



## Clinical trial results:

**A randomized, double-blind, placebo-controlled, dose-ranging, parallel-group study to evaluate the efficacy, safety, tolerability, pharmacokinetics and pharmacodynamics of BCX7353 as a preventative treatment to reduce the frequency of attacks in subjects with hereditary angioedema**

### Summary

EudraCT number	2016-001272-29
Trial protocol	GB DE HU ES AT DK GR
Global end of trial date	08 August 2017

### 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	BCX7353-203
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#### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02870972
WHO universal trial number (UTN)	-
Other trial identifiers	205417: IRAS

Notes:

### Sponsors

Sponsor organisation name	BioCryst Pharmaceuticals Inc
Sponsor organisation address	4505 Emperor Blvd., Suite 200, Durham, United States, 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	Final
Date of interim/final analysis	30 July 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	08 August 2017
Global end of trial reached?	Yes
Global end of trial date	08 August 2017
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

To evaluate the efficacy of once-daily prophylactic berotralstat at up to 5 dose levels, as measured by the number of attacks of hereditary angioedema (HAE) observed in patients with HAE enrolled in each treatment group.

Protection of trial subjects:

This trial was designed and monitored in accordance with sponsor procedures, which comply with the ethical principles of Good Clinical Practice (GCP) as required by the major regulatory authorities, and in accordance with the Declaration of Helsinki. A signed ICF was obtained from each subject before performing any study-related procedures; subjects were not screened or treated until the subject had signed an approved ICF in a language in which the subject was fluent. Each subject was given both verbal and written information describing the nature and duration of the clinical study. The investigator or designee explained to potential subjects the aims, methods, objectives, reasonably anticipated benefits, and potential hazards of the study prior to performing any study-related procedures. Subjects were informed that they were free not to participate in the trial and that they may have withdrawn consent to participate at any time. Before entry into the trial, consent was recorded by means of the subject's dated signature. The subject received a copy of the signed and dated ICF, and the original signed ICF was retained in the study files. The protocol, informed consent form (ICF), and other relevant study documentation were submitted by each investigator to an appropriate independent ethics committee (IEC)/institutional review board (IRB) for review and approval before study initiation.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	11 August 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 3
Country: Number of subjects enrolled	Macedonia, the former Yugoslav Republic of: 9
Country: Number of subjects enrolled	Switzerland: 5
Country: Number of subjects enrolled	Spain: 6
Country: Number of subjects enrolled	United Kingdom: 11
Country: Number of subjects enrolled	Austria: 6
Country: Number of subjects enrolled	Denmark: 8
Country: Number of subjects enrolled	France: 5
Country: Number of subjects enrolled	Germany: 12
Country: Number of subjects enrolled	Hungary: 3
Country: Number of subjects enrolled	Italy: 7

Worldwide total number of subjects	75
EEA total number of subjects	58

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)	75
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

HAE subjects with a documented recent history of frequent angioedema attacks were evaluated for participation in this study at a screening visit, which occurred within 21 days of Day 1.

### Period 1

Period 1 title	Parallel-group dose response study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

In order to make informed decisions about the conduct of the study, sponsor employees were unblinded at the time that the administrative interim data packages were available for review for each interim analysis.

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Placebo

Arm description:

- Part 1: 36 Subjects were randomized in a 1:1 ratio to placebo:berotralstat
- Part 2: 15 Subjects were randomized in a 1:3:3 ratio to placebo:berotralstat:berotralstat, with 2 different doses of berotralstat.
- Part 3: 24 Subjects were randomized in a 1:3:3:3 ratio to placebo:berotralstat:berotralstat:berotralstat, with 3 different doses of berotralstat.

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

Dosage and administration details:

The reference in this study was placebo to match berotralstat capsules. Capsules were administered orally QD for 28 days.

<b>Arm title</b>	berotralstat
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Arm description:

- Part 1: 36 Subjects were randomized in a 1:1 ratio of placebo:berotralstat
- Part 2: 15 Subjects were randomized in a 1:3:3 ratio of placebo:berotralstat (125mg):berotralstat (250mg).
- Part 3: 24 Subjects were randomized in a 1:3:3:3 ratio of placebo:berotralstat (125mg):berotralstat (250mg):berotralstat (62.5mg).

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:

The test drug in this study was berotralstat powder in capsules that were administered orally QD for 28

days.

<b>Number of subjects in period 1</b>	Placebo	berotralstat
Started	22	53
Completed	22	52
Not completed	0	1
Adverse event, non-fatal	-	1

## Baseline characteristics

### Reporting groups

Reporting group title	Parallel-group dose response study
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Reporting group description: -

Reporting group values	Parallel-group dose response study	Total	
Number of subjects	75	75	
Age categorical			
Units: Subjects			
Adults (18-64 years)	75	75	
Age continuous			
Units: years			
arithmetic mean	44.5		
standard deviation	± 12.5	-	
Gender categorical			
Units: Subjects			
Female	46	46	
Male	29	29	
Race			
Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	2	2	
Black or African American	0	0	
Native Hawaiian or other Pacific Islander	0	0	
White	68	68	
Other	5	5	
Ethnicity			
Units: Subjects			
Hispanic or Latino	6	6	
Not Hispanic or Latino	61	61	
Not Reported	5	5	
Unknown	3	3	
Weight			
Units: kilogram(s)			
arithmetic mean	78.13		
standard deviation	± 17.98	-	
Height			
Units: centimetres			
arithmetic mean	168.61		
standard deviation	± 9.72	-	
Body Mass Index			
Units: kilograms/metre			
arithmetic mean	27.44		
standard deviation	± 5.58	-	

**Subject analysis sets**

Subject analysis set title	berotralstat 350 mg
Subject analysis set type	Per protocol
Subject analysis set description: Capsules of berotralstat (350 mg) administered orally QD for 28 days.	
Subject analysis set title	berotralstat 250 mg
Subject analysis set type	Per protocol
Subject analysis set description: Capsules of berotralstat (250 mg) administered QD for 28 days.	
Subject analysis set title	berotralstat 125 mg
Subject analysis set type	Per protocol
Subject analysis set description: Capsules of berotralstat (125 mg) administered QD for 28 days.	
Subject analysis set title	berotralstat 62.5 mg
Subject analysis set type	Per protocol
Subject analysis set description: Capsules of berotralstat (62.5 mg) administered QD for 28 days.	

Reporting group values	berotralstat 350 mg	berotralstat 250 mg	berotralstat 125 mg
Number of subjects	18	14	14
Age categorical Units: Subjects			
Adults (18-64 years)	18	14	14
Age continuous Units: years			
arithmetic mean	43.8	40.9	48.1
standard deviation	± 11.6	± 13.4	± 12.6
Gender categorical Units: Subjects			
Female	11	6	10
Male	7	8	4
Race Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	1	1	0
Black or African American	0	0	0
Native Hawaiian or other Pacific Islander	0	0	0
White	15	12	14
Other	2	1	0
Ethnicity Units: Subjects			
Hispanic or Latino	1	1	0
Not Hispanic or Latino	14	10	14
Not Reported	0	3	0
Unknown	3	0	0
Weight Units: kilogram(s)			
arithmetic mean	80.13	76.88	84.28
standard deviation	± 15.83	± 13.57	± 24.44
Height			

Units: centimetres			
arithmetic mean	166.60	171.91	165.81
standard deviation	± 6.2	± 9.68	± 11.03
Body Mass Index			
Units: kilograms/metre			
arithmetic mean	28.75	25.88	30.43
standard deviation	± 4.78	± 2.97	± 6.99

<b>Reporting group values</b>	berotralstat 62.5 mg		
Number of subjects	7		
Age categorical			
Units: Subjects			
Adults (18-64 years)	7		
Age continuous			
Units: years			
arithmetic mean	38.9		
standard deviation	± 16.6		
Gender categorical			
Units: Subjects			
Female	6		
Male	1		
Race			
Units: Subjects			
American Indian or Alaska Native	0		
Asian	0		
Black or African American	0		
Native Hawaiian or other Pacific Islander	0		
White	7		
Other	0		
Ethnicity			
Units: Subjects			
Hispanic or Latino	1		
Not Hispanic or Latino	5		
Not Reported	1		
Unknown	0		
Weight			
Units: kilogram(s)			
arithmetic mean	65.66		
standard deviation	± 14.86		
Height			
Units: centimetres			
arithmetic mean	165.00		
standard deviation	± 5.13		
Body Mass Index			
Units: kilograms/metre			
arithmetic mean	24.08		
standard deviation	± 5.07		



## End points

### End points reporting groups

Reporting group title	Placebo
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Reporting group description:

- Part 1: 36 Subjects were randomized in a 1:1 ratio to placebo:berotralstat
- Part 2: 15 Subjects were randomized in a 1:3:3 ratio to placebo:berotralstat:berotralstat, with 2 different doses of berotralstat.
- Part 3: 24 Subjects were randomized in a 1:3:3:3 ratio to placebo:berotralstat:berotralstat:berotralstat, with 3 different doses of berotralstat.

