



Clinical trial results:

A randomized, double-blind, placebo-controlled, dose-ranging, study to evaluate the efficacy, safety and tolerability of single doses of BCX7353 as an acute attack treatment in subjects with hereditary angioedema

Summary

| | |
|--------------------------|-------------------|
| EudraCT number | 2016-001424-55 |
| Trial protocol | DE DK GB AT HU PL |
| Global end of trial date | 03 January 2019 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v1 (current) |
| This version publication date | 07 November 2020 |
| First version publication date | 07 November 2020 |

Trial information

Trial identification

| | |
|-----------------------|-------------|
| Sponsor protocol code | BCX7353-202 |
|-----------------------|-------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03240133 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | BioCryst Pharmaceuticals Inc. |
| Sponsor organisation address | 4505 Emperor Blvd., Durham, United States, NC 27703 |
| Public contact | Study Director, BioCryst Pharmaceuticals Inc., +1 919-859-1302, clinicaltrials@biocryst.com |
| Scientific contact | Study Director, BioCryst Pharmaceuticals Inc., +1 919-859-1302, clinicaltrials@biocryst.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 | Interim |
| Date of interim/final analysis | 12 November 2019 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 03 January 2019 |
| Global end of trial reached? | Yes |
| Global end of trial date | 03 January 2019 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of single oral doses of berotralstat in treating acute attacks in subjects with hereditary angioedema

Protection of trial subjects:

This trial was conducted in compliance with International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines for conducting, recording, and reporting trials, and in accordance with the Declaration of Helsinki. The informed consent form (ICF), protocol and amendments for this trial were submitted to and approved by an appropriate Independent Ethics Committee (IEC). Routine monitoring was performed to verify that rights and well-being of subjects were protected. Emergency equipment and medications were available within the clinical unit as per current standard procedures. Any medication considered necessary for the subject's safety and well-being was given at the discretion of the Investigator. A signed informed consent form (ICF) was obtained from each subject prior to performing any study-related procedures. The informed consent process took place under conditions where the subject had adequate time to consider the risks and benefits associated with his/her participation in the study. The Investigator explained to potential subjects the aims, methods, reasonably anticipated benefits, and potential hazards of the trial and any discomfort it may entail.

Background therapy: -

Evidence for comparator: -

| | |
|---|--------------|
| Actual start date of recruitment | 11 July 2017 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|---|
| Country: Number of subjects enrolled | Italy: 9 |
| Country: Number of subjects enrolled | Macedonia, the former Yugoslav Republic of: 2 |
| Country: Number of subjects enrolled | Israel: 6 |
| Country: Number of subjects enrolled | Romania: 4 |
| Country: Number of subjects enrolled | Switzerland: 2 |
| Country: Number of subjects enrolled | Poland: 6 |
| Country: Number of subjects enrolled | United Kingdom: 13 |
| Country: Number of subjects enrolled | Austria: 1 |
| Country: Number of subjects enrolled | Denmark: 3 |
| Country: Number of subjects enrolled | France: 1 |
| Country: Number of subjects enrolled | Germany: 9 |
| Country: Number of subjects enrolled | Hungary: 2 |
| Worldwide total number of subjects | 58 |
| EEA total number of subjects | 48 |

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) | 0 |
| Adults (18-64 years) | 57 |
| From 65 to 84 years | 1 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

HAE subjects attended a Screening Visit up to 35 days before the baseline visit, for assessment of eligibility to participate in the study.

Period 1

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

Blinding implementation details:

Study drug assignment was blinded to the investigator and clinical site personnel, study subjects, contract research organization staff, and sponsor employee(s) with the exception of those responsible for managing clinical supplies

Arms

| | |
|------------------------------|---|
| Are arms mutually exclusive? | No |
| Arm title | Part 1: Berotralstat (750 mg) Treated HAE attacks |

Arm description:

Subjects randomized 1:1:1 to treat 3 HAE attacks with 1 of 3 treatment sequences:

Sequence 1: berotralstat - placebo - berotralstat

Sequence 2: placebo - berotralstat - berotralstat

Sequence 3: berotralstat - berotralstat - placebo

| | |
|--|--------------------------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | berotralstat |
| Investigational medicinal product code | |
| Other name | BCX7353 |
| Pharmaceutical forms | Powder and solvent for oral solution |
| Routes of administration | Oral use |

Dosage and administration details:

Following investigator's approval that subject's HAE attack was suitable for treatment with IMP, subject reconstituted berotralstat powder with liquid vehicle before oral administration.

| | |
|------------------|---|
| Arm title | Part 2: Berotralstat (500 mg) Treated HAE attacks |
|------------------|---|

Arm description:

Subjects randomized 1:1:1 to treat 3 HAE attacks with 1 of 3 treatment sequences:

Sequence 1: berotralstat - placebo - berotralstat

Sequence 2: placebo - berotralstat - berotralstat

Sequence 3: berotralstat - berotralstat - placebo

| | |
|--|--------------------------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | berotralstat |
| Investigational medicinal product code | |
| Other name | BCX7353 |
| Pharmaceutical forms | Powder and solvent for oral solution |
| Routes of administration | Oral use |

Dosage and administration details:

Following investigator's approval that subject's HAE attack was suitable for treatment with IMP, subject reconstituted berotralstat powder with liquid vehicle before oral administration.

| | |
|------------------|---|
| Arm title | Part 3: Berotralstat (250 mg) Treated HAE attacks |
|------------------|---|

Arm description:

Subjects randomized 1:1:1 to treat 3 HAE attacks with 1 of 3 treatment sequences:

Sequence 1: berotralstat - placebo - berotralstat

Sequence 2: placebo - berotralstat - berotralstat

Sequence 3: berotralstat - berotralstat - placebo

| | |
|--|--------------------------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | berotralstat |
| Investigational medicinal product code | |
| Other name | BCX7353 |
| Pharmaceutical forms | Powder and solvent for oral solution |
| Routes of administration | Oral use |

Dosage and administration details:

Following investigator's approval that subject's HAE attack was suitable for treatment with IMP, subject reconstituted berotralstat powder with liquid vehicle before oral administration.

| | |
|------------------|-------------------------------------|
| Arm title | Part 1: Placebo Treated HAE attacks |
|------------------|-------------------------------------|

Arm description:

Subjects randomized 1:1:1 to treat 3 HAE attacks with 1 of 3 treatment sequences:

Sequence 1: berotralstat - placebo - berotralstat

Sequence 2: placebo - berotralstat - berotralstat

Sequence 3: berotralstat - berotralstat - placebo

| | |
|--|--------------------------------------|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder and solvent for oral solution |
| Routes of administration | Oral use |

Dosage and administration details:

Following investigator's approval that subject's HAE attack was suitable for treatment with IMP, subject reconstituted placebo powder with liquid vehicle before oral administration.

| | |
|------------------|-------------------------------------|
| Arm title | Part 2: Placebo Treated HAE attacks |
|------------------|-------------------------------------|

Arm description:

Subjects randomized 1:1:1 to treat 3 HAE attacks with 1 of 3 treatment sequences:

Sequence 1: berotralstat - placebo - berotralstat

Sequence 2: placebo - berotralstat - berotralstat

Sequence 3: berotralstat - berotralstat - placebo

| | |
|--|--------------------------------------|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder and solvent for oral solution |
| Routes of administration | Oral use |

Dosage and administration details:

Following investigator's approval that subject's HAE attack was suitable for treatment with IMP, subject reconstituted placebo powder with liquid vehicle before oral administration.

| | |
|------------------|-------------------------------------|
| Arm title | Part 3: Placebo Treated HAE attacks |
|------------------|-------------------------------------|

Arm description:

Subjects randomized 1:1:1 to treat 3 HAE attacks with 1 of 3 treatment sequences:

Sequence 1: berotralstat - placebo - berotralstat

Sequence 2: placebo - berotralstat - berotralstat

Sequence 3: berotralstat - berotralstat - placebo

| | |
|----------|---------|
| Arm type | Placebo |
|----------|---------|

| | |
|--|--------------------------------------|
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder and solvent for oral solution |
| Routes of administration | Oral use |

Dosage and administration details:

Following investigator's approval that subject's HAE attack was suitable for treatment with IMP, subject reconstituted placebo powder with liquid vehicle before oral administration.

| Number of subjects in period 1 | Part 1: Berotralstat (750 mg) Treated HAE attacks | Part 2: Berotralstat (500 mg) Treated HAE attacks | Part 3: Berotralstat (250 mg) Treated HAE attacks |
|---------------------------------------|---|---|---|
| Started | 33 | 14 | 11 |
| Completed | 33 | 14 | 11 |

| Number of subjects in period 1 | Part 1: Placebo Treated HAE attacks | Part 2: Placebo Treated HAE attacks | Part 3: Placebo Treated HAE attacks |
|---------------------------------------|-------------------------------------|-------------------------------------|-------------------------------------|
| Started | 31 | 11 | 11 |
| Completed | 31 | 11 | 11 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|---------------|
| Reporting group title | Overall Study |
|-----------------------|---------------|

Reporting group description: -

| Reporting group values | Overall Study | Total | |
|------------------------|---------------|-------|--|
| Number of subjects | 58 | 58 | |
| Age categorical | | | |
| Units: Subjects | | | |
| Adults (18-64 years) | 57 | 57 | |
| From 65-84 years | 1 | 1 | |
| Age continuous | | | |
| Units: years | | | |
| geometric mean | 41.6 | | |
| standard deviation | ± 12.0 | - | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 35 | 35 | |
| Male | 23 | 23 | |

End points

End points reporting groups

| | |
|---|---|
| Reporting group title | Part 1: Berotralstat (750 mg) Treated HAE attacks |
| Reporting group description: Subjects randomized 1:1:1 to treat 3 HAE attacks with 1 of 3 treatment sequences: Sequence 1: berotralstat - placebo - berotralstat Sequence 2: placebo - berotralstat - berotralstat Sequence 3: berotralstat - berotralstat - placebo | |
| Reporting group title | Part 2: Berotralstat (500 mg) Treated HAE attacks |
| Reporting group description: Subjects randomized 1:1:1 to treat 3 HAE attacks with 1 of 3 treatment sequences: Sequence 1: berotralstat - placebo - berotralstat Sequence 2: placebo - berotralstat - berotralstat Sequence 3: berotralstat - berotralstat - placebo | |
| Reporting group title | Part 3: Berotralstat (250 mg) Treated HAE attacks |
| Reporting group description: Subjects randomized 1:1:1 to treat 3 HAE attacks with 1 of 3 treatment sequences: Sequence 1: berotralstat - placebo - berotralstat Sequence 2: placebo - berotralstat - berotralstat Sequence 3: berotralstat - berotralstat - placebo | |
| Reporting group title | Part 1: Placebo Treated HAE attacks |
| Reporting group description: Subjects randomized 1:1:1 to treat 3 HAE attacks with 1 of 3 treatment sequences: Sequence 1: berotralstat - placebo - berotralstat Sequence 2: placebo - berotralstat - berotralstat Sequence 3: berotralstat - berotralstat - placebo | |
| Reporting group title | Part 2: Placebo Treated HAE attacks |
| Reporting group description: Subjects randomized 1:1:1 to treat 3 HAE attacks with 1 of 3 treatment sequences: Sequence 1: berotralstat - placebo - berotralstat Sequence 2: placebo - berotralstat - berotralstat Sequence 3: berotralstat - berotralstat - placebo | |
| Reporting group title | Part 3: Placebo Treated HAE attacks |
| Reporting group description: Subjects randomized 1:1:1 to treat 3 HAE attacks with 1 of 3 treatment sequences: Sequence 1: berotralstat - placebo - berotralstat Sequence 2: placebo - berotralstat - berotralstat Sequence 3: berotralstat - berotralstat - placebo | |
| Subject analysis set title | Part 1: Berotralstat 750 mg - pre-dose |
| Subject analysis set type | Full analysis |
| Subject analysis set description: Subjects completed a 3-component VAS on a 100 mm scale for severity of abdominal pain, skin pain and skin swelling associated with the HAE attack immediately prior to study drug administration, then at 1, 2, 3, 4, approximately 8 & at 24 hours post-dose. The number of subjects in analysis set corresponds to number of HAE attacks treated with 750 mg berotralstat in part 1. | |
| Subject analysis set title | Part 1: Placebo - Pre-dose |
| Subject analysis set type | Full analysis |
| Subject analysis set description: Subjects completed a 3-component VAS on a 100 mm scale for severity of abdominal pain, skin pain and skin swelling associated with the HAE attack immediately prior to study drug administration, then at 1, 2, 3, 4, approximately 8 & at 24 hours post-dose. The number of subjects in analysis set corresponds to number of HAE attacks treated with placebo in part 1. | |
| Subject analysis set title | Part 1: Berotralstat 750 mg - 4hr post-dose |
| Subject analysis set type | Full analysis |
| Subject analysis set description: Subjects completed a 3-component VAS on a 100 mm scale for severity of abdominal pain, skin pain | |

and skin swelling associated with the HAE attack immediately prior to study drug administration, then at 1, 2, 3, 4, approximately 8 & at 24 hours post-dose. The number of subjects in analysis set corresponds to number of HAE attacks treated with 750 mg berotralstat in part 1.

| | |
|----------------------------|---------------------------------|
| Subject analysis set title | Part 1: Placebo - 4hr post-dose |
| Subject analysis set type | Full analysis |

Subject analysis set description:

Subjects completed a 3-component VAS on a 100 mm scale for severity of abdominal pain, skin pain and skin swelling associated with the HAE attack immediately prior to study drug administration, then at 1, 2, 3, 4, approximately 8 & at 24 hours post-dose. The number of subjects in analysis set corresponds to number of HAE attacks treated with placebo in part 1.

| | |
|----------------------------|--|
| Subject analysis set title | Part 2: Berotralstat 500 mg - pre-dose |
| Subject analysis set type | Full analysis |

Subject analysis set description:

Subjects completed a 3-component VAS on a 100 mm scale for severity of abdominal pain, skin pain and skin swelling associated with the HAE attack immediately prior to study drug administration, then at 1, 2, 3, 4, approximately 8 & at 24 hours post-dose. The number of subjects in analysis set corresponds to number of HAE attacks treated with 500 mg berotralstat in part 2

| | |
|----------------------------|----------------------------|
| Subject analysis set title | Part 2: Placebo - pre-dose |
| Subject analysis set type | Full analysis |

Subject analysis set description:

Subjects completed a 3-component VAS on a 100 mm scale for severity of abdominal pain, skin pain and skin swelling associated with the HAE attack immediately prior to study drug administration, then at 1, 2, 3, 4, approximately 8 & at 24 hours post-dose. The number of subjects in analysis set corresponds to number of HAE attacks treated with placebo in part 2.

| | |
|----------------------------|---|
| Subject analysis set title | Part 2: Berotralstat 500 mg - 4hr post-dose |
| Subject analysis set type | Full analysis |

Subject analysis set description:

Subjects completed a 3-component VAS on a 100 mm scale for severity of abdominal pain, skin pain and skin swelling associated with the HAE attack immediately prior to study drug administration, then at 1, 2, 3, 4, approximately 8 & at 24 hours post-dose. The number of subjects in analysis set corresponds to number of HAE attacks treated with 500 mg berotralstat in part 2

| | |
|----------------------------|---------------------------------|
| Subject analysis set title | Part 2: Placebo - 4hr post-dose |
| Subject analysis set type | Full analysis |

Subject analysis set description:

Subjects completed a 3-component VAS on a 100 mm scale for severity of abdominal pain, skin pain and skin swelling associated with the HAE attack immediately prior to study drug administration, then at 1, 2, 3, 4, approximately 8 & at 24 hours post-dose. The number of subjects in analysis set corresponds to number of HAE attacks treated with placebo in part 2.

| | |
|----------------------------|--|
| Subject analysis set title | Part 3: Berotralstat 250 mg - pre-dose |
| Subject analysis set type | Full analysis |

Subject analysis set description:

Subjects completed a 3-component VAS on a 100 mm scale for severity of abdominal pain, skin pain and skin swelling associated with the HAE attack immediately prior to study drug administration, then at 1, 2, 3, 4, approximately 8 & at 24 hours post-dose. The number of subjects in analysis set corresponds to number of HAE attacks treated with 250 mg berotralstat in part 3.

| | |
|----------------------------|----------------------------|
| Subject analysis set title | Part 3: Placebo - pre-dose |
| Subject analysis set type | Full analysis |

Subject analysis set description:

Subjects completed a 3-component VAS on a 100 mm scale for severity of abdominal pain, skin pain and skin swelling associated with the HAE attack immediately prior to study drug administration, then at 1, 2, 3, 4, approximately 8 & at 24 hours post-dose. The number of subjects in analysis set corresponds to number of HAE attacks treated with placebo in part 3.

| | |
|----------------------------|---|
| Subject analysis set title | Part 3: Berotralstat 250 mg - 4hr post-dose |
| Subject analysis set type | Full analysis |

Subject analysis set description:

Subjects completed a 3-component VAS on a 100 mm scale for severity of abdominal pain, skin pain and skin swelling associated with the HAE attack immediately prior to study drug administration, then at 1, 2, 3, 4, approximately 8 & at 24 hours post-dose. The number of subjects in analysis set corresponds to number of HAE attacks treated with 250 mg berotralstat in part 3.

| | |
|--|---|
| Subject analysis set title | Part 3: Placebo - 4hr post-dose |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| Subjects completed a 3-component VAS on a 100 mm scale for severity of abdominal pain, skin pain and skin swelling associated with the HAE attack immediately prior to study drug administration, then at 1, 2, 3, 4, approximately 8 & at 24 hours post-dose. The number of subjects in analysis set corresponds to number of HAE attacks treated with placebo in part 3. | |
| Primary: Composite VAS HAE Attack Symptom Severity | |
| End point title | Composite VAS HAE Attack Symptom Severity |
| End point description: | |
| End point type | Primary |
| End point timeframe: | |
| Mean composite VAS for HAE attack symptoms severity prior to IMP treatment and 4 hours post-dose | |

| End point values | Part 1: Berotralstat 750 mg - pre- dose | Part 1: Placebo - Pre-dose | Part 1: Berotralstat 750 mg - 4hr post-dose | Part 1: Placebo - 4hr post-dose |
|--------------------------------------|--|-------------------------------|--|------------------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 59 ^[1] | 28 | 59 ^[2] | 28 |
| Units: millimeter(s) | | | | |
| arithmetic mean (standard deviation) | 13.96 (± 9.84) | 15.04 (± 11.90) | 10.54 (± 11.39) | 18.42 (± 14.19) |

Notes:

[1] - 59 HAE attacks treated with IMP for 33 subjects

[2] - 59 HAE attacks treated with IMP for 33 subjects

| End point values | Part 2: Berotralstat 500 mg - pre- dose | Part 2: Placebo - pre-dose | Part 2: Berotralstat 500 mg - 4hr post-dose | Part 2: Placebo - 4hr post-dose |
|--------------------------------------|--|-------------------------------|--|------------------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 24 ^[3] | 9 | 24 ^[4] | 9 |
| Units: millimeter(s) | | | | |
| arithmetic mean (standard deviation) | 17.69 (± 15.25) | 13.48 (± 16.11) | 11.31 (± 15.75) | 9.26 (± 11.53) |

Notes:

[3] - 24 HAE attacks treated with IMP for 14 subjects

[4] - 24 HAE attacks treated with IMP for 14 subjects

| End point values | Part 3: Berotralstat 250 mg - pre- dose | Part 3: Placebo - pre-dose | Part 3: Berotralstat 250 mg - 4hr post-dose | Part 3: Placebo - 4hr post-dose |
|--------------------------------------|--|-------------------------------|--|------------------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 21 ^[5] | 11 | 21 ^[6] | 11 |
| Units: millimeter(s) | | | | |
| arithmetic mean (standard deviation) | 14.57 (± 11.78) | 11.33 (± 10.17) | 10.92 (± 10.31) | 9.21 (± 9.67) |

Notes:

[5] - 21 HAE attacks treated with IMP for 11 subjects

[6] - 21 HAE attacks treated with IMP for 11 subjects

Statistical analyses

| | |
|---|---|
| Statistical analysis title | VAS change at 4 hr - placebo vs 750mg berotralstat |
| Statistical analysis description: | |
| Comparisons were performed separately at each time point using a mixed effect linear model including treatment, period and sequence as fixed effects, subject within sequence as a random effect, and pre-dose 3-symptom composite VAS score as a covariate. Compared to baseline, VAS at 4 hours post-dose was significantly different for attacks treated with 750 mg berotralstat compared to placebo. | |
| Comparison groups | Part 1: Berotralstat 750 mg - pre-dose v Part 1: Placebo - Pre-dose v Part 1: Berotralstat 750 mg - 4hr post-dose v Part 1: Placebo - 4hr post-dose |
| Number of subjects included in analysis | 174 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[7] |
| P-value | = 0.0024 |
| Method | Mixed effect linear model |
| Parameter estimate | Difference in Least Square Means |
| Point estimate | -6.98 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -11.37 |
| upper limit | -2.6 |

Notes:

[7] - 'Subjects in analysis' refers to 'Treated HAE attacks in analysis'. Additionally, as analysis for each treated HAE attack was conducted pre-dose and 4 hours post-dose in a separate comparison group, each HAE attack is counted twice; i.e. 87 HAE attacks analysed pre-dose and 4 hours post dose.

| | |
|---|---|
| Statistical analysis title | VAS change at 4 hr - placebo vs 500mg berotralstat |
| Statistical analysis description: | |
| Comparisons were performed separately at each time point using a mixed effect linear model including treatment, period and sequence as fixed effects, subject within sequence as a random effect, and pre-dose 3-symptom composite VAS score as a covariate. Compared to baseline, VAS at 4 hours post-dose was not significantly different for attacks treated with 500 mg berotralstat compared to placebo. | |
| Comparison groups | Part 2: Berotralstat 500 mg - pre-dose v Part 2: Placebo - pre-dose v Part 2: Berotralstat 500 mg - 4hr post-dose v Part 2: Placebo - 4hr post-dose |
| Number of subjects included in analysis | 66 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[8] |
| P-value | = 0.6424 |
| Method | Mixed effect linear model |
| Parameter estimate | Difference in Least Square Means |
| Point estimate | -2.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -11.49 |
| upper limit | 7.29 |

Notes:

[8] - 'Subjects in analysis' refers to 'Treated HAE attacks in analysis'. Additionally, as analysis for each treated HAE attack was conducted pre-dose and 4 hours post-dose in a separate comparison group, each HAE attack is counted twice; i.e. 33 HAE attacks analysed pre-dose and 4 hours post dose.

| | |
|---|---|
| Statistical analysis title | VAS change at 4 hr - placebo vs 250mg berotralstat |
| Statistical analysis description: | |
| Comparisons were performed separately at each time point using a mixed effect linear model including treatment, period and sequence as fixed effects, subject within sequence as a random effect, and pre-dose 3-symptom composite VAS score as a covariate. Compared to baseline, VAS at 4 hours post-dose was not significantly different for attacks treated with 250 mg berotralstat compared to placebo. | |
| Comparison groups | Part 3: Placebo - pre-dose v Part 3: Berotralstat 250 mg - pre-dose v Part 3: Berotralstat 250 mg - 4hr post-dose v Part 3: Placebo - 4hr post-dose |
| Number of subjects included in analysis | 64 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[9] |
| P-value | = 0.8283 |
| Method | Mixed effect linear model |
| Parameter estimate | Difference in Least Square Means |
| Point estimate | 0.57 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -4.9 |
| upper limit | 6.03 |

Notes:

[9] - 'Subjects in analysis' refers to 'Treated HAE attacks in analysis'. Additionally, as analysis for each treated HAE attack was conducted pre-dose and 4 hours post-dose in a separate comparison group, each HAE attack is counted twice; i.e. 32 HAE attacks analysed pre-dose and 4 hours post dose.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events (AEs) collected from informed consent signature until 16 to 19 days after 3rd or final HAE attack treated with IMP. AEs were assigned to attack treated with placebo or berotralstat depending on IMP used most recently prior to AE onset.

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 19.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---|
| Reporting group title | Part 1: Berotralstat (750 mg) Treated HAE attacks |
|-----------------------|---|

Reporting group description:

Subjects randomized 1:1:1 to treat 3 HAE attacks with 1 of 3 treatment sequences:

Sequence 1: berotralstat - placebo - berotralstat

Sequence 2: placebo - berotralstat - berotralstat

Sequence 3: berotralstat - berotralstat - placebo

| | |
|-----------------------|---|
| Reporting group title | Part 2: Berotralstat (500 mg) Treated HAE attacks |
|-----------------------|---|

Reporting group description:

Subjects randomized 1:1:1 to treat 3 HAE attacks with 1 of 3 treatment sequences:

Sequence 1: berotralstat - placebo - berotralstat

Sequence 2: placebo - berotralstat - berotralstat

Sequence 3: berotralstat - berotralstat - placebo

| | |
|-----------------------|---|
| Reporting group title | Part 3: Berotralstat (250 mg) Treated HAE attacks |
|-----------------------|---|

Reporting group description:

Subjects randomized 1:1:1 to treat 3 HAE attacks with 1 of 3 treatment sequences:

Sequence 1: berotralstat - placebo - berotralstat

Sequence 2: placebo - berotralstat - berotralstat

Sequence 3: berotralstat - berotralstat - placebo

| | |
|-----------------------|-------------------------------------|
| Reporting group title | Part 1: Placebo Treated HAE attacks |
|-----------------------|-------------------------------------|

Reporting group description:

Subjects randomized 1:1:1 to treat 3 HAE attacks with 1 of 3 treatment sequences:

Sequence 1: berotralstat - placebo - berotralstat

Sequence 2: placebo - berotralstat - berotralstat

Sequence 3: berotralstat - berotralstat - placebo

| | |
|-----------------------|-------------------------------------|
| Reporting group title | Part 2: Placebo Treated HAE attacks |
|-----------------------|-------------------------------------|

Reporting group description:

Subjects randomized 1:1:1 to treat 3 HAE attacks with 1 of 3 treatment sequences:

Sequence 1: berotralstat - placebo - berotralstat

Sequence 2: placebo - berotralstat - berotralstat

Sequence 3: berotralstat - berotralstat - placebo

| | |
|-----------------------|-------------------------------------|
| Reporting group title | Part 3: Placebo Treated HAE attacks |
|-----------------------|-------------------------------------|

Reporting group description:

Subjects randomized 1:1:1 to treat 3 HAE attacks with 1 of 3 treatment sequences:

Sequence 1: berotralstat - placebo - berotralstat

Sequence 2: placebo - berotralstat - berotralstat

Sequence 3: berotralstat - berotralstat - placebo

| Serious adverse events | Part 1: Berotralstat (750 mg) Treated HAE attacks | Part 2: Berotralstat (500 mg) Treated HAE attacks | Part 3: Berotralstat (250 mg) Treated HAE attacks |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 14 (7.14%) | 0 / 11 (0.00%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Injury, poisoning and procedural complications | | | |
| kidney contusion | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 14 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ankle fracture | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 14 (7.14%) | 0 / 11 (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 |
| Ligament sprain | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 14 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| Serious adverse events | Part 1: Placebo Treated HAE attacks | Part 2: Placebo Treated HAE attacks | Part 3: Placebo Treated HAE attacks |
|---|--|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 31 (3.23%) | 0 / 11 (0.00%) | 0 / 11 (0.00%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Injury, poisoning and procedural complications | | | |
| kidney contusion | | | |
| subjects affected / exposed | 1 / 31 (3.23%) | 0 / 11 (0.00%) | 0 / 11 (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 |
| Ankle fracture | | | |
| subjects affected / exposed | 0 / 31 (0.00%) | 0 / 11 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ligament sprain | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 31 (3.23%) | 0 / 11 (0.00%) | 0 / 11 (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 |

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

| Non-serious adverse events | Part 1: Berotralstat (750 mg) Treated HAE attacks | Part 2: Berotralstat (500 mg) Treated HAE attacks | Part 3: Berotralstat (250 mg) Treated HAE attacks |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 12 / 33 (36.36%) | 8 / 14 (57.14%) | 7 / 11 (63.64%) |
| Investigations | | | |
| Blood creatine phosphokinase increased | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 14 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Dysplastic naevus | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 14 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 0 | 1 |
| Injury, poisoning and procedural complications | | | |
| Ankle fracture | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 14 (7.14%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Arthropod bite | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 14 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 0 | 1 |
| Fall | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 14 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 0 | 1 |
| Limb injury | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 14 (7.14%) | 2 / 11 (18.18%) |
| occurrences (all) | 0 | 1 | 0 |
| Muscle contusion | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 14 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Kidney contusion | | | |

| | | | |
|--|---------------------|----------------------|---------------------|
| subjects affected / exposed occurrences (all) | 0 / 33 (0.00%) 0 | 0 / 14 (0.00%) 0 | 0 / 11 (0.00%) 0 |
| Ligament sprain subjects affected / exposed occurrences (all) | 0 / 33 (0.00%) 0 | 0 / 14 (0.00%) 0 | 0 / 11 (0.00%) 0 |
| Nervous system disorders Dysgeusia subjects affected / exposed occurrences (all) | 0 / 33 (0.00%) 0 | 1 / 14 (7.14%) 1 | 1 / 11 (9.09%) 1 |
| General disorders and administration site conditions Pyrexia subjects affected / exposed occurrences (all) | 0 / 33 (0.00%) 0 | 1 / 14 (7.14%) 1 | 0 / 11 (0.00%) 0 |
| Vessel puncture site reaction subjects affected / exposed occurrences (all) | 0 / 33 (0.00%) 0 | 1 / 14 (7.14%) 1 | 0 / 11 (0.00%) 0 |
| Fatigue subjects affected / exposed occurrences (all) | 0 / 33 (0.00%) 0 | 0 / 14 (0.00%) 0 | 1 / 11 (9.09%) 1 |
| Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all) | 0 / 33 (0.00%) 0 | 0 / 14 (0.00%) 0 | 0 / 11 (0.00%) 0 |
| Gastrointestinal disorders Abdominal discomfort subjects affected / exposed occurrences (all) | 1 / 33 (3.03%) 1 | 0 / 14 (0.00%) 0 | 1 / 11 (9.09%) 1 |
| Abdominal pain upper subjects affected / exposed occurrences (all) | 0 / 33 (0.00%) 0 | 0 / 14 (0.00%) 0 | 1 / 11 (9.09%) 1 |
| Faeces discoloured subjects affected / exposed occurrences (all) | 0 / 33 (0.00%) 0 | 0 / 14 (0.00%) 0 | 1 / 11 (9.09%) 1 |
| Abdominal pain subjects affected / exposed occurrences (all) | 1 / 33 (3.03%) 2 | 2 / 14 (14.29%) 3 | 0 / 11 (0.00%) 0 |

| | | | |
|---|----------------|-----------------|----------------|
| Diarrhoea | | | |
| subjects affected / exposed | 3 / 33 (9.09%) | 2 / 14 (14.29%) | 0 / 11 (0.00%) |
| occurrences (all) | 3 | 3 | 0 |
| Nausea | | | |
| subjects affected / exposed | 2 / 33 (6.06%) | 2 / 14 (14.29%) | 1 / 11 (9.09%) |
| occurrences (all) | 2 | 2 | 2 |
| Epigastric discomfort | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 14 (7.14%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 14 (7.14%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Vomiting | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 1 / 14 (7.14%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Hepatobiliary disorders | | | |
| Cholelithiasis | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 14 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 14 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 0 | 1 |
| Cough | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 14 (7.14%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 14 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Muscle spasms | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 14 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Infections and infestations | | | |
| Infection | | | |

| | | | |
|-----------------------------------|-----------------|----------------|-----------------|
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 14 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 4 / 33 (12.12%) | 1 / 14 (7.14%) | 0 / 11 (0.00%) |
| occurrences (all) | 4 | 1 | 0 |
| Rhinitis | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 14 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 0 | 1 |
| Sinusitis | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 14 (0.00%) | 2 / 11 (18.18%) |
| occurrences (all) | 0 | 0 | 2 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 14 (7.14%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 14 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Contusion | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 14 (0.00%) | 2 / 11 (18.18%) |
| occurrences (all) | 0 | 0 | 2 |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 14 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Tooth infection | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 14 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| Non-serious adverse events | Part 1: Placebo Treated HAE attacks | Part 2: Placebo Treated HAE attacks | Part 3: Placebo Treated HAE attacks |
|---|--|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 7 / 31 (22.58%) | 6 / 11 (54.55%) | 4 / 11 (36.36%) |
| Investigations | | | |
| Blood creatine phosphokinase increased | | | |
| subjects affected / exposed | 1 / 31 (3.23%) | 1 / 11 (9.09%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |

| | | | |
|---|---------------------|---------------------|---------------------|
| Dysplastic naevus subjects affected / exposed occurrences (all) | 0 / 31 (0.00%) 0 | 0 / 11 (0.00%) 0 | 0 / 11 (0.00%) 0 |
| Injury, poisoning and procedural complications | | | |
| Ankle fracture subjects affected / exposed occurrences (all) | 0 / 31 (0.00%) 0 | 0 / 11 (0.00%) 0 | 0 / 11 (0.00%) 0 |
| Arthropod bite subjects affected / exposed occurrences (all) | 0 / 31 (0.00%) 0 | 0 / 11 (0.00%) 0 | 1 / 11 (9.09%) 1 |
| Fall subjects affected / exposed occurrences (all) | 0 / 31 (0.00%) 0 | 0 / 11 (0.00%) 0 | 0 / 11 (0.00%) 0 |
| Limb injury subjects affected / exposed occurrences (all) | 0 / 31 (0.00%) 0 | 1 / 11 (9.09%) 1 | 0 / 11 (0.00%) 0 |
| Muscle contusion subjects affected / exposed occurrences (all) | 0 / 31 (0.00%) 0 | 1 / 11 (9.09%) 1 | 0 / 11 (0.00%) 0 |
| Kidney contusion subjects affected / exposed occurrences (all) | 1 / 31 (3.23%) 1 | 0 / 11 (0.00%) 0 | 0 / 11 (0.00%) 0 |
| Ligament sprain subjects affected / exposed occurrences (all) | 1 / 31 (3.23%) 1 | 0 / 11 (0.00%) 0 | 0 / 11 (0.00%) 0 |
| Nervous system disorders | | | |
| Dysgeusia subjects affected / exposed occurrences (all) | 0 / 31 (0.00%) 0 | 0 / 11 (0.00%) 0 | 1 / 11 (9.09%) 1 |
| General disorders and administration site conditions | | | |
| Pyrexia subjects affected / exposed occurrences (all) | 0 / 31 (0.00%) 0 | 0 / 11 (0.00%) 0 | 0 / 11 (0.00%) 0 |
| Vessel puncture site reaction subjects affected / exposed occurrences (all) | 0 / 31 (0.00%) 0 | 0 / 11 (0.00%) 0 | 0 / 11 (0.00%) 0 |

| | | | |
|--|---------------------|----------------------|---------------------|
| Fatigue subjects affected / exposed occurrences (all) | 0 / 31 (0.00%) 0 | 0 / 11 (0.00%) 0 | 1 / 11 (9.09%) 1 |
| Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all) | 1 / 31 (3.23%) 1 | 0 / 11 (0.00%) 0 | 0 / 11 (0.00%) 0 |
| Gastrointestinal disorders Abdominal discomfort subjects affected / exposed occurrences (all) | 0 / 31 (0.00%) 0 | 0 / 11 (0.00%) 0 | 0 / 11 (0.00%) 0 |
| Abdominal pain upper subjects affected / exposed occurrences (all) | 0 / 31 (0.00%) 0 | 0 / 11 (0.00%) 0 | 0 / 11 (0.00%) 0 |
| Faeces discoloured subjects affected / exposed occurrences (all) | 0 / 31 (0.00%) 0 | 0 / 11 (0.00%) 0 | 0 / 11 (0.00%) 0 |
| Abdominal pain subjects affected / exposed occurrences (all) | 1 / 31 (3.23%) 1 | 0 / 11 (0.00%) 0 | 0 / 11 (0.00%) 0 |
| Diarrhoea subjects affected / exposed occurrences (all) | 0 / 31 (0.00%) 0 | 2 / 11 (18.18%) 2 | 0 / 11 (0.00%) 0 |
| Nausea subjects affected / exposed occurrences (all) | 0 / 31 (0.00%) 0 | 0 / 11 (0.00%) 0 | 0 / 11 (0.00%) 0 |
| Epigastric discomfort subjects affected / exposed occurrences (all) | 0 / 31 (0.00%) 0 | 0 / 11 (0.00%) 0 | 0 / 11 (0.00%) 0 |
| Gastrooesophageal reflux disease subjects affected / exposed occurrences (all) | 0 / 31 (0.00%) 0 | 0 / 11 (0.00%) 0 | 0 / 11 (0.00%) 0 |
| Vomiting subjects affected / exposed occurrences (all) | 0 / 31 (0.00%) 0 | 0 / 11 (0.00%) 0 | 0 / 11 (0.00%) 0 |
| Hepatobiliary disorders | | | |

| | | | |
|--|--|--|--|
| Cholelithiasis subjects affected / exposed occurrences (all) | 0 / 31 (0.00%) 0 | 1 / 11 (9.09%) 1 | 0 / 11 (0.00%) 0 |
| Respiratory, thoracic and mediastinal disorders Oropharyngeal pain subjects affected / exposed occurrences (all) Cough subjects affected / exposed occurrences (all) | 0 / 31 (0.00%) 0 0 / 31 (0.00%) 0 | 0 / 11 (0.00%) 0 0 / 11 (0.00%) 0 | 1 / 11 (9.09%) 1 0 / 11 (0.00%) 0 |
| Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all) Muscle spasms subjects affected / exposed occurrences (all) | 0 / 31 (0.00%) 0 1 / 31 (3.23%) 1 | 2 / 11 (18.18%) 2 0 / 11 (0.00%) 0 | 0 / 11 (0.00%) 0 0 / 11 (0.00%) 0 |
| Infections and infestations Infection subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all) Rhinitis subjects affected / exposed occurrences (all) Sinusitis subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all) Urinary tract infection subjects affected / exposed occurrences (all) | 0 / 31 (0.00%) 0 1 / 31 (3.23%) 1 0 / 31 (0.00%) 0 0 / 31 (0.00%) 0 0 / 31 (0.00%) 0 0 / 31 (0.00%) 0 | 0 / 11 (0.00%) 0 0 / 11 (0.00%) 0 1 / 11 (9.09%) 1 0 / 11 (0.00%) 0 0 / 11 (0.00%) 0 1 / 11 (9.09%) 1 | 1 / 11 (9.09%) 1 0 / 11 (0.00%) 0 1 / 11 (9.09%) 1 0 / 11 (0.00%) 0 0 / 11 (0.00%) 0 0 / 11 (0.00%) 0 |

| | | | |
|-----------------------------|----------------|----------------|----------------|
| Contusion | | | |
| subjects affected / exposed | 0 / 31 (0.00%) | 0 / 11 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Bronchitis | | | |
| subjects affected / exposed | 1 / 31 (3.23%) | 0 / 11 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Tooth infection | | | |
| subjects affected / exposed | 1 / 31 (3.23%) | 0 / 11 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 24 February 2017 | Removal of inclusion criterion requiring male subjects to abstain from sperm donation. QTcF exclusion criterion was updated for men to QTcF > 450 msec. Family of sponsor employees, investigator, or study site employees were excluded from participation in the study. Formal stopping criteria was clarified |
| 02 August 2017 | Additional efficacy endpoints: time to almost complete symptom relief, time to initial symptom relief & time to complete symptom relief. Clarification of criteria for what constituted a protocol-qualified attack for study drug treatment. Additional diary time point added at approximately 8 hours after study drug administration. Inclusion criterion for the clinical diagnosis of HAE was updated (defined as C1 INH functional < 50% of normal and a C4 level below the LLN reference range). Added C1 INH antigen level testing for subjects enrolled in the study |
| 16 March 2018 | Updated active ingredient name. Study design and methodology text were clarified to update the interim analysis |

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.

This interim analysis focuses on safety findings, 3-symptom composite VAS at 4 hours post-dose and proportion of subject attacks requiring standard of care treatment by 24 hours. All other efficacy endpoints will be discussed at final analysis.

Notes: