Results from Part A of the Hemoglobin Oxygen Affinity Modulation to Inhibit HbS Polymerization (HOPE) Trial (GBT440-031), a Placebo-Controlled Randomized Study Evaluating Voxelotor (GBT440) in Adults and Adolescents with Sickle Cell Disease

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On behalf of all HOPE investigators
Disclosures

Consultant/advisory boards:

- Global Blood Therapeutics
- Bluebird Bio
- Protagonist
Voxelotor, a Novel Inhibitor of HbS Polymerization

• Novel mechanism that inhibits HbS polymerization and RBC sickling, the underlying pathophysiologic mechanism of SCD

• Preclinical and clinical studies to date demonstrated:
  • Improved red blood cell deformability and decreased blood viscosity\textsuperscript{1}
  • Rapid, sustained, and clinically meaningful increases in Hb and reduction of hemolysis\textsuperscript{2,3}
  • Favorable safety profile with once-daily oral dosing\textsuperscript{2,3}
  • Improved blood oxygen carrying capacity and tissue oxygen delivery\textsuperscript{4,5}

• Potential to modify morbidity and mortality by improving anemia and hemolysis

Hb, hemoglobin; HbS, sickle hemoglobin; RBC, red blood cell; SCD, sickle cell disease.
Voxelotor Acts Upstream: Potential to be Disease Modifying

HbS Polymerization

Voxelotor

Red Blood Cell Damage

Hemolytic Anemia

Organ Damage
- Stroke
- Renal failure
- Pulmonary HTN
- Priapism
- Leg ulcers
- Mortality

Fatigue

Vaso-occlusion

Organ Damage
- Osteonecrosis
- Retinopathy

Pain / VOC

HTN, hypertension; VOC, vaso-occlusive crisis.
Adapted from Eaton WA, Bunn HF. Blood 2017;129(20):2719-2726.
HOPE Study Design—Part A

Key Eligibility Criteria
- 1-10 VOCs in prior year
- Hb ≥5.5 to ≤10.5 g/dL
- ≥12 years old
- Concomitant hydroxyurea allowed

Primary Endpoints
- Proportion of patients who achieve a >1 g/dL Hb improvement
- Safety

Key Secondary Endpoints
- Hemolysis measures
- VOC
- Patient-reported outcome

Stratification
- Hydroxyurea use
- Age
- Geographic region

Part A
- Voxelotor 1500 mg N=52
- Voxelotor 900 mg N=52
- Placebo N=50

1:1:1 Randomization

- Part A included 154 treated patients through Week 24
- Primary analysis of all patients (n=271) is planned in early 2019
## Baseline Characteristics

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Voxelotor 1500 mg N=52</th>
<th>Voxelotor 900 mg N=52</th>
<th>Placebo N=50</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years (range)</td>
<td>23 (12, 59)</td>
<td>26 (13, 59)</td>
<td>26 (12, 52)</td>
</tr>
<tr>
<td>12 to &lt; 18 years, n (%)</td>
<td>8 (15)</td>
<td>7 (13)</td>
<td>6 (12)</td>
</tr>
<tr>
<td>18 to 65 years, n (%)</td>
<td>44 (85)</td>
<td>45 (87)</td>
<td>44 (88)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>16 (31)</td>
<td>24 (46)</td>
<td>25 (50)</td>
</tr>
<tr>
<td>Region, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>North America</td>
<td>21 (40)</td>
<td>22 (42)</td>
<td>20 (40)</td>
</tr>
<tr>
<td>Europe</td>
<td>7 (13)</td>
<td>6 (12)</td>
<td>7 (14)</td>
</tr>
<tr>
<td>Other&lt;sup&gt;a&lt;/sup&gt;</td>
<td>24 (46)</td>
<td>24 (46)</td>
<td>23 (46)</td>
</tr>
<tr>
<td>Genotype, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HbSS/HbSβ&lt;sup&gt;0&lt;/sup&gt; thalassemia</td>
<td>48 (92)</td>
<td>49 (94)</td>
<td>45 (90)</td>
</tr>
<tr>
<td>HbSC</td>
<td>1 (2)</td>
<td>1 (2)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Other&lt;sup&gt;b&lt;/sup&gt;</td>
<td>3 (6)</td>
<td>2 (4)</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Current hydroxyurea use, n (%)</td>
<td>32 (62)</td>
<td>35 (67)</td>
<td>32 (64)</td>
</tr>
<tr>
<td>Median baseline hemoglobin, g/dL (range)</td>
<td>8.6 (5.9, 10.8)</td>
<td>8.3 (6.3, 10.8)</td>
<td>8.5 (6.1, 10.4)</td>
</tr>
<tr>
<td>VOC episodes in previous 12 months&lt;sup&gt;c&lt;/sup&gt;, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>23 (44)</td>
<td>21 (40)</td>
<td>22 (44)</td>
</tr>
<tr>
<td>2-5</td>
<td>25 (48)</td>
<td>27 (52)</td>
<td>24 (48)</td>
</tr>
<tr>
<td>6-10</td>
<td>4 (8)</td>
<td>4 (8)</td>
<td>4 (8)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Other regions: Lebanon, Turkey, Oman, Egypt, Kenya, Jamaica.

<sup>b</sup>Other genotypes include: HbSβ<sup>+</sup> thalassemia, other sickle cell syndrome variant.

<sup>c</sup>Baseline VOC defined as document episode of ACS or acute painful crisis that required prescription or healthcare professional-instructed use of analgesics for moderate to severe pain.
65% of Patients Receiving Voxelotor 1500 mg Achieved >1 g/dL Increase in Hemoglobin

Baseline = average of screening and Day 1; 24 Weeks = average of Weeks 20 and 24. P values are based on comparison with placebo.
Voxelotor Demonstrates a Rapid, Robust, and Sustained Improvement in Anemia at Target Hemoglobin Occupancy

![Graph showing mean change in Hb from baseline in g/dL over weeks for Voxelotor 1500 mg, Voxelotor 900 mg, and Placebo]

### Table: Hemoglobin Occupancy

<table>
<thead>
<tr>
<th>Value</th>
<th>Voxelotor 900 mg</th>
<th>Voxelotor 1500 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Hb occupancy(a) ((C_{\text{min}}))</td>
<td>13.8% (46.5)</td>
<td>25.3% (32.8)</td>
</tr>
</tbody>
</table>

SE, standard error

\(a\)Hb occupancy geometric mean (%CV) = calculated % of RBC Hb bound by voxelotor.
Voxelotor 1500 mg Increased Hemoglobin to Mean of 10 g/dL, Consistent With Substantial Improvement in Anemia

Voxelotor 1500 mg (n=43)  
Voxelotor 900 mg (n=43)  
Placebo (n=42)

Mean (±SE) Hb, g/dL

Baseline  | 24 Weeks
---|---
8.6 | 10.0
8.4 | 9.0
8.6 | 8.7

Mean (±SE) Change From Baseline to 24 Weeks in Hb, g/dL

Baseline 24 Weeks
---
1.4 | 0.6
0.1

Baseline = average of screening and day of randomization; 24 Weeks = average of Weeks 20 and 24.
Hemoglobin Improvement With or Without Hydroxyurea (HU)

Baseline = average of screening and day of randomization; 24 Weeks = average of Weeks 20 and 24.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mean (±SE) Change From Baseline in Hb, g/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Voxelotor 1500 mg</td>
<td>1.6 ± 0.1</td>
</tr>
<tr>
<td>No HU</td>
<td>1.1 ± 0.1</td>
</tr>
<tr>
<td>Voxelotor 900 mg</td>
<td>0.7 ± 0.1</td>
</tr>
<tr>
<td>No HU</td>
<td>0.5 ± 0.1</td>
</tr>
<tr>
<td>Placebo</td>
<td>0.0 ± 0.0</td>
</tr>
</tbody>
</table>

HU n=25, No HU n=18, HU n=29, No HU n=14, HU n=28, No HU n=14
Hemoglobin Improvement Regardless of Baseline Anemia Severity

Baseline = average of screening and day of randomization; 24 Weeks = average of Weeks 20 and 24.
Absolute Reticulocyte Count Improvement Consistent With Decreased Hemolysis

Baseline = average of screening and day of randomization; 24 Weeks = average of Weeks 20 and 24.
Percent Reticulocyte Count Improvement Consistent With Decreased Hemolysis

Baseline = average of screening and day of randomization; 24 Weeks = average of Weeks 20 and 24.
Indirect Bilirubin Improvement Consistent With Decreased Hemolysis

Baseline = average of screening and day of randomization; 24 Weeks = average of Weeks 20 and 24.
LDH Improvement Consistent With Decreased Intravascular Hemolysis

Mean (±SE) LDH

- **Voxelotor 1500 mg (n=43)**
  - Baseline: [Graph]
  - 24 Weeks: [Graph]

- **Voxelotor 900 mg (n=42)**
  - Baseline: [Graph]
  - 24 Weeks: [Graph]

- **Placebo (n=41)**
  - Baseline: [Graph]
  - 24 Weeks: [Graph]

**Mean (±SE) % Change From Baseline to 24 Weeks in LDH**

LDH, lactate dehydrogenase.
Baseline = average of screening and day of randomization; 24 Weeks = average of Weeks 20 and 24.
## Treatment-Emergent Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>Voxelotor 1500 mg N=52</th>
<th>Voxelotor 900 mg N=52</th>
<th>Placebo N=50</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>48 (92%)</td>
<td>46 (88%)</td>
<td>47 (94%)</td>
</tr>
<tr>
<td>Grade ≥3</td>
<td>29 (56%)</td>
<td>31 (60%)</td>
<td>27 (54%)</td>
</tr>
<tr>
<td>AE leading to treatment discontinuation</td>
<td>5 (10%)</td>
<td>3 (6%)</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>SAE (not including VOC or ACS)</td>
<td>25 (48%)</td>
<td>29 (56%)</td>
<td>24 (48%)</td>
</tr>
<tr>
<td>Fatal SAE</td>
<td>0</td>
<td>0</td>
<td>1 (2%)</td>
</tr>
</tbody>
</table>

ACS, acute chest syndrome; AE, adverse event; SAE, serious adverse event.
## Treatment-Emergent Adverse Events Occurring in ≥10% of Subjects

<table>
<thead>
<tr>
<th>Preferred Term, n (%)</th>
<th>Voxelotor 1500 mg N=52</th>
<th>Voxelotor 900 mg N=52</th>
<th>Placebo N=50</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with ≥1 event (not including SCD events)</td>
<td>48 (92)</td>
<td>46 (88)</td>
<td>47 (94)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>11 (21)</td>
<td>10 (19)</td>
<td>5 (10)</td>
</tr>
<tr>
<td>Headache</td>
<td>15 (29)</td>
<td>6 (12)</td>
<td>13 (26)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>7 (13)</td>
<td>11 (21)</td>
<td>5 (10)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>9 (17)</td>
<td>7 (13)</td>
<td>5 (10)</td>
</tr>
<tr>
<td>Nausea</td>
<td>8 (15)</td>
<td>8 (15)</td>
<td>6 (12)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>7 (13)</td>
<td>6 (12)</td>
<td>4 (8)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>5 (10)</td>
<td>7 (13)</td>
<td>6 (12)</td>
</tr>
<tr>
<td>Pain</td>
<td>5 (10)</td>
<td>7 (13)</td>
<td>4 (8)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>7 (13)</td>
<td>5 (10)</td>
<td>7 (14)</td>
</tr>
<tr>
<td>Back pain</td>
<td>5 (10)</td>
<td>6 (12)</td>
<td>4 (8)</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>4 (8)</td>
<td>7 (13)</td>
<td>8 (16)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>4 (8)</td>
<td>6 (12)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>3 (6)</td>
<td>6 (12)</td>
<td>6 (12)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>5 (10)</td>
<td>4 (8)</td>
<td>7 (14)</td>
</tr>
<tr>
<td>Cough</td>
<td>5 (10)</td>
<td>2 (4)</td>
<td>3 (6)</td>
</tr>
</tbody>
</table>
VOC definition includes ACS

- Moderate to severe pain lasting ≥2 hours
- No explanation other than VOC
- Requires medication prescribed/directed by a healthcare professional
- Patient was seen in medical facility or contacted site within 1 business day

Median follow up = 41.6 weeks for all patients (N=154)
No Treatment-Related Increase in Erythropoietin, Indicating Preserved Tissue Oxygenation

CFB, change from baseline; EPO, erythropoietin; HCT, hematocrit; LOCR, last observation carried forward
Conclusions

- Rapid, robust, and sustained improvement in hemoglobin and hemolysis
- Voxelotor 1500 mg dose demonstrated:
  - Hemoglobin increase of >1 g/dL in 65% of patients
  - Anemia improvement irrespective of baseline anemia severity or HU use
- Voxelotor was safe and well tolerated
- Fewer VOC with substantial increase in hemoglobin
- Preserved tissue oxygenation as indicated by reduction in reticulocyte counts and stable erythropoietin levels

Voxelotor has the potential to modify the morbidity of chronic organ damage associated with SCD by improving anemia and hemolysis
Thank You to All the HOPE Investigators


*Indicates change of Principal Investigator
Acknowledgments

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

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