Incidence of Vaso-occlusive Crisis Does Not Increase With Achieving Higher Hemoglobin Levels on Voxelotor Treatment or After Discontinuation: Analyses of the HOPE Study

Elliott Vichinsky, MD[1]; Paul Telfer, DM, FRCP[2]; Adlette Inati, MD, FAAP[3]; Margaret Tonda, PharmD[4]; Barbara Tong, PhD[4]; Irene Agodoa, MD[4]; Joshua Lehrer-Graiwer, MD, MPhil, FACC[4]; Kenneth I. Ataga, MD[5]

[1]UCSF Benioff Children's Hospital Oakland, Oakland, CA, USA; [2]Barts Health NHS Trust, London, UK; [3]Lebanese American University, Beirut, Lebanon; [4]Global Blood Therapeutics, South San Francisco, CA, USA; [5]University of Tennessee Health Science Center at Memphis, Memphis, TN, USA

BACKGROUND

- Sickle cell disease (SCD) is an inherited disorder in which pathology is driven by hemoglobin (Hb) polymerization and red blood cell sickling, leading to chronic hemolytic anemia, and intermittent vaso-occlusion with subsequent ischemic-reperfusion injury.[1]
  - Hemolytic anemia has been associated with innate immune system and endothelial cell activation resulting in an inflammatory, pro-adhesive state that leads to vaso-occlusive crisis (VOC) and damage to organs.[1,2]
- Voxelotor is a first-in-class sickle hemoglobin (HbS) polymerization inhibitor in development for the treatment of SCD (**Figure 1**).[3]
- In the phase 3 HOPE trial, voxelotor 1500 mg and 900 mg daily demonstrated robust, rapid, and sustained dose-dependent improvements in patients' Hb levels, with numerically fewer VOCs compared with placebo, which suggests that viscosity was not increased with voxelotor treatment.[4]

Figure 1. Voxelotor Inhibits HbS Polymerization and Is Potentially Disease Modifying

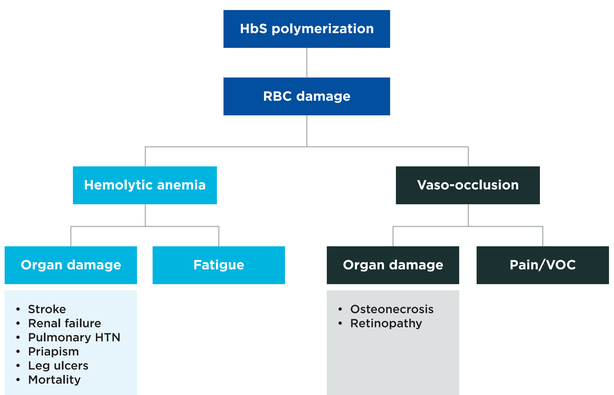


Figure adapted from Eaton WA, Bunn HF. *Blood.* 2017;129(20):2719-2726.
HbS, sickle hemoglobin; HTN, hypertension; RBC, red blood cell; VOC, vaso-occlusive crisis.

OBJECTIVES

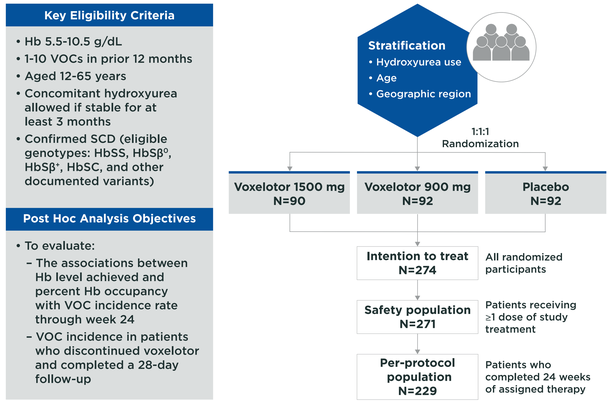
- To evaluate the associations between VOC incidence rate and absolute Hb level achieved and percent Hb occupancy achieved with voxelotor treatment.

METHODS

Study Design

- A post hoc analysis of data from the HOPE trial (a phase 3, randomized, placebo-controlled, double-blind, multicenter study) was conducted to compare VOC incidence by Hb level and Hb occupancy among patients with SCD who were aged 12 to 65 years and receiving 2 different doses of voxelotor or placebo (**Figure 2**).

Figure 2. HOPE Study Design



Hb, hemoglobin; HbSC, hemoglobin SC disease; HbSS, sickle cell anemia; HbSβ, sickle cell beta thalassemia; SCD, sickle cell disease; VOC, vaso-occlusive crisis.

- Patients in the per-protocol population who completed 24 weeks of their assigned therapy were stratified by Hb level (<8 g/dL, 8 to <10 g/dL, 10 to <12 g/dL, or ≥12 g/dL) and by Hb occupancy (<20%, 20% to <30%, or ≥30%) at 24 weeks and assessed up to week 72 of the study.
  - Hb levels at week 24 were calculated as the mean of values collected at weeks 20 and 24.
- In patients who initiated hydroxyurea post randomization, VOC data were censored as of hydroxyurea treatment initiation.
  - A VOC event during the treatment period was defined as a composite of acute pain crisis or acute chest syndrome with moderate to severe pain lasting ≥2 hours, no explanation other than VOC, pain requiring analgesic use, or documented doctor visit within a day of the event.
  - For patients who discontinued treatment, data on VOC events occurring in the 28 days post treatment are presented separately.
- Mean cumulative functions of VOC events are presented by treatment group.

RESULTS

Baseline Characteristics

- Baseline characteristics were similar among patients receiving voxelotor 1500 mg and 900 mg and those receiving placebo, as previously reported.[4]

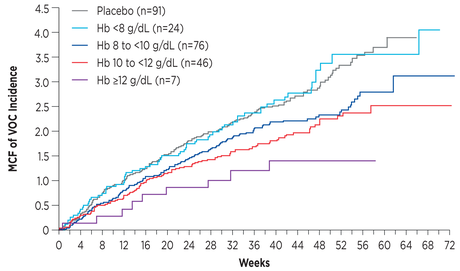
Treatment With Voxelotor Was Associated With Reduced Rates of VOCs

- The proportion of patients with ≥1 VOC was 67.0% (59 of 88) in the voxelotor 1500 mg group, 66.3% (61 of 92) in the voxelotor 900 mg group, and 69.2% (63 of 91) in the placebo group.
- The annualized adjusted incidence rate of VOCs (the number of crises per person-year) was 2.77 in the voxelotor 1500 mg group, 2.76 in the voxelotor 900 mg group, and 3.19 in the placebo group.

Higher Hb Levels Achieved With Voxelotor Were Associated With Reduced Rates of VOCs

- When stratified by absolute Hb level after 24 weeks of treatment, the incidence of VOCs was generally lower in patients who achieved higher Hb levels in the pooled voxelotor (1500 mg and 900 mg) group than in those who achieved lower Hb levels or who were receiving placebo (**Figure 3**).

Figure 3. Cumulative Incidence of VOCs by Hb Level During Treatment Period



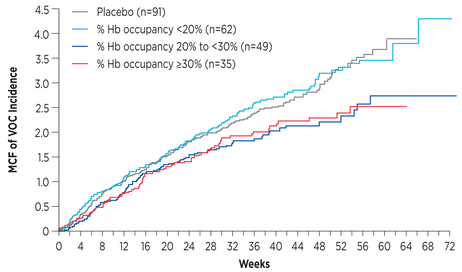
No. at Risk	Hb at Week 24	Week: 0	4	8	12	16	20	24	36	48	60	72
Placebo	All	91	90	87	84	82	79	75	45	24	5	0
Voxelotor pooled	Hb <8 g/dL	24	24	24	24	24	24	24	16	7	2	0
	Hb 8 to <10 g/dL	76	76	76	76	76	76	74	45	23	5	1
	Hb 10 to <12 g/dL	46	46	46	46	46	46	46	34	19	4	1
	Hb ≥12 g/dL	7	7	7	7	7	7	7	5	3	0	0

Hb, hemoglobin; MCF, mean cumulative function; VOC, vaso-occlusive crisis.

Higher Hb Occupancy With Voxelotor Treatment Was Associated With Reduced Rates of VOCs

- Among patients receiving voxelotor, those who had Hb occupancy of ≥20% with voxelotor after 24 weeks experienced numerically fewer VOCs compared with placebo, consistent with a treatment-induced inhibition of HbS polymerization (**Figure 4**).

Figure 4. Cumulative Incidence of VOCs by Percent Hb Occupancy During Treatment Period



No. at Risk	% Hb Occupancy	Week: 0	4	8	12	16	20	24	36	48	60	72
Placebo	All	91	90	87	84	82	79	75	45	24	5	0
Voxelotor pooled	<20%	62	61	60	58	57	57	55	34	18	3	1
	20% to <30%	49	49	47	47	46	45	44	26	12	4	2
	≥30%	35	35	33	31	30	29	28	22	12	2	0

Among patients receiving voxelotor, the <20% Hb occupancy group (n=62) included 50 patients treated with the 900 mg dose and 12 patients treated with the 1500 mg dose. The 20% to <30% Hb occupancy group (n=49) included 21 patients treated with voxelotor 900 mg and 28 treated with voxelotor 1500 mg. The ≥30% Hb occupancy group (n=35) included 3 patients treated with voxelotor 900 mg and 32 patients treated with voxelotor 1500 mg.
Hb, hemoglobin; MCF, mean cumulative function; VOC, vaso-occlusive crisis.

A Numerically Lower Incidence of VOCs Was Observed in the Voxelotor Groups Than in the Placebo Group After Discontinuation

- At the time of data cutoff, 55 patients had discontinued treatment and had post-treatment follow-up.
- In the 28 days post treatment discontinuation:
  - Five of 21 patients in the voxelotor 1500 mg group reported a total of 6 VOCs.
  - Three of 17 patients in the voxelotor 900 mg group reported a total of 3 VOCs.
  - Five of 17 patients in the placebo group reported a total of 8 VOCs.

CONCLUSIONS

- There was no evidence that increased Hb with voxelotor treatment led to an increased risk of VOC. Patients who achieved the greatest absolute Hb levels after 24 weeks of treatment with voxelotor had numerically fewer VOCs than patients who received placebo.
- Patients who reached a Hb occupancy of ≥20% and those with Hb levels of ≥12 g/dL with voxelotor experienced the lowest VOC rates and fewer VOCs compared with those receiving placebo, consistent with a treatment-induced inhibition of HbS polymerization.
- Although the patient population of the HOPE study was not enriched or powered to evaluate VOCs as an efficacy endpoint, the results of this safety analysis provide important reassurance regarding the safety of voxelotor and are consistent with voxelotor treatment safely raising Hb without causing a viscosity-related increase in risk of VOC.

References

1. Kato GJ, Piel FB, Reid CD, et al. Sickle cell disease. *Nat Rev Dis Primers.* 2018;4:18010.
2. Kato GJ, Steinberg MH, Gladwin MT. Intravascular hemolysis and the pathophysiology of sickle cell disease. *J Clin Invest.* 2017;127(3):750-760.
3. Estepp JH. Voxelotor (GBT440), a first-in-class hemoglobin oxygen-affinity modulator, has promising and reassuring preclinical and clinical data. *Am J Hematol.* 2018;93(3):326-329.
4. 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.

Acknowledgments

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

Disclosures

- **Elliott Vichinsky:** Global Blood Therapeutics, consultant; Agios, Pfizer, research funding. **Paul Telfer:** Bluebird Bio, research funding; Global Blood Therapeutics, Terumo, Bluebird Bio, honoraria; Global Blood Therapeutics, Pfizer, ApoPharma, membership. **Adlette Inati:** Global Blood Therapeutics, AstraZeneca, Novartis, research funding; Novo Nordisk, Pfizer, Roche, Novartis, advisory board. **Margaret Tonda, Barbara Tong, Irene Agodoa, Joshua Lehrer-Graiwer:** Global Blood Therapeutics, employees and stockholders. **Kenneth I. Ataga:** Novartis, consultant; Global Blood Therapeutics, Pfizer, research funding; Global Blood Therapeutics, Novartis, Modus Therapeutics, Bioverativ, honoraria; Global Blood Therapeutics, Bioverativ, membership.
- Nelson Jen, PhD (Healthcare Consultancy Group, with funding from Global Blood Therapeutics) provided editorial assistance in the preparation of this report.
- This study was sponsored by Global Blood Therapeutics.

For a copy of this poster, scan the QR code with your Android™ phone, Blackberry®, or iPhone®. No personal information will be collected. This is not associated with any marketing or promotional activity.

https://bit.ly/2qgsbkV

Presented at: 61st ASH Annual Meeting and Exposition; December 7-10, 2019; Orlando, FL, USA

© 2019 Global Blood Therapeutics