Clinical trial results:
Human pasteurized C1 esterase inhibitor concentrate (CE1145) in subjects with congenital C1-INH deficiency and acute abdominal or facial HAE attacks

Summary

EudraCT number	2004-001186-17
Trial protocol	HU GB ES CZ SE BG
Global end of trial date	28 December 2007

Results information

Result version number	v1 (current)
This version publication date	13 July 2016
First version publication date	06 August 2015

Trial information

Trial identification

Sponsor protocol code	CE1145_3001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00168103
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	CSL Behring GmbH
Sponsor organisation address	Emil-von-Behring-Strasse 76, Marburg, Germany, 35041
Public contact	Trial Disclosure Manager, CSL Behring GmbH, clinicaltrials@cslbehring.com
Scientific contact	Trial Disclosure Manager, CSL Behring GmbH, 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	28 December 2007
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	28 December 2007
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To show that pasteurized C1 esterase inhibitor (C1-INH) concentrate (Berinert® P) shortens the time to onset of relief of symptoms of abdominal or facial hereditary angioedema (HAE) attack compared to placebo .

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.
Before undergoing screening procedures for possible enrollment into 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	14 August 2005
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	Spain: 1
Country: Number of subjects enrolled	Sweden: 2
Country: Number of subjects enrolled	Bulgaria: 7
Country: Number of subjects enrolled	Czech Republic: 2
Country: Number of subjects enrolled	Hungary: 1
Country: Number of subjects enrolled	Argentina: 3
Country: Number of subjects enrolled	Australia: 1
Country: Number of subjects enrolled	Canada: 6
Country: Number of subjects enrolled	United Kingdom: 1
Country: Number of subjects enrolled	Israel: 5
Country: Number of subjects enrolled	Macedonia, the former Yugoslav Republic of: 4
Country: Number of subjects enrolled	Poland: 8
Country: Number of subjects enrolled	Romania: 4
Country: Number of subjects enrolled	Russian Federation: 3
Country: Number of subjects enrolled	United States: 78

Worldwide total number of subjects	126
EEA total number of subjects	26

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)	3
Adolescents (12-17 years)	15
Adults (18-64 years)	104
From 65 to 84 years	4
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Subjects with C1-INH deficiency with an acute moderate to severe abdominal or facial attack were eligible for this study. For each subject, only a single abdominal or facial attack was treated and evaluated in this study. A screening visit was performed before the subject presented with his/her abdominal/facial attack at the study center.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Participants received a placebo intravenous injection or infusion within 5 hours after the status of the HAE attack became moderate/severe.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Placebo was a commercially available physiological saline solution.

Arm title	C1-INH 10 U/kg

Arm description:

Participants received C1 Esterase Inhibitor (C1-INH) concentrate 10 Units (U)/kg of body weight by i.v. injection or infusion within 5 hours after the status of the HAE attack became moderate/severe.

Arm type	Experimental
Investigational medicinal product name	C1 esterase inhibitor concentrate
Investigational medicinal product code	CE1145
Other name	Berinert® P
Pharmaceutical forms	Powder and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Lyophilized C1-INH containing approximately 500 U C1-INH reconstituted with 10 mL water for injection

Arm title	C1-INH 20 U/kg

Arm description:

Participants received C1 Esterase Inhibitor (C1-INH) concentrate 20 Units (U)/kg of body weight by i.v. injection or infusion within 5 hours after the status of the HAE attack became moderate/severe.

Arm type	Experimental

Investigational medicinal product name	C1 esterase inhibitor concentrate
Investigational medicinal product code	CE1145
Other name	Berinert® P
Pharmaceutical forms	Powder and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Lyophilized C1-INH containing approximately 500 U C1-INH reconstituted with 10 mL water for injection

Number of subjects in period 1	Placebo	C1-INH 10 U/kg	C1-INH 20 U/kg
Started	42	40	43
Intent-to-treat population	42	39	43
Completed	41	38	40
Not completed	1	2	4
Consent withdrawn by subject	1	1	2
Lost to follow-up	-	1	2
Joined	0	0	1
Treated but not randomized	-	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Participants received a placebo intravenous injection or infusion within 5 hours after the status of the HAE attack became moderate/severe.	
Reporting group title	C1-INH 10 U/kg
Reporting group description:	
Participants received C1 Esterase Inhibitor (C1-INH) concentrate 10 Units (U)/kg of body weight by i.v. injection or infusion within 5 hours after the status of the HAE attack became moderate/severe.	
Reporting group title	C1-INH 20 U/kg
Reporting group description:	
Participants received C1 Esterase Inhibitor (C1-INH) concentrate 20 Units (U)/kg of body weight by i.v. injection or infusion within 5 hours after the status of the HAE attack became moderate/severe.	

Reporting group values	Placebo	C1-INH 10 U/kg	C1-INH 20 U/kg
Number of subjects	42	40	44
Age categorical			
Data provided for all randomized participants and one subject who was treated but not randomized (126 subjects).			
Units: Subjects			
3 to < 12 years	2	0	1
12 to < 17 years	3	3	4
17 to < 65 years	37	36	36
>= 65 years	0	1	3
Age continuous			
Data are provided for the Intent-to-treat population (124 subjects).			
Units: years			
arithmetic mean	31.5	33.1	34.6
standard deviation	± 13.57	± 12.77	± 14.91
Gender categorical			
Data provided for all randomized participants and one subject who was treated but not randomized (126 subjects).			
Units: Subjects			
Female	28	27	30
Male	14	13	14
Race			
Data provided for all randomized participants and one subject who was treated but not randomized (126 subjects).			
Units: Subjects			
American Indian or Alaska Native	1	0	0
Black	1	0	3
White	37	36	39
Hispanic	1	3	2
Asian	2	1	0

Reporting group values	Total		
Number of subjects	126		

Age categorical			
Data provided for all randomized participants and one subject who was treated but not randomized (126 subjects).			
Units: Subjects			
3 to < 12 years	3		
12 to < 17 years	10		
17 to < 65 years	109		
>= 65 years	4		
Age continuous			
Data are provided for the Intent-to-treat population (124 subjects).			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Data provided for all randomized participants and one subject who was treated but not randomized (126 subjects).			
Units: Subjects			
Female	85		
Male	41		
Race			
Data provided for all randomized participants and one subject who was treated but not randomized (126 subjects).			
Units: Subjects			
American Indian or Alaska Native	1		
Black	4		
White	112		
Hispanic	6		
Asian	3		

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Participants received a placebo intravenous injection or infusion within 5 hours after the status of the HAE attack became moderate/severe.	
Reporting group title	C1-INH 10 U/kg
Reporting group description:	
Participants received C1 Esterase Inhibitor (C1-INH) concentrate 10 Units (U)/kg of body weight by i.v. injection or infusion within 5 hours after the status of the HAE attack became moderate/severe.	
Reporting group title	C1-INH 20 U/kg
Reporting group description:	
Participants received C1 Esterase Inhibitor (C1-INH) concentrate 20 Units (U)/kg of body weight by i.v. injection or infusion within 5 hours after the status of the HAE attack became moderate/severe.	

Primary: Time to Start of Relief of Symptoms From HAE Attack

End point title	Time to Start of Relief of Symptoms From HAE Attack
End point description:	
The start of symptom relief was determined by subject self-assessment. Time to start of symptom relief was set to 24 hours if the subject received rescue medication (blinded study medication, narcotic analgesics, antiemetics, open-label C1-INH, or fresh frozen plasma) at any time point after the start of study treatment but before start of relief.	
End point type	Primary
End point timeframe:	
Up to 24 hours after start of study treatment	

End point values	Placebo	C1-INH 10 U/kg	C1-INH 20 U/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	42[1]	39[2]	43[3]	
Units: hours				
median (full range (min-max))	1.5 (0.2 to 24)	1.17 (0.17 to 24)	0.5 (0.17 to 24)	

Notes:

[1] - Intent-to-treat (ITT) population

[2] - ITT population

[3] - ITT population

Statistical analyses

Statistical analysis title	Primary analysis
Comparison groups	Placebo v C1-INH 20 U/kg

Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.00253 [4]
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	-0.525
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.217
upper limit	-0.033

Notes:

[4] - 1-sided P-value. The a priori threshold was 0.024 (overall Type 1 error 0.025 adjusted for alpha spending for an interim analysis).

Secondary: Number of Subjects With Worsened Intensity of Clinical HAE Symptoms

End point title	Number of Subjects With Worsened Intensity of Clinical HAE Symptoms

End point description:

Includes any worsening of intensity of at least one of the HAE symptoms present at Baseline. Routinely checked symptoms included pain, nausea, vomiting, cramps, and diarrhea.

End point type	Secondary

End point timeframe:

Baseline and between 2 and 4 h after start of study treatment

End point values	Placebo	C1-INH 10 U/kg	C1-INH 20 U/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	42[5]	39[6]	43[7]	
Units: subjects	13	8	2	

Notes:

[5] - ITT population

[6] - ITT population

[7] - ITT population

Statistical analyses

Statistical analysis title	Secondary analysis
Comparison groups	C1-INH 20 U/kg v Placebo
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0014 [8]
Method	Fisher exact
Parameter estimate	Odds ratio (OR)
Point estimate	0.1088

Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0.0392
upper limit	0.3023

Notes:

[8] - 1-sided P-value. The a priori threshold for significance was 0.1 (trend).

Secondary: Number of Vomiting Episodes per Subject

End point title	Number of Vomiting Episodes per Subject

End point description:

End point type	Secondary

End point timeframe:

Within 4 hours after the start of study treatment

End point values	Placebo	C1-INH 10 U/kg	C1-INH 20 U/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	42[9]	39[10]	43[11]	
Units: vomiting episodes per subject				
median (full range (min-max))	0 (0 to 16)	0 (0 to 4)	0 (0 to 2)	

Notes:

[9] - ITT population

[10] - ITT population

[11] - ITT population

Statistical analyses

Statistical analysis title	Secondary analysis
Comparison groups	Placebo v C1-INH 20 U/kg
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0329 [12]
Method	Wilcoxon (Mann-Whitney)

Notes:

[12] - 1-sided P-value. The a priori threshold for significance was 0.1 (trend).

Other pre-specified: Time to Complete Resolution of All HAE Symptoms, Including Pain

End point title	Time to Complete Resolution of All HAE Symptoms, Including Pain

End point description:

Complete resolution of symptoms was determined by subject self-assessment. The investigator asked the subject if all symptoms of the HAE attack have resolved completely, and if so at what time.

End point type	Other pre-specified

End point timeframe:

Up to 24 hours after start of study treatment

End point values	Placebo	C1-INH 10 U/kg	C1-INH 20 U/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	42[13]	39[14]	43[15]	
Units: hours				
median (full range (min-max))	7.79 (0.33 to 1486.17)	20 (0.47 to 1486.17)	4.92 (0.47 to 1486.17)	

Notes:

[13] - ITT population

[14] - ITT population

[15] - ITT population

Statistical analyses

Statistical analysis title	Exploratory analysis
Comparison groups	C1-INH 20 U/kg v Placebo
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0237 [16]
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	-3.292
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-5.15
upper limit	-1.05

Notes:

[16] - 1-sided, exploratory test

Other pre-specified: Number of Subjects Receiving Rescue Study Medication	
End point title	Number of Subjects Receiving Rescue Study Medication
End point description:	
End point type	Other pre-specified
End point timeframe:	
Within 4 hours after the start of study treatment	

End point values	Placebo	C1-INH 10 U/kg	C1-INH 20 U/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	42[17]	39[18]	43[19]	
Units: subjects	24	13	8	

Notes:
[17] - ITT population
[18] - ITT population
[19] - ITT population

Statistical analyses

Statistical analysis title	Exploratory analysis
Comparison groups	Placebo v C1-INH 20 U/kg
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Odds ratio (OR)
Point estimate	0.1714
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.0642
upper limit	0.4575

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The first 4.0 hours after start of infusion

Adverse event reporting additional description:

In the 4-hour-safety-population, subjects were analyzed in the dose group according to their actual treatment (analysis "as treated"), i.e., subjects randomized to Placebo but receiving (not permitted) open-label Berinert within 4.0 hours after start of infusion were analyzed in the respective Berinert dosage group.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	10.0

Reporting groups

Reporting group title	Placebo

Reporting group description:

Participants received a placebo intravenous injection or infusion within 5 hours after the status of the HAE attack became moderate/severe.

Reporting group title	C1-INH 10 U/kg

Reporting group description:

Participants received C1 Esterase Inhibitor (C1-INH) concentrate 10 Units (U)/kg of body weight by i.v. injection or infusion within 5 hours after the status of the HAE attack became moderate/severe.

Reporting group title	C1-INH 20 U/kg

Reporting group description:

Participants received C1 Esterase Inhibitor (C1-INH) concentrate 20 Units (U)/kg of body weight by i.v. injection or infusion within 5 hours after the status of the HAE attack became moderate/severe.

Serious adverse events	Placebo	C1-INH 10 U/kg	C1-INH 20 U/kg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 41 (0.00%)	0 / 39 (0.00%)	0 / 46 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

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

Non-serious adverse events	Placebo	C1-INH 10 U/kg	C1-INH 20 U/kg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	18 / 41 (43.90%)	10 / 39 (25.64%)	9 / 46 (19.57%)
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	0 / 41 (0.00%)	1 / 39 (2.56%)	2 / 46 (4.35%)
occurrences (all)	0	1	2

Headache			
subjects affected / exposed	2 / 41 (4.88%)	1 / 39 (2.56%)	0 / 46 (0.00%)
occurrences (all)	2	2	0
General disorders and administration site conditions			
Pain			
subjects affected / exposed	1 / 41 (2.44%)	4 / 39 (10.26%)	1 / 46 (2.17%)
occurrences (all)	1	4	1
Edema peripheral			
subjects affected / exposed	0 / 41 (0.00%)	1 / 39 (2.56%)	1 / 46 (2.17%)
occurrences (all)	0	1	1
Face edema			
subjects affected / exposed	1 / 41 (2.44%)	1 / 39 (2.56%)	0 / 46 (0.00%)
occurrences (all)	1	1	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	3 / 41 (7.32%)	1 / 39 (2.56%)	2 / 46 (4.35%)
occurrences (all)	5	1	3
Nausea			
subjects affected / exposed	5 / 41 (12.20%)	1 / 39 (2.56%)	3 / 46 (6.52%)
occurrences (all)	6	1	4
Diarrhea			
subjects affected / exposed	4 / 41 (9.76%)	1 / 39 (2.56%)	0 / 46 (0.00%)
occurrences (all)	4	1	0
Vomiting			
subjects affected / exposed	3 / 41 (7.32%)	1 / 39 (2.56%)	1 / 46 (2.17%)
occurrences (all)	3	1	1
Lip swelling			
subjects affected / exposed	1 / 41 (2.44%)	1 / 39 (2.56%)	0 / 46 (0.00%)
occurrences (all)	1	1	0
Musculoskeletal and connective tissue disorders			
Muscle spasms			
subjects affected / exposed	2 / 41 (4.88%)	4 / 39 (10.26%)	1 / 46 (2.17%)
occurrences (all)	2	4	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 May 2005	Amendment 1 provided for 2 changes to the protocol, including integration of a screening visit to confirm the diagnosis of HAE and to perform a toxicology screening and integration of further time points for photographic documentation of facial edema, as well as additional clarifications to the protocol.
27 July 2005	Amendment 2 provided for 3 changes to the protocol, including specification of screening visit procedures, specification of inclusion/exclusion criteria, and changes in the planned statistical analyses, as well as additional clarifications to the protocol.
23 May 2007	Amendment 3 provided for 6 changes to the protocol, including integration of a second interim analysis to be conducted when 25 subjects in each of the Berinert 20 U/kg bw and Placebo groups completed the study (ITT population), ceasing of the Berinert 10 U/kg bw group according to recommendation of the DSMB after the first interim analysis, definition of the final analysis to be performed when 42 subject in each group (Berinert 20 U/kg bw and Placebo) completed the study (ITT population), and changes required due to European Union (EU) directive (Item 42), as well as additional clarifications to the protocol.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/19767078