



## Clinical trial results:

**A Phase 3, randomized, double-blind, placebo-controlled, parallel group study to evaluate the efficacy and safety of two dose levels of BCX7353 as an oral treatment for the prevention of attacks in subjects with hereditary angioedema**

### Summary

EudraCT number	2017-003966-29
Trial protocol	BG IE GB FR DE DK HU CZ AT NL BE ES IT RO
Global end of trial date	06 April 2022

### Results information

Result version number	v1 (current)
This version publication date	22 October 2022
First version publication date	22 October 2022

### Trial information

#### Trial identification

Sponsor protocol code	BCX7353-302
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#### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03485911
WHO universal trial number (UTN)	-
Other trial identifiers	IND: 135,058

Notes:

### Sponsors

Sponsor organisation name	BioCryst Pharmaceuticals Inc.
Sponsor organisation address	4505 Emperor Blvd., Suite 200, Durham, United States, NC 27703
Public contact	Study Director, BioCryst Pharmaceuticals Inc., 001 919859 1302, clinicaltrials@biocryst.com
Scientific contact	Study Director, BioCryst Pharmaceuticals Inc., 001 919859 1302, clinicaltrials@biocryst.com

Notes:

### Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMA-002449-PIP02-18
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?	Yes

Notes:

## Results analysis stage

Analysis stage	Final
Date of interim/final analysis	22 June 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	06 April 2022
Global end of trial reached?	Yes
Global end of trial date	06 April 2022
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

Part 1 - To determine the efficacy of prophylactic BCX7353 110 mg and 150 mg administered once daily (QD) for 24 weeks compared to placebo in subjects with hereditary angioedema (HAE)

Part 2 - To evaluate the long-term safety and tolerability of BCX7353 110 mg and 150 mg administered QD over a 24- to 48-week administration period in subjects with HAE

Part 3 - To evaluate the long-term safety and tolerability of BCX7353 administered QD over a 48 up to 240-week administration period in subjects with HAE

Protection of trial subjects:

This trial was conducted in compliance with International Conference on Harmonisation (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), assent, 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 adult 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	01 February 2018
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	Romania: 1
Country: Number of subjects enrolled	Spain: 2
Country: Number of subjects enrolled	United Kingdom: 7
Country: Number of subjects enrolled	Austria: 4
Country: Number of subjects enrolled	Czechia: 8
Country: Number of subjects enrolled	France: 3
Country: Number of subjects enrolled	Germany: 5
Country: Number of subjects enrolled	Hungary: 2
Country: Number of subjects enrolled	North Macedonia: 2
Country: Number of subjects enrolled	Canada: 10
Country: Number of subjects enrolled	United States: 77

Worldwide total number of subjects	121
EEA total number of subjects	25

Notes:

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**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)	6
Adults (18-64 years)	106
From 65 to 84 years	9
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

Subjects with HAE Type 1 or 2 were eligible for the study following assessment of data obtained from screening procedures, including demonstration of a minimum number of qualifying HAE attacks documented during a prospective run-in period of 14 to 56 days from the date of the screening visit.

### 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, Carer, Subject

Blinding implementation details:

Only Part 1 and Part 2 were blinded. As part 3 was open-label, no blinding was used

### Arms

Are arms mutually exclusive?	Yes
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<b>Arm title</b>	Treatment Group 1 (110 mg berotralstat QD)
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Arm description: -

Arm type	Experimental
Investigational medicinal product name	berotralstat
Investigational medicinal product code	
Other name	BCX7353
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Parts 1 and 2: two 55 mg capsules of berotralstat QD × 48 weeks

Part 3: one 110 mg capsule of berotralstat QD until the subject can be transitioned to the 150 mg dose

<b>Arm title</b>	Treatment Group 2 (150 mg berotralstat QD)
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Arm description: -

Arm type	Experimental
Investigational medicinal product name	berotralstat
Investigational medicinal product code	
Other name	BCX7353
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Parts 1 and 2: two 75 mg capsules of berotralstat QD × 48 weeks

Part 3: one 150 mg capsule of berotralstat QD × up to 96 weeks

<b>Arm title</b>	Treatment Group 3a
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Arm description:

Subjects were treated with placebo in Part 1 and 110 mg berotralstat in part 2. In part 3, subjects were treated with 110 mg berotralstat QD until the subject could transition to the 150 mg dose.

Arm type	Experimental
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Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Placebo was administered as two matching capsules, orally QD for up to 24 weeks (Days 1 to 168).

Investigational medicinal product name	berotralstat
Investigational medicinal product code	
Other name	BCX7353
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Part 2: two 55 mg capsules of berotralstat QD × 24 weeks (Days 169 to 337)

Part 3: one 110 mg capsule of berotralstat QD until the subject can be transitioned to the 150 mg dose

<b>Arm title</b>	Treatment Group 3b
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Arm description:

Subjects were treated with placebo in Part 1 and 150 mg berotralstat in part 2 and 3.

Arm type	Experimental
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Placebo was administered as two matching capsules, orally QD for up to 24 weeks (Days 1 to 168).

Investigational medicinal product name	berotralstat
Investigational medicinal product code	
Other name	BCX7353
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Part 2: two 75 mg capsules of berotralstat QD × 24 weeks (Days 169 to 337)

Part 3: one 150 mg capsule of berotralstat QD × up to 96 weeks

<b>Number of subjects in period 1</b>	Treatment Group 1 (110 mg berotralstat QD)	Treatment Group 2 (150 mg berotralstat QD)	Treatment Group 3a
Started	41	40	20
Completed Part 1	37	37	17
Started Part 2	37	37	17
Completed Part 2	28	31	15
Started Part 3	26	26	15
Completed	7	4	5
Not completed	34	36	15
Part 1: perceived lack of efficacy	1	1	2
Part 1: subject withdrew consent	-	1	-

Part 2: Investigator judgement	1	-	-
Part 2: Subject non-compliance	1	-	-
Part 1: Other	-	-	-
Part 2: Other	1	3	-
Part 3: Sponsor discontinuation	1	-	-
Part 3: perceived lack of efficacy	2	2	2
Part 3: subject withdrew consent	1	4	-
Part 3: Berotralstat provided by alternative means	13	13	7
Part 3: Other	1	1	-
Part 1: Reimbursement decision	-	-	-
Part 2: lab abnormalities/AEs	1	2	-
Part 2: subject withdrew consent	1	1	2
Part 3: Intercurrent illness/new medical condition	-	1	1
Part 3: lab abnormalities/AEs	1	1	-
Part 2: perceived lack of efficacy	5	5	-
Part 1: lab abnormalities/AEs	3	1	1
Part 2: Intercurrent illness/new medical condition	1	-	-

<b>Number of subjects in period 1</b>	Treatment Group 3b
Started	20
Completed Part 1	17
Started Part 2	17
Completed Part 2	14
Started Part 3	14
Completed	4
Not completed	16
Part 1: perceived lack of efficacy	-
Part 1: subject withdrew consent	1
Part 2: Investigator judgement	-
Part 2: Subject non-compliance	-
Part 1: Other	1
Part 2: Other	-
Part 3: Sponsor discontinuation	-
Part 3: perceived lack of efficacy	-
Part 3: subject withdrew consent	1
Part 3: Berotralstat provided by alternative means	7
Part 3: Other	-
Part 1: Reimbursement decision	1

Part 2: lab abnormalities/AEs	-
Part 2: subject withdrew consent	1
Part 3: Intercurrent illness/new medical condition	-
Part 3: lab abnormalities/AEs	2
Part 2: perceived lack of efficacy	2
Part 1: lab abnormalities/AEs	-
Part 2: Intercurrent illness/new medical condition	-

## Baseline characteristics

### Reporting groups

Reporting group title	Overall Study
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Reporting group description:

Overall Study group corresponds to the intent to treat (ITT) population and included all randomized subjects, regardless of whether study treatment was administered. This population was the primary population for the analysis of the efficacy and health outcomes data.

Reporting group values	Overall Study	Total	
Number of subjects	121	121	
Age categorical			
Units: Subjects			
Adolescents (12-17 years)	6	6	
Adults (18-64 years)	106	106	
From 65-84 years	9	9	
Age continuous			
Units: years			
arithmetic mean	41.6	-	
standard deviation	± 15.32	-	
Gender categorical			
Units: Subjects			
Female	80	80	
Male	41	41	
Baseline Investigator-confirmed attack rate			
Units: Subjects			
< 2 HAE attacks/month	35	35	
≥ 2 HAE attacks/month	86	86	

## End points

### End points reporting groups

Reporting group title	Treatment Group 1 (110 mg berotralstat QD)
Reporting group description: -	
Reporting group title	Treatment Group 2 (150 mg berotralstat QD)
Reporting group description: -	
Reporting group title	Treatment Group 3a
Reporting group description: Subjects were treated with placebo in Part 1 and 110 mg berotralstat in part 2. In part 3, subjects were treated with 110 mg berotralstat QD until the subject could transition to the 150 mg dose.	
Reporting group title	Treatment Group 3b
Reporting group description: Subjects were treated with placebo in Part 1 and 150 mg berotralstat in part 2 and 3.	
Subject analysis set title	Part 1: 110 mg berotralstat
Subject analysis set type	Intention-to-treat
Subject analysis set description: Berotralstat administered as two 55mg capsules, orally QD for 24weeks.	
Subject analysis set title	Part 1: 150 mg berotralstat
Subject analysis set type	Intention-to-treat
Subject analysis set description: Berotralstat administered as two 75mg capsules, orally QD for 24weeks.	
Subject analysis set title	Part 1: Placebo
Subject analysis set type	Intention-to-treat
Subject analysis set description: Placebo administered as two matching capsules, orally QD for 24 weeks.	
Subject analysis set title	Part 2: 110mg berotralstat
Subject analysis set type	Safety analysis
Subject analysis set description: The safety population included all subjects who received at least 1 capsule of study treatment - 110 mg berotralstat - in part 2.	
Subject analysis set title	Part 2: Placebo, 110mg berotralstat
Subject analysis set type	Safety analysis
Subject analysis set description: The safety population included all subjects who received at least 1 capsule of study treatment - 110 mg berotralstat - in part 2, following prior treatment with placebo in part 1.	
Subject analysis set title	Part 2: 150mg berotralstat
Subject analysis set type	Safety analysis
Subject analysis set description: The safety population included all subjects who received at least 1 capsule of study treatment - 150 mg berotralstat - in part 2.	
Subject analysis set title	Part 2: Placebo, 150mg berotralstat
Subject analysis set type	Safety analysis
Subject analysis set description: The safety population included all subjects who received at least 1 capsule of study treatment - 150 mg berotralstat - in part 2, following treatment with placebo in part 1.	
Subject analysis set title	Part 3: berotralstat
Subject analysis set type	Safety analysis
Subject analysis set description: The safety data was assessed for the safety population, for subjects who entered Part 3, and includes TEAEs that began in Part 3 for these subjects.	

## Primary: Part 1: Rate of Investigator-confirmed HAE Attacks

End point title	Part 1: Rate of Investigator-confirmed HAE Attacks
End point description:	Investigator-confirmed attacks were reported as the negative binomial analysis estimated attack rates per 28 days, where the number of investigator-confirmed attacks was included as the dependent variable, the treatment was included as a fixed effect, baseline investigator-confirmed attack rate was included as a covariate, and the logarithm of duration on treatment was included as an offset variable.
End point type	Primary
End point timeframe:	24 week treatment period (Days 1-168)

End point values	Part 1: 110 mg berotralstat	Part 1: 150 mg berotralstat	Part 1: Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	41	40	40	
Units: HAE attack rate per 28 days number (not applicable)	1.65	1.31	2.35	

## Statistical analyses

<b>Statistical analysis title</b>	HAE Attack Rate - 110mg Berotralstat vs Placebo
Statistical analysis description:	Treatment comparisons between 110mg berotralstat & placebo in the rate of investigator confirmed HAE attacks were analyzed using a negative binomial model. The number of investigator-confirmed attacks was included as the dependent variable, the treatment was included as a fixed effect, the stratification variable (baseline attack rate) was included as a covariate, & the logarithm of duration on treatment was included as an offset variable.
Comparison groups	Part 1: 110 mg berotralstat v Part 1: Placebo
Number of subjects included in analysis	81
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.024
Method	negative binomial regression model
Parameter estimate	negative binomial regression model
Point estimate	-30
Confidence interval	
level	95 %
sides	2-sided
lower limit	-48.7
upper limit	-4.6

<b>Statistical analysis title</b>	HAE Attack Rate - 150mg Berotralstat vs placebo
Statistical analysis description:	Treatment comparisons between 150mg berotralstat & placebo in the rate of investigator confirmed HAE attacks were analyzed using a negative binomial model. The number of investigator-confirmed attacks was included as the dependent variable, the treatment was included as a fixed effect, the stratification variable (baseline attack rate) was included as a covariate, & the logarithm of duration on treatment

was included as an offset variable.

Comparison groups	Part 1: Placebo v Part 1: 150 mg berotralstat
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	negative binomial regression model
Parameter estimate	negative binomial regression model
Point estimate	-44.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-59.5
upper limit	-23

### Primary: Part 2 & 3: Safety & Tolerability

End point title	Part 2 & 3: Safety & Tolerability <sup>[1]</sup>
End point description: The safety data was assessed for the safety population, for subjects who entered Part 2 and Part 3, and includes TEAEs that began in Part 2 or 3, respectively, for these subjects.	
End point type	Primary
End point timeframe: Part 2: 24 weeks (Days 169 to 337) Part 3: 48 weeks (Days 338 to 674)	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Primary endpoint for Part 2 & 3 was safety and tolerability; no statistical analysis is considered applicable

End point values	Part 2: 110mg berotralstat	Part 2: Placebo, 110mg berotralstat	Part 2: 150mg berotralstat	Part 2: Placebo, 150mg berotralstat
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	37	17	37	17
Units: subjects				
TEAE	22	13	27	12
Drug-related TEAE	4	5	7	7
TESAE	0	0	1	1
Drug-related TESAE	0	0	0	0
DMID grade 3 or 4 TEAE	1	1	2	1
Drug-related DMID grade 3or 4 TEAE	0	0	1	0
TEAE leading to interruption of study drug	0	1	2	1
TEAE leading to discontinuation of study drug	1	0	2	2
Drug-related investigator-identified rash	0	0	1	0
GI abdominal-related TEAE	5	4	10	9
GI abdominal-related TEAE -study drug discontinued	1	0	1	1

<b>End point values</b>	Part 3: berotralstat			
Subject group type	Subject analysis set			
Number of subjects analysed	81			
Units: subjects				
TEAE	67			
Drug-related TEAE	12			
TESAE	7			
Drug-related TESAE	0			
DMID grade 3 or 4 TEAE	10			
Drug-related DMID grade 3 or 4 TEAE	1			
TEAE leading to interruption of study drug	5			
TEAE leading to discontinuation of study drug	3			
Drug-related investigator-identified rash	0			
GI abdominal-related TEAE	18			
GI abdominal-related TEAE -study drug discontinued	2			

## Statistical analyses

No statistical analyses for this end point

### Secondary: Part 2: Rate of Investigator-confirmed HAE Attacks - month 12 change from baseline

End point title	Part 2: Rate of Investigator-confirmed HAE Attacks - month 12 change from baseline
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End point description:

Monthly Attack Rate was defined as the total number of investigator-confirmed HAE attacks experienced during the treatment period adjusted for the length of a month (defined as 28 days) and the number of days the subject was on treatment during that month.

Baseline investigator-confirmed attack rate was defined as the total number of investigator-confirmed HAE attacks experienced in the period between screening and first dose of study drug adjusted for the length of a month (defined as 28 days) and the number of days during that period.

End point type	Secondary
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End point timeframe:

24 weeks (Days 169 to 337)

<b>End point values</b>	Part 2: 110mg berotralstat	Part 2: 150mg berotralstat		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	32	32		
Units: HAE attack rate -change from baseline				
arithmetic mean (standard deviation)	-1.543 (± 1.6539)	-1.910 (± 1.5330)		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Part 1: Change From Baseline in Angioedema Quality of Life Questionnaire

End point title	Part 1: Change From Baseline in Angioedema Quality of Life Questionnaire
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End point description:

Change in Quality of Life, on a 1-100 scale, where higher scores indicate more impairment and a decrease (change with a negative value) in AE-QoL questionnaire scores indicates an improvement in the subject's QoL. The minimum clinically important difference (MCID) for the AE-QoL questionnaire is -6 (total score). The AE-QoL is only validated for adults; however, data were collected on all adult and adolescent study subjects.

End point type	Secondary
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End point timeframe:

Baseline & 24 weeks

End point values	Part 1: 110 mg berotralstat	Part 1: 150 mg berotralstat	Part 1: Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	40	38	36	
Units: AE-QoL TotalScore Change from baseline				
least squares mean (standard error)	-12.46 ( $\pm$ 2.530)	-14.59 ( $\pm$ 2.592)	-9.69 ( $\pm$ 2.643)	

## Statistical analyses

Statistical analysis title	AE-QoL - 110mg Berotralstat vs Placebo
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Statistical analysis description:

Numerical difference in change from baseline of AE-QoL total score between treatment groups.

Comparison groups	Part 1: 110 mg berotralstat v Part 1: Placebo
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Number of subjects included in analysis	76
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Analysis specification	Pre-specified
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Analysis type	superiority
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P-value	= 0.453
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Method	mixed-model repeated measures analysis
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Parameter estimate	mixed-model repeated measures analysis
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Point estimate	-2.77
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Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.08
upper limit	4.53

<b>Statistical analysis title</b>	AE-QoL - 150mg Berotralstat vs Placebo
Statistical analysis description:	
Numerical difference in change from baseline of AE-QoL total score between treatment groups.	
Comparison groups	Part 1: Placebo v Part 1: 150 mg berotralstat
Number of subjects included in analysis	74
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.188
Method	mixed-model repeated measures analysis
Parameter estimate	mixed-model repeated measures analysis
Point estimate	-4.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.23
upper limit	2.43

### Secondary: Part 1: Days with Angioedema Symptoms

End point title	Part 1: Days with Angioedema Symptoms
End point description:	
Assessment of proportion of days subjects had angioedema symptoms from expert-confirmed HAE attacks during Part 1.	
End point type	Secondary
End point timeframe:	
24 weeks	

End point values	Part 1: 110 mg berotralstat	Part 1: 150 mg berotralstat	Part 1: Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	41	40	40	
Units: Proportion days with angioedema symptoms				
least squares mean (standard error)	0.134 (± 0.0191)	0.119 (± 0.0194)	0.197 (± 0.0196)	

### Statistical analyses

<b>Statistical analysis title</b>	HAE Symptoms - 110mg Berotralstat vs Placebo
Statistical analysis description:	
Numerical differences from the placebo treatment in the LSM proportion of the 169 days of treatment with angioedema symptoms. In the event that the first secondary endpoint did not meet statistical significance in the hierarchical testing scheme, testing of the second secondary endpoint of proportion of days with angioedema symptoms through to 24 weeks for statistical significance would not be completed. P-values that are reported are nominal.	
Comparison groups	Part 1: 110 mg berotralstat v Part 1: Placebo
Number of subjects included in analysis	81
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.025
Method	ANCOVA
Parameter estimate	Difference in Least Square Means
Point estimate	-0.062
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.117
upper limit	-0.008

<b>Statistical analysis title</b>	HAE Symptoms - 1150mg Berotralstat vs Placebo
Statistical analysis description:	
Numerical differences from the placebo treatment in the LSM proportion of the 169 days of treatment with angioedema symptoms. In the event that the first secondary endpoint did not meet statistical significance in the hierarchical testing scheme, testing of the second secondary endpoint of proportion of days with angioedema symptoms through to 24 weeks for statistical significance would not be completed. P-values that are reported are nominal.	
Comparison groups	Part 1: Placebo v Part 1: 150 mg berotralstat
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.006
Method	ANCOVA
Parameter estimate	Difference in Least Square Means
Point estimate	-0.078
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.133
upper limit	-0.023

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse Events (AEs) were reported from ICF signature until the last follow-up visit, approximately 3 weeks following the last dose of study drug, or until the AE was resolved or the subject was in a clinically stable condition with regard to the AE.

Adverse event reporting additional description:

Non-serious AEs are reported where the incidence in either the all Active (berotralstat) treatment group or all Placebo subject group was greater than 5%

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	19.1
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### Reporting groups

Reporting group title	110/150 mg berotralstat
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Reporting group description:

Subjects received 110 mg berotralstat during part 1 & 2 followed by 150 mg berotralstat in part 3

Reporting group title	Placebo, 110/150mg berotralstat
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Reporting group description:

Subjects received placebo in part 1, 110 mg berotralstat during part 2 followed by 150 mg berotralstat in part 3

Reporting group title	150 mg berotralstat
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Reporting group description:

Subjects received 150 mg berotralstat during part 1, 2 & 3

Reporting group title	Placebo, 150mg berotralstat
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Reporting group description:

Subjects received placebo during part 1, followed by 150 mg berotralstat in part 2 & 3

Reporting group title	Placebo
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Reporting group description:

Subjects received placebo during part 1

<b>Serious adverse events</b>	110/150 mg berotralstat	Placebo, 110/150mg berotralstat	150 mg berotralstat
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 41 (7.32%)	2 / 17 (11.76%)	2 / 40 (5.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Plasma cell myeloma			
subjects affected / exposed	1 / 41 (2.44%)	0 / 17 (0.00%)	0 / 40 (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
Uterine leiomyoma			

subjects affected / exposed	0 / 41 (0.00%)	0 / 17 (0.00%)	0 / 40 (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>Investigations</b>			
Medical observation			
subjects affected / exposed	0 / 41 (0.00%)	0 / 17 (0.00%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Cardiac disorders</b>			
Acute myocardial infarction			
subjects affected / exposed	0 / 41 (0.00%)	0 / 17 (0.00%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Nervous system disorders</b>			
Syncope			
subjects affected / exposed	0 / 41 (0.00%)	0 / 17 (0.00%)	0 / 40 (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
Transient ischaemic attack			
subjects affected / exposed	0 / 41 (0.00%)	0 / 17 (0.00%)	0 / 40 (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>General disorders and administration site conditions</b>			
Vascular stent occlusion			
subjects affected / exposed	0 / 41 (0.00%)	0 / 17 (0.00%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Gastrointestinal disorders</b>			
Diverticulum intestinal haemorrhagic			
subjects affected / exposed	0 / 41 (0.00%)	0 / 17 (0.00%)	0 / 40 (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
Gastritis alcoholic			

subjects affected / exposed	1 / 41 (2.44%)	0 / 17 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Respiratory, thoracic and mediastinal disorders</b>			
Pleural effusion			
subjects affected / exposed	0 / 41 (0.00%)	1 / 17 (5.88%)	0 / 40 (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
<b>Psychiatric disorders</b>			
Bipolar disorder			
subjects affected / exposed	0 / 41 (0.00%)	1 / 17 (5.88%)	0 / 40 (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
<b>Infections and infestations</b>			
Pneumonia			
subjects affected / exposed	0 / 41 (0.00%)	1 / 17 (5.88%)	0 / 40 (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
Pyelonephritis			
subjects affected / exposed	0 / 41 (0.00%)	0 / 17 (0.00%)	0 / 40 (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>Metabolism and nutrition disorders</b>			
Obesity			
subjects affected / exposed	1 / 41 (2.44%)	0 / 17 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Serious adverse events</b>	Placebo, 150mg berotralstat	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 17 (17.65%)	2 / 39 (5.13%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			

Plasma cell myeloma			
subjects affected / exposed	0 / 17 (0.00%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine leiomyoma			
subjects affected / exposed	1 / 17 (5.88%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Medical observation			
subjects affected / exposed	0 / 17 (0.00%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 17 (0.00%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Syncope			
subjects affected / exposed	1 / 17 (5.88%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	0 / 17 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Vascular stent occlusion			
subjects affected / exposed	0 / 17 (0.00%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diverticulum intestinal haemorrhagic			

subjects affected / exposed	0 / 17 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Gastritis alcoholic</b>			
subjects affected / exposed	0 / 17 (0.00%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Respiratory, thoracic and mediastinal disorders</b>			
<b>Pleural effusion</b>			
subjects affected / exposed	0 / 17 (0.00%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Psychiatric disorders</b>			
<b>Bipolar disorder</b>			
subjects affected / exposed	0 / 17 (0.00%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Infections and infestations</b>			
<b>Pneumonia</b>			
subjects affected / exposed	0 / 17 (0.00%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Pyelonephritis</b>			
subjects affected / exposed	1 / 17 (5.88%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Metabolism and nutrition disorders</b>			
<b>Obesity</b>			
subjects affected / exposed	0 / 17 (0.00%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

<b>Non-serious adverse events</b>	110/150 mg berotralstat	Placebo, 110/150mg berotralstat	150 mg berotralstat
Total subjects affected by non-serious adverse events			
subjects affected / exposed	39 / 41 (95.12%)	17 / 17 (100.00%)	38 / 40 (95.00%)
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	2 / 41 (4.88%)	0 / 17 (0.00%)	1 / 40 (2.50%)
occurrences (all)	2	0	1
Limb injury			
subjects affected / exposed	1 / 41 (2.44%)	0 / 17 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 41 (9.76%)	0 / 17 (0.00%)	5 / 40 (12.50%)
occurrences (all)	4	0	5
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	4 / 41 (9.76%)	0 / 17 (0.00%)	4 / 40 (10.00%)
occurrences (all)	4	0	4
Chest pain			
subjects affected / exposed	0 / 41 (0.00%)	0 / 17 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	3
Oedema peripheral			
subjects affected / exposed	0 / 41 (0.00%)	1 / 17 (5.88%)	0 / 40 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	9 / 41 (21.95%)	1 / 17 (5.88%)	8 / 40 (20.00%)
occurrences (all)	11	1	13
Dyspepsia			
subjects affected / exposed	5 / 41 (12.20%)	3 / 17 (17.65%)	5 / 40 (12.50%)
occurrences (all)	5	3	5
Abdominal pain			
subjects affected / exposed	3 / 41 (7.32%)	1 / 17 (5.88%)	8 / 40 (20.00%)
occurrences (all)	7	1	13
Diarrhoea			

