Initial Results From a Cohort in a Phase 2a Study (GBT440-007) Evaluating Adolescents With Sickle Cell Disease Treated With Multiple Doses of Voxelotor, a Sickle Hemoglobin Polymerization Inhibitor

#301

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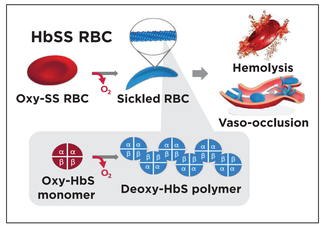
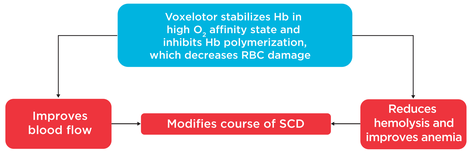
BACKGROUND

- Sickle cell disease (SCD) is an autosomal recessive disorder caused by a mutation in the β-chain of hemoglobin (Hb) that leads to the production of sickle hemoglobin (HbS)[1]
- When deoxygenated, HbS polymerizes and deforms red blood cells (RBCs) into a sickle shape and damages cell membranes. These damaged RBCs block capillaries and undergo hemolysis, which triggers downstream effects of anemia, fatigue, tissue ischemia, vaso-occlusive crisis (VOC), vascular injury, and organ damage, leading to a diminished quality of life (**Figure 1**)[1]
- SCD affects approximately 100,000 patients in the United States and millions globally[2,3]
- Voxelotor (previously called GBT440) is a first-in-class, oral, once-daily therapy designed to modulate the affinity of Hb for oxygen and is in clinical development for the treatment of SCD.[4] By maintaining HbS in an oxygenated state, voxelotor inhibits polymerization and the resultant sickling of RBCs, potentially interrupting the molecular pathogenesis of the disease[5,6]
- With the potential to improve anemia and reduce vaso-occlusive events, it is hypothesized that voxelotor will modify the course of SCD
- GBT440-007 is an ongoing phase 2a study in children aged 6 to 17 years with SCD. Results of the interim analysis of a cohort of adolescents (aged 12 to 17 years) receiving 900 mg/d voxelotor for up to 24 weeks are summarized here

Figure 1. Voxelotor Clinical Hypothesis: Increase in Hb O_2 Affinity Inhibits HbS Polymerization



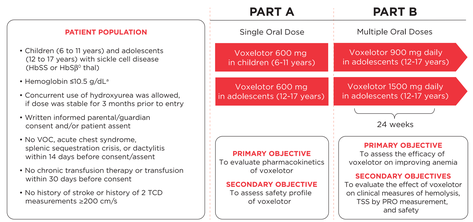


Deoxy, deoxygenated; HbSS, sickle cell anemia; O_2, oxygen; oxy, oxygenated.

- There is 1:1 stoichiometry of voxelotor to Hb tetramer binding
- Voxelotor preferentially partitions into RBCs (75:1)
- Voxelotor PK supports once-daily dosing

OBJECTIVES AND STUDY DESIGN

Figure 2. GBT440-007: Study Design



HbSβ⁰ thal, sickle beta zero thalassemia; PRO, patient-reported outcome; TSS, total symptom score.
[a]One patient had a baseline Hb level >10.5 g/dL.

- This ongoing study is being conducted in 2 parts (**Figure 2**)
  - Part A: a single dose of voxelotor 600 mg in pediatric and adolescent patients (ASPHO Poster #305)
  - Part B: multiple doses of voxelotor 900 mg/d or 1500 mg/d for 24 weeks in adolescent patients
- Data presented are results of the 900-mg/d dose cohort in Part B

RESULTS

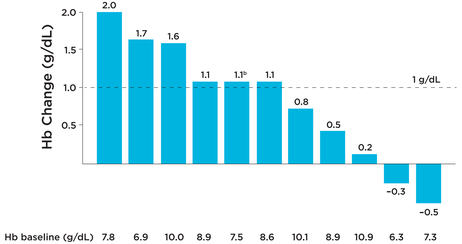
Table 1. Baseline Characteristics

Baseline Characteristics	900 mg N=12 Patients Treated 16 Weeks to Date[a] (Efficacy Population)	900 mg N=24 All Treated Patients to Date[a] (Safety Population)
Male, n (%)	6 (50)	14 (58)
Age, median (range), y	13 (12-17)	14 (12-17)
HbSS genotype,[b] n (%)	11 (92)	23 (96)
Number of VOCs in prior year, n (%)		
0	7 (59)	11 (46)
1-4	4 (33)	11 (46)
>4	1 (8)	2 (8)
Baseline Hb, median (range), g/dL	8.7 (6.3-11.0)	8.9 (6.3-11.0)
Current HU use, n (%)	11 (92)	21 (88)
Baseline HbF, median (range), %	10.7 (5.5-29.0)	11.2 (3.7-29.0)
Baseline TAMM for TCD, median (range), cm/s	120 (89-143)	120 (74-149)[c]

HbF, fetal hemoglobin; HU, hydroxyurea; TAMM, time-averaged mean of maximum velocity; TCD, transcranial Doppler ultrasound.
[a]As of November 6, 2017.
[b]1 patient with HbSβ⁰ thal.
[c]n=20.

Efficacy

Figure 3. Hb Response >1 g/dL Achieved in 55% of Patients (6 of 11)[a] at 16 Weeks



[a]Data not available on 1 patient at 16 weeks because blood sample could not be drawn.
[b]Not receiving concurrent hydroxyurea.

- Data for hemolysis measures are available for 11 patients who received voxelotor for 16 weeks (**Figure 3**)

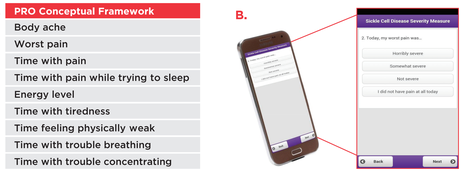
Table 2. Change in Hemolysis Measures at 16 Weeks Compared With Baseline

Parameter, median (25th, 75th percentile)	Change From Baseline N=11[a]
Hb, g/dL	1.1 (0.2, 1.6)
Reticulocytes, %	−10.5 (−42.3, 6.2)
Unconjugated bilirubin, %	−39.8[b] (−67.9, −10.0)

[a]16-week data not available for 1 patient because blood sample could not be drawn.
[b]n=10.

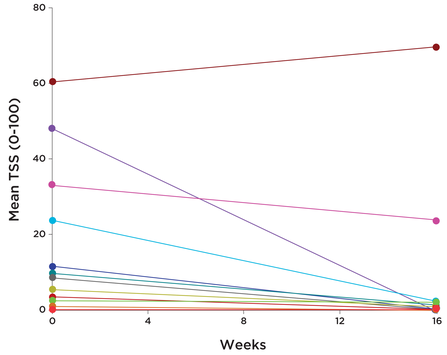
- Laboratory measures of hemolysis improved concordantly; the median reductions in reticulocytes and unconjugated bilirubin were 11% and 40%, respectively

Figure 4. Daily SCD Symptoms Assessed Using Total Symptom Score (TSS)



- The TSS is the sum of 9 questions (**Figure 4A**), with each question having a score ranging from 0 (no symptoms) to 3 (severe symptoms)
- Daily SCD symptoms were recorded using a handheld patient-reported outcome (PRO) instrument (**Figure 4B**)
- Potential TSS range from 0 (no SCD symptoms) to 27 (severe symptoms) for any given day, rescaled to a 100-point scale

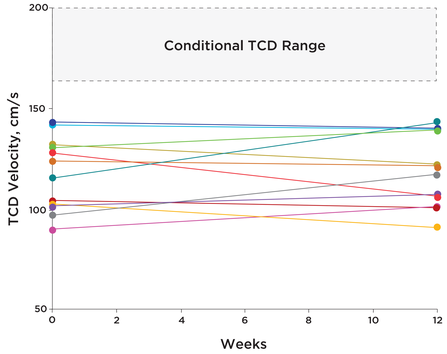
Figure 5. Voxelotor Reduced TSS at Week 16 (n=12)



Each dot represents mean daily TSS averaged over preceding study period (2-week screening and 12-16 weeks of treatment).

- 83% of patients (10 of 12) showed reduction in TSS from baseline to week 16 (**Figure 5**)
- There was a 94% median reduction in TSS from baseline
- 42% of patients (5 of 12) had a mean TSS of 0 (no symptoms) at week 16 (**Figure 5**)
- 1 patient had a mean TSS of 0 at baseline and at week 16 (no change)

Figure 6. TCD Velocity



- All patients were normal at baseline, with TCD <170 cm/s
- 58% of patients (7 of 12) had a numerical decrease in TCD velocity at week 12 (**Figure 6**)

Safety and Tolerability

Table 3. Drug-Related AEs Occurring in ≥2 Patients

Adverse Event	Voxelotor 900 mg N=24
Nausea, n (%)	3 (12.5)
Headache, n (%)	2 (8.3)
Rash, n (%)	2 (8.3)

AE, adverse event.

- Voxelotor 900 mg was well tolerated up to 24 weeks of dosing
- Drug-related AEs were grade 1 or 2 (except one grade 3 rash that did not recur with continued dosing)
- There were no treatment-related serious AEs or drug discontinuations due to AEs

CONCLUSIONS

- Voxelotor 900 mg given daily for 16 weeks in adolescents with SCD, the majority of whom were taking hydroxyurea, demonstrated consistent and sustained efficacy on Hb levels and measures of hemolysis
  - 55% (6 of 11 patients) achieved >1 g/dL Hb response and a median Hb change of 1.1 g/dL at 16 weeks
  - Reduction in clinical measures of hemolysis in adolescents was consistent with results in adults
- Improvement in TSS in mildly symptomatic patients suggests that the PRO is sensitive to treatment effect and supports its use in the ongoing **H**emoglobin **O**xygen Affinity Modulation to Inhibit HbS **P**olym**E**rization (HOPE) phase 3 study
  - 83% of patients (10 of 12) achieved improvement in SCD TSS after 16 weeks of voxelotor 900 mg treatment
- In adolescents, voxelotor 900 mg was well tolerated and most AEs were grade 1 or 2. The safety and tolerability profile of voxelotor in adolescents is consistent with that of adults
- Future studies to assess the effect of voxelotor on TCD velocity are planned to include patients with conditional/abnormal TCD at baseline
- These interim results support ongoing clinical evaluation of voxelotor as a potential disease-modifying therapy for patients with SCD

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