CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

Clinical Studies

NDA #:	213137
Supplement #:	006
Drug Name:	Oxbryta (voxelotor)
Indication(s):	To reduce the pediatric age limit from 12 years and older to 4 years and older for the treatment of sickle cell disease (SCD).
Applicant:	Global Blood Therapeutics
Receipt Date:	06/25/2021
PDUFA Date:	12/25/2021
Review Priority:	Priority
Biometrics Division:	Division of Biometrics IX
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Link to keywords:
http://intranetapps.fda.gov/scripts/ob_apps/ob/eWork/uploads/eWork/2009/Keywords-in-DFS.htm

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EXECUTIVE SUMMARY

On 25 June 2021, the applicant, Global Blood Therapeutics (GBT), submitted supplemental 6 of the new drug application 213137 (sNDA213137 s006) for the study drug, Oxbryta (voxelotor).

Voxelotor was given an accelerated approval by FDA for the treatment of sickle cell disease (SCD) in adults and pediatric patients 12 years of age and older on 25 November 2019.

In this submission, the applicant proposes to lower the indicated age range for voxelotor in treatment of patients with SCD from 12 years or older to 4 years or older. The clinical study that may support this claim is the ongoing study, GBT440-007 Part C.

GBT440-007 is a phase 2a, single-arm, open-label study. Part C is designed to assess voxelotor administered for up to 48 weeks in subjects 4 to 17 years of age, inclusive, with SCD. Treatment in Part C is ongoing, and the data included in this submission has a cutoff date of 30 September 2020. There is no formal hypothesis testing and sample size calculation. No inferential statistical analyses are performed. Primary endpoint is the hemoglobin (Hb) response at Week 24. A response is defined as an increase of more than 1 g/dL in Hb from baseline at Week 24. The pre-defined primary analysis population is the efficacy evaluation (EE) population, which is defined as enrolled subjects who received at least one dose of study drug.

A total of 56 subjects (45 subjects aged 4 to 11 years and 11 subjects aged 12 to 17 years) were enrolled. As of the data cutoff date, 73.2% (41/56) of subjects (77.8% [35/45] aged 4 to 11 years and 54.5% [6/11] aged 12 to 17 years) had completed 24 weeks of study treatment. Since the objective of the submission is to lower the voxelotor indicated age from 12 years or older to 4 years or older, the subjects aged 4 – 11 years are the focus of this review.

There were 34 out of 45 subjects aged 4 to 11 years who took at least one dose of study drug and have a valid assessment at week 24. These 34 subjects were used for the efficacy analysis by the applicant. The 11 subjects who were also treated but either have missing value or dropped out the study before Week 24 were excluded from the analysis. Out of these 34 subjects, 16 achieved a Hb response. This corresponds to an estimated response rate of 47.1% (95% CI: 29.8, 64.9). However, for a single arm trial such as Part C of Study GBT440-007, we are interested in treated population, which is defined as all enrolled subjects who took at least one dose of study drug. Hence, the Hb response was recalculated using the 45 subjects as the analysis population. The 11 subjects who had missing values at week 24 were considered non-responders. The estimated response rate for the treated population was 35.6% (95% CI: 21.6, 49.5).

There is a noticeable difference (35.6% vs. 47.1%) in the estimated Hb response between the treated population and the applicant's primary analysis population, respectively. This is due to the sizable missing data (24%) who were considered non-responders in the treated population analysis but were excluded from the applicant's primary analysis.

INTRODUCTION

1.1 Overview

Investigational drug and intended indication
Voxelotor was granted an accelerated approval by FDA for the treatment of SCD in adults and children 12 years of age and older on 25 November 2019.

This indication is approved under accelerated approval based on increase in hemoglobin (Hb). The full approval for this indication will be contingent upon verification and description of clinical benefit in confirmatory trial(s).

In this supplemental submission, GBT proposes to lower the indicated age range for voxelotor in treatment of patients with SCD from 12 years or older to 4 years or older.

Proposed Indication:

- For the treatment of sickle cell disease (SCD) in adults and pediatric patients 4 years of age and older.

Clinical Study to support the new indication:

Study submitted:

- GBT440-007 Part C: a phase 2a, single-arm, open-label, single- and multiple-dose study to evaluate the pharmacokinetic (PK), safety, tolerability, and efficacy of voxelotor in pediatric subjects with SCD. Subjects 4 to 17 years of age, inclusive, were enrolled in Part c.

  This study is ongoing, the data have a cutoff date of 30 September 2020.

1.2 Data Sources

Data were provided electronically with the standard analysis data formats. SAS programs used to create key efficacy and safety outputs for the study were submitted with this application.

The link of this submission, including the data and SAS programs is:
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1.3 Overview of Sickle Cell Disease (SCD)

SCD is a rare, inherited disorder caused by a point mutation in the β-globin gene leading to the production of sickle hemoglobin (HbS). A primary and obligatory event in the molecular pathogenesis of SCD is the polymerization of deoxygenated HbS, which leads to sickling of red blood cells (RBCs). The resulting hemolytic anemia is experienced by all patients with SCD and is a defining and serious feature of the disease. Hemolytic anemia leads to reduced oxygen-carrying capacity, tissue hypoxia, and clinical manifestations of end-organ damage, such as stroke, silent cerebral infarction, chronic kidney disease, leg ulcers, and pulmonary hypertension. The disease course is also characterized by lifelong pain and frequent health-care interactions.

Voxelotor is a novel, first-in-class small-molecule HbS polymerization inhibitor. Voxelotor binds covalently and reversibly via a Schiff-base to the N-terminal valine of one of the α-chains of Hb. The mechanism of action of voxelotor specifically targets the underlying mechanism of SCD by increasing the affinity of Hb for oxygen and stabilizing Hb in the oxyhemoglobin state, thereby inhibiting polymerization of HbS and RBC sickling.

The mechanism of action of Hb modification by voxelotor in the RBCs is independent of patient age. Therefore, the treatment effect of voxelotor (with a therapeutic target of 20% to 30% Hb occupancy) on the exposure-response in younger pediatric subjects with SCD is expected to be the same as that observed in pediatric subjects aged 12 to 17 years and adult subjects with SCD.

STATISTICAL EVALUATION

1.4 Data and Analysis Quality

Data of this submission, provided with SDTM and ADaM formats, are acceptable. The sponsor also provided clear definition file for datasets and, reviewer guide and detailed analysis SAS programs for assisting review.

1.5 Evaluation of Efficacy

1.5.1 GBT440-007 Part C

1.5.1.1 Study Design and Endpoints

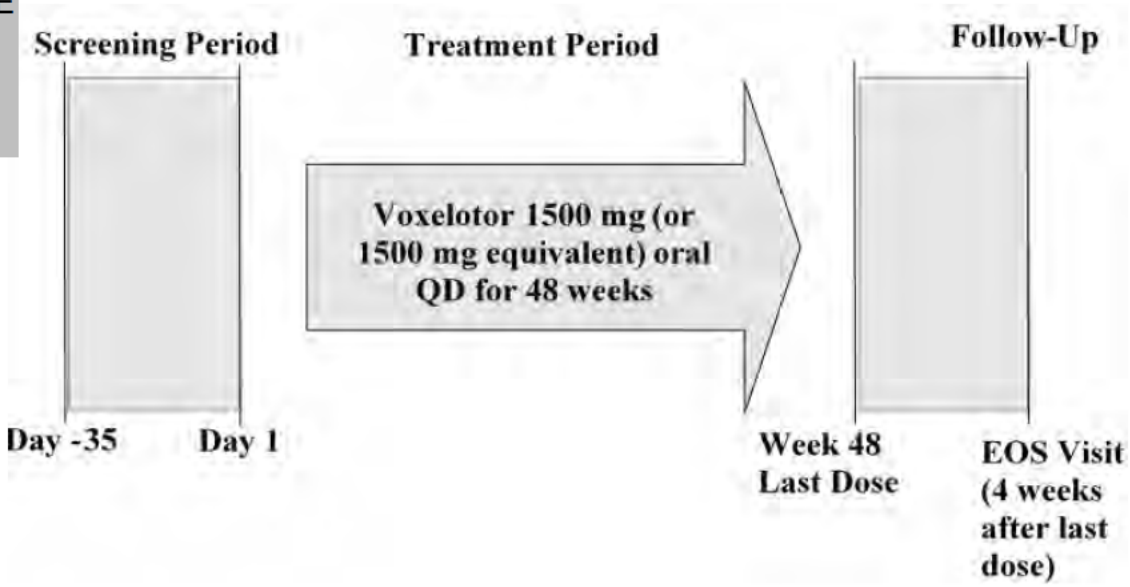
GBT440-007 is a phase 2a, open-label, single- and multiple-dose study to evaluate the pharmacokinetic (PK), safety, tolerability, and efficacy of voxelotor in pediatric subjects with SCD. Subjects 4 to 17 year so age, inclusive, were enrolled in Part C.

Part C of the study was designed to assess the safety, tolerability, PK, and efficacy of multiple doses of voxelotor administered for up to 48 weeks in pediatric subjects with SCD. Treatment in Part C is ongoing at the time of submission and the data included has a cutoff date of 30 September 2020.

Primary Efficacy Objective:

- To evaluate the effect of voxelotor on clinical measures of anemia and hemolysis
- To evaluate the effect of voxelotor on cerebral hemodynamics as measured by TCD flow velocity

Figure 1: Study Schema



Source: Figure 1 of Applicant's CSR

Selection of Doses in the Study:
Subjects aged 4 to 17 years, inclusive, were enrolled in ongoing Part C. Subjects aged 12 to 17 years are receiving voxelotor at 1500 mg QD. Subjects aged 4 to 11 years are receiving voxelotor weight-based dosing.

Table 1: Voxelotor Weight-Based Doses Determined for Pediatric Subjects Aged 4 to 11 years

Population	Voxelotor Doses
5 to < 10 kg	400 mg
10 to < 20 kg	600 mg
20 to < 40 kg	900 mg
≥ 40 kg	1500 mg

Source: Table 3 of Applicant's CSR

These weight-based doses of voxelotor are based on targeting the same exposure and Hb modification (target 20% to 30%) as achieved with the therapeutic dose of 1500 mg voxelotor in subjects 12 years and older.

Primary Efficacy Endpoint:
- Hemoglobin (Hb) response (an increase in Hb >1 g/dL from baseline) at Week 24.

Secondary Efficacy Endpoints:

- Change from baseline to Week 24 in Hb.
- Percent change from baseline to Week 24 in LDH, indirect bilirubin, and reticulocyte count.
- Change from baseline to Week 24 in cerebral blood flow as measured by the time-averaged mean of the maximum (TAMM) transcranial Doppler (TCD) flow velocity.

1.5.1.2 Statistical Methodologies

Sample Size Calculation
A total of 56 subjects had been enrolled in GBT440-007 as of 30 September 2020, including 45 subjects who were 4-11 years of age and 11 subjects who were 12-17 years of age.

Efficacy Analysis Set*:*
Efficacy Evaluable (EE) Population: all subjects who received at least one dose of study drug will be included in this population. All efficacy analyses will be based on the EE population.

Enrolled Population: all subjects who were enrolled.

Treated Population: all subjects who were enrolled and received at least one dose of study drug.

Statistical Methods:
Hb response, defined as an increase in Hb > 1 g/dL, were summarized descriptively at Week 24. Subjects who dropped out early or did not have a Week 24 visit, were not included in the analysis for Hb response at Week 24 by the applicant. No missing data imputation or adjustment for RBC transfusion was performed for this endpoint.

Hematology parameters (hemoglobin, reticulocyte count, indirect bilirubin, and LDH) and cerebral blood flow as measured by TAMM TCD flow velocity were summarized at Week 24 for observed values and changes (absolute and percent) from baseline using appropriate descriptive statistics. If indirect bilirubin was missing and direct and total bilirubin are collected, indirect bilirubin can be calculated as:

Indirect Bilirubin = Total Bilirubin – Direct Bilirubin.

1.5.1.3 Patient Disposition, Demographic and Baseline Characteristics

Patient Disposition:
A total of 56 subjects (45 subjects aged 4 to 11 years and 11 subjects aged 12 to 17 years) were enrolled.

Fifty percent (28/56) of subjects (60% [27/45] aged 4 to 11 years and 9.1% [1/11] aged 12 to 17 years) had completed the study as of the data cutoff date of 30 September 2020. The most common primary reason for early discontinuation of the study was withdrawal of consent (6 subjects aged 4 to 11 years and 3 subjects 12 to 17 years); 3 subjects aged 4 to 11 years and 2 subjects aged 12 to 17 years discontinued due to an AE).

As of the cutoff date, 73.2% (41/56) of subjects (77.8% [35/45] aged 4 to 11 years and 54.5% [6/11] aged 12 to 17 years) had completed 24 weeks of study treatment.

Table 2: Patient Disposition

	4-11 Years N = 45	12-17 Years N = 11	Total N = 56

Did the subject complete the study?			
Yes	27 (60.0)	1 (9.1)	28 (50.0)
No	10 (22.2)	7 (63.6)	17 (30.4)
Ongoing	8 (17.8)	3 (27.3)	11 (19.6)
Primary Reason for early study termination			
Discretion of Investigator	1 (2.2)	0	1 (1.8)
Adverse event	3 (6.7)	2 (18.2)	5 (8.9)
Withdrawal of consent	6 (13.3)	3 (27.3)	9 (16.1)
Other	0	2 (18.2)	2 (3.6)
Did the subjects completed 24 weeks of treatment			
Yes	35 (77.8)	6 (54.5)	41 (73.2)
No	10 (22.2)	5 (45.5)	15 (26.8)
Did the subject complete assigned treatment (48 weeks) with study drug?			
Yes	26 (57.8)	1 (9.1)	27 (48.2)
No	11 (24.4)	7 (63.6)	18 (32.1)
Ongoing	8 (17.8)	3 (27.3)	11 (19.6)
Primary reason for early discontinuation of treatment			
Adverse event	4 (8.9)	2 (18.2)	6 (10.7)
Withdrawal of consent	5 (11.1)	3 (27.3)	8 (14.3)
Discretion of Investigator	1 (2.2)	2 (18.2)	3 (5.4)
Other	1 (2.2)	0	1 (1.8)

Source: Reviewer analysis

Baseline Demographic and Disease Characteristics:
For subjects aged 4 to 11 years, the median age of subjects was 7 years, approximately one-half of subjects (51.1% [23/45 subjects]) were female, and 91.1% (41/45) of subjects were black or African American. 2 were Middle Eastern or North African (2/45) and 2 were white (2/45). 84.4% of subjects had baseline hydroxyurea (HU) use and 75.6% had no blood transfusions in the previous 12 months.

For subjects aged 12 to 17 years, the median age of subjects was 13 years, the majority of subjects (63.6% [7/11]) were male, and all subjects were Black or African American. 63.6% of subjects had baseline HU use and 72.7% had no blood transfusions in the previous 12 months.

Table 3: Demographic Characteristics

	4 – 11 Years N = 45	12 – 17 Years N = 11	Total N = 56
Age at Screening (years)			
Median	7	13	8
Min, max	4, 11	12, 15	4, 15
Sex, n (%)			
Female	23 (51.1)	4 (36.4)	27 (48.2)
Male	22 (48.9)	7 (63.6)	29 (51.8)
Race, n (%)			
Black or African American	41 (91.1)	11 (100.0)	52 (92.9)

Middle Eastern or North African	2 (4.4)	0	2 (3.6)
White	2 (4.4)	0	2 (3.6)
Baseline Hydroxyurea (HU) Use			
Yes	38 (84.4)	7 (63.6)	45 (80.4)
No	7 (15.6)	4 (36.4)	11 (19.6)
Blood Transfusions in the Previous 12 months, n (%)			
0	34 (75.6)	8 (72.7)	42 (75.0)
≥ 1	11 (24.4)	3 (27.3)	14 (25.0)

Source: Reviewer analysis

The mean Hb, Fetal Hb, percent reticulocyte count and transcranial Doppler (TCD) at baseline are presented below.

Table 4: Disease Characteristics

	4 – 11 Years N = 45	12 – 17 Years N = 11	Total N = 56
Baseline Hb (g/dL)			
N	45	11	56
Mean (SD)	8.6 (1.01)	8.1 (0.78)	8.5 (0.98)
Min, max	6.1, 10.5	7.2, 9.4	6.1, 10.5
Baseline HbF (%)			
N	43	11	54
Mean (SD)	17.7 (7.86)	11.0 (8.69)	16.4 (8.41)
Min, max	2.3, 38.4	0.9, 22.3	0.9, 38.4
Baseline Percent Reticulocyte Count			
N	43	9	52
Mean (SD)	10.4 (4.45)	8.8 (4.71)	10.1 (4.49)
Min, max	2.1, 19.5	3.4, 17.6	2.1, 19.5
Baseline TCD, n (%)			
Normal	18 (40.0)	0	18 (32.1)
Elevated	15 (33.3)	7 (63.6)	22 (39.3)
Conditional	12 (26.7)	4 (36.4)	16 (28.6)

Source: Reviewer analysis

1.5.1.4 Efficacy Results

Primary Efficacy Endpoint: Hb Response:
The primary analysis included subjects who were in the EE population and had a valid Hb assessment at Week 24. For subjects who did not have a valid Hb value at Week 24, they were excluded from the calculation of the response rate.

Sixteen out of 34 subjects in the EE population aged 4 to 11 years and had a valid Hb value at Week 24 achieved a Hb response. This corresponds to an estimated response rate of 47.1% (95% CI: 29.8, 64.9) (Table 5).

Two out of 6 subjects in the EE population aged 12 to 17 years and had a valid Hb value at Week 24 achieved a Hb response and that corresponds to a 33.3% response rate (95% CI: 4.3, 77.7). However, the interpretation of the results for this age group is limited by the small sample size (Table 5).

Table 5: Hb Response (>1 g/dL) – EE Population

> 1 g/dL in Hb from Baseline	4 – 11 Years N = 45	12 – 17 Years N = 11
Week 12		
n	37	6
Hb Responder, n (%)	14 (37.8)	1 (16.7)
(95% CI)	(22.2, 53.5)	(0, 46.5)
Week 24		
n	34	6
Hb Responder, n (%)	16 (47.1)	2 (33.3)
(95% CI)	(30.3, 63.8)	(0, 71.1)
Week 48		
n	25	1
Hb Responder, n (%)	9 (36.0)	0
(95% CI)	(17.2, 54.8)	NA
Note: Responder from Voxelotor 1500 mg arm in Study GBT440-031 was 46/90. It corresponds to 51.2% (95%CI: 40.6, 61.8).		

Source: Reviewer analysis

Sensitivity Analysis:
In a single arm trial, the treated population, which includes all enrolled subjects who took at least one dose of study drug, is of interest and all subjects in this population should be accounted for in the analysis. Therefore, this reviewer re-estimated the Hb response with the treated population. The subjects who did not have a valid Hb value at week 24 were considered non-responders. Since all enrolled subjects took the study drug, this is the same as the enrolled population.

The estimated Hb response for the treated subjects was 35.6% (95% CI: 21.6, 49.5). 18.2% (2/11) (95% CI: 4.3, 77.7) enrolled subjects aged 12 to 17 years achieved a Hb response. Again, Interpretation of results for the group is limited by the small sample size (Table 6).

Review Comment: The response rate dropped approximately 11% in the treated population compared with the EE population who had valid Hb assessments. During the applicant orientation meeting, the sponsor stated that the results from this pediatric study is consistent with the results from Study 031. In Study 031, the response rate was 51.2% (46/90). Since Study

031used ITT population, it should be compared with the estimated response rate in the treated population in GBT440-007 Part C, which was 35.6%. Further, the lower bound of the 95% CI of the response rate in the treated population was 21.6%. This shows that voxelotor has some benefit in Hb response for the 4-11 years, however, this is half of the lower bound of the 95% CI of Study 03, 40.6%.

Table 6: Hb Response (> 1 g/dL) - Treated Population

> 1 g/dL in Hb from Baseline	4 – 11 Years N = 45	12 – 17 Years N = 11
Week 12		
Hb Responder, n (%)	14 (31.1)	1 (9.1)
(95% CI)	(17.6, 44.6)	(0, 26.1)
Week 24		
Hb Responder, n (%)	16 (35.6)	2 (18.2)
(95% CI)	(21.6, 49.5)	(0, 41.0)
Week 48		
Hb Responder, n (%)	9 (20.0)	0
(95% CI)	(8.3, 31.7)	NA
Note: Responder from Voxelotor 1500 mg arm in Study GBT440-031 was 46/90. It corresponds to 51.2% (95%CI: 40.6, 61.8).		

Source: Reviewer analysis

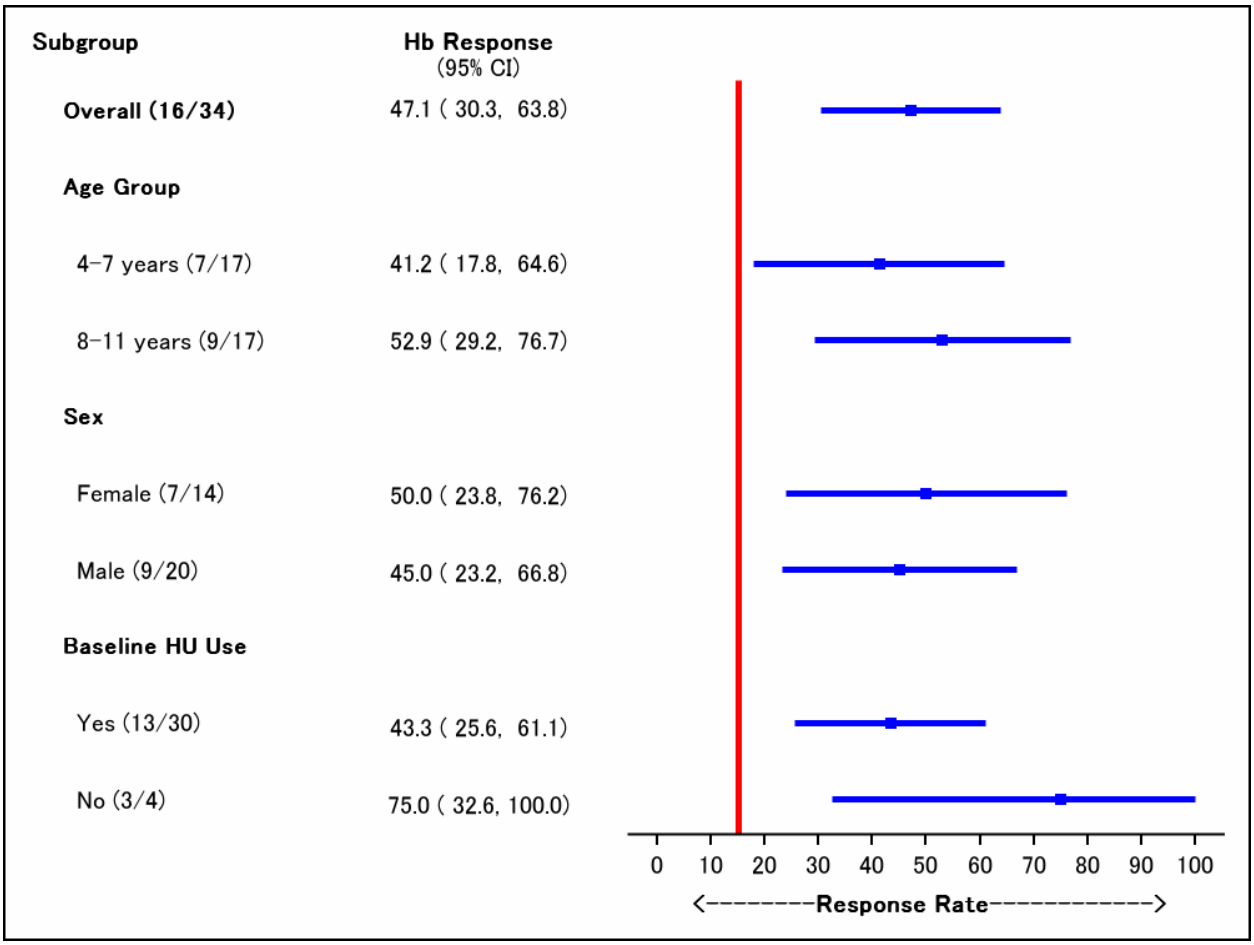
Subgroup Analysis:
Subgroup analyses by age group (4-7 vs 8-11), sex (female vs male), and baseline HU use (Yes vs. no). No outlier subgroups were observed (Table 7; Figure 2).

Table 7: Subgroup Analyses for Subjects Who is Aged 4-11 Years - EE Population

		Response (%) and 95% CI
Overall (N=45)	16/34	47.1 (30.3, 63.8)
Age Group		
4-7 (N=23)	7/17	41.2 (17.8, 64.6)
8-11 (N=22)	9/17	52.9 (29.2, 76.7)
Sex		
Female (n=23)	7/14	50.0 (23.8, 76.2)
Male (n=22)	9/20	45.0 (23.2, 66.8)
Baseline HU Use		
Yes (n=38)	13/30	43.3 (25.6, 61.1)
No (n=7)	3/4	75.0 (32.6, 100)

Source: Reviewer analysis

Figure 2: Forest Plot for Subgroup Analyses in Subjects Aged 4-11 Years - EE Population



Source: Reviewer analysis

Secondary Efficacy Endpoints:

Change from Baseline in Hb

Change in Hb from baseline to Week 24 in EE population is presented here. In subjects aged 4-11 years, the mean change from baseline was 1.0 g/dL. Improvements in Hb were observed at Week 24.

Table 8: Change from Baseline to Week 24 in Hb

Hb (g/dL)	4 – 11 Years N = 45	12 – 17 Years N = 11
Baseline		
N	45	11
Mean (SD)	8.6 (1.01)	8.1 (0.78)
Min, max	6.1, 10.5	7.2, 9.4
Week 24		
N	34	6
Mean (SD)	9.7 (1.53)	8.4 (1.11)
Min, max	6.8, 13.1	6.9, 9.7

Change from Baseline to Week 24		
N	34	6
Mean (SD)	1.0 (1.21)	0.8 (1.14)
Min, max	-1.9, 3.8	-0.3, 2.3

Source: Reviewer analysis

Change from Baseline in Clinical Measures of Hemolysis

Consistent with changes in Hb, improvements in clinical measures of hemolysis were observed at Week 24 (i.e., indirect bilirubin and percent reticulocyte count and LDH)

At week 24, the mean indirect bilirubin observed a decrease of 38.6% from baseline for the 4-11 years age group. The 12-17 years age group observed a 45.7% decrease in mean indirect bilirubin. Keep in mind that the sample size is very small in the 12-17 years age group, hence, the results may not be reliable.

Table 9: Change from Baseline to Week 24 in Indirect Bilirubin

Indirect bilirubin (mg/dL)	4 – 11 Years N = 45	12 – 17 Years N = 11
Baseline		
N	38	11
Mean (SD)	2.1 (0.97)	3.1 (2.80)
Min, max	0.6, 4.6	0.7, 10.2
Week 24		
N	32	6
Mean (SD)	1.1 (0.46)	2.6 (2.70)
Min, max	0.3, 2.0	0.5, 7.4
Percent Change from Baseline to Week 24		
N	28	6
Mean (SD)	-38.6 (27.18)	-45.7 (24.93)
Min, max	-76.0, 40.0	-80.0, -10.5

Source: Reviewer analysis

For the reticulocyte count, at week 24, a decrease of 3.3% from the baseline for the 4-11 years age group and an increase of 7.7% in the 12-17 years age group in mean reticulocyte count were observed.

Table 10: Change from Baseline to Week 24 in Reticulocyte Count

Reticulocyte Count (%)	4 – 11 Years N = 45	12 – 17 Years N = 11
Baseline		
N	43	9
Mean (SD)	10.4 (4.45)	8.8 (4.71)
Min, max	2.1, 19.5	3.4, 17.6
Week 24		

N	32	6
Mean (SD)	8.8 (4.46)	10.2 (6.64)
Min, max	0.9, 19.1	4.4, 22.3
Percent Change from Baseline to Week 24		
N	31	5
Mean (SD)	-3.3 (45.89)	7.7 (44.80)
Min, max	-95.0, 110.3	-52.7, 70.9

Source: Reviewer analysis

The mean LDH decreased 2.6% from baseline in the 4-11 years age group. The 12-17 years age group observed a 22.4% decrease.

Table 11: Change from Baseline to Week 24 in Lactate Dehydrogenase

Lactate Dehydrogenase (U/L)	4 – 11 Years N = 45	12 – 17 Years N = 11
Baseline		
N	45	9
Mean (SD)	671.4 (425.60)	725.9 (483.10)
Min, max	282.0, 2613.0	281.0, 1852.0
Week 24		
N	32	5
Mean (SD)	551.0 (242.24)	567.6 (88.06)
Min, max	230.0, 1502.0	490.0, 710.0
Percent Change from Baseline to Week 24		
N	32	4
Mean (SD)	-2.6 (21.48)	-22.4 (22.08)
Min, max	-36.6, 44.2	-48.0, 2.1

Source: Reviewer analysis

Change from Baseline in transcranial Doppler (TCD) Flow Velocity:

For subjects aged 4 to 11 years, mean (SD) TCD flow velocity at baseline was 135.1 cm/sec (18.04) for subjects with normal TCD flow velocity (defined as < 170 cm/sec). The mean (SD) change from baseline to Week 24 with normal TCD flow velocity at baseline was -1.3 cm/sec (16.41). Mean (SD) baseline TCD flow velocity at baseline was 177.3 cm/sec (5.00) for subjects with conditional TCD flow velocity (defined as ≥ 170 to < 200 cm/sec). The mean (SD) change from baseline to Week 24 with conditional TCD flow velocity at baseline was -12.4 cm/sec (8.56). Overall, no subjects converted to abnormal TCD flow velocity (defined as ≥ 200 cm/sec) over the course of the study. Two subjects with normal TCD flow velocity at baseline converted to conditional during the study.

For subjects aged 12 to 17 years, no subjects converted to abnormal TCD flow velocity (defined as ≥ 200 cm/sec) over the course of the study. The mean (SD) change from baseline to Week 24 in TCD flow velocity was 0 cm/sec (18.25) with normal TCD at baseline. One subject with

normal TCD flow velocity at baseline (162 cm/sec) converted to conditional (183 cm/sec) at Week 24. The mean (SD) change from baseline to Week 24 in TCD flow velocity was -28.3 cm/sec (10.25) with conditional TCD at baseline.

Table 12: Change from Baseline to Week 24 in TCD Flow Velocity

	4 – 11 Years		12 – 17 Years	
	Normal TCD at Baseline [a]	Conditional TCD at Baseline [b]	Normal TCD at Baseline	Conditional TCD at Baseline
Baseline				
N	33	12	7	4
Mean (SD)	135.1 (18.04)	177.3 (5.00)	157.0 (8.29)	175.2 (4.01)
Min, max	80.0, 163.0	170.0, 189.0	148.9, 169.5	170.0, 179.7
Week 24				
N	28	5	3	3
Mean (SD)	132.2 (20.07)	166.6 (8.44)	159.0 (21.63)	148.6 (10.50)
Min, max	87.0, 173.0	157.0, 176.0	141.0, 183.0	138.0, 159.0
Change from Baseline to Week 24 [c]				
N	28	5	3	3
Mean (SD)	-1.3 (16.41)	-12.4 (8.56)	0.0 (18.25)	-28.3 (10.25)
Min, max	-39.6, 26.0	-24.0, 0.0	-12.0, 21.0	-37.0, -17.0

[a] Normal TCD at Baseline is defined as < 170 cm/sec.
[b] Conditional TCD at Baseline is defined as ≥ 170 to < 200 cm/sec.
[c] Change from Baseline to Week 24 calculation includes all subjects with values at both baseline and Week 24.
Source: Reviewer analysis

1.6 Other Special/Subgroup Populations

For the subgroup analyses of the primary efficacy endpoint, Hb response, refer to previous section. No analyses for other special populations were performed.

1.7 Statistical Issues and Collective Evidence

Study GBT440-007 Part C is ongoing. The data cutoff date for this submission was 30 September 2020.

The proportion of Hb response for subjects aged 4-11 years was 47.1% (95% CI: 30.3, 63.8) and 35.6% (95% CI: 21.6, 49.5) in the EE and treated population at Week 24, respectively. No outlier subgroups were observed.

Results summaries were based on descriptive statistics; no statistical adjustments were made for covariates, no statistical adjustments were made for multiple comparisons, and no inferential statistical analyses were performed. All results are descriptive.

1.8 Conclusions and Recommendations

Based on the descriptive evidence provided in study GBT440-007-part C, it appears that voxelotor demonstrated the benefit of voxelotor in treatment patients aged 4-11 years with SCD.

1.9 Labeling Recommendations

Since study GBT440-007 Part C was a single-arm, open-label, phase 2a study without a formal sample size calculation and a pre-specified statistical hypothesis, these efficacy results should only be included descriptively in the label. Further, the results from the treated population should be used (b) (4). This is because the EE population excluded 11 subjects who were treated with the study drug aged 4 – 11 years, hence, reduced the analysis sample size by 24%. As a result, the estimated Hb response from the EE population may not be reliable.

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