Higher Hemoglobin Levels Achieved with Voxelotor Are Associated with Lower Vaso-Occlusive Crisis Incidence: 72-Week Analysis from the HOPE Study

Elliott Vichinsky, MD; Victor R. Gordeuk, MD; Paul Telfer, DM, FRCP; Adlette Inati, MD, FAAP; Margaret Tonda, PharmD; Sarah Gray, PhD; Irene Agodoa, MD; Kenneth I. Ataga, MD

1UCSF Benioff Children’s Hospital, Oakland, CA, USA; 2University of Illinois at Chicago College of Medicine, Chicago, IL, USA; 3Barts Health NHS Trust, London, United Kingdom; 4Lebanese American University, Beirut and Nini Hospital, Tripoli, Lebanon; 5Global Blood Therapeutics, South San Francisco, CA, USA; 6University of Tennessee Health Science Center at Memphis, Memphis, TN, USA

ASH 2020
Disclosures

Elliot Vichinsky (presenting author)
• Consultancy: Global Blood Therapeutics
• Research funding: Agios, Pfizer

Victor R. Gordeuk
• Consultancy: Emmaus Medical, Global Blood Therapeutics, Modus Therapeutics
• Research funding: Emmaus Medical, Global Blood Therapeutics, Incyte, Novartis

Paul Telfer
• Honoraria: Bluebird Bio, Global Blood Therapeutics, Terumo
• Membership on entity’s Board of Directors or advisory committees: ApoPharma, Global Blood Therapeutics, Pfizer
• Research funding: Bluebird Bio

Adlette Inati
• Consultancy: Novartis
• Honoraria: Novartis, Novo Nordisk, Pfizer, Roche
• Membership on entity’s Board of Directors or advisory committees: Cyclerion, Novartis, Novo Nordisk, Pfizer, Roche
• Research funding: AstraZeneca, Cyclerion, Global Blood Therapeutics, Novartis, Octapharma

Margaret Tonda
• Current employment and current equity holder in a publicly traded company: Global Blood Therapeutics

Sarah Gray
• Current employment and current equity holder in a publicly traded company: Global Blood Therapeutics

Irene Agodoa
• Current employment and current equity holder in a publicly traded company: Global Blood Therapeutics

Kenneth I. Ataga
• Consultancy: Forma Therapeutics, Novartis
• Honoraria: Bioverativ, Editas Medicine, Global Blood Therapeutics, Modus Therapeutics, Novartis, Novo Nordisk
• Membership on entity’s Board of Directors or advisory committees: Bioverativ, Global Blood Therapeutics, Novo Nordisk
• Research funding: Global Blood Therapeutics, Novartis, Pfizer, Shire/Takeda
Background

SCD is a lifelong, inherited disorder characterized by sickle hemoglobin polymerization that results in red blood cell sickling and in complications such as hemolytic anemia, VOCs, endothelial dysfunction, and organ damage¹.

Large and rapid increases in hemoglobin concentration in response to red blood cell transfusions have raised concerns of hyperviscosity and the associated increased risk of vaso-occlusive complications²,³:

- Current transfusion guidelines recommend raising Hb to no higher than 10 g/dL in adults².

Voxelotor is an oral, once-daily sickle hemoglobin–polymerization inhibitor indicated for treatment of SCD in adults and adolescents aged ≥12 years⁴.

Here we report a post hoc analysis assessing the association between average on-treatment Hb and VOC incidence over 72 weeks.

Hb, hemoglobin; SCD, sickle cell disease; VOC, vaso-occlusive crisis.
**HOPE Trial: Study Design**

**Phase 3, randomized, double-blind, placebo-controlled, multicenter trial evaluating the efficacy and safety of voxelotor**

- Aged 12 to 65 years with confirmed SCD\(^4\)
- Hb 5.5 to 10.5 g/dL
- Between 1 and 10 VOCs in prior 12 months
- Concomitant HU, if stable for ≥3 months

![Diagram of study design]

**Primary efficacy endpoint**
- **Hb response rate**: percentage of participants with Hb increase >1.0 g/dL at 24 weeks

**Key secondary efficacy endpoints**
- **Hemolysis markers**: change from baseline to week 24
- **Hb level**: change from baseline to week 24
- **Annualized incidence of VOCs**: final analysis at 72 weeks

---

\(^4\)Eligible genotypes: HbSS, HbSβ\(^0\), HbSβ\(^+\), HbSC, and other documented variants.

Hb, hemoglobin; HbSβ\(^0\), sickle beta zero thalassemia; HbSβ\(^+\), sickle beta plus thalassemia; HbSC, hemoglobin SC disease; HbSS, homozygous for SCD; HU, hydroxyurea; R, randomization; SCD, sickle cell disease; VOC, vaso-occlusive crisis.

VOC Annualized Incidence Rates Were Numerically Lower with Voxelotor

VOC, vaso-occlusive crisis.
VOC Annualized Incidence Rates Were Numerically Lower with Voxelotor in Patients with ≥2 VOCs 12 Months prior to Screening

**Annualized Incidence Rate of VOCs**

(≥2 VOCs in 12 Months prior to Screening)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Events per person-year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>3.1</td>
</tr>
<tr>
<td>Voxelotor 1500 mg</td>
<td>2.5</td>
</tr>
<tr>
<td>Voxelotor 900 mg</td>
<td>3.0</td>
</tr>
</tbody>
</table>

**VOC IRR**

Voxelotor vs Placebo

- **Voxelotor 1500 mg**: IRR = 0.5
- **Voxelotor 900 mg**: IRR = 1.0

Favors treatment ➡️ Favors placebo

**IRR (95% CI)**

Favors treatment ➡️ Favors placebo

IRR, incidence rate ratio; VOC, vaso-occlusive crisis.
Incidence Rate of VOCs Was Lowest in Patients Achieving the Highest Hemoglobin Levels

Summary excludes VOC events after treatment discontinuation and events after HU initiation post randomization for patients with no HU use at baseline. Summary excludes patients without post-baseline Hb lab assessment. Hb values are as observed based on assessments collected through the end of the week 72 visit window. Hb values collected after treatment discontinuation (for patients with last dose prior to the week 72 visit window), after withdrawal of consent, after study discontinuation, and after HU initiation post randomization for patients with no HU use at baseline were excluded.

Hb, hemoglobin; HU, hydroxyurea; MCF, mean cumulative function; VOC, vaso-occlusive crisis; wk, week.

Baseline demographics were generally well balanced across Hb strata

Mean Cumulative Function for VOC Incidence (on Treatment) by Average Hb Post Baseline (Final Study Database)

No. at risk | Hb Average | Wk | 0 | 4 | 8 | 12 | 16 | 20 | 24 | 36 | 48 | 60 | 72 |
--- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
Placebo | All | 91 | 90 | 87 | 83 | 82 | 79 | 75 | 70 | 66 | 64 | 40 |
| Hb 5.9 to <8 g/dL | 23 | 21 | 20 | 19 | 19 | 19 | 17 | 15 | 14 | 14 | 14 | 6 |
| Hb 8 to <10 g/dL | 96 | 96 | 94 | 92 | 90 | 88 | 84 | 78 | 76 | 72 | 72 | 55 |
| Hb 10 to <12 g/dL | 50 | 50 | 46 | 43 | 42 | 41 | 41 | 40 | 39 | 39 | 39 | 30 |
| Hb 12 to ≤13.3 g/dL | 10 | 10 | 9 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 6 |
Conclusions

Treatment with once-daily voxelotor resulted in increases in average Hb concentrations that reached or exceeded 10 g/dL in a substantial number of study participants.

In contrast with the theoretical concern of higher VOC risk with higher Hb levels, patients who had the highest average Hb levels over 72 weeks with voxelotor experienced the fewest VOCs, with a stepwise reduction in VOC rate with each increase in Hb stratum.

These results suggest the mechanism of reducing hemolysis and raising Hb in individuals with SCD, such as via inhibition of polymerization, is important.

The improvement in red blood cell health, including increased deformability and decreased viscosity, suggest higher Hb thresholds could be considered in patients on voxelotor.

Hb, hemoglobin; SCD, sickle cell disease; VOC, vaso-occlusive crisis.
Acknowledgements

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

• This study was supported by Global Blood Therapeutics.