Clinical trial results:
A Phase 2, Open Label, Multiple Dose Escalation Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Voxelotor in Patients with Sickle Cell Disease

Summary

EudraCT number	2019-001838-34
Trial protocol	GB
Global end of trial date	08 June 2021

Results information

Result version number	v1 (current)
This version publication date	03 June 2022
First version publication date	03 June 2022
Summary attachment (see zip file)	GBT400-029_Clinical Study Report (GBT440-029_Clinical Study Report_Report Body_14Feb2022.pdf)

Trial information

Trial identification

Sponsor protocol code	GBT440-029

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04247594
WHO universal trial number (UTN)	-
Other trial identifiers	IND number: 121,691

Notes:

Sponsors

Sponsor organisation name	Global Blood Therapeutics, Inc.
Sponsor organisation address	181 Oyster Point Blvd, South San Francisco, California, United States, 94080
Public contact	Eleanor Lisbon, Global Blood Therapeutics, Inc., 001 650822 8731, elisbon@gbt.com
Scientific contact	Eleanor Lisbon, Global Blood Therapeutics, Inc., 001 650822 8731, elisbon@gbt.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
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	14 July 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	08 June 2021
Global end of trial reached?	Yes
Global end of trial date	08 June 2021
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To evaluate the tolerability and safety of voxelotor at daily doses of >1500 mg (2000 mg to 3000 mg) in participants with sickle cell disease (SCD)

Protection of trial subjects:

The Investigator informed, and obtained approval from, the Independent Ethics Committee (IEC)/Institutional Review Board (IRB) for the conduct of the study at named sites, for the protocol, the subject informed consent form (ICF), and any other written information that was provided to the subjects and any advertisements that were used. Proposed amendments to the protocol and documents were discussed with the Sponsor and contract research organization (CRO), and then submitted to the IEC/IRB for approval as well as submitted to regulatory authorities for approval prior to implementation.

The study was conducted according to the protocol; guidelines established by International Council for Harmonisation (ICH) for Good Clinical Practice (GCP) in clinical studies; United States (US) regulations (21 CFR Parts 50, 54, 56, and 312); and country-specific requirements, as applicable.

Each individual was provided with oral and written information describing the nature, purpose and duration of the study, participation/termination conditions, and risks and benefits. Prior to initiation of any study-related procedures, subjects signed and dated the ICF to participate in the study.

Background therapy:

None

Evidence for comparator:

None

Actual start date of recruitment	29 November 2019
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 Kingdom: 6
Worldwide total number of subjects	6
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	6
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study enrolled male and female patients aged 18 to <60 years inclusive who fulfilled all the inclusion criteria for study enrollment as per Section 4.1 of the GBT440-029 Study Protocol.

Pre-assignment

Screening details:

All patients completed the following study procedures prior to a confirmation of eligibility: Signed Informed Consent Form, Review inclusion/exclusion criteria, Medication and Medical History, Height/Weight/ BMI, Vital signs, ECG (12-lead) in triplicate, Physical examination, Serum pregnancy test (females of child-bearing potential only) and so on.

Pre-assignment period milestones[1][2]

Number of subjects started	9[3]
Intermediate milestone: Number of subjects	Signed Informed Consent: 9
Intermediate milestone: Number of subjects	Review Inclusion/exclusion criteria: 6
Intermediate milestone: Number of subjects	Medication and medical history: 6
Intermediate milestone: Number of subjects	Height/Weight/BMI: 6
Intermediate milestone: Number of subjects	Vital Signs: 6
Intermediate milestone: Number of subjects	ECG (12-lead) in triplicate: 6
Intermediate milestone: Number of subjects	Physical Examination: 6
Intermediate milestone: Number of subjects	Serum pregnancy test (females only): 3
Intermediate milestone: Number of subjects	Coagulation panel: 6
Intermediate milestone: Number of subjects	Serology panel (PT, PTT, INR): 6
Intermediate milestone: Number of subjects	Blood for hematology and chemistry: 6
Intermediate milestone: Number of subjects	Hemoglobin genotype testing: 6
Intermediate milestone: Number of subjects	Fetal hemoglobin: 6
Intermediate milestone: Number of subjects	Urinalysis: 6
Intermediate milestone: Number of subjects	Concomitant medications: 6
Intermediate milestone: Number of subjects	Adverse events: 6
Number of subjects completed	6

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Did not meet eligibility criteria: 3

Notes:

[1] - The number of subjects at the milestone is less than the number that completed the pre-assignment period. It is expected the number of subjects at the milestones will be greater than, or equal to the number that completed the pre-assignment period.

Justification: A total of 9 subjects were screened for inclusion in the study prior to study termination; of these, 3 subjects did not meet eligibility criteria

[2] - The number of subjects at the milestone exceeds the number at the preceding milestone. It is

expected the number of subjects at each milestone will be less than, or equal to the number at the preceding milestone in the pre-assignment period.
Justification: A total of 9 subjects were screened for inclusion in the study prior to study termination; of these, 3 subjects did not meet eligibility criteria
[3] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: A total of 9 subjects were screened for inclusion in the study prior to study termination; of these, 3 subjects did not meet eligibility criteria

Period 1

Period 1 title	Treatment (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Treatment

Arm description:

Treatment Period (Dose Escalation): Periods 1-4 of voxelotor administration at progressively higher cumulative daily dose levels from 1500 mg until either an MTD or 3000 mg cumulative daily dose was reached, whichever occurred first

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

Dosage and administration details:

Voxelotor was supplied as 500 mg tablets. Subjects received voxelotor tablets administered orally, once daily or twice daily. Study subjects were to undergo up to four periods of voxelotor administration at progressively higher cumulative daily dose levels from 1500 mg until either an MTD or 3000 mg cumulative daily dose was reached, whichever occurred first. The four periods were as follows:
• Period 1: 1500 mg per day: 1500 mg once daily (3 × 500 mg tablets) for 3 weeks (± 3 days)
• Period 2: 2000 mg per day: 1000 mg (2 × 500 mg) twice daily for 3 weeks (± 3 days)
• Period 3: 2500 mg per day: 1500 mg (3 × 500 mg) in the morning and 1000 mg (2 × 500 mg) in the evening daily for 3 weeks (± 3 days)
• Period 4: 3000 mg per day: 1500 mg (3 × 500 mg) twice daily for 3 weeks (± 3 days)

Number of subjects in period 1	Treatment
Started	6
Review Inclusion/Exclusion criteria	6
Medication and medical history	6
Height/weight/BMI	6
Vital Signs	6
ECG (12-lead) in triplicate	6
Physical examination	6
Urine pregnancy test (females only)	3
Blood for hematology and chemistry	6
Erythropoietin	6

RBC deformability, dense cells	6
Hemoximetry (P50 and P20)	6
Study drug administration	6
Blood for PK assessment	6
CGI-C and PGI-C	6
Concomitant medications	6
Adverse events	6
Completed	2
Not completed	4
Consent withdrawn by subject	4

Baseline characteristics

Reporting groups	
Reporting group title	Treatment
Reporting group description:	
Subjects treated with at least one dose of Voxelotor	

Reporting group values	Treatment	Total	
Number of subjects	6	6	
Age categorical Units: Subjects			
Adults (18-64 years)	6	6	
Age continuous Units: years			
median	32		
full range (min-max)	27 to 36	-	
Gender categorical Units: Subjects			
Female	3	3	
Male	3	3	
Race Units: Subjects			
Black or African American	6	6	
Ethnicity Units: Subjects			
Not Hispanic or Latino	6	6	
Weight			
Weight of subjects			
Units: kg			
median	66.45		
full range (min-max)	47 to 74.9	-	
Height Units: cm			
median	171		
full range (min-max)	163 to 190	-	
BMI Units: kg/m3			
median	22		
full range (min-max)	18 to 28	-	

