Clinical trial results:
A Phase 3, Double-blind, Randomized, Placebo-controlled, Multicenter Study of Voxelotor Administered Orally to Patients With Sickle Cell Disease

Summary

EudraCT number	2016-003370-40
Trial protocol	GB NL FR IT
Global end of trial date	08 October 2019

Results information

Result version number	v1 (current)
This version publication date	21 March 2021
First version publication date	21 March 2021

Trial information

Trial identification

Sponsor protocol code	GBT440-031

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03036813
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Global Blood Therapeutics, Inc.
Sponsor organisation address	181 Oyster Point Blvd, South San Francisco, United States, 94080
Public contact	Margaret Tonda, Global Blood Therapeutics, Inc., 1 650.741.7761, mtonda@gbt.com
Scientific contact	Sr. Director, Clinical Science, Global Blood Therapeutics, Inc., 1 650.741.7761, mtonda@gbt.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-002356-PIP02-20
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	22 November 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	08 October 2019
Global end of trial reached?	Yes
Global end of trial date	08 October 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to assess the efficacy of voxelotor (GBT440) in adolescents and adults with Sickle Cell Disease (SCD) as measured by improvement in hemoglobin.

Protection of trial subjects:

1. All approved therapies for SCD were allowed under this protocol including pain control, hydroxycarbamide (HU) therapy, L-glutamine, and blood transfusions. Other concomitant medications specifically permitted by the protocol included penicillin, folic acid, and codeine, as these are medications commonly used by subjects with SCD. In addition, the use of combined (estrogen- and progestogen-containing) or progestogen-only hormonal contraception associated with inhibition of ovulation was also permitted. All subjects used at least 1 concomitant medication.
2. Patients may be removed from the study at any time at the discretion of the investigator per his/her clinical judgement for reasons including severe AE.
3. An independent DSMB monitored the safety and conduct of the study.

Background therapy:

All approved therapies for SCD were allowed under this protocol including pain control, HU therapy, L-glutamine, and blood transfusions. Other concomitant medications specifically permitted by the protocol included penicillin, folic acid, and codeine, as these are medications commonly used by subjects with SCD.

Evidence for comparator:

This study used placebo as a comparator on the background of best clinical standard-of-care treatment. All approved therapies for SCD were allowed under the protocol; none were withheld. This included pain control, HU, L-glutamine, and blood transfusions. Agreeing to placebo treatment did not place subjects at any increased risk, because no standard of care (SOC) therapies were withheld as a result.

Actual start date of recruitment	13 December 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 101
Country: Number of subjects enrolled	Kenya: 49
Country: Number of subjects enrolled	Egypt: 44
Country: Number of subjects enrolled	Turkey: 12
Country: Number of subjects enrolled	Oman: 9
Country: Number of subjects enrolled	Lebanon: 7
Country: Number of subjects enrolled	Canada: 4
Country: Number of subjects enrolled	Jamaica: 4

Country: Number of subjects enrolled	Netherlands: 8
Country: Number of subjects enrolled	United Kingdom: 32
Country: Number of subjects enrolled	France: 3
Country: Number of subjects enrolled	Italy: 1
Worldwide total number of subjects	274
EEA total number of subjects	44

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	46
Adults (18-64 years)	228
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Overall, 449 subjects were screened for this study at 60 study sites. Between January 2017 and May 2018, a total of 274 subjects were randomized at 58 study sites across 12 countries. All 274 randomized subjects were included in the ITT Population. A total of 271 subjects received study drug and were included in the Safety Population.

Pre-assignment

Screening details:

Screening procedures were done within 35 days of randomization to assess eligibility.

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Assessor

Blinding implementation details:

This study was a double-blind study. The voxelotor and placebo capsules or tablets were matched for shape, size, and color. All individuals involved in the conduct of the study (ie, site staff and participants, Investigator, CRO personnel, Sponsor personnel) were blinded to randomized treatment assignment. Drug Supply personnel remained unblinded throughout the study. Other sponsor and CRO personnel may be unblinded as required per Regulatory reporting requirements of SUSARS.

Arms

Are arms mutually exclusive?	Yes
Arm title	Voxelotor 900mg

Arm description:

Participants received voxelotor 900mg; administered orally, once daily for 72 weeks.

Arm type	Experimental
Investigational medicinal product name	Voxelotor 900mg
Investigational medicinal product code	
Other name	GBT440
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

900mg administered orally once a day

Arm title	Voxelotor 1500mg

Arm description:

Participants received voxelotor 1500mg administered orally, once daily for 72 weeks

Arm type	Experimental
Investigational medicinal product name	Voxelotor 1500mg
Investigational medicinal product code	
Other name	GBT440
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

1500mg administered orally once a day

Arm title	Placebo

Arm description:

Matching placebo; administered orally, once daily for 72 weeks.

Arm type	Placebo
No investigational medicinal product assigned in this arm	

Number of subjects in period 1	Voxelotor 900mg	Voxelotor 1500mg	Placebo
Started	92	90	92
Completed	70	63	66
Not completed	22	27	26
Consent withdrawn by subject	12	6	10
Physician decision	2	1	1
Non-Compliance	1	5	3
Reason Not Categorized	-	3	5
Pregnancy	-	-	1
Adverse event	6	11	6
Lost to follow-up	1	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Voxelotor 900mg
Reporting group description:	
Participants received voxelotor 900mg; administered orally, once daily for 72 weeks.	
Reporting group title	Voxelotor 1500mg
Reporting group description:	
Participants received voxelotor 1500mg administered orally, once daily for 72 weeks	
Reporting group title	Placebo
Reporting group description:	
Matching placebo; administered orally, once daily for 72 weeks.	

Reporting group values	Voxelotor 900mg	Voxelotor 1500mg	Placebo
Number of subjects	92	90	92
Age categorical			
Overall Number of Baseline Participants			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	15	14	17
Adults (18-64 years)	77	76	75
From 65-84 years	0	0	0
85 years and over	0	0	0
Gender categorical			
Sex: Female, Male			
Units: Subjects			
Female	51	58	50
Male	41	32	42

Reporting group values	Total		
Number of subjects	274		
Age categorical			
Overall Number of Baseline Participants			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	46		
Adults (18-64 years)	228		
From 65-84 years	0		

85 years and over	0		

Gender categorical			
Sex: Female, Male			
Units: Subjects			
Female	159		
Male	115		

End points

End points reporting groups	
Reporting group title	Voxelotor 900mg
Reporting group description:	
Participants received voxelotor 900mg; administered orally, once daily for 72 weeks.	
Reporting group title	Voxelotor 1500mg
Reporting group description:	
Participants received voxelotor 1500mg administered orally, once daily for 72 weeks	
Reporting group title	Placebo
Reporting group description:	
Matching placebo; administered orally, once daily for 72 weeks.	

Primary: Number of Participants with Increased in Hb>1 g/dL	
End point title	Number of Participants with Increased in Hb>1 g/dL
End point description:	
Number of participants with increased in Hb>1 g/dL from baseline to week 24.	
End point type	Primary
End point timeframe:	
Baseline to Week 24	

End point values	Voxelotor 900mg	Voxelotor 1500mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	92	90	92	
Units: Count of Participants	30	46	6	

Statistical analyses

Statistical analysis title	Primary Endpoint (voxelotor 1500mg vs Placebo)
Statistical analysis description:	
Hemoglobin response of > 1 g/dl change from baseline was derived based on change from baseline to the average of the values for Weeks 20 and 24. Subjects with any of the following scenarios were counted as non-responders: 1) hemoglobin missing at both Weeks 20 and 24; 2) post-randomization HU use prior to Week 24 for subjects with no HU use at baseline; 3) received transfusion due to anemia within 8 weeks prior to Week 24 Hb assessment.	
Comparison groups	Voxelotor 1500mg v Placebo
Number of subjects included in analysis	182
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	< 0.001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in adjusted response rate
Point estimate	45

Confidence interval	
level	95 %
sides	2-sided
lower limit	33.4
upper limit	56.7

Notes:

[1] - Comparison adjusted for baseline HU use, age group, and geographic region.

