



## 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<sup>[1][2]</sup>

|  |  |
|--|--|
| Number of subjects started                 | 9 <sup>[3]</sup>                       |
| 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

|                  |           |
|------------------|-----------|
| <b>Arm title</b> | 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/m <sup>3</sup>  |            |       |  |
| 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

|   |                     |  |  |
|---|---------------------|--|--|
| <b>Reporting group values</b>                                     | Safety Population   |  |  |
| Number of subjects  | 6                   |  |  |
| Age categorical<br>Units: Subjects                                |                     |  |  |
| Adults (18-64 years)  | 6                   |  |  |
| Age continuous<br>Units: years<br>median<br>full range (min-max)  | 32<br>27 to 36      |  |  |
| Gender categorical<br>Units: Subjects                             |                     |  |  |
| Female  | 3                   |  |  |
| Male  | 3                   |  |  |
| Race<br>Units: Subjects   |                     |  |  |
| Black or African American   | 6                   |  |  |
| Ethnicity<br>Units: Subjects                                      |                     |  |  |
| Not Hispanic or Latino  | 6                   |  |  |
| Weight  |                     |  |  |
| Weight of subjects  |                     |  |  |
| Units: kg<br>median<br>full range (min-max)                       | 66.45<br>47 to 74.9 |  |  |
| Height<br>Units: cm<br>median<br>full range (min-max)             | 171<br>163 to 190   |  |  |
| BMI<br>Units: kg/m <sup>3</sup><br>median<br>full range (min-max) | 22<br>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) <sup>[1]</sup> |
| 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         |

|   |                 |  |  |
|---|-----------------|--|--|
| <b>Serious adverse events</b>                     | 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 %

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

|   |                 |  |  |
|---|-----------------|--|--|
| <b>Non-serious adverse events</b>                     | 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<br>occurrences (all)  | 0 / 1 (0.00%)<br>0                             |  |  |
| Skin and subcutaneous tissue disorders<br>Dry skin<br>subjects affected / exposed<br>occurrences (all)<br><br>Pruritus allergic<br>subjects affected / exposed<br>occurrences (all)           | 0 / 1 (0.00%)<br>0<br><br>0 / 1 (0.00%)<br>0   |  |  |
| Musculoskeletal and connective tissue disorders<br>Pain in extremity<br>subjects affected / exposed<br>occurrences (all)<br><br>Back pain<br>subjects affected / exposed<br>occurrences (all) | 1 / 1 (100.00%)<br>1<br><br>0 / 1 (0.00%)<br>0 |  |  |
| Infections and infestations<br>Urinary tract infection<br>subjects affected / exposed<br>occurrences (all)  | 0 / 1 (0.00%)<br>0                             |  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date              | Amendment  |
|-------------------|--|
| 13 September 2019 | <p>Change 1.:</p> <ul style="list-style-type: none"><li>- Excluded patients who require strong inducers of CYP2B6, CYP2C9, CYP2C19, and CYP3A4/CYP3A5, and patients who use astemizole, cisapride, or terfenadine</li></ul> <p>Rationale:</p> <ul style="list-style-type: none"><li>- To align with the Investigator Brochure list of contraindicated medications</li></ul> <p>Change 2.:</p> <p>Excluded patients who use strong inhibitors of CYP3A4</p> <p>Rationale:</p> <ul style="list-style-type: none"><li>- 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.</li></ul>  |
| 05 October 2020   | <p>The purpose of this amendment was as follows:</p> <ol style="list-style-type: none"><li>1. The study design was streamlined to reduce the burden on investigator sites as directed by the Health Authority (MHRA):<ol style="list-style-type: none"><li>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.</li><li>b. Multi-dose PK analysis (serial PK sampling) was changed to population PK approach (sparse sampling)</li><li>c. No overnight stay in the Research unit</li><li>d. Removal of Cohort B and associated evaluations, including magnetic resonance imaging (MRI) and cardiopulmonary exercise testing (CPET), from the study design</li><li>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.</li></ol></li><li>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.</li></ol> |

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