Subject analysis sets	
Subject analysis set title	Safety Population
Subject analysis set type	Full analysis
Subject analysis set description:	
Subjects treated with at least one dose of voxelotor	

Reporting group values	Safety Population		
Number of subjects	6		
Age categorical Units: Subjects			
Adults (18-64 years)	6		
Age continuous Units: years median full range (min-max)	 32 27 to 36		
Gender categorical Units: Subjects			
Female Male	3 3		
Race Units: Subjects			
Black or African American	6		
Ethnicity Units: Subjects			
Not Hispanic or Latino	6		
Weight			
Weight of subjects			
Units: kg median full range (min-max)	 66.45 47 to 74.9		
Height Units: cm median full range (min-max)	 171 163 to 190		
BMI Units: kg/m3 median full range (min-max)	 22 18 to 28		

End points

End points reporting groups

Reporting group title	Treatment
Reporting group description:	
Treatment Period (Dose Escalation): Periods 1-4 of voxelotor administration at progressively higher cumulative daily dose levels from 1500 mg until either an MTD or 3000 mg cumulative daily dose was reached, whichever occurred first	
Subject analysis set title	Safety Population
Subject analysis set type	Full analysis
Subject analysis set description:	
Subjects treated with at least one dose of voxelotor	

Primary: Treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs)

End point title	Treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs)[1]
End point description:	
Sickle cell disease (SCD)-related Treatment-emergent Adverse Events—Safety Population taken 1500mg daily dose of Voxelotor	
End point type	Primary
End point timeframe:	
Any new or worsening events which occurs after first dose or through 28 days after study drug discontinuation	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical testing was ever planned for this study as per the study protocol

End point values	Treatment	Safety Population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	6	6		
Units: Number of subjects				
Number of subjects with at least one TEAE	5	5		
Number of subjects with at least one TEAE ≥ Grade	3	3		
Number of subjects with at least one SAE	3	3		
Number of SAEs	4	4		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All adverse events were recorded from the time the study participant signs the informed consent form (ICF) until 28 days after the last dose of study drug.

Adverse event reporting additional description:

Adverse events were coded using the Medical Dictionary for Regulatory Activities Dictionary (MedDRA) version 24.0 and were categorized by system organ class (SOC) and preferred term (PT). National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03 was used to determine the grade.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24

Reporting groups

Reporting group title	1500mg

Reporting group description:

Adverse events occurring in subjects treated with voxelotor 1500 mg once daily in Period 1

Reporting group title	2000mg

Reporting group description:

Adverse events occurring in subjects treated with voxelotor cumulative daily dose of 2000 mg in Period 2

Reporting group title	2500mg

Reporting group description:

Adverse events occurring in subjects treated with voxelotor cumulative daily dose of 2500 mg in Period 3

Reporting group title	3000mg

Reporting group description:

Adverse events occurring in subjects treated with voxelotor cumulative daily dose of 3000 mg in Period 4

Serious adverse events	1500mg	2000mg	2500mg
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 6 (100.00%)	4 / 4 (100.00%)	3 / 3 (100.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Blood and lymphatic system disorders			
Sickle cell anaemia with crisis			
subjects affected / exposed	5 / 6 (83.33%)	1 / 4 (25.00%)	1 / 3 (33.33%)
occurrences causally related to treatment / all	0 / 5	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Priapism			

subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	0 / 3 (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

Serious adverse events	3000mg		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 1 (100.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Blood and lymphatic system disorders			
Sickle cell anaemia with crisis			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Priapism			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	1500mg	2000mg	2500mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 6 (100.00%)	4 / 4 (100.00%)	3 / 3 (100.00%)
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	2 / 3 (66.67%)
occurrences (all)	1	0	2
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	2 / 3 (66.67%)
occurrences (all)	0	0	2
Nervous system disorders			
Headache			

subjects affected / exposed	1 / 6 (16.67%)	2 / 4 (50.00%)	1 / 3 (33.33%)
occurrences (all)	1	2	1
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 6 (33.33%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	2	0	0
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	2 / 6 (33.33%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	2	0	0
Constipation			
subjects affected / exposed	2 / 6 (33.33%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	2	0	0
Diarrhoea			
subjects affected / exposed	4 / 6 (66.67%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	4	0	0
Dry mouth			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	1 / 3 (33.33%)
occurrences (all)	1	0	1
Nausea			
subjects affected / exposed	2 / 6 (33.33%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	2	0	0
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Pruritus allergic			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	0 / 6 (0.00%)	1 / 4 (25.00%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Back pain			
subjects affected / exposed	2 / 6 (33.33%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	2	0	0

Infections and infestations			
Urinary tract infection			
subjects affected / exposed	1 / 6 (16.67%)	1 / 4 (25.00%)	0 / 3 (0.00%)
occurrences (all)	1	1	0

Non-serious adverse events	3000mg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 1 (100.00%)		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Constipation			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Diarrhoea			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Dry mouth			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Nausea			

subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0		
Skin and subcutaneous tissue disorders Dry skin subjects affected / exposed occurrences (all) Pruritus allergic subjects affected / exposed occurrences (all)	 0 / 1 (0.00%) 0 0 / 1 (0.00%) 0		
Musculoskeletal and connective tissue disorders Pain in extremity subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all)	 1 / 1 (100.00%) 1 0 / 1 (0.00%) 0		
Infections and infestations Urinary tract infection subjects affected / exposed occurrences (all)	 0 / 1 (0.00%) 0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 September 2019	Change 1.: - Excluded patients who require strong inducers of CYP2B6, CYP2C9, CYP2C19, and CYP3A4/CYP3A5, and patients who use astemizole, cisapride, or terfenadine Rationale: - To align with the Investigator Brochure list of contraindicated medications Change 2.: Excluded patients who use strong inhibitors of CYP3A4 Rationale: - Since GBT440-029 study will be evaluating higher doses that were not previously tested; the concomitant use of strong CYP3A4 inhibitors was prohibited as a precautionary measure.
05 October 2020	The purpose of this amendment was as follows: 1. The study design was streamlined to reduce the burden on investigator sites as directed by the Health Authority (MHRA): a. A reduction in the duration of treatment for participants in Cohort A – the duration of Periods 1 and 4 (originally Cohort A, Periods 1 and 4) was reduced from 9 weeks to 3 weeks. Each period now represents a 3week safety evaluation period/dose-limiting toxicity window followed by a 24-week observation period at the maximum tolerated dose or 3000 mg daily, followed by a 28day safety follow-up period. b. Multi-dose PK analysis (serial PK sampling) was changed to population PK approach (sparse sampling) c. No overnight stay in the Research unit d. Removal of Cohort B and associated evaluations, including magnetic resonance imaging (MRI) and cardiopulmonary exercise testing (CPET), from the study design e. Streamline of ECG recordings – ECG recordings was aligned with PK samples to allow for a combined evaluation of overall safety and QTc analysis. In addition, exclusion criteria based on ECG intervals were added and analyses of ECG intervals were specified. 2. Protocol Amendment 2 also introduced a 24-week observational period into the study design. Participants will enter this longer observation period after 3 weeks of voxelotor at the maximum tolerated dose (MTD) or 3000mg daily, followed by a 28 day safety follow-up period. The longer observational period coincides with the 24-week duration of treatment in the pivotal trial for voxelotor in order to establish efficacy and safety for a similar period of time.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date

08 June 2021	Due to events arising from COVID-19 Pandemic and the challenges to recruitment, the Sponsor took the decision to halt further recruitment from February 2021, at that time three patients were ongoing study treatment. Following consultation with the patient's primary consultant and the Principal Investigator in collaboration with the Sponsor, it was determined to permit ongoing patients to continue their treatment with the study drug per the protocol due to clinical benefit. It was declared that the date of the last subject last visit occurred on 08 June 2021.	-

Notes:

Limitations and caveats

None reported