subjects affected / exposed occurrences (all)	6 / 41 (14.63%) 6	1 / 17 (5.88%) 1	7 / 40 (17.50%) 10
Vomiting subjects affected / exposed occurrences (all)	4 / 41 (9.76%) 6	1 / 17 (5.88%) 1	7 / 40 (17.50%) 12
Abdominal discomfort subjects affected / exposed occurrences (all)	1 / 41 (2.44%) 1	2 / 17 (11.76%) 6	6 / 40 (15.00%) 8
Gastrooesophageal reflux disease subjects affected / exposed occurrences (all)	7 / 41 (17.07%) 7	0 / 17 (0.00%) 0	2 / 40 (5.00%) 2
Flatulence subjects affected / exposed occurrences (all)	3 / 41 (7.32%) 3	0 / 17 (0.00%) 0	3 / 40 (7.50%) 3
Toothache subjects affected / exposed occurrences (all)	4 / 41 (9.76%) 8	0 / 17 (0.00%) 0	3 / 40 (7.50%) 3
Abdominal distension subjects affected / exposed occurrences (all)	2 / 41 (4.88%) 3	1 / 17 (5.88%) 1	1 / 40 (2.50%) 1
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	4 / 41 (9.76%) 5	0 / 17 (0.00%) 0	1 / 40 (2.50%) 1
Oropharyngeal pain subjects affected / exposed occurrences (all)	3 / 41 (7.32%) 4	1 / 17 (5.88%) 1	2 / 40 (5.00%) 2
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all)	2 / 41 (4.88%) 2	1 / 17 (5.88%) 1	2 / 40 (5.00%) 3
Depression subjects affected / exposed occurrences (all)	2 / 41 (4.88%) 2	0 / 17 (0.00%) 0	1 / 40 (2.50%) 1
Irritability			

subjects affected / exposed occurrences (all)	0 / 41 (0.00%) 0	0 / 17 (0.00%) 0	0 / 40 (0.00%) 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 41 (4.88%)	0 / 17 (0.00%)	5 / 40 (12.50%)
occurrences (all)	2	0	5
Arthralgia			
subjects affected / exposed	1 / 41 (2.44%)	1 / 17 (5.88%)	3 / 40 (7.50%)
occurrences (all)	1	1	3
Pain in extremity			
subjects affected / exposed	1 / 41 (2.44%)	0 / 17 (0.00%)	1 / 40 (2.50%)
occurrences (all)	1	0	1
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	9 / 41 (21.95%)	6 / 17 (35.29%)	15 / 40 (37.50%)
occurrences (all)	20	13	40
Upper respiratory tract infection			
subjects affected / exposed	7 / 41 (17.07%)	1 / 17 (5.88%)	8 / 40 (20.00%)
occurrences (all)	12	1	9
Gastroenteritis viral			
subjects affected / exposed	4 / 41 (9.76%)	1 / 17 (5.88%)	2 / 40 (5.00%)
occurrences (all)	4	1	2
Urinary tract infection			
subjects affected / exposed	4 / 41 (9.76%)	3 / 17 (17.65%)	1 / 40 (2.50%)
occurrences (all)	6	6	4
Sinusitis			
subjects affected / exposed	1 / 41 (2.44%)	1 / 17 (5.88%)	4 / 40 (10.00%)
occurrences (all)	1	1	5
Influenza			
subjects affected / exposed	3 / 41 (7.32%)	1 / 17 (5.88%)	2 / 40 (5.00%)
occurrences (all)	3	1	2

<b>Non-serious adverse events</b>	Placebo, 150mg berotralstat	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 17 (88.24%)	30 / 39 (76.92%)	

Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 17 (5.88%)	2 / 39 (5.13%)	
occurrences (all)	1	2	
Limb injury			
subjects affected / exposed	1 / 17 (5.88%)	2 / 39 (5.13%)	
occurrences (all)	1	2	
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 17 (0.00%)	2 / 39 (5.13%)	
occurrences (all)	0	2	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 17 (5.88%)	1 / 39 (2.56%)	
occurrences (all)	1	1	
Chest pain			
subjects affected / exposed	0 / 17 (0.00%)	2 / 39 (5.13%)	
occurrences (all)	0	2	
Oedema peripheral			
subjects affected / exposed	1 / 17 (5.88%)	2 / 39 (5.13%)	
occurrences (all)	1	2	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	3 / 17 (17.65%)	7 / 39 (17.95%)	
occurrences (all)	3	8	
Dyspepsia			
subjects affected / exposed	2 / 17 (11.76%)	3 / 39 (7.69%)	
occurrences (all)	4	6	
Abdominal pain			
subjects affected / exposed	2 / 17 (11.76%)	2 / 39 (5.13%)	
occurrences (all)	2	2	
Diarrhoea			
subjects affected / exposed	1 / 17 (5.88%)	0 / 39 (0.00%)	
occurrences (all)	2	0	
Vomiting			

subjects affected / exposed occurrences (all)	2 / 17 (11.76%) 2	1 / 39 (2.56%) 2	
Abdominal discomfort subjects affected / exposed occurrences (all)	2 / 17 (11.76%) 2	3 / 39 (7.69%) 3	
Gastroesophageal reflux disease subjects affected / exposed occurrences (all)	2 / 17 (11.76%) 3	0 / 39 (0.00%) 0	
Flatulence subjects affected / exposed occurrences (all)	3 / 17 (17.65%) 3	1 / 39 (2.56%) 1	
Toothache subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	2 / 39 (5.13%) 2	
Abdominal distension subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	2 / 39 (5.13%) 2	
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1	0 / 39 (0.00%) 0	
Oropharyngeal pain subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	3 / 39 (7.69%) 3	
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	3 / 39 (7.69%) 3	
Depression subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1	2 / 39 (5.13%) 2	
Irritability subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	2 / 39 (5.13%) 2	
Musculoskeletal and connective tissue disorders			

Back pain			
subjects affected / exposed	1 / 17 (5.88%)	1 / 39 (2.56%)	
occurrences (all)	1	1	
Arthralgia			
subjects affected / exposed	1 / 17 (5.88%)	1 / 39 (2.56%)	
occurrences (all)	1	1	
Pain in extremity			
subjects affected / exposed	1 / 17 (5.88%)	3 / 39 (7.69%)	
occurrences (all)	1	3	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	4 / 17 (23.53%)	9 / 39 (23.08%)	
occurrences (all)	6	15	
Upper respiratory tract infection			
subjects affected / exposed	1 / 17 (5.88%)	1 / 39 (2.56%)	
occurrences (all)	1	1	
Gastroenteritis viral			
subjects affected / exposed	0 / 17 (0.00%)	3 / 39 (7.69%)	
occurrences (all)	0	3	
Urinary tract infection			
subjects affected / exposed	1 / 17 (5.88%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
Sinusitis			
subjects affected / exposed	0 / 17 (0.00%)	2 / 39 (5.13%)	
occurrences (all)	0	2	
Influenza			
subjects affected / exposed	1 / 17 (5.88%)	0 / 39 (0.00%)	
occurrences (all)	1	0	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 October 2018	<p>Amendment to allow patients continued access to BCX7353 for up to 96 weeks. This change was in accordance with the Sponsor's commitment made to the VHP Initial Assessment request to allow continued access. Treatment post 48 weeks was to be open-label, continuing at the dose which patients had been receiving in a blinded manner from Week 24 to Week 48. The diary collection requirements were reduced from Week 48 to 96, to lower the patient burden. Inclusion criteria for C1-INH Function confirmation of HAE diagnosis were clarified further.</p> <p>Subject Discontinuation Criteria associated with raised liver enzymes were amended to reflect regulatory guidance on Drug-induced Liver Injury: Premarketing Clinical Evaluation.</p> <p>Following further clinical investigations, the medications which were prohibited throughout the trial were reduced to a definitive list.</p> <p>Requirement for monthly pregnancy testing was included in accordance with the Sponsor's commitment on VHP Initial Assessment.</p> <p>Statistical Section updated for the inclusion of Part 3, and additions/ clarifications in accordance with the Sponsor's commitments at VHP Initial Assessment.</p> <p>Administrative changes were included throughout the protocol for updated contact information and consistency.</p>
11 September 2019	<p>Length of treatment extended to 240 weeks OR until the IMP became available to the subject through another method i.e. marketed product or local access program.</p> <p>Following the evaluation of the Week 24 primary interim analysis, it was confirmed that all patients would take 150mg berotralstat daily.</p> <p>Regarding male contraception requirements, male subjects and their female partners were no longer be required to take acceptable effective contraceptive measures. The nonclinical data supported this change, in accordance with the CTFG guidelines published 2014.</p> <p>The definition of Events of Special Interest (EOSI) was narrowed to only drug-related maculopapular rashes. The sponsor, having collected a large body of safety evidence was confident that this narrowing of the definition would capture all events of interest.</p>
10 February 2020	<p>US-specific protocol amendment to reduce part 3 length of treatment to 144 days, in response to an FDA request that the study be extended by 1-year increments.</p>

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported