#PF709

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

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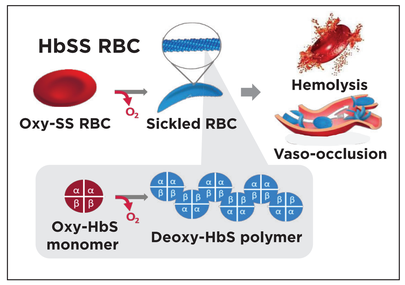
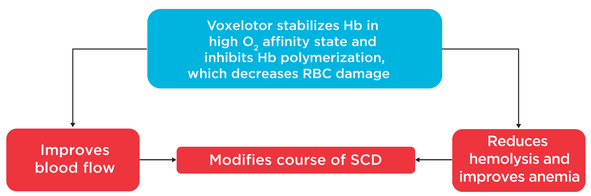
BACKGROUND

- Sickle cell disease (SCD) is an autosomal recessive disorder caused by a mutation in the β-chain of hemoglobin 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]
- More than 300,000 infants are born with SCD worldwide each year[2]
- Voxelotor (previously called GBT440) is a first-in-class, oral, once-daily therapy that is designed to modulate Hb's affinity for oxygen and is in clinical development for the treatment of SCD[3]
- With the potential to improve RBC function and reduce VOC, it is hypothesized that voxelotor will modify the course of SCD
- GBT440-007 is an ongoing phase 2a study in pediatric patients aged 6 to 17 years with SCD. The data presented are a summary of the analysis of a cohort of adolescents (aged 12–17 years) receiving 900 mg/d voxelotor for up to 24 weeks

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





Deoxy, deoxygenated; Hb, hemoglobin; HbS; sickle hemoglobin; HbSS, sickle cell anemia; O_2, oxygen; oxy, oxygenated; RBC, red blood cell; SCD, sickle cell disease.

- There is 1:1 stoichiometry of voxelotor to Hb tetramer binding
- Voxelotor preferentially partitions into RBCs compared with plasma (75:1)
- Voxelotor pharmacokinetics support once-daily dosing

OBJECTIVES AND STUDY DESIGN

Figure 2. GBT440-007: Study Design

PATIENT POPULATION

- Children (6 to 11 years) and adolescents (12 to 17 years) with sickle cell disease (HbSS or HbSβ⁰ thal)
- Hemoglobin ≤10.5 g/dL[a]
- Concurrent use of hydroxyurea was allowed, if dose was stable for 3 months prior to entry
- Written informed parental/guardian consent +/- patient assent
- No VOC, acute chest syndrome, splenic sequestration crisis, or dactylitis within 14 days before consent/assent
- No chronic transfusion therapy or transfusion within 30 days before consent
- No history of stroke or history of 2 TCD measurements ≥200 cm/s

PART A	PART B
Single Oral Dose	Multiple Oral Doses
Voxelotor 600 mg in children (6-11 years)	Voxelotor 900 mg daily in adolescents (12-17 years)
Voxelotor 600 mg in adolescents (12-17 years)	Voxelotor 1500 mg daily in adolescents (12-17 years)
	24 weeks
PRIMARY OBJECTIVE To evaluate pharmacokinetics of voxelotor; **SECONDARY OBJECTIVE** To assess safety profile of voxelotor	**PRIMARY OBJECTIVE** To assess the efficacy of voxelotor on improving anemia; **SECONDARY OBJECTIVES** To evaluate the effect of voxelotor on clinical measures of hemolysis, TSS by PRO measurement, and safety

HbSβ⁰ thal, sickle beta zero thalassemia; HbSS, sickle cell anemia; PRO, patient-reported outcome; TCD, transcranial Doppler; TSS, total symptom score; VOC, vaso-occlusive crisis.
[a]One patient had a baseline Hb level >10.5 g/dL.