Secondary: Percent Change From Baseline in Hemolysis Measures

End point title	Percent Change From Baseline in Hemolysis Measures

End point description:

Percentage change from baseline to week 24 in indirect bilirubin

End point type	Secondary

End point timeframe:

Baseline to Week 24

End point values	Voxelotor 900mg	Voxelotor 1500mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	88[2]	85[3]	85[4]	
Units: Percent Change				
least squares mean (standard error)	-20.1 (± 3.41)	-29.1 (± 3.46)	-2.8 (± 3.51)	

Notes:

[2] - analysis pop includes all randomized with baseline and at least one baseline value

[3] - analysis pop includes all randomized with baseline and at least one baseline value

[4] - analysis pop includes all randomized with baseline and at least one baseline value

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Hemolysis Measures

End point title	Change from Baseline in Hemolysis Measures

End point description:

Percentage change from Baseline to Week 24 in reticulocytes percentage

End point type	Secondary

End point timeframe:

Baseline to week 24

End point values	Voxelotor 900mg	Voxelotor 1500mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	92	88	91	
Units: Percent Change				
least squares mean (standard error)	-1.4 (± 4.65)	-18.0 (± 4.70)	6.8 (± 4.73)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage Change From Baseline in Hemolysis Measures

End point title	Percentage Change From Baseline in Hemolysis Measures

End point description:

Percent Change from Baseline to week 24 in absolute reticulocytes.

End point type	Secondary

End point timeframe:

Baseline to Week 24

End point values	Voxelotor 900mg	Voxelotor 1500mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	92	88[5]	91[6]	
Units: percent				
least squares mean (standard error)	4.7 (± 5.13)	-6.4 (± 5.17)	4.17 (± 5.19)	

Notes:

[5] - Population excludes 2 subjects that were not treated

[6] - Population excludes 1 subject that was not treated.

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Hemolysis Measures

End point title	Percent Change From Baseline in Hemolysis Measures

End point description:

Percentage change from Baseline to Week 24 in Lactate Dehydrogenase (LDH)

End point type	Secondary

End point timeframe:

Baseline to week 24

End point values	Voxelotor 900mg	Voxelotor 1500mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	90[7]	88[8]	87[9]	
Units: Percent Change				
least squares mean (standard error)	1.6 (± 3.68)	-4.6 (± 3.69)	3.0 (± 3.75)	

Notes:

[7] - analysis pop includes all randomized with baseline and at least one baseline value

[8] - analysis pop includes all randomized with baseline and at least one baseline value

[9] - analysis pop includes all randomized with baseline and at least one baseline value

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized Vaso-Occlusive Crisis (VOC) Incidence Rate

End point title	Annualized Vaso-Occlusive Crisis (VOC) Incidence Rate

End point description:

Number of Vaso-Occlusive Crisis (VOC) events per year.

End point type	Secondary

End point timeframe:

Baseline to week 72

End point values	Voxelotor 900mg	Voxelotor 1500mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	92	88[10]	91[11]	
Units: Adjusted Annualized Incidence Rate				
number (confidence interval 95%)	2.4 (1.9 to 3.1)	2.4 (1.8 to 3.1)	2.8 (2.2 to 3.6)	

Notes:

[10] - Population excludes 2 subjects that were not treated

[11] - Population excludes 1 subject that was not treated

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From Baseline to 72 Weeks	
Adverse event reporting additional description:	
Non-sickle cell disease (Non-SCD) related Adverse Events. For number of deaths (all causes) the total of all deaths is reported (non-SCD and SCD related). For the number of deaths resulting from adverse events, only non-SCD adverse events are reported below.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups	
Reporting group title	Voxelotor 900mg
Reporting group description:	
Participants received voxelotor 900 mg; administered orally, once daily for 72 weeks.	
Reporting group title	Voxelotor 1500mg
Reporting group description:	
Participants received voxelotor 1500 mg administered orally, once daily for 72 weeks.	
Reporting group title	Placebo
Reporting group description:	
Matching placebo; administered orally, once daily for 72 weeks.	

Serious adverse events	Voxelotor 900mg	Voxelotor 1500mg	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	20 / 92 (21.74%)	25 / 88 (28.41%)	23 / 91 (25.27%)
number of deaths (all causes)	2	2	2
number of deaths resulting from adverse events	1	2	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Uterine leiomyoma			
subjects affected / exposed	1 / 92 (1.09%)	0 / 88 (0.00%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Cholecystectomy			
subjects affected / exposed	0 / 92 (0.00%)	1 / 88 (1.14%)	1 / 91 (1.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			

Non-cardiac chest pain			
subjects affected / exposed	0 / 92 (0.00%)	1 / 88 (1.14%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral swelling			
subjects affected / exposed	0 / 92 (0.00%)	0 / 88 (0.00%)	1 / 91 (1.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	3 / 92 (3.26%)	2 / 88 (2.27%)	3 / 91 (3.30%)
occurrences causally related to treatment / all	0 / 4	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death unknown etiology			
subjects affected / exposed	1 / 92 (1.09%)	0 / 88 (0.00%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 92 (0.00%)	1 / 88 (1.14%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 92 (0.00%)	1 / 88 (1.14%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	0 / 92 (0.00%)	2 / 88 (2.27%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 92 (0.00%)	2 / 88 (2.27%)	1 / 91 (1.10%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Respiratory failure			
subjects affected / exposed	0 / 92 (0.00%)	1 / 88 (1.14%)	1 / 91 (1.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Haemoglobin decreased			
subjects affected / exposed	1 / 92 (1.09%)	0 / 88 (0.00%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oxygen saturation decreased			
subjects affected / exposed	0 / 92 (0.00%)	1 / 88 (1.14%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Lower limb fracture			
subjects affected / exposed	1 / 92 (1.09%)	0 / 88 (0.00%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Medication error			
subjects affected / exposed	0 / 92 (0.00%)	1 / 88 (1.14%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Patella fracture			
subjects affected / exposed	0 / 92 (0.00%)	1 / 88 (1.14%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal compression fracture			
subjects affected / exposed	0 / 92 (0.00%)	0 / 88 (0.00%)	1 / 91 (1.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiac arrest			

subjects affected / exposed	0 / 92 (0.00%)	0 / 88 (0.00%)	1 / 91 (1.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cardiac failure high output			
subjects affected / exposed	0 / 92 (0.00%)	1 / 88 (1.14%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Supraventricular tachycardia			
subjects affected / exposed	1 / 92 (1.09%)	0 / 88 (0.00%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebral microhaemorrhage			
subjects affected / exposed	0 / 92 (0.00%)	0 / 88 (0.00%)	1 / 91 (1.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	1 / 92 (1.09%)	0 / 88 (0.00%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depressed level of consciousness			
subjects affected / exposed	0 / 92 (0.00%)	0 / 88 (0.00%)	1 / 91 (1.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Encephalopathy			
subjects affected / exposed	0 / 92 (0.00%)	1 / 88 (1.14%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Headache			
subjects affected / exposed	0 / 92 (0.00%)	1 / 88 (1.14%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperaesthesia			

subjects affected / exposed	0 / 92 (0.00%)	0 / 88 (0.00%)	1 / 91 (1.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	0 / 92 (0.00%)	1 / 88 (1.14%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 92 (3.26%)	0 / 88 (0.00%)	2 / 91 (2.20%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemolytic anaemia			
subjects affected / exposed	0 / 92 (0.00%)	0 / 88 (0.00%)	1 / 91 (1.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypersplenism			
subjects affected / exposed	0 / 92 (0.00%)	2 / 88 (2.27%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reticulocytopenia			
subjects affected / exposed	0 / 92 (0.00%)	1 / 88 (1.14%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Splenic infarction			
subjects affected / exposed	0 / 92 (0.00%)	0 / 88 (0.00%)	1 / 91 (1.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	1 / 92 (1.09%)	0 / 88 (0.00%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytosis			

subjects affected / exposed	0 / 92 (0.00%)	0 / 88 (0.00%)	1 / 91 (1.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Blindness			
subjects affected / exposed	0 / 92 (0.00%)	1 / 88 (1.14%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinal haemorrhage			
subjects affected / exposed	0 / 92 (0.00%)	1 / 88 (1.14%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vitreous haemorrhage			
subjects affected / exposed	0 / 92 (0.00%)	1 / 88 (1.14%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 92 (1.09%)	0 / 88 (0.00%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	2 / 92 (2.17%)	0 / 88 (0.00%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis haemorrhagic			
subjects affected / exposed	1 / 92 (1.09%)	0 / 88 (0.00%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 92 (0.00%)	1 / 88 (1.14%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Odynophagia			

subjects affected / exposed	0 / 92 (0.00%)	0 / 88 (0.00%)	1 / 91 (1.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 92 (0.00%)	1 / 88 (1.14%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	1 / 92 (1.09%)	0 / 88 (0.00%)	1 / 91 (1.10%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic sequestration			
subjects affected / exposed	0 / 92 (0.00%)	1 / 88 (1.14%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis acute			
subjects affected / exposed	1 / 92 (1.09%)	0 / 88 (0.00%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Rash generalized			
subjects affected / exposed	1 / 92 (1.09%)	0 / 88 (0.00%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 92 (0.00%)	1 / 88 (1.14%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthritis			
subjects affected / exposed	0 / 92 (0.00%)	1 / 88 (1.14%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Back pain			
subjects affected / exposed	1 / 92 (1.09%)	0 / 88 (0.00%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Costochondritis			
subjects affected / exposed	0 / 92 (0.00%)	0 / 88 (0.00%)	1 / 91 (1.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal chest pain			
subjects affected / exposed	2 / 92 (2.17%)	0 / 88 (0.00%)	1 / 91 (1.10%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal pain			
subjects affected / exposed	0 / 92 (0.00%)	0 / 88 (0.00%)	1 / 91 (1.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			
subjects affected / exposed	1 / 92 (1.09%)	0 / 88 (0.00%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 92 (0.00%)	1 / 88 (1.14%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Brain abscess			
subjects affected / exposed	0 / 92 (0.00%)	1 / 88 (1.14%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Cellulitis			
subjects affected / exposed	1 / 92 (1.09%)	0 / 88 (0.00%)	1 / 91 (1.10%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			

subjects affected / exposed	0 / 92 (0.00%)	0 / 88 (0.00%)	1 / 91 (1.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis viral			
subjects affected / exposed	0 / 92 (0.00%)	0 / 88 (0.00%)	1 / 91 (1.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal viral infection			
subjects affected / exposed	0 / 92 (0.00%)	1 / 88 (1.14%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	0 / 92 (0.00%)	0 / 88 (0.00%)	1 / 91 (1.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	1 / 92 (1.09%)	0 / 88 (0.00%)	1 / 91 (1.10%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung Infection			
subjects affected / exposed	0 / 92 (0.00%)	0 / 88 (0.00%)	1 / 91 (1.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malaria			
subjects affected / exposed	3 / 92 (3.26%)	1 / 88 (1.14%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	0 / 5	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pharyngitis			
subjects affected / exposed	1 / 92 (1.09%)	0 / 88 (0.00%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary sepsis			

subjects affected / exposed	0 / 92 (0.00%)	1 / 88 (1.14%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Sepsis			
subjects affected / exposed	1 / 92 (1.09%)	0 / 88 (0.00%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis syndrome			
subjects affected / exposed	1 / 92 (1.09%)	0 / 88 (0.00%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tonsillitis			
subjects affected / exposed	0 / 92 (0.00%)	1 / 88 (1.14%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	0 / 92 (0.00%)	1 / 88 (1.14%)	1 / 91 (1.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	1 / 92 (1.09%)	0 / 88 (0.00%)	1 / 91 (1.10%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Gout			
subjects affected / exposed	1 / 92 (1.09%)	0 / 88 (0.00%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	1 / 92 (1.09%)	0 / 88 (0.00%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Type 2 diabetes mellitus			

subjects affected / exposed	1 / 92 (1.09%)	0 / 88 (0.00%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Voxelotor 900mg	Voxelotor 1500mg	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	85 / 92 (92.39%)	85 / 88 (96.59%)	81 / 91 (89.01%)
Nervous system disorders			
Dizziness			
subjects affected / exposed	8 / 92 (8.70%)	4 / 88 (4.55%)	9 / 91 (9.89%)
occurrences (all)	10	4	9
Headache			
subjects affected / exposed	20 / 92 (21.74%)	27 / 88 (30.68%)	23 / 91 (25.27%)
occurrences (all)	22	33	34
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	13 / 92 (14.13%)	12 / 88 (13.64%)	12 / 91 (13.19%)
occurrences (all)	16	14	15
Non-cardiac chest pain			
subjects affected / exposed	13 / 92 (14.13%)	9 / 88 (10.23%)	10 / 91 (10.99%)
occurrences (all)	15	10	10
Pain			
subjects affected / exposed	15 / 92 (16.30%)	15 / 88 (17.05%)	18 / 91 (19.78%)
occurrences (all)	27	27	22
Pyrexia			
subjects affected / exposed	10 / 92 (10.87%)	11 / 88 (12.50%)	4 / 91 (4.40%)
occurrences (all)	13	13	5
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	6 / 92 (6.52%)	4 / 88 (4.55%)	2 / 91 (2.20%)
occurrences (all)	9	4	2
Gastrointestinal disorders			
Abdominal pain			

subjects affected / exposed	13 / 92 (14.13%)	13 / 88 (14.77%)	10 / 91 (10.99%)
occurrences (all)	15	17	12
Abdominal pain upper			
subjects affected / exposed	14 / 92 (15.22%)	8 / 88 (9.09%)	6 / 91 (6.59%)
occurrences (all)	19	9	10
Constipation			
subjects affected / exposed	9 / 92 (9.78%)	6 / 88 (6.82%)	9 / 91 (9.89%)
occurrences (all)	9	7	9
Diarrhoea			
subjects affected / exposed	17 / 92 (18.48%)	20 / 88 (22.73%)	10 / 91 (10.99%)
occurrences (all)	24	22	12
Gastritis			
subjects affected / exposed	5 / 92 (5.43%)	3 / 88 (3.41%)	4 / 91 (4.40%)
occurrences (all)	7	8	4
Nausea			
subjects affected / exposed	17 / 92 (18.48%)	16 / 88 (18.18%)	9 / 91 (9.89%)
occurrences (all)	21	21	17
Vomiting			
subjects affected / exposed	13 / 92 (14.13%)	11 / 88 (12.50%)	15 / 91 (16.48%)
occurrences (all)	20	17	24
Hepatobiliary disorders			
Ocular icterus			
subjects affected / exposed	9 / 92 (9.78%)	6 / 88 (6.82%)	8 / 91 (8.79%)
occurrences (all)	15	7	14
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	6 / 92 (6.52%)	8 / 88 (9.09%)	10 / 91 (10.99%)
occurrences (all)	7	10	11
Dyspnoea			
subjects affected / exposed	5 / 92 (5.43%)	2 / 88 (2.27%)	4 / 91 (4.40%)
occurrences (all)	5	2	6
Oropharyngeal pain			
subjects affected / exposed	1 / 92 (1.09%)	7 / 88 (7.95%)	1 / 91 (1.10%)
occurrences (all)	1	9	1
Skin and subcutaneous tissue disorders			

Pruritus			
subjects affected / exposed	5 / 92 (5.43%)	4 / 88 (4.55%)	3 / 91 (3.30%)
occurrences (all)	8	4	6
Rash			
subjects affected / exposed	5 / 92 (5.43%)	6 / 88 (6.82%)	8 / 91 (8.79%)
occurrences (all)	5	9	8
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	14 / 92 (15.22%)	18 / 88 (20.45%)	13 / 91 (14.29%)
occurrences (all)	24	33	17
Back pain			
subjects affected / exposed	12 / 92 (13.04%)	15 / 88 (17.05%)	12 / 91 (13.19%)
occurrences (all)	25	17	16
Bone pain			
subjects affected / exposed	1 / 92 (1.09%)	5 / 88 (5.68%)	8 / 91 (8.79%)
occurrences (all)	5	9	22
Musculoskeletal chest pain			
subjects affected / exposed	0 / 92 (0.00%)	2 / 88 (2.27%)	5 / 91 (5.49%)
occurrences (all)	0	3	5
Musculoskeletal pain			
subjects affected / exposed	4 / 92 (4.35%)	6 / 88 (6.82%)	4 / 91 (4.40%)
occurrences (all)	4	6	4
Pain in extremity			
subjects affected / exposed	20 / 92 (21.74%)	12 / 88 (13.64%)	19 / 91 (20.88%)
occurrences (all)	33	19	22
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	6 / 92 (6.52%)	2 / 88 (2.27%)	3 / 91 (3.30%)
occurrences (all)	6	2	5
Influenza			
subjects affected / exposed	4 / 92 (4.35%)	3 / 88 (3.41%)	5 / 91 (5.49%)
occurrences (all)	5	3	6
Malaria			
subjects affected / exposed	2 / 92 (2.17%)	5 / 88 (5.68%)	3 / 91 (3.30%)
occurrences (all)	5	8	6
Tonsillitis			

subjects affected / exposed	3 / 92 (3.26%)	5 / 88 (5.68%)	8 / 91 (8.79%)
occurrences (all)	5	7	10
Upper respiratory tract infection			
subjects affected / exposed	22 / 92 (23.91%)	12 / 88 (13.64%)	13 / 91 (14.29%)
occurrences (all)	26	13	18
Urinary tract infection			
subjects affected / exposed	5 / 92 (5.43%)	9 / 88 (10.23%)	13 / 91 (14.29%)
occurrences (all)	8	10	15
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	6 / 92 (6.52%)	2 / 88 (2.27%)	0 / 91 (0.00%)
occurrences (all)	6	2	0
Hypokalaemia			
subjects affected / exposed	3 / 92 (3.26%)	2 / 88 (2.27%)	5 / 91 (5.49%)
occurrences (all)	3	4	5

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 November 2016	Herein is a summary of the major changes made to the original protocol, dated 19 October 2016, and reflected in this Amendment 1, dated 09 November 2016: 1. Inclusion and Exclusion Criteria relevant to vaso-occlusive crisis (VOC) have been revised/clarified. 2. Certain laboratory tests results may suggest the treatment assignment; clarification has been made that these results may be redacted to the Investigator and monitored by the DSMB. 3. Study endpoints relevant to vaso-occlusive crisis (VOC) have been revised/clarified. 4. Additional instructions/clarifications have been included in the Schedule of Assessments.
19 January 2017	Herein is a summary of the major changes made to the Amendment 1 of this protocol, dated 09 November 2016 and reflected in this Amendment 2, dated 19 January 2017: 1. The duration of the study was clarified 2. The rationale for the placebo comparator arm was clarified 3. The unblinding language for medical need was revised to clarify that the investigator has authority to unblind for medical necessity
18 August 2017	Herein is a summary of the major changes made to the Amendment 2 of this protocol, dated 19 January 2017, and reflected in this Amendment 2.1, dated 18 August 2017: 1. Inclusion of Section Heading 1.1.1: Available Treatment for Patients with SCD: 2. Inclusion of Section 5.13: Imaging 3. Revision of Exclusion Criteria Number 8
21 September 2017	This protocol has been amended to address typos, provide updates regarding the development of GBT440, and to provide clarification and additional information/guidance. This amendment also includes changes to the design/operational aspects of the trial.
03 January 2019	This protocol has been amended to address changes to planned analyses, to provide updates regarding the development of voxelotor, and to provide clarification and additional information/guidance.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Group 3 was not enrolled, GBT submitted an NDA to US FDA under subpart H for voxelotor based on data collect from subjects in Groups 1 and 2 of this study.

Notes: