
- Data in this study were limited to 9 clinical sites in the United States.
- The incidences of non–SCD-related adverse events in RETRO differed from those observed in the phase 3 HOPE trial, which is not unexpected given the retrospective nature of this study.

CONCLUSIONS

- RETRO is the largest multicenter study to collect and analyze retrospective data from patients with SCD treated with voxelotor in a real-world setting, providing essential information on the clinical use of voxelotor in patients aged ≥12 years.
- Results were consistent with the pivotal HOPE trial, demonstrating that voxelotor increases Hb levels and decreases hemolytic markers in clinical practice.
- Fewer than 40% of participants reported a TEAE unrelated to SCD, and most TEAEs were mild to moderate in severity; no new safety signals were identified.

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ACKNOWLEDGMENTS

- **We thank the patients with sickle cell disease, their families and caregivers, physicians, research nurses, study coordinators, and support staff who contributed to this study.**

DISCLOSURES

- **Biree Andemariam:** Consultant, advisory board: Agios, Aruvant, Bluebird Bio, CRISPR, Emmaus, Forma Therapeutics, Global Blood Therapeutics, Hemanext, Novartis, Novo Nordisk, Sanofi Genzyme, Shenox, Terumo BCT, Vertex; research funding: Forma Therapeutics, Global Blood Therapeutics, Hemanext, Imara, Novartis. **Modupe Idowu:** Research funding: Pfizer, Ironwood, Forma Therapeutics; advisory board: Novartis; advisory board, speaker: Global Blood Therapeutics. **Nirmish Shah:** Speaker, research funding, consultant: Global Blood Therapeutics; speaker, research funding: Novartis; consultant: Bluebird Bio, CSL Behring; speaker: Alexion. **Richard Drachtman:** Speaker, consultant: Global Blood Therapeutics; consultant: Bluebird Bio, Agios. **Archana Sharma:** Nothing to disclose. **Alexander Glaros:** Advisory board: Global Blood Therapeutics. **Maureen Achebe:** Advisory board: Fulcrum Therapeutics, Pharmacosmos. **Alecia Nero:** Consultant: Global Blood Therapeutics, Editas Medicine, Bluebird Bio, Novartis. **Rong Michelle Xu:** Employee, equity ownership: Global Blood Therapeutics. **Susanna Curtis:** Consultant: Global Blood Therapeutics. **Caterina Minniti:** Consultant: Global Blood Therapeutics, Novartis, Novo Nordisk, Roche, Forma, Agios, Chiesi, Emmaus Life Sciences, Sanguine Bio.
- Medical writing and editorial assistance was provided by Brittany Ulrich, PhD (Healthcare Consultancy Group, funded by Global Blood Therapeutics).
- This study was supported by Global Blood Therapeutics.