- This ongoing study is being conducted in 2 parts
  - Part A: a single dose of voxelotor 600 mg in pediatric and adolescent patients (EHA Poster #PF713)
  - Part B: multiple doses of voxelotor 900 mg/d or 1500 mg/d for 24 weeks in adolescent patients (**Figure 2**)
- Data presented are complete results of the 900 mg/d cohort in Part B

RESULTS

Table 1. Baseline Characteristics

Baseline Characteristics	900 mg/d N=25 All Treated Patients to Date[a] (Safety Population)
Male, n (%)	14 (56)
Age, median (range), y	14 (12-17)
HbSS genotype,[b] n (%)	24 (96)
Number of VOCs in prior year, n (%) 0 1-4 >4	11 (44) 12 (48) 2 (8)
Current HU use, n (%)	22 (88)
Baseline[c] Hb, median (range), g/dL	8.9 (6.3-11.0[d])
Baseline[c] HbF, median (range), %	10.8 (3.7-29.0)
Baseline[c] TAMM for TCD, median (range), cm/s	110 (74-149)

HbF, fetal hemoglobin; HU, hydroxyurea; TAMM, time-averaged mean of maximum velocity; TCD, transcranial Doppler ultrasound.
[a]As of April 16, 2018.
[b]1 patient with HbSβ⁰ thal.
[c]Baseline is the average of the values obtained prior to the first dose.
[d]One patient had a baseline Hb level >10.5 g/dL.

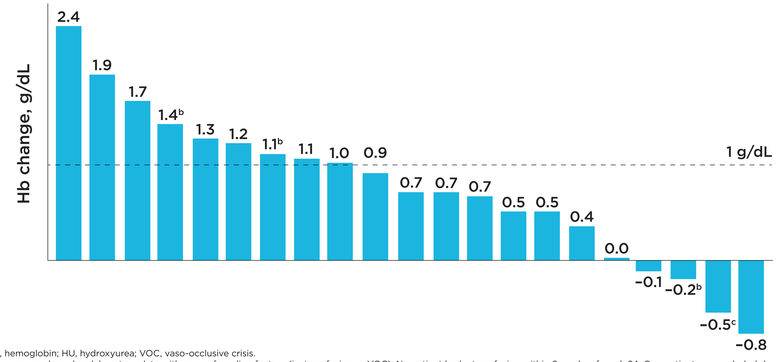
Table 2. Dose Dispensations (900 mg/d)

Treatment Status	N
Dosed	25
Discontinued dosing prior to 24 weeks	3
Completed 24 weeks of dosing	22

- Reasons for discontinuation
  - n=1: withdrew consent (on study 28 days)
  - n=1: lost to follow-up (on study approximately 4 months)
  - n=1: noncompliance (on study approximately 4 months)

EFFICACY

Figure 3. Hb Response ≥1 g/dL Achieved in 43% of Patients (9 of 21[a]) at 24 Weeks (900 mg/d)



Hb, hemoglobin; HU, hydroxyurea; VOC, vaso-occlusive crisis.
[a]Hb response based on laboratory data with no confounding factors (ie, transfusion or VOC). No patient had a transfusion within 8 weeks of week 24. One patient was excluded due to a concurrent acute chest syndrome at week 24.
[b]Not receiving concurrent HU.
[c]Documented noncompliance.

Table 3. Change in Hemolysis Measures from Baseline to Week 24

Parameter Median (25th, 75th Percentile)	Change From Baseline N=21
Hb, g/dL	0.7 (0.4, 1.2)
Reticulocytes, % change	−22.9 (−35.4, −2.8)
Unconjugated bilirubin, % change	−38.6 (−57.8, −27.3)

Hb, hemoglobin.

- Clinical measures of hemolysis improved concordantly; the median reductions in reticulocytes and unconjugated bilirubin were 23% and 39%, respectively (Table 3)

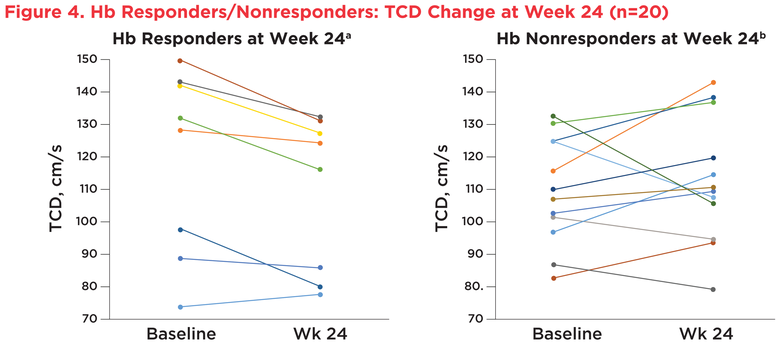
Daily SCD Symptoms Assessed Using Total Symptom Score (TSS)

- The TSS is the sum of 9 questions (related to pain, energy level, and ability to concentrate), with each question having a score ranging from 0 (no symptoms) to 3 (severe symptoms)
- Daily SCD symptoms were recorded using a handheld PRO instrument
- Potential TSSs range from 0 (no SCD symptoms) to 27 (severe symptoms) for any given day, rescaled to a 100-point scale
- TSS score was determined at baseline (average of 2-week screening period) and week 24 (average of 20-24 weeks)

Changes in TSS at 24 weeks (n=21)

- 62% (13 of 21 patients) showed reduction in TSS from baseline to week 24
- There was a 39% median reduction in TSS from baseline
- 1 patient had a mean TSS of 0 at baseline and at week 24 (no change)

Figure 4. Hb Responders/Nonresponders: TCD Change at Week 24 (n=20)



Hb, hemoglobin; TCD, transcranial Doppler.
[a]One Hb responder did not have a TCD assessment performed at 24 weeks.
[b]One Hb nonresponder did not have a TCD assessment performed at 24 weeks.

- Overall, 11 of 20 patients had a numerical decrease at week 24
- 88% (7 of 8) Hb responders at week 24 (≥1 g/dL increase) had a numerical decrease in TCD (**Figure 4**)

SAFETY AND TOLERABILITY

Table 4. Drug-Related Adverse Events Occurring in ≥2 Patients

AE	All Grade 900 mg/d (n=25)	Grade 3 900 mg/d (n=25)
Nausea, n (%)	3 (12)	0
Vomiting, n (%)	2 (8)	0
Headache, n (%)	2 (8)	0
Rash,[a] n (%)	2 (8)	1 (14)

AE, adverse event.
[a]Includes grade 1 rash papular and grade 3 urticaria, (which resolved and did not recur with continued dosing).

- Voxelotor 900 mg/d was well tolerated for up to 24 weeks of dosing
- There were no drug discontinuations due to AEs

CONCLUSIONS

- Voxelotor 900 mg given once daily for 24 weeks in adolescents with SCD, most of whom were on stable hydroxyurea treatment, demonstrated sustained and durable improvements in Hb and reduction in clinical measures of hemolysis in the majority of patients
  - 43% (9 of 21 patients) achieved ≥1 g/dL Hb response at 24 weeks
  - Reduction in clinical measures of hemolysis in adolescents were consistent with results in adults
- Improvement in TSS in mildly symptomatic patients suggests that the PRO may be sensitive to treatment
  - 62% (13 of 21 patients) achieved improvement in SCD TSS after 24 weeks of voxelotor 900 mg/d treatment
- Most hemoglobin responders (88%) showed a temporal reduction in TCD, consistent with the known correlation between TCD and anemia
  - This suggests that voxelotor may reduce TCD and stroke risk, which warrants further investigation in controlled studies in patients with baseline elevated TCD
- Voxelotor was generally safe and well tolerated, consistent with results in adults
- These results are consistent with in vivo inhibition of HbS polymerization by voxelotor and support the ongoing clinical evaluation of voxelotor as a potential disease-modifying therapy for adults and adolescents with SCD

References

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