Reporting group title	berotralstat
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Reporting group description:

- Part 1: 36 Subjects were randomized in a 1:1 ratio of placebo:berotralstat
- Part 2: 15 Subjects were randomized in a 1:3:3 ratio of placebo:berotralstat (125mg):berotralstat (250mg).
- Part 3: 24 Subjects were randomized in a 1:3:3:3 ratio of placebo:berotralstat (125mg):berotralstat (250mg):berotralstat (62.5mg).

Subject analysis set title	berotralstat 350 mg
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Subject analysis set type	Per protocol
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Subject analysis set description:

Capsules of berotralstat (350 mg) administered orally QD for 28 days.

Subject analysis set title	berotralstat 250 mg
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Subject analysis set type	Per protocol
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Subject analysis set description:

Capsules of berotralstat (250 mg) administered QD for 28 days.

Subject analysis set title	berotralstat 125 mg
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Subject analysis set type	Per protocol
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Subject analysis set description:

Capsules of berotralstat (125 mg) administered QD for 28 days.

Subject analysis set title	berotralstat 62.5 mg
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Subject analysis set type	Per protocol
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Subject analysis set description:

Capsules of berotralstat (62.5 mg) administered QD for 28 days.

### Primary: Difference in HAE Attack Rate

End point title	Difference in HAE Attack Rate
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End point description:

Efficacy was evaluated by the number of acute angioedema attacks. To ensure that consistent, objective assessments were used in accepting subject-reported attack data, a panel of expert physicians in the treatment of HAE patients adjudicated all subject-reported attacks prior to their inclusion in primary efficacy analyses.

End point type	Primary
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End point timeframe:

Investigators collected data from patient diaries from the first day of dosing through Day 29 (the effective dosing period).

End point values	Placebo	berotralstat	berotralstat 350 mg	berotralstat 250 mg
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	22	53	18	14
Units: attacks/week				
least squares mean (standard error)				
HAE Attack Rate: Entire Dosing Period	0.952 ( $\pm$ 0.104)	0.494 ( $\pm$ 0.067)	0.519 ( $\pm$ 0.115)	0.527 ( $\pm$ 0.130)

End point values	berotralstat 125 mg	berotralstat 62.5 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	14	7		
Units: attacks/week				
least squares mean (standard error)				
HAE Attack Rate: Entire Dosing Period	0.249 ( $\pm$ 0.130)	0.852 ( $\pm$ 0.185)		

## Statistical analyses

Statistical analysis title	Difference vs Placebo: All berotralstat
Statistical analysis description:	
The primary analysis of treatment-effect was performed using an ANCOVA with the adjusted qualifying attack rate as the covariate. Statistically significant and clinically meaningful reductions in the rate of attacks were observed in subjects treated with berotralstat compared to placebo at doses $\geq$ 125 mg QD.	
Comparison groups	Placebo v berotralstat
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Difference Least Mean Square
Point estimate	-0.458
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.703
upper limit	-0.214

Statistical analysis title	Difference vs Placebo: berotralstat 350 mg
Statistical analysis description:	
The primary analysis of treatment-effect was performed using an ANCOVA with the adjusted qualifying attack rate as the covariate. Statistically significant and clinically meaningful reductions in the rate of attacks were observed in subjects treated with 350 mg berotralstat compared to placebo.	
Comparison groups	Placebo v berotralstat 350 mg

Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.006
Method	ANCOVA
Parameter estimate	Difference Least Mean Square
Point estimate	-0.433
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.74
upper limit	-0.127

<b>Statistical analysis title</b>	Difference vs Placebo: berotralstat 250 mg
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Statistical analysis description:

The primary analysis of treatment-effect was performed using an ANCOVA with the adjusted qualifying attack rate as the covariate. Statistically significant and clinically meaningful reductions in the rate of attacks were observed in subjects treated with 250 mg berotralstat compared to placebo.

Comparison groups	Placebo v berotralstat 250 mg
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.012
Method	ANCOVA
Parameter estimate	Difference Least Mean Square
Point estimate	-0.425
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.755
upper limit	-0.095

<b>Statistical analysis title</b>	Difference vs Placebo: berotralstat 125 mg
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Statistical analysis description:

The primary analysis of treatment-effect was performed using an ANCOVA with the adjusted qualifying attack rate as the covariate. Statistically significant and clinically meaningful reductions in the rate of attacks were observed in subjects treated with 125 mg berotralstat compared to placebo.

Comparison groups	Placebo v berotralstat 125 mg
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Difference Least Mean Square
Point estimate	-0.703

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.033
upper limit	-0.373

<b>Statistical analysis title</b>	Difference vs Placebo: berotralstat 62.5 mg
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Statistical analysis description:

The primary analysis of treatment-effect was performed using an ANCOVA with the adjusted qualifying attack rate as the covariate. Statistically significant reductions in the rate of attacks were not observed in subjects treated with 62.5 mg berotralstat compared to placebo.

Comparison groups	Placebo v berotralstat 62.5 mg
Number of subjects included in analysis	29
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.639
Method	ANCOVA
Parameter estimate	Difference Least Mean Square
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.52
upper limit	0.32

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse event data were collected from Day 1 of the treatment period of the study through the last dose plus 30 days.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

### Reporting groups

Reporting group title	Placebo
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Reporting group description:

The reference in this study was placebo capsules to match berotralstat capsules.

Reporting group title	berotralstat
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Reporting group description:

Part 1: Subjects were randomized in a 1:1 ratio to placebo:berotralstat. A total of 36 subjects were enrolled and treated in Part 1: 18 berotralstat (350 mg) and 18 placebo subjects.

Part 2: Subjects were randomized in a 1:3:3 ratio. A total of 15 subjects were enrolled and treated in Part 2: 6 berotralstat (250mg), 7 berotralstat (125mg) and 2 placebo subjects.

Part 3: Subjects were randomized in a 1:3:3:3 ratio to placebo:berotralstat (125mg):berotralstat (250mg):berotralstat (62.5mg). A total of 24 subjects were enrolled and treated in Part 3: 8 berotralstat (250mg), 7 berotralstat (125mg), 7 berotralstat (62.5mg) and 2 placebo subjects.

Serious adverse events	Placebo	berotralstat	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 22 (0.00%)	1 / 53 (1.89%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Gastrointestinal disorders			
Gastrointestinal infection			
subjects affected / exposed	0 / 22 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Placebo	berotralstat	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 22 (68.18%)	36 / 53 (67.92%)	
Investigations			

Alanine aminotransferase increased subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	2 / 53 (3.77%) 2	
Injury, poisoning and procedural complications Contusion subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1	1 / 53 (1.89%) 1	
Nervous system disorders Headache subjects affected / exposed occurrences (all)  Migraine subjects affected / exposed occurrences (all)	4 / 22 (18.18%) 4  0 / 22 (0.00%) 0	6 / 53 (11.32%) 6  2 / 53 (3.77%) 2	
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all)  Influenza like illness subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1  1 / 22 (4.55%) 1	3 / 53 (5.66%) 3  1 / 53 (1.89%) 1	
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all)  Abdominal pain upper subjects affected / exposed occurrences (all)  Diarrhoea subjects affected / exposed occurrences (all)  Flatulence subjects affected / exposed occurrences (all)  Nausea	0 / 22 (0.00%) 0  0 / 22 (0.00%) 0  2 / 22 (9.09%) 2  0 / 22 (0.00%) 0	6 / 53 (11.32%) 6  3 / 53 (5.66%) 3  6 / 53 (11.32%) 6  2 / 53 (3.77%) 2	

subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	6 / 53 (11.32%) 6	
Vomiting subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	2 / 53 (3.77%) 2	
Constipation subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1	1 / 53 (1.89%) 1	
Gastrooesophageal reflux disease subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1	1 / 53 (1.89%) 1	
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	2 / 22 (9.09%) 2	0 / 53 (0.00%) 0	
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1	1 / 53 (1.89%) 1	
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	6 / 22 (27.27%) 6	8 / 53 (15.09%) 8	
Pharyngitis subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	2 / 53 (3.77%) 2	
Gastrointestinal infection subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	2 / 53 (3.77%) 2	
Upper respiratory tract infection subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1	1 / 53 (1.89%) 1	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 September 2016	Protocol Amendment 1.0 * The follow-up visit was changed from Day 42 to Day 44. *In the inclusion criteria, clinical diagnosis for Type 1 HAE was modified. *The contraceptive requirements were updated. *Summary findings for Study BCX7353 101 were updated based on final data for the study.
30 December 2016	Protocol Amendment 2.0 Additional safety laboratory analyses were added.
21 March 2017	Protocol Amendment 3.0 *The power assessment based on sample size and study attack rate was corrected. *Reference to the collection of a blood sample for cleaved HK as a possible exploratory PD analysis was removed..

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported

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### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/30044938>