



Clinical trial results:

An open-label, randomized study to evaluate the long-term clinical safety and efficacy of subcutaneous administration of human plasma-derived C1-esterase inhibitor in the prophylactic treatment of hereditary angioedema.

Summary

EudraCT number	2014-001054-42
Trial protocol	DE GB HU CZ ES IT
Global end of trial date	21 September 2017

Results information

Result version number	v1 (current)
This version publication date	05 April 2018
First version publication date	05 April 2018

Trial information

Trial identification

Sponsor protocol code	CSL830_3002
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02316353
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 Registration Coordinator, CSL Behring GmbH, clinicaltrials@cslbehring.com
Scientific contact	Trial Registration Coordinator, 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	09 November 2017
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	21 September 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the clinical safety of subcutaneously administered C1-INH in the long-term prophylactic treatment of hereditary angioedema (HAE).

Protection of trial subjects:

This study was conducted in accordance with standards of Good Clinical Practice as defined by the International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ethical principles that have their origin in the Declaration of Helsinki, and applicable national and local regulations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	31 December 2014
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	Australia: 3
Country: Number of subjects enrolled	Canada: 12
Country: Number of subjects enrolled	Israel: 14
Country: Number of subjects enrolled	United States: 54
Country: Number of subjects enrolled	Romania: 1
Country: Number of subjects enrolled	Spain: 4
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	Czech Republic: 4
Country: Number of subjects enrolled	Germany: 22
Country: Number of subjects enrolled	Hungary: 6
Country: Number of subjects enrolled	Italy: 4
Worldwide total number of subjects	126
EEA total number of subjects	43

Notes:

Subjects enrolled per age group

In utero	0
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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)	7
Adults (18-64 years)	106
From 65 to 84 years	10
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The study enrolled patients who participated in prior Study 3001. Because subjects were enrolled into Study 3002 while Study 3001 was still ongoing, all subjects enrolled into Study 3002 were randomized to the treatment arms to eliminate premature unblinding. In addition, also naive subjects were screened and randomized.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
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Arm title	CSL830 (40)
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Arm description:

A low-volume dose of C1-INH (40 IU/kg) administered subcutaneously twice a week

Arm type	Experimental
Investigational medicinal product name	C1-esterase inhibitor
Investigational medicinal product code	
Other name	CSL830
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Administered subcutaneously twice a week

Arm title	CSL830 (60)
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Arm description:

A high-volume dose of C1-INH (60 IU/kg) administered subcutaneously twice a week

Arm type	Experimental
Investigational medicinal product name	C1-esterase inhibitor
Investigational medicinal product code	
Other name	CSL830
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Administered subcutaneously twice a week

Number of subjects in period 1	CSL830 (40)	CSL830 (60)
Started	63	63
Completed	55	55
Not completed	8	8
Consent withdrawn by subject	6	2
Adverse event, non-fatal	1	3
Pregnancy	1	3

Baseline characteristics

Reporting groups

Reporting group title	CSL830 (40)
Reporting group description: A low-volume dose of C1-INH (40 IU/kg) administered subcutaneously twice a week	
Reporting group title	CSL830 (60)
Reporting group description: A high-volume dose of C1-INH (60 IU/kg) administered subcutaneously twice a week	

Reporting group values	CSL830 (40)	CSL830 (60)	Total
Number of subjects	63	63	126
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	2	1	3
Adolescents (12-17 years)	3	4	7
Adults (18-64 years)	56	50	106
From 65-84 years	2	8	10
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	40.8	40.3	
standard deviation	± 14.96	± 16.26	-
Gender categorical Units: Subjects			
Female	40	36	76
Male	23	27	50

End points

End points reporting groups

Reporting group title	CSL830 (40)
Reporting group description: A low-volume dose of C1-INH (40 IU/kg) administered subcutaneously twice a week	
Reporting group title	CSL830 (60)
Reporting group description: A high-volume dose of C1-INH (60 IU/kg) administered subcutaneously twice a week	

Primary: Person-time Incidence Rates (subject-based)

End point title	Person-time Incidence Rates (subject-based) ^[1]
End point description: Subject-based Analysis for Person-Time Incidence Rate = (the total number of subjects who experienced the event during the respective treatment) / (the sum of the date each subject experienced the event – the subject's start date + 1 day) / (365.25 days). The analysis population for this endpoint was the Safety Population: The Safety Population comprised all subjects who provided informed consent / assent, who were randomized, and who received at least 1 dose or a partial dose of CSL830.	
End point type	Primary
End point timeframe: Up to 146 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: Only descriptive statistics were collected for this endpoint.	

End point values	CSL830 (40)	CSL830 (60)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63	63 ^[2]		
Units: Rate/Year				
number (not applicable)				
AEs Leading to Premature Study Discontinuation	0.01	0.03		
Thromboembolic Events	0.00	0.01		
Anaphylaxis	0.00	0.00		
HAE Attacks Resulting in In-patient Hospitalization	0.00	0.00		
Solicited AEs Graded as Severe	0.00	0.00		
Related SAEs Other Than Specified Above	0.00	0.00		
Antibodies to C1-INH (Inhibitory + Non-inhibitory)	0.06	0.06		

Notes:

[2] - Actual n=70 because 7 subjects titrated up from the 40 IU/kg arm and will be displayed in both arms

Statistical analyses

No statistical analyses for this end point

Primary: Person-time Incidence Rates (event-based)

End point title	Person-time Incidence Rates (event-based) ^[3]
End point description:	
Event-based Analysis for Person-Time Incidence Rate = (the total number of events documented during the respective treatment) / (the sum of each subject's end date – the subject's start date + 1 day) / (365.25 days). The analysis population for this endpoint was the Safety Population: The Safety Population comprised all subjects who provided informed consent / assent, who were randomized, and who received at least 1 dose or a partial dose of CSL830.	
End point type	Primary
End point timeframe:	
Up to 146 weeks	

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: Only descriptive statistics were collected for this endpoint.

End point values	CSL830 (40)	CSL830 (60)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63	63 ^[4]		
Units: Rate/Year				
number (not applicable)				
AEs Leading to Premature Study Discontinuation	0.01	0.03		
Thromboembolic Events	0.00	0.01		
Anaphylaxis	0.00	0.00		
HAE Attacks Resulting in In-patient Hospitalization	0.00	0.00		
Solicited AEs Graded as Severe	0.00	0.00		
Related SAEs Other Than Specified Above	0.00	0.00		
Antibodies to C1-INH (Inhibitory + Non-inhibitory)	0.06	0.09		

Notes:

[4] - Actual n=70 because 7 subjects titrated up from the 40 IU/kg arm and will be displayed in both arms

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Who have Solicited Adverse Events (AEs)

End point title	Percentage of Subjects Who have Solicited Adverse Events (AEs)
End point description:	
The number of subjects having at least 1 solicited local AE during a treatment were divided by the number of subjects in the corresponding treatment. The analysis population for this endpoint was the Safety Population: The Safety Population comprised all subjects who provided informed consent / assent, who were randomized, and who received at least 1 dose or a partial dose of CSL830.	
End point type	Secondary
End point timeframe:	
Up to 146 weeks	

End point values	CSL830 (40)	CSL830 (60)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63	63 ^[5]		
Units: Percent				
number (not applicable)	55.6	45.7		

Notes:

[5] - Actual n=70 because 7 subjects titrated up from the 40 IU/kg arm and will be displayed in both arms

Statistical analyses

No statistical analyses for this end point

Secondary: Percent of Injections Followed by at Least One Solicited Adverse Event

End point title	Percent of Injections Followed by at Least One Solicited Adverse Event
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End point description:

The percent of injections followed by at least one solicited adverse event. The analysis population for this endpoint was the Safety Population: The Safety Population comprised all subjects who provided informed consent / assent, who were randomized, and who received at least 1 dose or a partial dose of CSL830.

End point type	Secondary
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End point timeframe:

Up to 146 weeks

End point values	CSL830 (40)	CSL830 (60)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63	63 ^[6]		
Units: Percent of injections				
number (not applicable)	6.3	5.1		

Notes:

[6] - Actual n=70 because 7 subjects titrated up from the 40 IU/kg arm and will be displayed in both arms

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Who Become Seropositive for Human Immunodeficiency virus (HIV-1/-2), Hepatitis B virus, or Hepatitis C virus

End point title	Percentage of Subjects Who Become Seropositive for Human Immunodeficiency virus (HIV-1/-2), Hepatitis B virus, or Hepatitis C virus
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End point description:

Blood samples to be tested for HIV-1/-2, HBV, and HCV. The analysis population for this endpoint was the Safety Population: The Safety Population comprised all subjects who provided informed consent / assent, who were randomized, and who received at least 1 dose or a partial dose of CSL830.

End point type	Secondary
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End point timeframe:

Up to 146 weeks

End point values	CSL830 (40)	CSL830 (60)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63	63 ^[7]		
Units: Percent				
number (not applicable)	0	0		

Notes:

[7] - Actual n=70 because 7 subjects titrated up from the 40 IU/kg arm and will be displayed in both arms

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects who Experience a Time-normalized HAE Attack Frequency of <1 HAE Attack per 4-Week Period

End point title	Percentage of Subjects who Experience a Time-normalized HAE Attack Frequency of <1 HAE Attack per 4-Week Period
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End point description:

The proportion of subjects with a time-normalized merged HAE attack frequency of < 1 HAE attack per 4-week period. The analysis population for this endpoint was the Intent-to-Treat (ITT) Population: The ITT Population comprised all subjects who provided informed consent / assent and were randomized, regardless of whether or not they received CSL830.

End point type	Secondary
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End point timeframe:

Up to 146 weeks

End point values	CSL830 (40)	CSL830 (60)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63	63		
Units: Percent				
number (not applicable)	79.4	85.7		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects who are Responders

End point title	Percentage of Subjects who are Responders
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End point description:

A responder was defined as a subject with a $\geq 50\%$ reduction in the time-normalized number of HAE attacks on CSL830 relative to the time-normalized number of HAE attacks used to qualify for participation in the current study. The analysis population for this endpoint was the Intent-to-Treat (ITT) Population: The ITT Population comprised all subjects who provided informed consent / assent and were randomized, regardless of whether or not they received CSL830.

End point type	Secondary
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End point timeframe:

Up to 146 weeks

End point values	CSL830 (40)	CSL830 (60)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	60		
Units: Percent				
number (confidence interval 95%)	93.5 (84.6 to 97.5)	91.7 (81.9 to 96.4)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

146 weeks per subject

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	18.0
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Reporting groups

Reporting group title	CSL830 (40)
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Reporting group description:

A low-volume dose of C1-INH (40 IU/kg) administered subcutaneously twice a week

Reporting group title	CSL830 (60)
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Reporting group description:

A high-volume dose of C1-INH (60 IU/kg) administered subcutaneously twice a week

Serious adverse events	CSL830 (40)	CSL830 (60)	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 63 (6.35%)	5 / 70 (7.14%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Diffuse large B-cell lymphoma			
subjects affected / exposed	1 / 63 (1.59%)	0 / 70 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 63 (1.59%)	0 / 70 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 63 (0.00%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration			

site conditions			
Chest pain			
subjects affected / exposed	0 / 63 (0.00%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Diplopia			
subjects affected / exposed	0 / 63 (0.00%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 63 (0.00%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 63 (0.00%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 63 (1.59%)	0 / 70 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 63 (1.59%)	0 / 70 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	1 / 63 (1.59%)	0 / 70 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Non-serious adverse events	CSL830 (40)	CSL830 (60)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	33 / 63 (52.38%)	28 / 70 (40.00%)	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	5 / 63 (7.94%)	1 / 70 (1.43%)	
occurrences (all)	5	1	
Nervous system disorders			
Headache			
subjects affected / exposed	10 / 63 (15.87%)	10 / 70 (14.29%)	
occurrences (all)	22	19	
Migraine			
subjects affected / exposed	4 / 63 (6.35%)	0 / 70 (0.00%)	
occurrences (all)	8	0	
General disorders and administration site conditions			
Injection site pain			
subjects affected / exposed	17 / 63 (26.98%)	10 / 70 (14.29%)	
occurrences (all)	211	51	
Injection site erythema			
subjects affected / exposed	10 / 63 (15.87%)	12 / 70 (17.14%)	
occurrences (all)	45	331	
Injection site bruising			
subjects affected / exposed	9 / 63 (14.29%)	7 / 70 (10.00%)	
occurrences (all)	56	22	
Injection site reaction			
subjects affected / exposed	5 / 63 (7.94%)	8 / 70 (11.43%)	
occurrences (all)	75	72	
Injection site haematoma			
subjects affected / exposed	6 / 63 (9.52%)	4 / 70 (5.71%)	
occurrences (all)	11	12	
Injection site induration			
subjects affected / exposed	4 / 63 (6.35%)	3 / 70 (4.29%)	
occurrences (all)	19	4	
Injection site swelling			

subjects affected / exposed occurrences (all)	4 / 63 (6.35%) 19	2 / 70 (2.86%) 2	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	5 / 63 (7.94%)	4 / 70 (5.71%)	
occurrences (all)	10	14	
Diarrhoea			
subjects affected / exposed	4 / 63 (6.35%)	2 / 70 (2.86%)	
occurrences (all)	12	2	
Toothache			
subjects affected / exposed	1 / 63 (1.59%)	4 / 70 (5.71%)	
occurrences (all)	1	4	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	6 / 63 (9.52%)	5 / 70 (7.14%)	
occurrences (all)	6	5	
Back pain			
subjects affected / exposed	7 / 63 (11.11%)	3 / 70 (4.29%)	
occurrences (all)	7	4	
Myalgia			
subjects affected / exposed	4 / 63 (6.35%)	1 / 70 (1.43%)	
occurrences (all)	6	6	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	12 / 63 (19.05%)	21 / 70 (30.00%)	
occurrences (all)	23	36	
Upper respiratory tract infection			
subjects affected / exposed	8 / 63 (12.70%)	8 / 70 (11.43%)	
occurrences (all)	10	10	
Urinary tract infection			
subjects affected / exposed	3 / 63 (4.76%)	6 / 70 (8.57%)	
occurrences (all)	4	6	
Bronchitis			
subjects affected / exposed	7 / 63 (11.11%)	2 / 70 (2.86%)	
occurrences (all)	7	2	
Sinusitis			

subjects affected / exposed	4 / 63 (6.35%)	4 / 70 (5.71%)	
occurrences (all)	4	7	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported