Interim Results From a Phase 2a Study (GBT440-007) Evaluating Adolescents With Sickle Cell Disease Treated with Multiple Doses of Voxelotor (GBT440)

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Disclosures

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- Novartis
- Pfizer

Voxelotor, A Novel Inhibitor of HbS Polymerization

- Novel mechanism that inhibits HbS polymerization and RBC sickling, the underlying pathophysiologic mechanism of SCD
- Preclinical and clinical studies to date demonstrated:
  - Improved red blood cell deformability and decreased blood viscosity[1]
  - Rapid, sustained, and clinically meaningful increases in Hb and reduction of hemolysis[2,3]
  - Favorable safety profile with once-daily oral dosing[2,3]
  - Improved blood oxygen carrying capacity and tissue oxygen delivery[4,5]
- Potential to modify morbidity and mortality by improving anemia and hemolysis

Hb, hemoglobin; HbS, sickled hemoglobin; RBC, red blood cell; SCD, sickle cell disease.

1. Dufu K, et al. *Clin Hemorheol Microcirc*. 2018;70(1):95-105. 2. Lehrer-Graiwer J, et al. ASH 2016. Poster/Abstract #2488. 3. Brown C, et al. EHA 2018. Poster/Abstract #PF709. 4. Smith G, et al. ATS 2018. Poster (hypoxic maximal conditions). 5. Smith G, et al. ATS 2018. Poster (submaximal hypoxic conditions).

GBT440-007: Objectives and Study Design

KEY ELIGIBILITY CRITERIA:

- Children (aged 6 to 11 years) and adolescents (aged 12 to 17 years) with sickle cell disease (HbSS or HbSβ^0-thalassemia)
- Concurrent use of hydroxyurea was allowed, if stable dose for 3 months prior to entry
- Screening hemoglobin ≤10.5 g/dL
- No VOC, acute chest syndrome, or splenic sequestration crisis within 14 days prior to 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 (Daily for 24 Weeks)
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)**
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 (>1g/dL increase) **SECONDARY OBJECTIVES** To evaluate the effect of voxelotor on clinical measures of hemolysis

TCD, transcranial Doppler; VOC, vaso-occlusive crisis.

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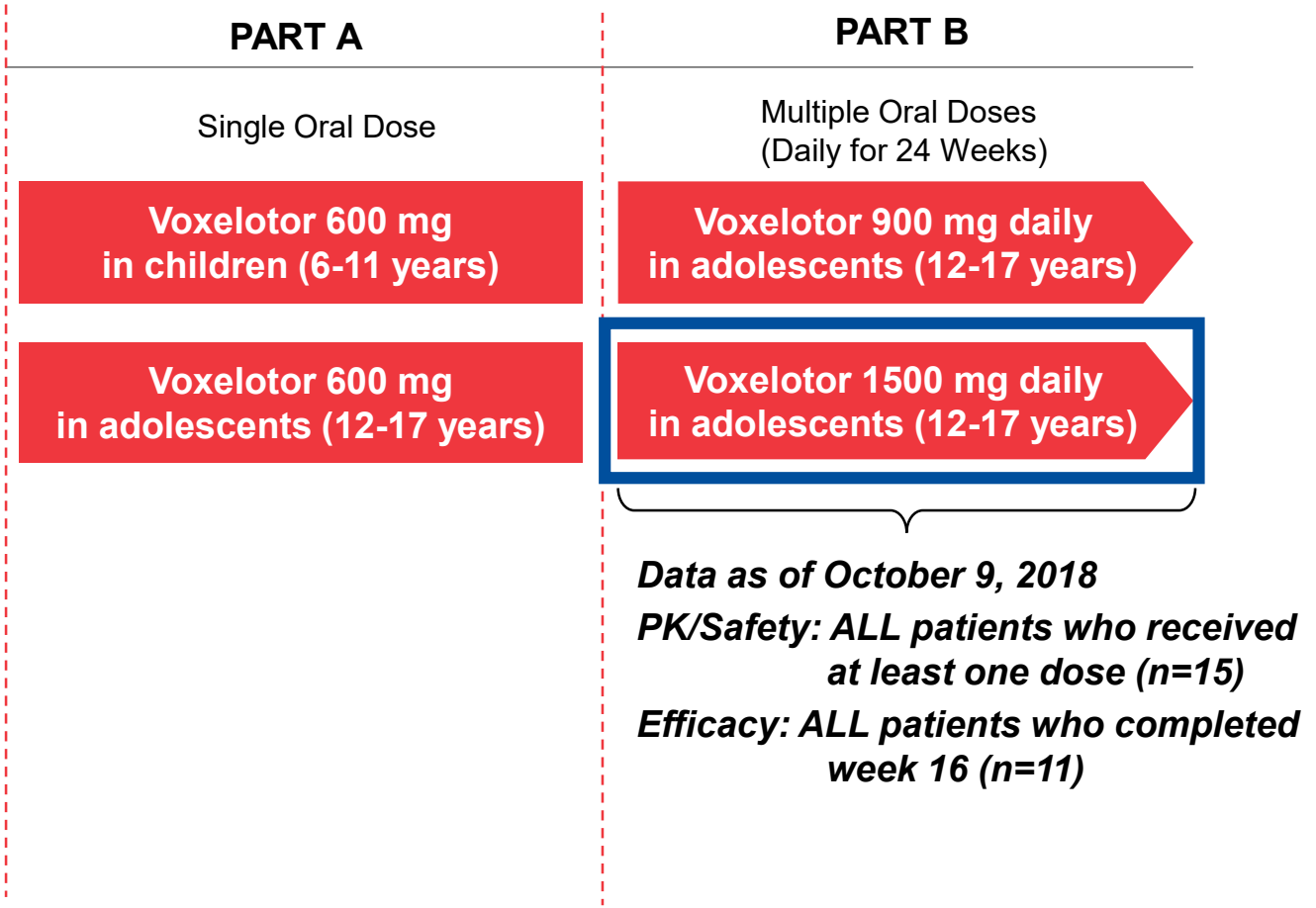


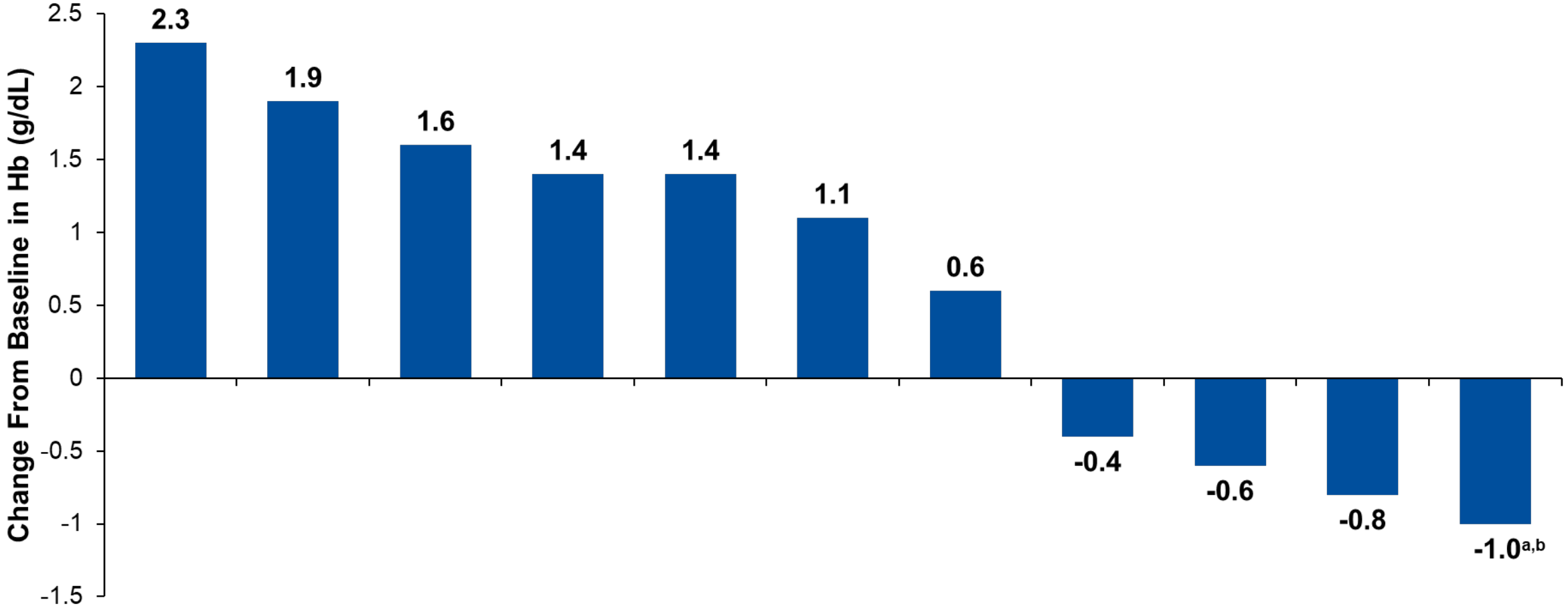
PK, pharmacokinetics; TCD, transcranial Doppler; VOC, vaso-occlusive crisis.

Baseline Characteristics

Baseline Characteristics	Voxelotor Safety Population (N=15)[b]
Male n (%)	5 (33)
Age (years, median, range)	14 (12-17)
HbSS, n (%)	12 (80)
HbSβ^0-thalassemia, n (%)	3 (20)
Number of VOCs in prior year, n (%)	
0	5 (33)
1-4	6 (40)
>4	4 (27)
Baseline[a] Hb (g/dL, median, range)	8.8 (6.2-10.6)[c]
Current hydroxyurea use, n (%)	15 (100)
Baseline HbF (%, median, range)	14.0 (4.7-25.6)
Baseline* TAMM by TCD (cm/sec, median, range)	112 (92-177)
Normal (<170 cm/sec)[d]	14 patients
Conditional (≥170 cm/sec to <200 cm/sec)	1 patient

HbF, fetal hemoglobin; TAMM, time-averaged mean of maximum velocity; TCD, transcranial Doppler; VOC, vaso-occlusive crisis.
[a]Baseline is the average of the values prior to the first dose. [b]Safety population includes all patients who receive at least one dose of study medication.
[c]All patients were eligible for the study with screening Hb ≤10.5 g/dL; one subject had screening Hb = 10.5 g/dL and day 1 Hb = 10.6 g/dL.
[d]All 14 patients with normal TCD velocity were <135 cm/sec. Data as of October 9, 2018.

55% of Subjects Achieved >1 g/dL Increase in Hemoglobin



[a]Low PK exposure.
[b]Previous Hb change from baseline at week 12 was 1.7 g/dL, acute Hb decrease temporally associated with concomitant viral infection.
Data as of October 9, 2018.

Improvement in Anemia and Hemolysis

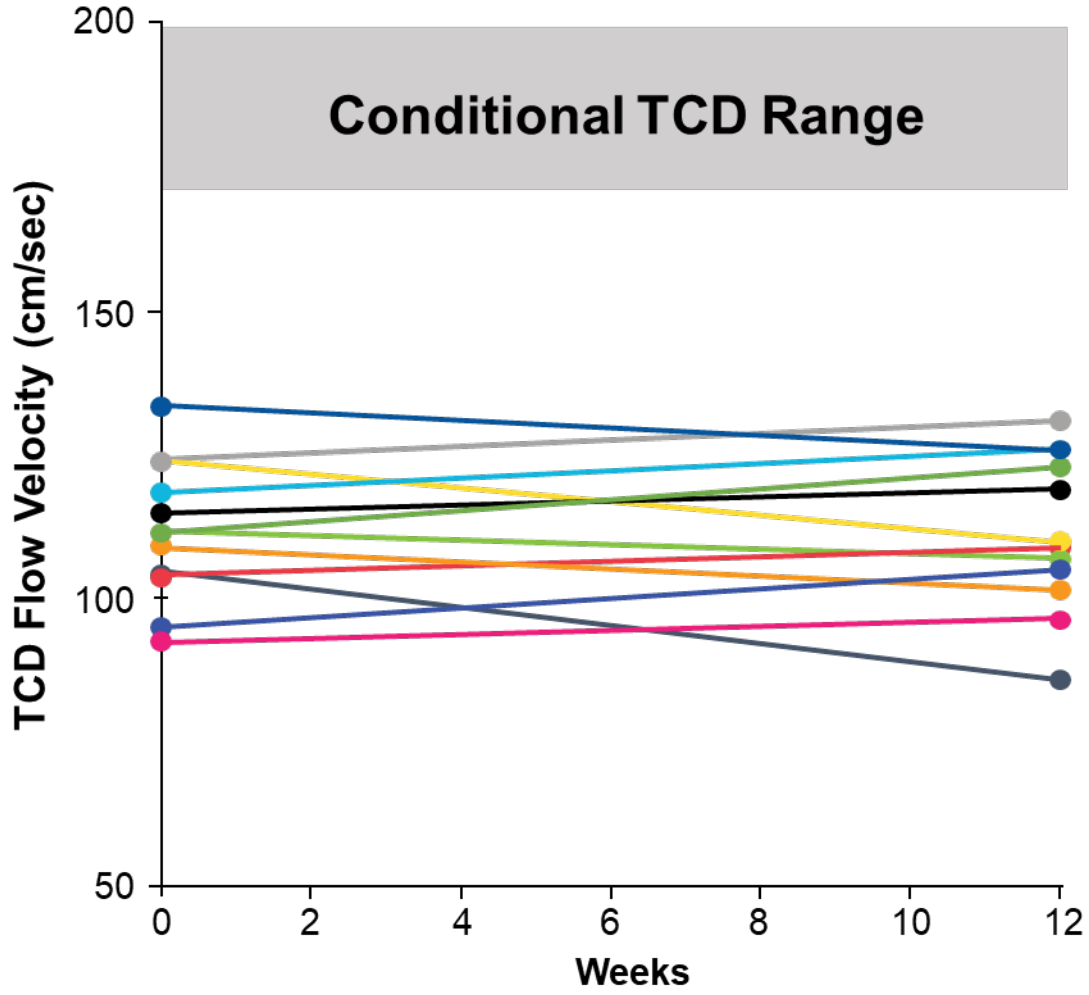
Parameter	Voxelotor 1500 mg Median Change From Baseline N=11	25th, 75th Percentile
Hemoglobin (g/dL)	1.1	-0.6, 1.6
Percent reticulocytes (% change)	-5.8	-42.1, 14.7
Unconjugated bilirubin (% change)	-36.9[a]	-58.5, -5.9
LDH (% change)	-23.1	-33.2, 10.9

LDH, lactate dehydrogenase.
[a]n=10.
Data as of October 9, 2018.

TCD Remained Normal at Midpoint

13 patients had data at week 12

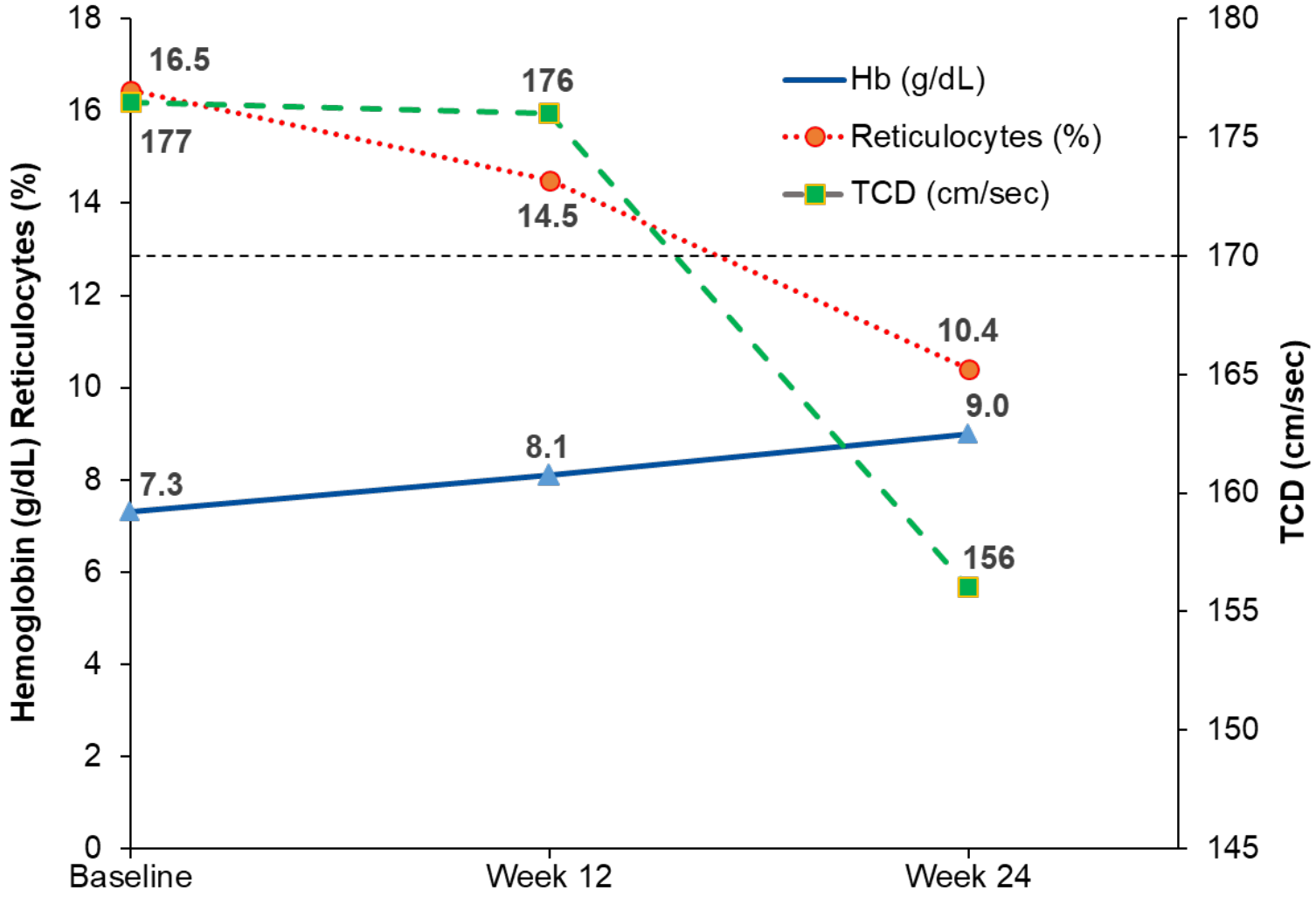
- 12 with normal baseline TCD
  - <135 cm/s at baseline
  - All 12 remained normal at midpoint
- 1 with conditional baseline TCD



Data as of October 9, 2018.

Case Study of Patient With Conditional TCD Velocity

- Subject B01040 had conditional TCD despite hydroxyurea at MTD
- TCD normalized at week 24 with concordant improvements in Hb and reticulocytes



MTD, maximum tolerated dose.
Data as of October 9, 2018.

Safety and Tolerability in Adolescents Treated at 1500 mg

- Voxelotor 1500 mg was well tolerated
- The majority of drug-related AEs related to voxelotor were Grade 1 or 2
  - One Grade 3 event (rash[a])
- No drug discontinuations due to AEs

Drug-related AEs occurring in ≥2 subject

Adverse Event	Voxelotor 1500 mg n (%) N=15
Nausea	3 (20)
Diarrhea	2 (13)

AEs, adverse events.
[a]Did not recur with continued dosing.
Data as of October 9, 2018.

Decrease in Erythropoietin

Erythropoietin (mU/mL)	Voxelotor 1500 mg Median N=11	25th, 75th Percentile
Baseline	139	86, 187
Week 12	91	43, 196
% Change from baseline to week 12	-15.3	-46.8, 0.5

Data as of October 9, 2018.

Adolescent PK as Predicted and Similar to Adults: Target Hb Occupancy Achieved at 1500 mg

	Adolescents (GBT440-007)[a]
Number of patients	14[b]
C_{max}, µg/mL, geometric mean (%CV)	175 (30)
AUC, h*µg/mL, geometric mean (%CV)	3740 (31)
Half-life, h, geometric mean (%CV)	33.6 (24)
% Hb occupancy based on C_{min} geometric mean (%CV)	25.7 (44)

AUC, area under the curve.
[a]Exposures simulated based on individual PK parameters from models estimated for pooled dataset from GBT440-001, GBT440-031, and GBT440-007.
[b]GBT440-007: One patient was excluded from the PK analysis for whole blood due to potential PK timepoint error.
Data as of October 9, 2018.

Conclusions

- Majority of adolescents receiving daily dosing of 1500mg voxelotor achieved robust and sustained improvement in hemoglobin and reduction in hemolysis, consistent with results from RCT HOPE study
  - 55% (6 of 11) of patients achieved >1 g/dL response in Hb
- Voxelotor was safe and well tolerated at the higher 1500mg dose
- Adolescents with normal TCD velocity at baseline remained within the normal range; one subject with conditional TCD normalized at week 24

Since anemia is a strong predictor of stroke, these results support a potential for voxelotor to reduce stroke risk in children and warrants further investigation

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