Compassionate-use Voxelotor (GBT440) for up to 2 Years in Patients With Severe Sickle Cell Disease and Life-Threatening Comorbidities

Gershwin Blyden, MD¹, Kenneth Bridges, MD², Lanetta Bronté, MD¹

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

• Dr. Bridges is an employee of Global Blood Therapeutics and has equity in the company
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Background

• Current treatments SCD
  o inadequately control disease-related complications
  o do not address the primary pathogenesis of SCD
  o leave a high unmet need for more effective treatment options

• Patients with severe SCD are routinely excluded from clinical trials of investigational agents for SCD

• The FDA provides expanded access—“compassionate use”—of an investigational drug for treatment of patients with serious or immediately life-threatening diseases/conditions who lack therapeutic alternatives

3. Investigational New Drug Application, Subpart I—Expanded Access to Investigational Drugs for Treatment Use. (Food and Drugs, 21 C.F.R. §312.300–312.320. 2009.)
Key FDA Requirements for Expanded Access for Life-Threatening Conditions

- No comparable or satisfactory therapy exists for the patient’s disease or condition
- Conditions must be serious and immediately life-threatening
- Potential benefit justifies potential risk
- The investigational drug is unavailable under another IND or clinical trial

IND, investigational new drug.

US Food & Drug Administration. Investigational New Drug Application, Subpart I—Expanded Access to Investigational Drugs for Treatment Use. (Food and Drugs, 21 C.F.R. §312.300–312.320. 2009.)
Voxelotor Interruption of HbS Polymerization Could Modify Disease

- HbS Polymerization
  - RBC Damage
    - Hemolytic Anemia
    - Vaso-occlusion
      - Organ Damage
        - Stroke
        - Renal failure
        - Pulmonary HTN
        - Priapism
        - Leg Ulcers
      - Pain / VOC
        - Organ Damage
        - Osteonecrosis
        - Retinopathy

Eaton W, Bunn F. Targeting HbS Polymerization, Blood 2017, Kato JCI 2017
• Patient treatment begun between May 2016 and June 2017
• All had advanced SCD with multiple organ injury predicting high risk of death and one or more of the following complications:
  • End stage renal disease in SCD
  • Recurrent multi-organ failure
  • Pulmonary hypertension/diastolic dysfunction
  • History of severe anemia
  • Advanced age
  • Low $O_2$ saturation
  • Frequent pain crises
Patient Disposition and Characteristics

- 7 patients: 4 females and 3 males
- Treatment duration ranged from 6 months to 2 years
- Key comorbidities
  - 5 patients had frequent transfusions
  - 4 patients had severe fatigue
  - All patients had iron overload
- Patient C hospitalized twice with multiorgan failure and coma in the 18 months prior to treatment
- Patients A and E required continuous supplemental oxygen therapy

### Patient Characteristics

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<th>Age</th>
<th>Gender</th>
<th>Type</th>
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<th>Refractory to transfusion</th>
<th>Severe fatigue</th>
<th>Iron overload</th>
<th>Chronic O₂ supplementation</th>
<th>Progressive severe renal dysfunction</th>
<th>Multi-organ failure</th>
<th>Treatment (months)</th>
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Voxelotor Produced Substantial Hb Rises at 24 weeks

- Hb values increased rapidly in all patients, with increments ranging from 0.5 to 5.4 g/dL at 24 weeks
- Hb values increased by ≥1 g/dL in 5 of 7 patients
Voxelotor Lowered Hospitalizations for VOC and Number of Transfusions

- In the 24 weeks before and after voxelotor treatment:
  - Total hospitalizations for VOC pain decreased by 67% (from 28 to 9, respectively)
    - Per patient hospitalizations ranged from 2 to 5
  - Total RBC transfusions decreased by 60% (from 33 to 13, respectively)
    - 6 of 7 patients received transfusions before voxelotor, while 2 of 6 received no transfusions after\(^a\)

\(^a\)Patient A, who was alloimmunized to RBCs to the point of being refractory to any transfusion.
Voxelotor Improved Oxygenation

- 4 patients had low room air oxygen saturations of <95% at baseline that improved to 98%–99% with voxelotor treatment.
  - Patients A and E no longer required continuous supplemental oxygen.

Room air O₂ saturation after 24 weeks of voxelotor treatment.
Voxelotor Improved 6-minute Walk Test in Patient A for 2 Years

- Patient A, who was initially on continuous supplemental oxygen, had a 6-minute walk test at baseline and again after 14, 24 and 48 weeks of voxelotor treatment.
- Post-walk pulse rate and room air SpO₂ improved rapidly and was maintained.

**Graph**

- Pulse rate
- Room Air SpO₂
- Walk Distance

**Axes**
- X-axis: Baseline, 14 weeks, 24 weeks, 2 years
- Y-axis: 6MWT, Oxygen Saturation (%), Pulse Rate

**Values**
- Baseline: 86, 330
- 14 weeks: 96, 93
- 24 weeks: 375, 96, 93
- 2 years: 102, 387, 369

BPM, beats per minute; RA, room air; SpO₂, oxygen saturation.
Voxelotor Improved Patient-Related Outcome

- At baseline, by the PHQ-9 scale:
  - Patient D had moderate depression
  - Patient A had moderately severe depression
  - 5 patients had no or minimal depression
- After 24 weeks of treatment with voxelotor, PHQ-9 scores improved in patients A and D
  - Patient A showed no or minimal depression
  - Patient D showed only mild depression

PHQ-9, Patient Health Questionnaire-9.
Safety Summary

• Voxelotor was well-tolerated for up to 17 months at a dose of 900 mg with no dose reductions or discontinuations.

• Patients B and C, each with extensive preexisting end-organ injury, died after starting voxelotor treatment due to end organ failure.

• The dose for Patient A was increased to 1500 mg, which caused grade 2 diarrhea that resolved with a return to the 900 mg dose. The 1500 mg voxelotor dose produced no problems in any other patient.

• Patient F had transient grade 1 diarrhea at the 900 mg dose that resolved with no treatment change.

• No voxelotor-related serious adverse events occurred.
Conclusions

- In 7 patients with severe SCD who were not eligible for the HOPE study, voxelotor administered by compassionate use substantially improved a variety of clinical, laboratory, and patient-reported parameters, including:
  - Hb levels, hospital admissions related to VOC, frequency of blood transfusions, daily pain, overall well-being, and depression

- Controlled clinical trials are needed to confirm the benefits of voxelotor in patients with severe SCD
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