Clinical trial results:
Open-label extension study of CE1145 (Human pasteurized C1 esterase inhibitor concentrate) in subjects with congenital C1-INH deficiency and acute HAE attacks

Summary

EudraCT number	2005-003139-38
Trial protocol	Outside EU/EEA
Global end of trial date	26 February 2010

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_3003

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00292981
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	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	17 May 2010
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	26 February 2010
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To document the use of CE1145 in the treatment of all types of HAE attacks.

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	31 August 2005
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	United States: 55
Country: Number of subjects enrolled	Canada: 2
Worldwide total number of subjects	57
EEA total number of subjects	0

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)	1
Adolescents (12-17 years)	8

Adults (18-64 years)	48
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This was a multicenter, open-label extension study enrolling subjects at 15 sites in North America that had participated in study CE1145_3001. Enrollment occurred between August 2005 and January 2008.

Pre-assignment

Screening details:

Subjects with hereditary angioedema (HAE) who had participated in study CE1145_3001, or who were eligible, but not treated in study CE1145_3001 because they developed a laryngeal edema were eligible to participate in this extension 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

Arm title	C1 Esterase Inhibitor

Arm description:

Participants received C1 Esterase Inhibitor (C1-INH) concentrate 20 Units (U)/kg of body weight by slow intravenous infusion for each acute HAE attack.

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

Dosage and administration details:

20 U/kg body weight administered by slow intravenous infusion for each acute HAE attack

Number of subjects in period 1	C1 Esterase Inhibitor
Started	57
Completed	18
Not completed	39
Consent withdrawn by subject	22
Adverse event, non-fatal	1
Other	3
Lost to follow-up	13

Baseline characteristics

Reporting groups	
Reporting group title	C1 Esterase Inhibitor
Reporting group description:	
Participants received C1 Esterase Inhibitor (C1-INH) concentrate 20 Units (U)/kg of body weight by slow intravenous infusion for each acute HAE attack.	

Reporting group values	C1 Esterase Inhibitor	Total	
Number of subjects	57	57	
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 31.9 ± 11.98	 -	
Gender categorical Units: Subjects			
Female	38	38	
Male	19	19	
Type of HAE Units: Subjects			
HAE type I	49	49	
HAE type II	7	7	
Unknown	1	1	

End points

End points reporting groups

Reporting group title	C1 Esterase Inhibitor

Reporting group description:

Participants received C1 Esterase Inhibitor (C1-INH) concentrate 20 Units (U)/kg of body weight by slow intravenous infusion for each acute HAE attack.

Subject analysis set title	Intention-to-treat populations
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The Intention-to-treat populations include the ITT subject population and the ITT attack population. The ITT subject population includes all subjects admitted to the study who received any portion of the study medication. The ITT attack population includes all attacks in subjects admitted to the study for which any portion of study medication was administered.

Primary: Time to Onset of Relief of Symptoms From HAE Attack, per subject

End point title	Time to Onset of Relief of Symptoms From HAE Attack, per subject[1]

End point description:

Time between start of study medication administration and onset of relief of symptoms from HAE attack, determined by subject self-assessment. Subjects were asked by the investigator if, taking into account all of the symptoms associated with this HAE attack, they were confident that it was starting to improve. The time of onset of relief from attack was defined by the time determined at the first of the two consecutive "yes" responses. The per-subject analysis used the average of the attacks of each subject.

Intention-to-treat (ITT) population included all subjects admitted to the study who received any portion of the study medication.

End point type	Primary

End point timeframe:

Up to 24 hours after start of study treatment

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: No formal hypotheses were tested for this endpoint.

End point values	C1 Esterase Inhibitor			
Subject group type	Reporting group			
Number of subjects analysed	57[2]			
Units: hours				
median (confidence interval 95%)	0.46 (0.39 to 0.53)			

Notes:

[2] - ITT subjects

Statistical analyses

No statistical analyses for this end point

Primary: Time to Onset of Relief of Symptoms From HAE Attack, per attack

End point title	Time to Onset of Relief of Symptoms From HAE Attack, per attack[3]

End point description:

Time between start of study medication administration and onset of relief of symptoms from HAE attack, determined by subject self-assessment. Subjects were asked by the investigator if, taking into account

all of the symptoms associated with this HAE attack, they were confident that it was starting to improve. The time of onset of relief from attack was defined by the time determined at the first of the two consecutive "yes" responses.

The ITT attack population included all attacks in subjects admitted to the study for which any portion of study medication was administered.

End point type	Primary

End point timeframe:

Up to 24 hours after start of study treatment

Notes:

[3] - 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: No formal hypotheses were tested for this endpoint.

End point values	Intention-to-treat populations			
Subject group type	Subject analysis set			
Number of subjects analysed	57[4]			
Units: hours				
median (confidence interval 95%)	0.37 (0.33 to 0.42)			

Notes:

[4] - ITT attack population
Number of HAE Attacks Analyzed: 1085

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Complete Resolution of All HAE Symptoms, per Subject

End point title	Time to Complete Resolution of All HAE Symptoms, per Subject

End point description:

Complete resolution of symptoms was determined by subject self-assessment and documented on a diary card.

End point type	Secondary

End point timeframe:

Up to Day 9 following an attack

End point values	C1 Esterase Inhibitor			
Subject group type	Reporting group			
Number of subjects analysed	57[5]			
Units: hours				
median (confidence interval 95%)	15.48 (11.64 to 21.59)			

Notes:

[5] - ITT subject population

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Complete Resolution of All HAE Symptoms, per Attack

End point title	Time to Complete Resolution of All HAE Symptoms, per Attack

End point description:

Complete resolution of symptoms was determined by subject self-assessment and documented on a diary card.

End point type	Secondary

End point timeframe:

Up to Day 9 following an attack

End point values	Intention-to-treat populations			
Subject group type	Subject analysis set			
Number of subjects analysed	57[6]			
Units: hours				
median (confidence interval 95%)	14.28 (12.07 to 15.8)			

Notes:

[6] - ITT attack population
Number of HAE Attacks Analyzed: 1085

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

For each HAE attack, the AE reporting period comprised the time period from the subject's enrollment (Day 1) until Day 7 to 9. The reporting period for serious adverse events (SAEs) was 12 Weeks from the time of the first HAE attack.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	13.0

Reporting groups

Reporting group title	C1 Esterase Inhibitor

Reporting group description:

Participants received C1 Esterase Inhibitor (C1-INH) concentrate 20 Units (U)/kg of body weight by slow intravenous infusion for each acute HAE attack.

Serious adverse events	C1 Esterase Inhibitor		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 57 (1.75%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Congenital, familial and genetic disorders			
Hereditary angioedema	Additional description: A hereditary angioedema attack was reported as an adverse event if it represented a worsening of symptoms during a treated attack.		
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Staphylococcal infection			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	C1 Esterase Inhibitor		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	24 / 57 (42.11%)		
General disorders and administration site conditions			
Influenza like illness			
subjects affected / exposed	2 / 57 (3.51%)		
occurrences (all)	2		
Local swelling			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences (all)	1		
Pyrexia			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences (all)	1		
Infusion related reaction			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences (all)	1		
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences (all)	4		
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences (all)	1		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences (all)	1		
Investigations			
Blood potassium decreased			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences (all)	1		
Red blood cells urine positive			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences (all)	1		
Urine leukocyte esterase positive			

subjects affected / exposed	1 / 57 (1.75%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Clavicle fracture			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences (all)	1		
Hand fracture			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences (all)	1		
Muscle strain			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences (all)	2		
Congenital, familial and genetic disorders			
Hereditary angioedema	Additional description: hereditary angioedema attack was reported as an adverse event if it represented a worsening of symptoms during a treated attack.		
subjects affected / exposed	1 / 57 (1.75%)		
occurrences (all)	1		
Nervous system disorders			
Headache			
subjects affected / exposed	5 / 57 (8.77%)		
occurrences (all)	9		
Dizziness			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences (all)	1		
Eye disorders			
Conjunctivitis			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences (all)	2		
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	2 / 57 (3.51%)		
occurrences (all)	2		
Abdominal pain			
subjects affected / exposed	2 / 57 (3.51%)		
occurrences (all)	9		
Abdominal distension			

subjects affected / exposed	1 / 57 (1.75%)		
occurrences (all)	3		
Abdominal tenderness			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences (all)	3		
Constipation			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences (all)	1		
Dry mouth			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences (all)	7		
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	2 / 57 (3.51%)		
occurrences (all)	2		
Dermatitis contact			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences (all)	1		
Pruritus			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences (all)	1		
Joint swelling			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences (all)	1		
Muscle spasms			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences (all)	1		
Myalgia			

subjects affected / exposed	1 / 57 (1.75%)		
occurrences (all)	1		
Neck pain			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences (all)	1		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	3 / 57 (5.26%)		
occurrences (all)	3		
Upper respiratory tract infection			
subjects affected / exposed	2 / 57 (3.51%)		
occurrences (all)	5		
Vulvovaginal mycotic infection			
subjects affected / exposed	2 / 57 (3.51%)		
occurrences (all)	2		
Erythema infectiosum			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences (all)	1		
Herpes zoster			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences (all)	1		
Periodontal infection			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences (all)	1		
Pharyngitis streptococcal			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences (all)	1		
Sinusitis			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences (all)	1		
Urinary tract infection			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences (all)	2		
Viral infection			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences (all)	1		

Gastroenteritis bacterial subjects affected / exposed occurrences (all)	1 / 57 (1.75%) 1		
Vaginitis bacterial subjects affected / exposed occurrences (all)	1 / 57 (1.75%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 July 2006	The treatment of laryngeal attacks for subjects screened for, but not treated in, study CE1145_3001 was included. When this amendment was implemented, 17 subjects had already been treated in this extension study.
19 March 2008	The duration of the study period was changed from 24 months after enrollment of the last subject or until the approval in the US (whichever occurred first) to 36 months after treatment of the first attack or until product launch (whichever occurred first). The end of the enrollment period was changed from the end of study CE1145_3001 to 2 months after the end of the study CE1145_3001. Screening could take place on the day of the first attack if the subject was informed about the study in detail prior to Day 1. Attacks were to be excluded from the PP population if <75% of the planned amount of study medication was administered (<90% previously). Additional criteria that led to exclusion of attacks from the PP population were defined. The definition of age groups for subgroup analyses was changed from "<18 years and 18 to <65 years" to "3 to <12 years, 12 to <17 years, and 17 to <65 years". For the subgroup analysis of subjects with/without androgens, androgens were defined as concomitant danazol and/or stanazolol or ongoing oxandrolone. When the amendment was implemented, all 57 subjects had already been treated in this extension study.
29 October 2008	The assessment of additional safety variables (anti-C1-INH antibodies and hematology, biochemistry, and urinalysis parameters) at different time points was included. An additional sample for viral safety at the end of the study was also included. The study medication storage temperature was changed from a range of +2°C to +8°C (+36°F to +46°F) to +2°C to +25°C (+36°F to +77°F), based on additional stability tests. Additional subgroup analyses of AEs were included (AEs starting within 24 hours or 72 hours of administration of study medication; AEs by the number of previous infusions of the product at onset of the AE; and AEs except those representing symptoms of abdominal HAE attacks). When the amendment was implemented, all 57 subjects had already been treated in this extension study.

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/21195947

http://www.ncbi.nlm.nih.gov/pubmed/21884533

http://www.ncbi.nlm.nih.gov/pubmed/20635155

http://www.ncbi.nlm.nih.gov/pubmed/24661784

http://www.ncbi.nlm.nih.gov/pubmed/23987198

http://www.ncbi.nlm.nih.gov/pubmed/22856636