Clinical trial results:
Prospective open-label uncontrolled multi-center post-marketing study to assess inhibitory antibody formation in subjects with congenital C1-INH deficiency and acute hereditary angioedema (HAE) attacks treated with Berinert®, a C1-esterase inhibitor

Summary

EudraCT number	2010-024242-30
Trial protocol	PL HU BG
Global end of trial date	17 October 2014

Results information

Result version number	v1 (current)
This version publication date	13 July 2016
First version publication date	03 May 2015

Trial information

Trial identification

Sponsor protocol code	CE1145_4001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01467947
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	CSL Behring GmbH
Sponsor organisation address	Emil-von-Behring-Str. 76, Marburg, Germany, 35041
Public contact	Clinical Trial Disclosure Manager, CSL Behring, clinicaltrials@cslbehring.com
Scientific contact	Clinical Trial Disclosure Manager, CSL Behring, clinicaltrials@cslbehring.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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	23 January 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	17 October 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To document the formation of inhibitory anti-C1-esterase-inhibitor (anti-C1-INH) antibodies in subjects with hereditary angioedema (HAE) treated with C1 Esterase Inhibitor (Berinert).
The study evaluated the hypothesis that the incidence of inhibitory anti-C1-INH antibodies in subjects with HAE treated with C1 Esterase Inhibitor is less than 20% of the total study population.

Protection of trial subjects:

This study was carried out in accordance with the International Conference on Harmonisation (ICH) Good Clinical Practice guidelines, and standard operating procedures for clinical research and development at CSL Behring (CSLB). The study protocol and all amendments were approved by the Independent Ethics Committee(s) (IECs) /
Institutional Review Board(s) (IRBs) of the participating centers. Prior to entering the study, subjects were informed, in an understandable form, about the nature, scope, and possible consequences of the study. The investigator was responsible for obtaining a subject's written informed consent to participate in the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	23 November 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Romania: 15
Country: Number of subjects enrolled	Bulgaria: 10
Country: Number of subjects enrolled	Hungary: 8
Country: Number of subjects enrolled	Poland: 13
Worldwide total number of subjects	46
EEA total number of subjects	46

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)	2
Adults (18-64 years)	42
From 65 to 84 years	2
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

60 subjects were screened and enrolled in the study. 14 subjects did not experience an HAE attack before the study ended and so did not receive study treatment. 46 subjects started and completed the active treatment period of the study.

Period 1

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

Arms

Arm title	C1 Esterase Inhibitor

Arm description:

Subjects received 20 U C1 Esterase Inhibitor (C1-INH)/kg body weight by slow intravenous infusion for each acute HAE attack requiring treatment during a 9-month period beginning after their first HAE attack while on study.

Arm type	Experimental
Investigational medicinal product name	C1 Esterase Inhibitor
Investigational medicinal product code	CE1145
Other name	Berinert®, C1-INH
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

20 U of C1-INH/kg body weight for the treatment of each HAE attack

Number of subjects in period 1	C1 Esterase Inhibitor
Started	46
Completed	46

Baseline characteristics

Reporting groups	
Reporting group title	C1 Esterase Inhibitor
Reporting group description:	
Subjects received 20 U C1 Esterase Inhibitor (C1-INH)/kg body weight by slow intravenous infusion for each acute HAE attack requiring treatment during a 9-month period beginning after their first HAE attack while on study.	

Reporting group values	C1 Esterase Inhibitor	Total	
Number of subjects	46	46	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	2	2	
Adults (18-64 years)	42	42	
From 65-84 years	2	2	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	38.9		
standard deviation	± 14.42	-	
Gender categorical Units: Subjects			
Female	32	32	
Male	14	14	
HAE Type Units: Subjects			
HAE Type I	38	38	
HAE Type II	8	8	
Duration of HAE Units: years			
arithmetic mean	10.95		
standard deviation	± 7.603	-	
Number of Prior Attacks in Last 6 Months per Subject Units: HAE attacks			
arithmetic mean	4.3		
standard deviation	± 1.37	-	

End points

End points reporting groups

Reporting group title	C1 Esterase Inhibitor

Reporting group description:

Subjects received 20 U C1 Esterase Inhibitor (C1-INH)/kg body weight by slow intravenous infusion for each acute HAE attack requiring treatment during a 9-month period beginning after their first HAE attack while on study.

Primary: Number of subjects with inhibitory anti-C1-esterase-inhibitor antibodies

End point title	Number of subjects with inhibitory anti-C1-esterase-inhibitor antibodies[1]

End point description:

Subjects with no positive baseline result and at least one positive post-baseline result for inhibitory anti-C1-INH antibodies. Anti-C1-INH antibodies were detected using a direct binding enzyme-linked immunosorbent assay (ELISA). Positive samples were mixed with equal volumes of standard human plasma to assess neutralizing capacity by comparing with normal control samples.

End point type	Primary

End point timeframe:

Baseline to approximately 9 months

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: Statistical analyses cannot be entered when there is just one treatment group.

End point values	C1 Esterase Inhibitor			
Subject group type	Reporting group			
Number of subjects analysed	46			
Units: subjects	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with any (inhibitory or non-inhibitory) anti-C1-esterase-inhibitor antibodies

End point title	Number of subjects with any (inhibitory or non-inhibitory) anti-C1-esterase-inhibitor antibodies

End point description:

Subjects with at least one positive result for inhibitory or non-inhibitory anti-C1-INH antibodies. A direct binding enzyme-linked immunosorbent assay was used to detect inhibitory antibodies to C1-esterase inhibitor.

End point type	Secondary

End point timeframe:

Baseline to approximately 9 months

End point values	C1 Esterase Inhibitor			
Subject group type	Reporting group			
Number of subjects analysed	46			
Units: subjects				
Antibodies detected on Day 1 (Baseline)	9			
Antibodies detected post-baseline	10			
Antibodies first detected at Month 3	2			
Antibodies first detected at Month 6	1			
Antibodies first detected at Month 9	1			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Baseline to approximately 9 months	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	16.0
Reporting groups	
Reporting group title	C1 Esterase Inhibitor
Reporting group description:	
Subjects received 20 U C1 Esterase Inhibitor (C1-INH)/kg body weight by slow intravenous infusion for each acute HAE attack requiring treatment during a 9-month period beginning after their first HAE attack while on study.	

Serious adverse events	C1 Esterase Inhibitor		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 46 (4.35%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Congenital, familial and genetic disorders			
Hereditary angioedema			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Abortion spontaneous			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	C1 Esterase Inhibitor		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 46 (15.22%)		

Vascular disorders Hypotension subjects affected / exposed occurrences (all)	 3 / 46 (6.52%) 3		
Nervous system disorders Headache subjects affected / exposed occurrences (all)	 6 / 46 (13.04%) 26		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 March 2013	- Inclusion Criteria changed to: Diagnosis of congenital C1-INH deficiency (HAE type I or II) period and assessed by the investigator to likely require IV Berinert treatment during the study - Removal of requirement to confirm postmenopausal status with hormone levels - Pregnancy test required of all female subjects - At the discretion of the Investigator, the subject will be allowed to go home after onset of symptom relief - Microscopic sediment analysis to be completed for any abnormal results in Urinalysis - Typographical corrections, updates and clarifications in the document.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported