Clinical trial results:
An Open-Label study to Evaluate the Long-Term Safety of Daily Oral BCX7353 in subjects with Type I and II Hereditary Angioedema

Summary

EudraCT number	2017-003281-27
Trial protocol	GB DE HU DK AT ES SK PL BE NL IT
Global end of trial date	27 April 2022

Results information

Result version number	v1 (current)
This version publication date	15 December 2022
First version publication date	15 December 2022

Trial information

Trial identification

Sponsor protocol code	BCX7353-204

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03472040
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)	EMEA-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	15 July 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 April 2022
Global end of trial reached?	Yes
Global end of trial date	27 April 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the long-term safety and tolerability of daily dosing of oral BCX7353 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), 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. Signed informed consent was obtained from each adult subject or parent or guardian of adolescent subjects prior to performing any study-related procedures. Similarly, subject assent by subjects aged 12 to 17 was obtained from each adolescent prior to performing any study-related procedures. The informed consent/assent process took place under conditions where the subject and/or parent/guardian had adequate time to consider the risks and benefits associated with the subject's participation in the study. The Investigator explained 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	27 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	Australia: 20
Country: Number of subjects enrolled	United States: 165
Country: Number of subjects enrolled	Hong Kong: 7
Country: Number of subjects enrolled	Israel: 40
Country: Number of subjects enrolled	North Macedonia: 6
Country: Number of subjects enrolled	New Zealand: 7
Country: Number of subjects enrolled	Serbia: 6
Country: Number of subjects enrolled	South Africa: 22
Country: Number of subjects enrolled	Korea, Republic of: 12
Country: Number of subjects enrolled	Switzerland: 6
Country: Number of subjects enrolled	Netherlands: 3
Country: Number of subjects enrolled	Poland: 23
Country: Number of subjects enrolled	Slovakia: 13

Country: Number of subjects enrolled	Spain: 2
Country: Number of subjects enrolled	United Kingdom: 16
Country: Number of subjects enrolled	Austria: 4
Country: Number of subjects enrolled	Belgium: 1
Country: Number of subjects enrolled	Denmark: 7
Country: Number of subjects enrolled	France: 6
Country: Number of subjects enrolled	Germany: 10
Country: Number of subjects enrolled	Hungary: 3
Country: Number of subjects enrolled	Italy: 8
Worldwide total number of subjects	387
EEA total number of subjects	80

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	28
Adults (18-64 years)	346
From 65 to 84 years	13
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Subjects with a clinical diagnosis of HAE Type 1 or 2 who, in the opinion of the investigator, were expected to benefit from an oral treatment for the prevention of angioedema attacks were eligible for the study.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	110 mg followed by 150 mg Berotralstat

Arm description:

Subjects were initially treated with berotralstat 110 mg QD. Following the results from Part 1 of Study BCX7353-302, all subjects were transitioned to a berotralstat dose of 150 mg QD.

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:

Subjects initially received 1x 110 mg capsule of berotralstat QD. Once transitioned to the 150 mg dose, subjects received either 3x 50 mg capsules or 1x 150 mg capsules QD. Dosing continued for up to 96 weeks (US) / 240 weeks (ROW)

Arm title	150 mg Berotralstat

Arm description:

Subjects were treated with berotralstat 150 mg QD.

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:

Subjects received either 3x 50 mg capsules or 1x 150 mg capsules QD. Dosing continued for up to 96 weeks (US) / 240 weeks (ROW)

Number of subjects in period 1	110 mg followed by 150 mg Berotralstat	150 mg Berotralstat
Started	100	287
Completed	0	1
Not completed	100	286
Intercurrent illness/new medical condition	2	3
Consent withdrawn by subject	10	23
Physician decision	-	3
Subject non-compliance	2	5
Lab abnormality or AE	7	25
Perceived lack of efficacy	29	30
Other	4	19
Berotralstat provided by alternative means	46	175
Subsequent ineligibility	-	2
Discontinuation due to rash	-	1

Baseline characteristics

Reporting groups	
Reporting group title	110 mg followed by 150 mg Berotralstat
Reporting group description:	
Subjects were initially treated with berotralstat 110 mg QD. Following the results from Part 1 of Study BCX7353-302, all subjects were transitioned to a berotralstat dose of 150 mg QD.	

Reporting group title	150 mg Berotralstat
Reporting group description:	
Subjects were treated with berotralstat 150 mg QD.	

Reporting group values	110 mg followed by 150 mg Berotralstat	150 mg Berotralstat	Total
Number of subjects	100	287	387
Age categorical Units: Subjects			
Adolescents (12-17 years)	5	23	28
Adults (18-64 years)	93	253	346
From 65-84 years	2	11	13
Age continuous Units: years			
arithmetic mean	37.6	40.5	
standard deviation	± 14.04	± 15.26	-
Gender categorical Units: Subjects			
Female	62	180	242
Male	38	107	145

End points

End points reporting groups

Reporting group title	110 mg followed by 150 mg Berotralstat

Reporting group description:

Subjects were initially treated with berotralstat 110 mg QD. Following the results from Part 1 of Study BCX7353-302, all subjects were transitioned to a berotralstat dose of 150 mg QD.

Reporting group title	150 mg Berotralstat

Reporting group description:

Subjects were treated with berotralstat 150 mg QD.

Primary: Safety & Tolerability

End point title	Safety & Tolerability[1]

End point description:

The safety population included all subjects who received at least 1 dose of study drug. This population was used in the assessment and reporting of safety data.

End point type	Primary

End point timeframe:

Up to 96 weeks (US / 240 weeks (ROW).

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 was safety and tolerability; no statistical analysis is considered applicable

End point values	110 mg followed by 150 mg Berotralstat	150 mg Berotralstat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	100	287		
Units: subjects				
TEAE	94	240		
Drug-related TEAE	58	119		
TESAE	23	20		
Drug-related TESAE	3	1		
DMID Grade 3 or 4 TEAE	18	35		
Drug-related DMID Grade 3 or 4 TEAE	7	11		
TEAE leading to study drug discontinuation	8	28		
TEAE leading to study drug interruption	8	32		
Drug-related rash	5	5		
Drug-related rash leading to IMP discontinuation	1	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of HAE attacks

End point title	Number of HAE attacks

End point description:

Number of 'adjusted' attacks were assessed. Adjusted attacks included at least 1 symptom of swelling, had a response of 'no' to the diary question, 'In retrospect, could there be an alternative explanation for your symptoms other than an HAE attack (i.e., allergic reaction, viral cold etc.)?', and were considered unique (attack began > 24 hours from the end of the prior attack). Any attack that began within 24 hours from the end of a prior attack was combined with the prior attack.

End point type	Secondary

End point timeframe:

Up to 96 weeks (US) / 240 weeks (ROW)

End point values	110 mg followed by 150 mg Berotralstat	150 mg Berotralstat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	100	287		
Units: subjects				
Subjects reporting at least 1 attack	95	231		
Subjects reporting at least 1 treated attack	87	214		
Subjects reporting at least 1 untreated attack	59	99		

Statistical analyses

No statistical analyses for this end point

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.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	110 mg followed by 150 mg Berotralstat

Reporting group description:

Subjects were initially treated with berotralstat 110 mg QD. Following the results from Part 1 of Study BCX7353-302, all subjects were transitioned to a berotralstat dose of 150 mg QD.

Reporting group title	150 mg Berotralstat

Reporting group description:

Subjects were treated with berotralstat 150 mg QD.

Serious adverse events	110 mg followed by 150 mg Berotralstat	150 mg Berotralstat	
Total subjects affected by serious adverse events			
subjects affected / exposed	23 / 100 (23.00%)	20 / 287 (6.97%)	
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)			
Acute myelomonocytic leukaemia			
subjects affected / exposed	0 / 100 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	2 / 100 (2.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ruptured ectopic pregnancy			
subjects affected / exposed	0 / 100 (0.00%)	1 / 287 (0.35%)	
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			
Chest pain			
subjects affected / exposed	0 / 100 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 100 (1.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 100 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide attempt			
subjects affected / exposed	0 / 100 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Medical observation			
subjects affected / exposed	2 / 100 (2.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic enzyme increased			
subjects affected / exposed	1 / 100 (1.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver function test abnormal			
subjects affected / exposed	0 / 100 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			

Lower limb fracture			
subjects affected / exposed	1 / 100 (1.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radius fracture			
subjects affected / exposed	1 / 100 (1.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	0 / 100 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seroma			
subjects affected / exposed	0 / 100 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Hereditary angioedema			
subjects affected / exposed	11 / 100 (11.00%)	2 / 287 (0.70%)	
occurrences causally related to treatment / all	0 / 36	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Splenic hamartoma			
subjects affected / exposed	0 / 100 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 100 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 100 (1.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Nervous system disorders			
Facial paralysis			
subjects affected / exposed	1 / 100 (1.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Enteritis			
subjects affected / exposed	2 / 100 (2.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	1 / 100 (1.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 100 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 100 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 100 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary colic			
subjects affected / exposed	0 / 100 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			

subjects affected / exposed	0 / 100 (0.00%)	2 / 287 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Foot deformity			
subjects affected / exposed	0 / 100 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protrusion			
subjects affected / exposed	0 / 100 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	2 / 100 (2.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal abscess			
subjects affected / exposed	1 / 100 (1.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 100 (1.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	1 / 100 (1.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gingivitis			
subjects affected / exposed	1 / 100 (1.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Peritonsillar abscess			
subjects affected / exposed	0 / 100 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	0 / 100 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			
subjects affected / exposed	1 / 100 (1.00%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	110 mg followed by 150 mg Berotralstat	150 mg Berotralstat	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	94 / 100 (94.00%)	240 / 287 (83.62%)	
Nervous system disorders			
Headache			
subjects affected / exposed	23 / 100 (23.00%)	34 / 287 (11.85%)	
occurrences (all)	44	49	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	14 / 100 (14.00%)	42 / 287 (14.63%)	
occurrences (all)	17	51	
Abdominal pain			
subjects affected / exposed	14 / 100 (14.00%)	29 / 287 (10.10%)	
occurrences (all)	40	37	
Gastrooesophageal reflux disease			
subjects affected / exposed	8 / 100 (8.00%)	14 / 287 (4.88%)	
occurrences (all)	8	16	
Vomiting			
subjects affected / exposed	3 / 100 (3.00%)	17 / 287 (5.92%)	
occurrences (all)	3	17	

Nausea			
subjects affected / exposed	9 / 100 (9.00%)	28 / 287 (9.76%)	
occurrences (all)	10	32	
Abdominal pain upper			
subjects affected / exposed	10 / 100 (10.00%)	18 / 287 (6.27%)	
occurrences (all)	13	25	
Dyspepsia			
subjects affected / exposed	5 / 100 (5.00%)	19 / 287 (6.62%)	
occurrences (all)	5	21	
Abdominal discomfort			
subjects affected / exposed	6 / 100 (6.00%)	17 / 287 (5.92%)	
occurrences (all)	7	25	
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	10 / 100 (10.00%)	12 / 287 (4.18%)	
occurrences (all)	19	20	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	33 / 100 (33.00%)	59 / 287 (20.56%)	
occurrences (all)	84	140	
Upper respiratory tract infection			
subjects affected / exposed	14 / 100 (14.00%)	36 / 287 (12.54%)	
occurrences (all)	31	47	
COVID-19			
subjects affected / exposed	10 / 100 (10.00%)	20 / 287 (6.97%)	
occurrences (all)	10	20	
Influenza			
subjects affected / exposed	8 / 100 (8.00%)	20 / 287 (6.97%)	
occurrences (all)	8	25	
Urinary tract infection			
subjects affected / exposed	7 / 100 (7.00%)	21 / 287 (7.32%)	
occurrences (all)	10	33	
Sinusitis			
subjects affected / exposed	10 / 100 (10.00%)	15 / 287 (5.23%)	
occurrences (all)	20	19	
Gastroenteritis			

subjects affected / exposed occurrences (all)	10 / 100 (10.00%) 11	12 / 287 (4.18%) 17	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 December 2017	The protocol was adapted to allow patients to participate in LTSS, who had not previously participated in efficacy studies of berotralstat. An efficacy study (BCX7353-302) with the same doses was conducted in parallel to this study. Thus, the design was amended to two arms to collect safety data of for treatment with 110 mg and 150 mg berotralstat. To obtain significant safety data, the number of patients included was increased to 200. Exclusion criterion 13 regarding creatinine clearance and transaminases was broadened following regulatory authority feedback, to allow inclusion of patients in the study that were more representative of the general HAE patient population. Additional safety assessments were added to monitor transaminase elevation.
06 December 2017	Expansion of inclusions criteria to include adolescent subjects ≥ 12 to 17 years of age to screen and enroll in participating regions. Expansion of inclusion criteria to allow enrolment of subjects who had not previously participated in a berotralstat study; i.e., subjects with a clinical diagnosis of HAE Type 1 or 2 who, in the opinion of the Investigator, were expected to benefit from treatment with an oral treatment for the prevention of angioedema attacks.
05 October 2018	Introduction of additional stopping criteria associated with liver enzyme elevations to precisely reflect FDA Guidance on Drug-Induced Liver Injury: Premarketing Clinical Evaluation. Clarification of requirements for discontinuation due to QTcF increase. Study duration extended to 96 weeks. To obtain significant safety data, the number of patients included was increased to 225.
07 February 2019	US-Specific Protocol Amendment. Protocol was updated to reflect the addition of multiple centres in the US. Amendment to remove reference to participation in a prior berotralstat study for US subjects, since completed studies of BCX7353 were conducted in Europe only. Additional safety screening assessments to characterise liver function after cessation of androgens and prior to allocation to study drug. Number of subjects increased to 275 including approximately 50 subjects in the US. To provide updated guidance on the management of subjects with treatment emergent increases in serum aminotransferases, based on the accumulation of clinical experience with dosing berotralstat.
31 July 2019	US-specific Protocol Amendment. Based on the results of BCX7353-302, Part 1, all subjects were transitioned to the 150 mg berotralstat dose level. Number of subjects increased to 475 including approximately 250 subjects in the US. Inclusion criteria updated to allow historic lab diagnosis of HAE. Amendment to allow males to participate in the study, without the need for contraception. Berotralstat has no identifiable genotoxicity risks, no evidence of effects on male fertility and no evidence of fetotoxicity in animal studies. Female participants continued to be required to take acceptable effective contraception.

21 August 2019	Amendment to allow subjects to continue receiving berotralstat for up to 240 weeks OR until an alternative method was available for participants to access berotralstat (locally marketed or market access program). Amendment to allow males to participate in the study, without the need for contraception. Berotralstat has no identifiable genotoxicity risks, no evidence of effects on male fertility and no evidence of fetotoxicity in animal studies. Female participants continued to be required to take acceptable effective contraception. Based on the results of BCX7353-302, Part 1, all subjects were transitioned to the 150 mg berotralstat dose level. Number of subjects increased to 475 including approximately 250 subjects in the US. Updated guidance regarding stopping criteria associated with liver enzyme elevations based on the accumulation of clinical experience with berotralstat dosing.
06 February 2020	US-specific Protocol Amendment. Protocol provided interim results from the study as well as updated benefit/risk to reflect information from BCX7353-302. As a result of additional safety data, the number of clinic visits were reduced and DMC meeting frequency decreased to every 6 months. Exclusion criterion relating to potential prolongation removed following negative results in a thorough QT study and no other cardiac signal having been detected. Prohibited Concomitant Medications also updated as a result of this. Exclusion criterion regarding creatinine clearance and transaminases was removed, as cumulative safety data had determined no additional safety risk in subjects with severe renal or hepatic disease dosed with berotralstat. Protocol clarified regarding evaluation of rash events, which were confirmed as a delayed type hypersensitivity benign drug rash that does not result in T-cell memory. The rash phenotype and biopsy results had been consistent throughout the development program, making it unlikely that additional data collection on other types of skin conditions or rashes not suspected to be due to study drug would be useful in further understanding the drug rash. Drug rashes continued to require enhanced data collection, and the need to discontinue study drug with severe rash remained.
23 March 2020	US-specific Protocol Amendment. To require coagulation parameters to be collected for all patients as part of routine safety labs. Reintroduction of limited PK samples in the first 12 weeks for adolescent subjects, to gain additional data to support future paediatric development.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported