Clinical trial results:
A Phase 2a double-blind placebo-controlled 2-period crossover study to evaluate the safety and efficacy of BCX4161 as a prophylactic treatment to reduce the frequency of attacks in subjects with hereditary angioedema

Summary

EudraCT number	2013-002319-82
Trial protocol	DE GB
Global end of trial date	13 May 2014

Results information

Result version number	v1 (current)
This version publication date	11 March 2021
First version publication date	11 March 2021

Trial information

Trial identification

Sponsor protocol code	BCX4161-203

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01984788
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	BioCryst Pharmaceuticals Inc
Sponsor organisation address	4505 Emperor Blvd, Durham, United States, NC 27703
Public contact	Study Director, BioCryst Pharmaceuticals Inc, 001 919 859 1302, clinicaltrials@biocryst.com
Scientific contact	Study Director, BioCryst Pharmaceuticals Inc, 001 919 859 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	29 May 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	13 May 2014
Global end of trial reached?	Yes
Global end of trial date	13 May 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the effect of prophylactic Avoralstat (BCX4161) as measured by the frequency of attacks in subjects with hereditary angioedema (HAE)

Protection of trial subjects:

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

Background therapy:

Subjects used their prescribed standard of care medication to treat any breakthrough HAE attacks on study

Evidence for comparator: -

Actual start date of recruitment	23 October 2013
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	United Kingdom: 4
Country: Number of subjects enrolled	Germany: 20
Worldwide total number of subjects	24
EEA total number of subjects	24

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0

Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	24
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Subjects attended a Screening Visit up to 14 days before dosing for assessment of eligibility to participate in the study. Healthy male and healthy non-pregnant, non lactating female subjects aged 18 to 65 years who had a clinical diagnosis of hereditary angioedema with an average of 1 attack per week over at least a 3 month period were eligible.

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, Data analyst, Subject, Carer, Assessor

Arms

Are arms mutually exclusive?	No
Arm title	Avoralstat

Arm description:

Subjects who met all eligibility criteria were randomized to 1 of 2 treatment sequences. Treatment Sequence 1: Subjects received 28 days of Avoralstat at a dose of 400 mg administered 3 times per day, followed by 28 days of placebo treatment administered 3 times per day. Treatment Sequence 2: Subjects received 28 days of placebo treatment administered 3 times per day, followed by 28 days of Avoralstat at a dose of 400 mg administered 3 times per day. A washout period of at least 7 days was imposed between administration of each 28-day regimen of study drug (Avoralstat or placebo).

Arm type	Experimental
Investigational medicinal product name	Avoralstat
Investigational medicinal product code	
Other name	BCX4161
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Subjects received 28 days of Avoralstat 4× 100-mg capsules for oral administration 3 times per day (total daily dose of 1200 mg)

Arm title	Placebo

Arm description:

Subjects who met all eligibility criteria were randomized to 1 of 2 treatment sequences. Treatment Sequence 1: Subjects received 28 days of Avoralstat at a dose of 400 mg administered 3 times per day, followed by 28 days of placebo treatment administered 3 times per day. Treatment Sequence 2: Subjects received 28 days of placebo treatment administered 3 times per day, followed by 28 days of Avoralstat at a dose of 400 mg administered 3 times per day. A washout period of at least 7 days was imposed between administration of each 28-day regimen of study drug (Avoralstat or placebo).

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

Dosage and administration details:

Subjects received 28 days of matching placebo capsules administered as 4 capsules 3 times per day.

Number of subjects in period 1	Avoralstat	Placebo
Started	24	24
Completed	24	24

Baseline characteristics

Reporting groups	
Reporting group title	Overall Study

Reporting group description: -

Reporting group values	Overall Study	Total	
Number of subjects	24	24	
Age categorical Units: Subjects			
Adults (18-64 years)	24	24	
Age continuous Units: years			
arithmetic mean	42.4		
standard deviation	± 11.4	-	
Gender categorical Units: Subjects			
Female	15	15	
Male	9	9	

End points

End points reporting groups

Reporting group title	Avoralstat

Reporting group description:

Subjects who met all eligibility criteria were randomized to 1 of 2 treatment sequences. Treatment Sequence 1: Subjects received 28 days of Avoralstat at a dose of 400 mg administered 3 times per day, followed by 28 days of placebo treatment administered 3 times per day. Treatment Sequence 2: Subjects received 28 days of placebo treatment administered 3 times per day, followed by 28 days of Avoralstat at a dose of 400 mg administered 3 times per day. A washout period of at least 7 days was imposed between administration of each 28-day regimen of study drug (Avoralstat or placebo).

Reporting group title	Placebo

Reporting group description:

Subjects who met all eligibility criteria were randomized to 1 of 2 treatment sequences. Treatment Sequence 1: Subjects received 28 days of Avoralstat at a dose of 400 mg administered 3 times per day, followed by 28 days of placebo treatment administered 3 times per day. Treatment Sequence 2: Subjects received 28 days of placebo treatment administered 3 times per day, followed by 28 days of Avoralstat at a dose of 400 mg administered 3 times per day. A washout period of at least 7 days was imposed between administration of each 28-day regimen of study drug (Avoralstat or placebo).

Primary: Rate of Confirmed Acute Attacks

End point title	Rate of Confirmed Acute Attacks

End point description:

Efficacy was evaluated by the rate of acute HAE 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

End point timeframe:

Investigators collected data from patient diaries from the first day of dosing through to Day 28 of each dosing period.

End point values	Avoralstat	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	24		
Units: HAE attacks/week				
least squares mean (standard deviation)	0.821 (± 0.5514)	1.274 (± 0.5006)		

Statistical analyses

Statistical analysis title	Difference in HAE attack rates
Comparison groups	Avoralstat v Placebo

Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.001
Method	Fixed Effect
Parameter estimate	Difference Least Mean Square
Point estimate	-0.453
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.679
upper limit	-0.227

Secondary: Number of Attack Free Days

End point title	Number of Attack Free Days

End point description:

Assessment of the number of days each subject experienced no HAE attacks during each treatment period with Avoralstat or Placebo

End point type	Secondary

End point timeframe:

Investigators collected data on HAE attacks from patient diaries from the first day of dosing through to Day 28 of each dosing period.

End point values	Avoralstat	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	24		
Units: Attack-free Days				
least squares mean (standard deviation)	22.1 (± 4.88)	19.0 (± 3.82)		

Statistical analyses

Statistical analysis title	Difference in HAE attack-free Days
Comparison groups	Avoralstat v Placebo
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.008
Method	Fixed Effect
Parameter estimate	Difference Least Mean Square
Point estimate	3.083

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.888
upper limit	5.279

Secondary: Angioedema Quality of Life (AE-QoL)

End point title	Angioedema Quality of Life (AE-QoL)

End point description:

Quality of Life (QoL) specific to hereditary angioedema (HAE) was assessed at baseline and Day 29 of each treatment period by a questionnaire (i.e. AE-QoL) consisting of 17 questions that spanned 4 domains (functioning, fatigue/mood, fear/shame, and nutrition). Each AE-QoL question had 5 answer options (scored 1-5), with lower and higher scores indicting less and more adverse impact, respectively. Per-subject scores for each domain were computed using the appropriate scoring algorithm applied to the question response scores for each domain. Per-subject total scores (including all 4 domains) were similarly computed using the question response scores for all 17 questions. The outputs from the scoring algorithm were normalized on a scale ranging from 0 (less adverse impact) to 100 (most adverse impact). The statistical analysis of the AE-QoL total score change from baseline to Day 29 is presented below.

End point type	Secondary

End point timeframe:

Day 1 & 29 of each treatment period

End point values	Avoralstat	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	24		
Units: AE-QoL score - change from baseline				
arithmetic mean (standard deviation)	-8.5 (± 13.38)	-0.6 (± 8.76)		

Statistical analyses

Statistical analysis title	Total AE-QoL Change from Baseline Score
Comparison groups	Avoralstat v Placebo
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.004
Method	Fixed Effect
Parameter estimate	Difference Least Mean Square
Point estimate	-7.904
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.981
upper limit	-2.827

Secondary: Pharmacokinetics - Avoralstat Day 14 AUC(0-3)

End point title	Pharmacokinetics - Avoralstat Day 14 AUC(0-3)[1]

End point description:

Avoralstat plasma concentrations were evaluated in all 24 subjects during both treatment periods on Days 1 and 14 at pre-dose, 0.5, 1, 2 and 3 hours post morning dose and on Day 7 at pre-morning dose and also on Day 29. For 15 subjects who consented for the PK sub-study, Avoralstat plasma concentrations were also evaluated during both treatment periods on Day 14 at 4, 6, and 8 hours post-morning dose. Mean Avoralstat plasma concentration versus time profile after oral administration of multiple doses of Avoralstat was used to determine AUC(0-3) at Day 14.

End point type	Secondary

End point timeframe:

Both treatment periods: Day 1 & 14 pre-dose, 0.5, 1, 2 & 3 hrs post-morning dose; Day 7 pre-morning dose; Day 29. Optional - Both treatment periods: Day 14 at 4, 6 & 8 hrs post-morning dose

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Avoralstat PK parameters only reported for Avoralstat treatment periods; not applicable for placebo treatment periods.

End point values	Avoralstat			
Subject group type	Reporting group			
Number of subjects analysed	23[2]			
Units: hr*ng/mL				
arithmetic mean (standard deviation)	307.85 (± 250.63)			

Notes:

[2] - PK parameter cannot be estimated in 1 subject due to insufficient data.

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Kallikrein Inhibition - Day 29

End point title	Plasma Kallikrein Inhibition - Day 29

End point description:

Kallikrein activity was evaluated in all 24 subjects during Avoralstat treatment and in 22 subjects during placebo treatment on Days 1 & 14 at pre-dose, 0.5, 1, 2 and 3 hrs after the morning dose, on Day 7 prior to dosing and on Day 29. In addition, kallikrein activity was evaluated over the 8-hr dosing interval in a subset of 15 subjects on Day 14. Mean kallikrein inhibition was determined after oral administration of multiple doses of Avoralstat and placebo. Mean kallikrein inhibition at the end of each treatment period (Avoralstat or placebo) is presented below.

End point type	Secondary

End point timeframe:

Both treatment periods: Day 1 & 14 pre-dose, 0.5, 1, 2 & 3 hrs post-morning dose; Day 7 pre-morning dose; Day 29. Optional - Both treatment periods: Day 14 at 4, 6 & 8 hrs post-morning dose

End point values	Avoralstat	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	18		
Units: % Inhibition				
arithmetic mean (standard deviation)	19.10 (± 30.138)	-17.51 (± 43.878)		

Statistical analyses

No statistical analyses for this end point

Secondary: C1 Esterase Inhibitor (C1 INH) Levels - Day 29

End point title	C1 Esterase Inhibitor (C1 INH) Levels - Day 29

End point description:

C1 INH antigen levels were evaluated in 23 subjects during Avoralstat or placebo treatment on Days 1, 29, and 36. Mean C1 INH antigen level change from baseline on Day 29 of each treatment period (Avoralstat or placebo) is presented below.

End point type	Secondary

End point timeframe:

Days 1, 29 and 36.

End point values	Avoralstat	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	16		
Units: mg/dL				
arithmetic mean (standard deviation)	-1.28 (± 4.827)	0.26 (± 3.613)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events (AEs) reported from informed consent signature until the follow-up visit (8 days +/-2 days after last dose IMP) or until the AE is resolved or the subject is in a clinically stable condition with regards to the AE.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16

Reporting groups

Reporting group title	Avoralstat

Reporting group description:

Subjects who met all eligibility criteria were randomized to 1 of 2 treatment sequences. Treatment Sequence 1: Subjects received 28 days of Avoralstat at a dose of 400 mg administered 3 times per day, followed by 28 days of placebo treatment administered 3 times per day. Treatment Sequence 2: Subjects received 28 days of placebo treatment administered 3 times per day, followed by 28 days of Avoralstat at a dose of 400 mg administered 3 times per day. A washout period of at least 7 days was imposed between administration of each 28-day regimen of study drug (Avoralstat or placebo).

Reporting group title	Placebo

Reporting group description:

Subjects who met all eligibility criteria were randomized to 1 of 2 treatment sequences. Treatment Sequence 1: Subjects received 28 days of Avoralstat at a dose of 400 mg administered 3 times per day, followed by 28 days of placebo treatment administered 3 times per day. Treatment Sequence 2: Subjects received 28 days of placebo treatment administered 3 times per day, followed by 28 days of Avoralstat at a dose of 400 mg administered 3 times per day. A washout period of at least 7 days was imposed between administration of each 28-day regimen of study drug (Avoralstat or placebo).

Serious adverse events	Avoralstat	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 24 (0.00%)	1 / 24 (4.17%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Immune system disorders			
Hereditary angioedema			
subjects affected / exposed	0 / 24 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Avoralstat	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 24 (70.83%)	20 / 24 (83.33%)	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	2 / 24 (8.33%)	0 / 24 (0.00%)	
occurrences (all)	2	0	
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 24 (16.67%)	4 / 24 (16.67%)	
occurrences (all)	4	4	
Vertigo			
subjects affected / exposed	2 / 24 (8.33%)	0 / 24 (0.00%)	
occurrences (all)	2	0	
Blood and lymphatic system disorders			
Splenomegaly			
subjects affected / exposed	3 / 24 (12.50%)	0 / 24 (0.00%)	
occurrences (all)	3	0	
Gastrointestinal disorders			
Flatulence			
subjects affected / exposed	4 / 24 (16.67%)	6 / 24 (25.00%)	
occurrences (all)	4	6	
Diarrhoea			
subjects affected / exposed	3 / 24 (12.50%)	5 / 24 (20.83%)	
occurrences (all)	3	5	
Dyspepsia			
subjects affected / exposed	2 / 24 (8.33%)	1 / 24 (4.17%)	
occurrences (all)	2	1	
Nausea			
subjects affected / exposed	0 / 24 (0.00%)	3 / 24 (12.50%)	
occurrences (all)	0	3	
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	0 / 24 (0.00%)	2 / 24 (8.33%)	
occurrences (all)	0	2	
Skin and subcutaneous tissue disorders			

Cold sweat subjects affected / exposed occurrences (all)	2 / 24 (8.33%) 2	0 / 24 (0.00%) 0	
Musculoskeletal and connective tissue disorders Musculoskeletal pain subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	2 / 24 (8.33%) 2	
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	4 / 24 (16.67%) 4	7 / 24 (29.17%) 7	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 September 2013	An independent Data Monitoring Committee (DMC) was added to periodically review safety data in accordance with a separate DMC Charter. Inclusion criterion number 5a was modified to indicate that estrogen-containing hormonal contraception was only permitted if it had been used for at least 60 days prior to screening. The washout period between Periods 1 and 2 was expanded to indicate a minimum of 7 days and a maximum of 14 days to allow for flexibility.
01 November 2013	an intravenous or subcutaneous treatment indicated for treatment of acute attacks to treat symptoms. The ITT population was modified to include all subjects who were randomized and received at least 1 dose of study drug in both study periods.
11 February 2014	A Clinical Endpoint Adjudication Panel (CEAP) was implemented to review and confirm subject-reported attacks for inclusion in all efficacy analyses. The CEAP was defined in a separate charter that delineated membership, roles, and processes. Inclusion criterion number 5a was modified to indicate that progestin-containing hormonal contraception was only permitted if it had been used for at least 60 days prior to screening although IUDs with progestin would be permitted to be placed any time prior to or during screening. Temporary treatment interruptions were made permissible

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported