# 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:<br>1. Inclusion and Exclusion Criteria relevant to vaso-occlusive crisis (VOC) have been<br>revised/clarified.<br>2. Certain laboratory tests results may suggest the treatment assignment; clarification<br>has been made that these results may be redacted to the Investigator and monitored<br>by the DSMB.<br>3. Study endpoints relevant to vaso-occlusive crisis (VOC) have been revised/clarified.<br>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<br>November 2016 and reflected in this Amendment 2, dated 19 January 2017:<br>1. The duration of the study was clarified<br>2. The rationale for the placebo comparator arm was clarified<br>3. The unblinding language for medical need was revised to clarify that the investigator<br>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,<br>dated 19 January 2017, and reflected in this Amendment 2.1, dated 18 August 2017:<br>1. Inclusion of Section Heading 1.1.1: Available Treatment for Patients with SCD:<br>2. Inclusion of Section 5.13: Imaging<br>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.<br>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: