Improvement in the Clinical Global Impression of Change with Voxelotor in Patients with Sickle Cell Disease in the Phase 3 HOPE Trial

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ASH 2020
Disclosures

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- Research funding: Global Blood Therapeutics, NHLBI, PCORI, HRSA, Novartis, Imara, Shire

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- Research funding: Global Blood Therapeutics, NHLBI, The Links Incorporated, Novartis
- Honoraria: NHLBI, ASPHO, MJH Life Sciences

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- Honoraria: Global Blood Therapeutics, Terumo, Bluebird Bio
- Membership: Global Blood Therapeutics, Pfizer, ApoPharma
Tools Capturing the Broad Symptomatology of SCD Are Needed to Assess Patients’ Overall Disease Status

Pain and fatigue are readily identifiable symptoms of SCD – and often the focus of clinical trials.1-4

Current PRO assessments in SCD only focus on capturing domain-specific symptoms and impacts – such as pain, depression, and fatigue.4,5

However, patients with SCD can experience additional complications and symptoms that impact their health-related quality of life.1,6

PRO, patient-reported outcome; SCD, sickle cell disease.
Clinical Global Impression of Change Is a Clinician-Reported Outcome That Assesses a Patient’s Clinical Status

A single-item tool that evaluates a patient’s status based on the treating physician’s clinical judgment.¹

Physicians are asked:
“Compared with the patient’s clinical status at baseline before initiating treatment, the patient’s overall condition is...”¹

Analogous to the well-known Patient Global Impression of Change scale²

<table>
<thead>
<tr>
<th>Rating</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Very much improved</td>
<td>Nearly all better; good level of functioning; minimal symptoms</td>
</tr>
<tr>
<td></td>
<td>Represents a substantial change</td>
</tr>
<tr>
<td>2 Moderately improved</td>
<td>Notably better with considerable reduction of symptoms</td>
</tr>
<tr>
<td></td>
<td>Increase in the level of functioning but some symptoms remain</td>
</tr>
<tr>
<td>3 Minimally improved</td>
<td>Slightly better with little or no clinically meaningful reduction of symptoms</td>
</tr>
<tr>
<td></td>
<td>Represents little change in basic clinical status, level of care, or functional capacity</td>
</tr>
<tr>
<td>4 No change</td>
<td>Symptoms remain essentially unchanged</td>
</tr>
<tr>
<td>5 Minimally worse</td>
<td>Slightly worse but may not be clinically meaningful</td>
</tr>
<tr>
<td></td>
<td>Represents little change in basic clinical status or functional capacity</td>
</tr>
<tr>
<td>6 Moderately worse</td>
<td>Clinically significant increase in symptoms and diminished functioning</td>
</tr>
<tr>
<td>7 Very much worse</td>
<td>Severe exacerbation of symptoms and loss of functioning</td>
</tr>
</tbody>
</table>

Objective: To evaluate the impact of voxelotor on patient outcomes in SCD, as measured by the single-item CGI-C

CGI-C, Clinical Global Impression of Change; SCD, sickle cell disease.
HOPE Trial: Study Design\textsuperscript{1,2}

**Voxelotor** is a HbS polymerization inhibitor that was approved by the US Food and Drug Administration for the treatment of SCD in adults and pediatric patients 12 years of age and older\textsuperscript{3}

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

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

\textsuperscript{a}Eligible genotypes: HbSS, HbS\textsuperscript{β}0, HbS\textsuperscript{β}+, HbSC, and other documented variants.

CGI-C, Clinical Global Impression of Change; Hb, hemoglobin; HbS, sickle hemoglobin; HbS\textsuperscript{β}0, sickle beta zero thalassemia; HbS\textsuperscript{β}+, sickle beta plus thalassemia; HbSC, hemoglobin SC disease; HbSS, homozygous for SCD; HU, hydroxyurea; R, randomization; SCD, sickle cell disease; ULN, upper limit of normal; VOC, vaso-occlusive crisis.

Voxelotor Was Associated with Greater Improvements in Patient SCD Status as Measured by CGI-C at Week 72

Clinicians rated the overall change in the patient’s SCD status since the start of the study.

Patients rated “very much improved” or “moderately improved” by CGI-C (%)

<table>
<thead>
<tr>
<th>Week</th>
<th>Voxelotor 1500 mg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>24</td>
<td>59% (32/54)</td>
<td>44% (24/55)</td>
</tr>
<tr>
<td>72</td>
<td>74% (39/53)</td>
<td>47% (24/51)</td>
</tr>
</tbody>
</table>

P < 0.01

CGI-C, Clinical Global Impression of Change; SCD, sickle cell disease.
Voxelotor Was Associated with Greater Improvements in CGI-C Score at Week 72 Regardless of Baseline Hb

Patients rated “very much improved” or “moderately improved” by CGI-C (%) by Baseline Hb (g/dL)

- Voxelotor 1500 mg
  - <8: 67% (10/15)
  - 8 to <8.5: 80% (8/10)
  - 8.5 to <9.4: 60% (9/15)
  - ≥9.4: 92% (12/13)

- Placebo
  - <8: 42% (5/12)
  - 8 to <8.5: 36% (4/11)
  - 8.5 to <9.4: 53% (8/15)
  - ≥9.4: 54% (7/13)

CGI-C, Clinical Global Impression of Change; Hb, hemoglobin.
Voxelotor Was Associated with Greater Improvements in CGI-C Score at Week 72 Regardless of Hemolysis Markers

Patients rated "very much improved" or "moderately improved" by CGI-C (%)

Baseline indirect bilirubin (µmol/L)

- Voxelotor 1500 mg
- Placebo

Baseline percentage of reticulocytes (%)

Baseline reticulocyte count (×10⁹/L)

CGI-C, Clinical Global Impression of Change.
Conclusions

Voxelotor 1500 mg resulted in improved health status in patients with SCD as assessed by the CGI-C, a clinician-reported outcome.

Improvements were observed regardless of baseline Hb levels and baseline markers of hemolysis.

The CGI-C provides an overall clinician-determined summary measure of a patient’s SCD status that takes into account all available information, including the patient’s history, their symptoms, and the impact of those symptoms on daily functioning.¹

CGI-C assessments are being included in ongoing studies of voxelotor.

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.

• This study was supported by Global Blood Therapeutics.