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

#PF711

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BACKGROUND

- Sickle cell disease (SCD) is an autosomal recessive inherited disorder in which a mutation in the β-chain of hemoglobin (Hb) produces sickle hemoglobin (HbS). When deoxygenated, HbS polymerizes into rigid chains that deform red blood cells (RBCs) into a sickle shape and damage cell membranes[1]
  - Inflexible, sickled RBCs occlude the body's microvasculature and hemolyze. This causes downstream effects that include anemia, fatigue, tissue ischemia, painful vaso-occlusive crisis (VOC), vascular injury, reduced quality of life (QoL), significant end-organ damage, and early death
- Current treatments for SCD inadequately control these complications and do not address the primary pathogenesis of SCD, leaving a high unmet need for more effective treatment options[2]
- Voxelotor (GBT440) is a first-in-class, oral, once-daily therapy designed to modulate the affinity of Hb for oxygen and prevent sickle hemoglobin polymerization, thereby blocking subsequent RBC damage and complications from SCD[3,4]
  - In controlled clinical studies, including those with participants receiving concomitant hydroxyurea therapy, voxelotor rapidly and durably increases Hb and improves measures of hemolysis[5-7]
  - Adverse events (AEs) associated with voxelotor treatment have been mostly grades 1 and 2, with few drug discontinuations due to AEs and no concerning safety signals observed[5-7]
- Clinical trials assessing the safety and efficacy of voxelotor in patients with SCD are currently under way, including the phase 3 HOPE (**H**emoglobin **O**xygen Affinity Modulation to Inhibit HbS **P**olym**E**rization) study for patients with SCD aged ≥12 years (NCT03036813)[8]
  - Excluded from voxelotor clinical trials are patients with severe SCD, defined as those with severe anemia (Hb <6.0 g/dL), those with frequent recurrent VOC pain episodes, or those who receive frequent RBC transfusions. Patients with severe SCD constitute a subset of patients with a major unmet need for therapeutic options[8]

OBJECTIVE

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

METHODS

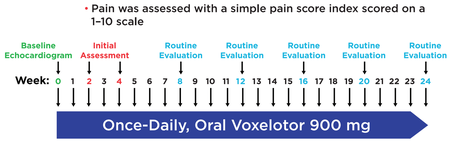
GBT COMPASSIONATE USE ACTIVITY

- Beginning in 2016, GBT granted voxelotor access to a limited number of adults with severe SCD
  - These 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 each 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 <6.0 g/dL or complications that were life-threatening. Patients were monitored over 24 weeks

COMPASSIONATE USE

- Patients received once-daily voxelotor 900 mg, with a possible increase to 1500 mg, according to a treatment plan developed by the patient's physician (**Figure 1**)

Figure 1. Compassionate Use Schema



Hb, hemoglobin; PHQ-9, 9-item Patient Health Questionnaire; RA SpO_2, room air oxygen saturation; VOC, vaso-occlusive crisis.

PATIENT QUESTIONNAIRE

- Depression was assessed at each clinical visit using the 9-item Patient Health Questionnaire (PHQ-9), a dual-purpose instrument that utilizes specific *Diagnostic and Statistical Manual of Mental Disorders,* 4th Edition, criteria to establish a diagnosis of depressive disorder and to grade depressive symptom severity[9]
- Diagnosis of depression was made by a board-certified psychiatrist
- A diagnosis of major depressive disorder was made if ≥5 symptoms, which must have included depressed mood or anhedonia, of the 9-symptom criteria were present for at least more than half the days in the preceding 2 weeks[9,10]
- Other depressive disorders were diagnosed if 2 to 4 depressive symptoms, which must have included depressed mood or anhedonia, were present for at least more than half the days in the preceding 2 weeks[9,10]
- The 9 items of the PHQ-9 are scored 0 to 3. This allows the PHQ-9 to serve as a measure of disease severity based on the total score, which ranges from 0 (no disease impact) to 27 (severe impact)[9-11]

PAIN SCORE INDEX

- At each clinical evaluation, patients were questioned about their pain, which was assessed by a simple pain index that was scored on a 0-10 scale (ranging from 0 = no pain to 10 = extreme pain)

RESULTS

PATIENT DISPOSITION AND CHARACTERISTICS

- Four female and 3 male patients aged 22 to 67 years were included in the compassionate use activity (ie, Patients A–G). Voxelotor treatment was initiated between May 2016 and June 2017 with treatment durations ranging from 6 to 17 months
- Key comorbidities included severe renal dysfunction, history of multiorgan failure, frequent transfusions, severe fatigue, and iron overload (**Table 1**)
- Of note, Patient C was hospitalized twice with multiorgan failure and coma in the 18 months prior to treatment
- Two patients (A and E) required continuous supplemental oxygen therapy

Table 1. Patient Characteristics

	Patient						
	A	B	C	D	E	F	G
Age	67	66	44	53	38	50	22
Sex	M	F	M	F	M	F	F
Type	SS	SS	Sβ⁰ thal	SS	SS	SS	SS
Frequent transfusion		X	X	X	X	X	
Refractory to transfusion	X						
Severe fatigue	X			X	X	X	
Iron overload	X	X	X	X	X	X	X
Chronic oxygen supplementation	X				X		
Progressive severe renal dysfunction		X					
Multiorgan failure			X				
Treatment (months)	17	16	7	15	6	6	6

Sβ⁰ thal, sickle beta zero thalassemia; SS, sickle cell anemia.

CLINICAL MEASURES OF EFFICACY

Summary of effects

- **Table 2** summarizes the changes in clinical parameters after 24 weeks of treatment. Substantial improvements occurred in Hb values, transfusion requirements, and hospitalizations for VOC. Reticulocyte counts fell in 3 of the 4 patients for whom values were available. Patients A and E discontinued continuous supplemental oxygen therapy
- Alleviation of clinical depression over the course of treatment as assessed by PHQ-9 score was observed in Patients A and D

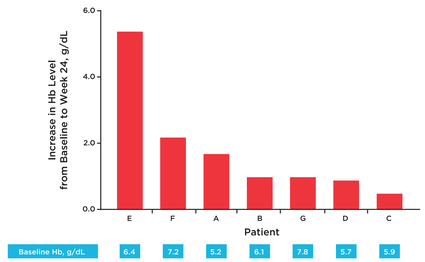
Table 2. Change in Clinical Parameters After Voxelotor Treatment for 24 Weeks

	Patient													
	A		B		C		D		E		F		G	
	B	24	B	24	B	24	B	24	B	24	B	24	B	24
Hb, g/dL	5.2	6.9	6.1	7.1	5.9	6.4	5.7	6.6	6.4	11.8	7.2	9.4	7.8	8.8
Reticulocytes, %	8.7	5.0	13.7	6.0	11.3	N/A	2.7	5.7	4.5	3.0	N/A	N/A	N/A	4.1
Indirect bilirubin, mg/dL	2.4	1.2	0.6	1.6	3.6	2.8	1.6	1.5	2.6	1.8	6.0	2.3	2.0	2.4
RA SpO_2, %	91	99	95	99	88	98	94	99	89	98	99	99	96	99
VOC hospitalizations, n	2	0	4	2	5	2	4	3	5	0	4	1	4	1
Transfusions, n	0	0	8	4	12	4	5	3	4	0	2	0	2	2
PHQ-9 score	18	2	2	2	0	4	10	4	3	2	3	2	3	2

24, 24 weeks; B, baseline; Hb, hemoglobin; N/A, not available; PHQ-9, 9-item Patient Health Questionnaire; RA SpO_2, room air oxygen saturation; VOC, vaso-occlusive crisis.

- Hb values rose rapidly in all patients, with increments ranging from 5.4 to 0.5 g/dL at 24 weeks. Hb values rose by ≥1 g/dL in 5 of the 7 patients (**Figure 2**)

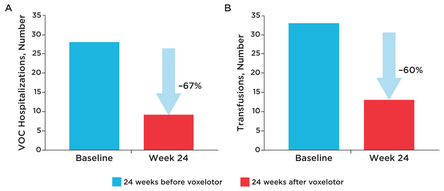
Figure 2. Hb Increase After 24 Weeks of Voxelotor Treatment



Hb, hemoglobin.

- Hospitalizations for VOC pain fell by 67% in the 24 weeks after voxelotor compared with the 24 weeks before treatment initiation (9 vs 28, respectively) (**Figure 3A**). Hospitalizations per patient ranged from 2 to 5 during the 24 weeks before voxelotor treatment, and the number fell in all patients during the 24 weeks of treatment
- Transfusions fell by 60% in the 24 weeks after voxelotor compared with the 24 weeks before treatment initiation (13 vs 33, respectively) (**Figure 3B**). Excepting Patient A, who was alloimmunized to RBCs to the point of being refractory to any transfusion, 6 patients received transfusions prior to voxelotor whereas 2 of 6 patients received no transfusions afterwards

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

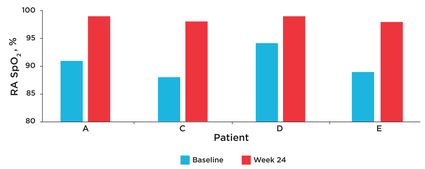


RBC, red blood cell; VOC, vaso-occlusive crisis.

Room air oxygen saturation

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

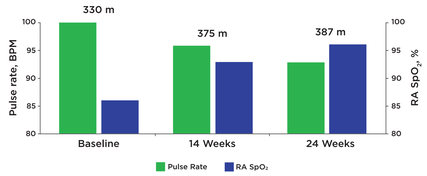
Figure 4. Room Air O_2 Saturation After 24 Weeks of Voxelotor Treatment



RA SpO_2, room air oxygen saturation.

- Patient A, who was initially on continuous supplemental oxygen, had a 6-minute walk test at baseline and again after 14 and 24 weeks of voxelotor treatment. His distance walked as well as his postwalk pulse rate and room air SpO_2 improved over the course of treatment (**Figure 5**)

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



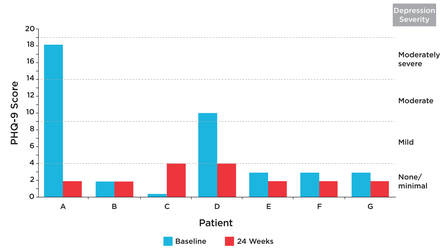
BPM, beats per minute; RA SpO_2, room air oxygen saturation.

PATIENT-REPORTED OUTCOMES

Depression

- At baseline, Patient D had moderate depression and Patient A had moderately severe depression, whereas 5 patients had no or minimal depression, as assessed by the PHQ-9 (**Figure 6**). After 24 weeks of treatment with voxelotor, PHQ-9 scores improved in Patients A and D, with both showing no or minimal depression

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



PHQ-9, 9-item Patient Health Questionnaire.

SAFETY

- Voxelotor was well-tolerated for up to 17 months at a dose of 900 mg with no dose reductions or discontinuations
- 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, which resolved with no treatment change
- No voxelotor-related serious AEs occurred

Patient deaths

- Patients B and C, each with extensive preexisting end-organ injury, died after starting voxelotor treatment
  - The treating physician deemed both deaths unrelated to voxelotor treatment
- Patient B's long-standing decline in renal function finally required hemodialysis several months into voxelotor treatment. Progressive hepatic failure from massive iron overload became critical at about month 15, and the patient died at month 16
- Patient C had experienced 3 episodes of multiorgan failure (2 with coma) over the 18 months prior to voxelotor treatment. He substantially improved with voxelotor treatment to the point that after 7 months he was able to engage in vigorous physical activity (eg, rock climbing). However, he developed an SCD pain crisis that deteriorated into multiorgan failure. He deteriorated over 3 days and died after a failed cardiac resuscitation

DISCUSSION

- The experiences of 7 patients with severe SCD treated with voxelotor through the GBT Compassionate Use Activity suggests the potential breadth and depth of clinical benefit of the drug. The patients were ineligible for ongoing trials due to their degree of anemia, frequency of VOC hospitalizations, or other comorbidities of severe SCD
- Hb values rose above baseline in all patients with the increase exceeding 1 g/dL in 5 of 7 patients
  - At a daily dose of 1500 mg, Patient E experienced a 5.4 g/dL rise in Hb to a level of 11.8 g/dL, the highest to date with voxelotor treatment. A theoretical concern in early development was that blood hyperviscosity might occur with Hb levels ≥10.5 g/dL, but Patient E had no evidence of hyperviscosity.[12,13] The patient's strength, fatigue, pain, and physical function all improved at this hemoglobin level, which would not be consistent with hyperviscosity
- Hospitalizations for VOC, the traditional yardstick of SCD pain,[14] fell by two-thirds during 24 weeks of voxelotor treatment as compared with the 24 weeks immediately prior to therapy. Therefore, clinical outcomes corroborated patient reports of improved well-being and quality of life with voxelotor treatment
- The 60% reduction in transfusions supports the dramatic effect of voxelotor on RBC destruction
  - Iron overload due to transfusion, a major, often underappreciated problem in SCD,[15] would be substantially mitigated by voxelotor treatment
- Voxelotor-related improvements with blood oxygenation, which were seen most dramatically in Patients A and E, are consistent with improved oxygenation of peripheral tissues due to inhibition of polymerization, improved rheology, and improved oxygen delivery with voxelotor
- Patients B and C died while on voxelotor therapy. Each had advanced organ injury, which was a direct cause of death for Patient B. The treating physicians concluded that voxelotor did not contribute to either death
- Voxelotor 900 mg 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

- **In this uncontrolled experience in 7 patients with severe SCD who were not eligible for the HOPE study, voxelotor administered via compassionate use demonstrated large improvements in anemia and hemolysis, including in patients with lower baseline Hb than studied in clinical trials to date**
- **Voxelotor also substantially improved a variety of other clinical and patient-reported parameters, including hospital admissions related to VOC, frequency of blood transfusions, daily pain, overall well-being, and depression**
- **These data are suggestive of meaningful improvement in clinical events and symptoms in patients with severe SCD and support ongoing investigation in controlled clinical trials to confirm the benefits of voxelotor in a broad range of patients with SCD**

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- **Kenneth R. Bridges** is an employee of and has equity ownership in Global Blood Therapeutics. **Gershwin Blyden** and **Lanetta Bronte** have nothing to disclose
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