Clinical trial results:
OPuS-4: An open-label study to evaluate the long-term safety of avoralstat in subjects with hereditary angioedema

Summary

EudraCT number	2015-003242-22
Trial protocol	DE HU BE FR GB IT
Global end of trial date	26 February 2016

Results information

Result version number	v1 (current)
This version publication date	24 March 2021
First version publication date	24 March 2021

Trial information

Trial identification

Sponsor protocol code	BCX4161-303

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02670720
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	BioCryst Pharmaceuticals, Inc
Sponsor organisation address	4505 Emperor Blvd. Suite 200, Durham, NC, United States, 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	19 January 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 February 2016
Global end of trial reached?	Yes
Global end of trial date	26 February 2016
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To determine the long-term safety and tolerability of oral avoralstat 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	14 December 2015
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	Belgium: 2
Country: Number of subjects enrolled	France: 4
Worldwide total number of subjects	6
EEA total number of subjects	6

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)	5
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Subjects who completed a previous avoralstat study did not require a Screening Visit if they had interrupted study drug for < 84 days. Avoralstat naïve subjects eligible for the study had a clinical diagnosis of hereditary angioedema (Type I or 2) and were considered a suitable candidate for prophylactic treatment of HAE attacks.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Overall study
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Avoralstat
Investigational medicinal product code	
Other name	BCX4161
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

5 × 100 mg avoralstat capsules for oral administration 3 times per day (total daily dose of 1500 mg)

Number of subjects in period 1	Overall study
Started	6
Completed	0
Not completed	6
sponsor terminated study	5
Adverse event, non-fatal	1

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial
Reporting group description: All subjects	

Reporting group values	Overall trial	Total	
Number of subjects	6	6	
Age categorical Units: Subjects			
Adults (18-64 years)	5	5	
From 65-84 years	1	1	
Age continuous Units: years			
arithmetic mean	44		
standard deviation	± 18.9	-	
Gender categorical			
males and females			
Units: Subjects			
Female	4	4	
Male	2	2	

End points

End points reporting groups

Reporting group title	Overall study

Reporting group description: -

Primary: Adverse Events

End point title	Adverse Events[1]

End point description:

Treatment-emergent AEs (TEAEs) were mapped to a Medical Dictionary for Regulatory Activities (MedDRA) preferred term and system organ class. The occurrence of TEAEs was summarized using MedDRA preferred terms, system organ classes, and severity. In addition to severity, AEs and serious AEs (SAEs) were also summarized based on Investigator or Sponsor assessment of relationship to study drug.

End point type	Primary

End point timeframe:

Planned: 72 weeks. Due to the OPuS-2 study failing to meet its primary endpoint, this study was terminated early. All 6 subjects received treatment for 4 weeks; 3 subjects received treatment for 6 weeks and 1 subject received treatment for 8 weeks

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	Overall study			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: Participants				
Any TEAE	3			
Drug-related TEAE	2			
Any SAE	0			
Discontinuation TEAE	1			
TEAE G3 or G4	2			
Death	0			

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 (2 weeks after last dose IMP) or until the AE is resolved or the subject is in a clinically stable condition with regards to the AE.

Adverse event reporting additional description:

Symptoms of HAE were not considered an AE unless they qualify as an SAE.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	Overall study

Reporting group description: -

Serious adverse events	Overall study		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 6 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Overall study		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 6 (50.00%)		
Investigations			
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Blood creatine increased			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		

Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) Mouth ulceration subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	 1 / 6 (16.67%) 1 1 / 6 (16.67%) 1 1 / 6 (16.67%) 1 1 / 6 (16.67%) 1		
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all) Musculoskeletal pain subjects affected / exposed occurrences (all)	 1 / 6 (16.67%) 1 1 / 6 (16.67%) 1		
Infections and infestations Urinary tract infection subjects affected / exposed occurrences (all)	 1 / 6 (16.67%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 August 2015	• Inclusion criteria were updated to match synopsis. • Section 11.2.2 (e-Diary) was updated to clarify subject compliance follow-up. • Section 12.2 (Toxicity Management) was updated to match withdrawal criteria.
07 December 2015	• Sites in Australia and South America were added. • Duration of treatment was modified to be up to 72 weeks (originally for as long as patients were deemed to derive clinical benefit). Week 72 Visit assessments were added to the protocol. • Descriptions of nonclinical toxicology studies were updated. • A description of the preceding OPuS-2 study was updated. • The inclusion criterion for women of childbearing potential was updated. • The inclusion criterion for male subjects regarding contraception was deleted. Recommendations for male subjects were added to Section 11.1 (Investigator-completed Assessments) of the protocol. • Section 12.2.1 (Management of Pancreatic Dysfunction) was updated to define how HAE attacks should be reported.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Due to the fact that the preceding OPuS-2 study failed to meet its primary endpoint, this study (OPuS-4) was terminated early. Efficacy endpoints and QoL were not analyzed.

Notes: