



## 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
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#### 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:

<b>Subjects enrolled per age group</b>	
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
<b>Arm title</b>	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.

<b>Arm title</b>	Part 2: Berotralstat (500 mg) Treated HAE attacks
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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.

<b>Arm title</b>	Part 3: Berotralstat (250 mg) Treated HAE attacks
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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.

<b>Arm title</b>	Part 1: Placebo Treated HAE attacks
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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.

<b>Arm title</b>	Part 2: Placebo Treated HAE attacks
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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.

<b>Arm title</b>	Part 3: Placebo Treated HAE attacks
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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
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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.

<b>Number of subjects in period 1</b>	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

<b>Number of subjects in period 1</b>	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
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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
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End point description:

End point type	Primary
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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 <sup>[1]</sup>	28	59 <sup>[2]</sup>	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 <sup>[3]</sup>	9	24 <sup>[4]</sup>	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 <sup>[5]</sup>	11	21 <sup>[6]</sup>	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

<b>Statistical analysis title</b>	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 <sup>[7]</sup>
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.

<b>Statistical analysis title</b>	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 <sup>[8]</sup>
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.

<b>Statistical analysis title</b>	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 <sup>[9]</sup>
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
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	19.0
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### Reporting groups

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

<b>Serious adverse events</b>	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

<b>Serious adverse events</b>	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 %

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

<b>Non-serious adverse events</b>	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 occurrences (all)	1 / 31 (3.23%) 1	1 / 11 (9.09%) 1	0 / 11 (0.00%) 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)	0 / 31 (0.00%) 0	0 / 11 (0.00%) 0	1 / 11 (9.09%) 1
Cough subjects affected / exposed occurrences (all)	0 / 31 (0.00%) 0	0 / 11 (0.00%) 0	0 / 11 (0.00%) 0
Musculoskeletal and connective tissue disorders			
Back pain subjects affected / exposed occurrences (all)	0 / 31 (0.00%) 0	2 / 11 (18.18%) 2	0 / 11 (0.00%) 0
Muscle spasms subjects affected / exposed occurrences (all)	1 / 31 (3.23%) 1	0 / 11 (0.00%) 0	0 / 11 (0.00%) 0
Infections and infestations			
Infection subjects affected / exposed occurrences (all)	0 / 31 (0.00%) 0	0 / 11 (0.00%) 0	1 / 11 (9.09%) 1
Nasopharyngitis subjects affected / exposed occurrences (all)	1 / 31 (3.23%) 1	0 / 11 (0.00%) 0	0 / 11 (0.00%) 0
Rhinitis subjects affected / exposed occurrences (all)	0 / 31 (0.00%) 0	1 / 11 (9.09%) 1	1 / 11 (9.09%) 1
Sinusitis subjects affected / exposed occurrences (all)	0 / 31 (0.00%) 0	0 / 11 (0.00%) 0	0 / 11 (0.00%) 0
Upper respiratory tract infection subjects affected / exposed occurrences (all)	0 / 31 (0.00%) 0	0 / 11 (0.00%) 0	0 / 11 (0.00%) 0
Urinary tract infection subjects affected / exposed occurrences (all)	0 / 31 (0.00%) 0	1 / 11 (9.09%) 1	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: