Compassionate-Use Experience With Voxelotor (GBT440) for Patients With Severe Sickle Cell Disease (SCD) and Life-Threatening Comorbidities

Kenneth R. Bridges1; Gershwin Blyden2; Lanetta Bronte2

1Global Blood Therapeutics, South San Francisco, CA; 2Foundation for Sickle Cell Disease Research, Hollywood, FL

BACKGROUND

- Sickle cell disease (SCD) is an autosomal recessive inherited disorder characterized by a mutation in the α-chain of hemoglobin (Hb) produces sickle hemoglobin (Hbs). When deoxygenated, Hbs polymerize and aggregate into rigid rods that enter red blood cells (RBCs) into a sickle shape and damage cell membranes.
- Infrequent, sickled RBCs occlude the body’s microcirculation and hematocrit. SCD-related complications that include anemia, fatigue, tissue ischemia, painful vaso-occlusive crises (VOC), venous thrombosis, stroke, and multiorgan failure, significant end-organ damage, and early death.
- Current treatments for SCD frequently control these complications and do not address the primary pathogenesis of SCD. A major unmet medical need for new treatments exists.
- Voxelotor (GBT440) is a first-in-class, oral, daily-vitamin therapy designed to modulate the affinity of Hb for oxygen and prevent sickle hemoglobin polymerization, thereby blocking subsequent RBC damage and complications from SCD.4–6
- In clinical studies, those with receiving concomitant hydroxyurea therapy, voxelotor substantially decreases Hb and improves measures of hemolysis7–9.
- Adverse events (AEs) associated with voxelotor treatment have been mostly grades 1 and 2, with few drug-related serious AEs and no AEs leading to discontinuation of treatment.

OBJECTIVE

- To report the results of a case study of 7 patients with severe SCD eligible for ongoing clinical trials because of high mortality risk from comorbidities who were provided compassionate-use access to voxelotor from the Global Blood Therapeutics (GBT) Compassionate Use Activity.

METHODS

GBT COMPASSIONATE USE ACTIVITY

- Beginning in 2016, GBT granted voxelotor access to a limited number of adults with severe SCD.
- Those patients had exhausted available treatment options and were ineligible for existing trials of voxelotor.
- Investigators obtained Investigational New Drug Applications from the US Food and Drug Administration for all of the patients, and their treatment was consistent with the guidelines for compassionate use.
- Patient inclusion criteria for the present compassionate use activity were severe SCD with Hb <8.0 g/dL or complications that limit life expectancy.

COMPASSIONATE USE

- Patients received once-daily voxelotor 900 mg, with a possible increase to 1500 mg for a treatment duration up to 17 months. A single case of diarrhea occurred at the 1500-mg voxelotor dose.
- The final 7-month duration was based on the safety and efficacy data from the phase 3 HOPE© study and discontinued continuous treatment for these patients. The plan developed by the patient’s physician (Figure 1).

RESULTS

PATIENT DISPOSITION AND CHARACTERISTICS

- Four female and 3 male patients aged 22 to 67 years were included in the compassionate use activity (Table 1). Patients A-D had a history of multiple severe complications, including chronic vaso-occlusive crises, multiorgan failure, and transfusions. Patients A and D had a history of severe renal dysfunction and hypertension. Moreover, all patients had core comorbidities, including multiorgan failure, transfusions, severe fatigue, and iron overload.
- Of note, Patient C was hospitalized twice with multiorgan failure and coma for 18 months prior to treatment with voxelotor. All patients had a severe haemoglobin level, with Hb levels ranging from 3.0 to 4.0 g/dL.
- No voxelotor-related serious AEs occurred. Two patients (A and E) required additional continuous supplemental oxygen therapy.

CLINICAL MEASURES OF EFFICACY

- Subsequent to the baseline visits, 24 weeks of voxelotor treatment, and safety monitoring, improvements in anemia and hemolysis, including in Hb levels, transfusion requirements, and hospitalizations for VOC were observed.
- The treatment was generally very well tolerated for a treatment duration up to 17 months. A single case of diarrhea occurred at the 1500-mg voxelotor dose.
- Both Patients A and E had a 5.4 g/dL rise in Hb to a level of 11.8 g/dL, with corrected PHQ-9 scores improving in Patients A and D, with both showing improvement in psychological depression.

PATIENT-REPORTED OUTCOMES

- At baseline, Patient D had moderate depression and Patient A had moderately severe depression. After 24 weeks of voxelotor treatment, both showed improvement in depression.
- Voxelotor was very well tolerated for a treatment duration up to 17 months. A single case of diarrhea occurred in a patient who received voxelotor 1500 mg, which resolved following dose reduction to 900 mg. No other voxelotor-related AEs occurred.

CONCLUSIONS

- These data support the meaningful treatment in clinical events and symptoms in patients with severe SCD and suggest voxelotor improves treatment of clinical trials to confirm the benefits of voxelotor in a broad range of patients with SCD.

TABLE 1. Change in Clinical Parameters After 24 Weeks of Voxelotor Treatment

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>24 Weeks</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb, g/dL</td>
<td>3.0-4.0</td>
<td>9.2-12.4</td>
<td>+5.2</td>
</tr>
<tr>
<td>Transfusions, Number</td>
<td>10 per patient</td>
<td>0 per patient</td>
<td>-10</td>
</tr>
<tr>
<td>Hospitalizations, Number</td>
<td>2 per patient</td>
<td>0 per patient</td>
<td>-2</td>
</tr>
<tr>
<td>PHQ-9 score</td>
<td>10</td>
<td>5</td>
<td>-5</td>
</tr>
</tbody>
</table>

Figure 2. Hb Increase After 24 Weeks of Voxelotor Treatment

Figure 3. Admissions for VOC and RBC Transfusions: 24 Weeks Before and After Voxelotor Treatment

Figure 4. Room Air O2 Saturation After 24 Weeks of Voxelotor Treatment

Figure 5. Voxelotor Treatment and the 6-minute Walk Test in Patient A

Figure 6. Self-Reported Depression Using the PHQ-9 at Baseline and After 24 Weeks of Voxelotor Treatment

REFERENCES


ACKNOWLEDGMENTS

- The authors thank all the participants, families, caregivers, research nurses, study coordinators, and Global Blood Therapeutics employees for their contributions to this compassionate-use activity. The authors are grateful to Global Blood Therapeutics for the generous financial support of this study.

DISCLOSURES

- The authors report no conflicts of interest. The authors are grateful to Global Blood Therapeutics for the generous financial support of this study.

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