



Clinical trial results:

A double-blind, randomized, placebo-controlled, cross-over study to evaluate the clinical efficacy and safety of subcutaneous administration of human plasma-derived C1-esterase inhibitor in the prophylactic treatment of hereditary angioedema

Summary

EudraCT number	2013-000916-10
Trial protocol	GB HU IT ES CZ
Global end of trial date	12 October 2015

Results information

Result version number	v1 (current)
This version publication date	17 November 2016
First version publication date	17 November 2016

Trial information

Trial identification

Sponsor protocol code	CSL830_3001
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01912456
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	CSL Behring
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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	04 December 2015
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	12 October 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the clinical efficacy of subcutaneous (SC) CSL830 in the prophylactic treatment of hereditary angioedema (HAE). To compare the clinical efficacy of 2 doses of SC CSL830.

Protection of trial subjects:

This study was carried out in accordance with the International Conference on Harmonisation Good Clinical Practice guidelines, standard operating procedures for clinical research and development at CSL Behring and any other relevant procedures and applicable international and national regulatory requirements. The study protocol and all amendments were approved by the Independent Ethics Committee / Institutional Review Board of the participating centers. Before undergoing Screening procedures for possible enrollment into the study, the subjects' legally acceptable representative was informed, in an understandable form, about the nature, scope, and possible consequences of the study. The investigator was responsible for obtaining a subject's legally acceptable representative written informed consent to participate in the study. The investigator could cease study treatment and withdraw the subject, or the subject could withdraw himself from participation in the study at any time. If a subject was withdrawn from the study or further participation was declined, the subject would continue to have access to medical care and would be treated according to routine medical practice, but would no longer receive the investigational medicinal product.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	18 December 2013
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: 1
Country: Number of subjects enrolled	Canada: 8
Country: Number of subjects enrolled	Israel: 9
Country: Number of subjects enrolled	Romania: 1
Country: Number of subjects enrolled	United States: 54
Country: Number of subjects enrolled	Spain: 4
Country: Number of subjects enrolled	United Kingdom: 3
Country: Number of subjects enrolled	Czech Republic: 1
Country: Number of subjects enrolled	Hungary: 4
Country: Number of subjects enrolled	Italy: 5
Worldwide total number of subjects	90
EEA total number of subjects	18

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)	7
Adults (18-64 years)	76
From 65 to 84 years	7
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

115 subjects were screened and 90 were randomized/enrolled

Period 1

Period 1 title	Period 1
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

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

In Period 1, a high-volume dose of placebo will be administered subcutaneously twice a week for up to 16 weeks, then in Period 2, a low-volume dose of C1-esterase inhibitor will be administered subcutaneously twice a week for up to 16 weeks.

Arm type	Experimental
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

A high-volume dose of placebo will be administered subcutaneously twice a week for up to 16 weeks

Arm title	CSL830 (40)/placebo high
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Arm description:

In Period 1, a low-volume dose of C1-esterase inhibitor will be administered subcutaneously twice a week for up to 16 weeks, then in Period 2, a high-volume dose of placebo will be administered subcutaneously twice a week for up to 16 weeks.

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

Dosage and administration details:

A low-volume dose of C1-esterase inhibitor (40 IU/kg) will be administered subcutaneously twice a week for up to 16 weeks

Arm title	Placebo low/CSL830 (60)
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Arm description:

In Period 1, a low-volume dose of placebo will be administered subcutaneously twice a week for up to 16 weeks, then in Period 2, a high-volume dose of C1-esterase inhibitor will be administered subcutaneously twice a week for up to 16 weeks.

Arm type	Experimental
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Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Subcutaneous use
Dosage and administration details:	
A low-volume dose of placebo will be administered subcutaneously twice a week for up to 16 weeks	
Arm title	CSL830 (60)/placebo low

Arm description:

In Period 1, a high-volume dose of C1-esterase inhibitor will be administered subcutaneously twice a week for up to 16 weeks, then in Period 2, a low-volume dose of placebo will be administered subcutaneously twice a week for up to 16 weeks.

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

Dosage and administration details:

A high-volume dose of C1-esterase inhibitor (60 IU/kg) will be administered subcutaneously twice a week for up to 16 weeks

Number of subjects in period 1	Placebo high/CSL830 (40)	CSL830 (40)/placebo high	Placebo low/CSL830 (60)
Started	22	23	23
Completed	20	22	21
Not completed	2	1	2
Consent withdrawn by subject	-	1	1
Physician decision	-	-	1
Adverse event, non-fatal	1	-	-
Non-compliance	1	-	-

Number of subjects in period 1	CSL830 (60)/placebo low
Started	22
Completed	19
Not completed	3
Consent withdrawn by subject	1
Physician decision	-
Adverse event, non-fatal	1
Non-compliance	1

Period 2

Period 2 title	Period 2
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

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

In Period 1, a high-volume dose of placebo will be administered subcutaneously twice a week for up to 16 weeks, then in Period 2, a low-volume dose of C1-esterase inhibitor will be administered subcutaneously twice a week for up to 16 weeks.

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

Dosage and administration details:

A low-volume dose of C1-esterase inhibitor (40 IU/kg) will be administered subcutaneously twice a week for up to 16 weeks

Arm title	CSL830 (40)/Placebo high
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Arm description:

In Period 1, a low-volume dose of C1-esterase inhibitor will be administered subcutaneously twice a week for up to 16 weeks, then in Period 2, a high-volume dose of placebo will be administered subcutaneously twice a week for up to 16 weeks.

Arm type	Experimental
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

A high-volume dose of placebo will be administered subcutaneously twice a week for up to 16 weeks

Arm title	Placebo low/CSL830 (60)
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Arm description:

In Period 1, a low-volume dose of placebo will be administered subcutaneously twice a week for up to 16 weeks, then in Period 2, a high-volume dose of C1-esterase inhibitor will be administered subcutaneously twice a week for up to 16 weeks.

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

Dosage and administration details:

A high-volume dose of C1-esterase inhibitor (60 IU/kg) will be administered subcutaneously twice a week for up to 16 weeks

Arm title	CSL830 (60)/Placebo low
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Arm description:

In Period 1, a high-volume dose of C1-esterase inhibitor will be administered subcutaneously twice a

week for up to 16 weeks, then in Period 2, a low-volume dose of placebo will be administered subcutaneously twice a week for up to 16 weeks.

Arm type	Experimental
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

A low-volume dose of placebo will be administered subcutaneously twice a week for up to 16 weeks

Number of subjects in period 2	Placebo high/CSL830 (40)	CSL830 (40)/Placebo high	Placebo low/CSL830 (60)
Started	20	22	21
Completed	20	20	21
Not completed	0	2	0
Adverse event, non-fatal	-	-	-
Lack of efficacy	-	2	-

Number of subjects in period 2	CSL830 (60)/Placebo low
Started	19
Completed	18
Not completed	1
Adverse event, non-fatal	1
Lack of efficacy	-

Baseline characteristics

Reporting groups

Reporting group title	Placebo high/CSL830 (40)
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Reporting group description:

In Period 1, a high-volume dose of placebo will be administered subcutaneously twice a week for up to 16 weeks, then in Period 2, a low-volume dose of C1-esterase inhibitor will be administered subcutaneously twice a week for up to 16 weeks.

Reporting group title	CSL830 (40)/placebo high
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Reporting group description:

In Period 1, a low-volume dose of C1-esterase inhibitor will be administered subcutaneously twice a week for up to 16 weeks, then in Period 2, a high-volume dose of placebo will be administered subcutaneously twice a week for up to 16 weeks.

Reporting group title	Placebo low/CSL830 (60)
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Reporting group description:

In Period 1, a low-volume dose of placebo will be administered subcutaneously twice a week for up to 16 weeks, then in Period 2, a high-volume dose of C1-esterase inhibitor will be administered subcutaneously twice a week for up to 16 weeks.

Reporting group title	CSL830 (60)/placebo low
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Reporting group description:

In Period 1, a high-volume dose of C1-esterase inhibitor will be administered subcutaneously twice a week for up to 16 weeks, then in Period 2, a low-volume dose of placebo will be administered subcutaneously twice a week for up to 16 weeks.

Reporting group values	Placebo high/CSL830 (40)	CSL830 (40)/placebo high	Placebo low/CSL830 (60)
Number of subjects	22	23	23
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)	0	0	0
Adolescents (12-17 years)	2	1	2
Adults (18-64 years)	17	21	19
From 65-84 years	3	1	2
85 years and over	0	0	0
Gender categorical			
Units: Subjects			
Female	14	14	17
Male	8	9	6

Reporting group values	CSL830 (60)/placebo low	Total	
Number of subjects	22	90	
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	7	
Adults (18-64 years)	19	76	
From 65-84 years	1	7	
85 years and over	0	0	
Gender categorical			
Units: Subjects			
Female	15	60	
Male	7	30	

End points

End points reporting groups

Reporting group title	Placebo high/CSL830 (40)
Reporting group description: In Period 1, a high-volume dose of placebo will be administered subcutaneously twice a week for up to 16 weeks, then in Period 2, a low-volume dose of C1-esterase inhibitor will be administered subcutaneously twice a week for up to 16 weeks.	
Reporting group title	CSL830 (40)/placebo high
Reporting group description: In Period 1, a low-volume dose of C1-esterase inhibitor will be administered subcutaneously twice a week for up to 16 weeks, then in Period 2, a high-volume dose of placebo will be administered subcutaneously twice a week for up to 16 weeks.	
Reporting group title	Placebo low/CSL830 (60)
Reporting group description: In Period 1, a low-volume dose of placebo will be administered subcutaneously twice a week for up to 16 weeks, then in Period 2, a high-volume dose of C1-esterase inhibitor will be administered subcutaneously twice a week for up to 16 weeks.	
Reporting group title	CSL830 (60)/placebo low
Reporting group description: In Period 1, a high-volume dose of C1-esterase inhibitor will be administered subcutaneously twice a week for up to 16 weeks, then in Period 2, a low-volume dose of placebo will be administered subcutaneously twice a week for up to 16 weeks.	
Reporting group title	Placebo high/CSL830 (40)
Reporting group description: In Period 1, a high-volume dose of placebo will be administered subcutaneously twice a week for up to 16 weeks, then in Period 2, a low-volume dose of C1-esterase inhibitor will be administered subcutaneously twice a week for up to 16 weeks.	
Reporting group title	CSL830 (40)/Placebo high
Reporting group description: In Period 1, a low-volume dose of C1-esterase inhibitor will be administered subcutaneously twice a week for up to 16 weeks, then in Period 2, a high-volume dose of placebo will be administered subcutaneously twice a week for up to 16 weeks.	
Reporting group title	Placebo low/CSL830 (60)
Reporting group description: In Period 1, a low-volume dose of placebo will be administered subcutaneously twice a week for up to 16 weeks, then in Period 2, a high-volume dose of C1-esterase inhibitor will be administered subcutaneously twice a week for up to 16 weeks.	
Reporting group title	CSL830 (60)/Placebo low
Reporting group description: In Period 1, a high-volume dose of C1-esterase inhibitor will be administered subcutaneously twice a week for up to 16 weeks, then in Period 2, a low-volume dose of placebo will be administered subcutaneously twice a week for up to 16 weeks.	
Subject analysis set title	CSL830 (40) - ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description: The ITT Population consisted of all subjects who provided informed consent / assent and were randomized, regardless of whether they received investigational product.	
Subject analysis set title	CSL830 (60) - ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description: The ITT Population consisted of all subjects who provided informed consent / assent and were randomized, regardless of whether they received investigational product.	
Subject analysis set title	Placebo high - ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The ITT Population consisted of all subjects who provided informed consent / assent and were randomized, regardless of whether they received investigational product.

Subject analysis set title	Placebo Low - ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The ITT Population consisted of all subjects who provided informed consent / assent and were randomized, regardless of whether they received investigational product.

Subject analysis set title	CSL830 (40) - Safety
Subject analysis set type	Safety analysis

Subject analysis set description:

The Safety Population consisted of all subjects who provided informed consent / assent, were randomized, and received at least 1 dose (or partial dose) of investigational product.

Subject analysis set title	CSL830 (60) - Safety
Subject analysis set type	Safety analysis

Subject analysis set description:

The Safety Population consisted of all subjects who provided informed consent / assent, were randomized, and received at least 1 dose (or partial dose) of investigational product.

Subject analysis set title	Placebo high - Safety
Subject analysis set type	Safety analysis

Subject analysis set description:

The Safety Population consisted of all subjects who provided informed consent / assent, were randomized, and received at least 1 dose (or partial dose) of investigational product.

Subject analysis set title	Placebo low - Safety
Subject analysis set type	Safety analysis

Subject analysis set description:

The Safety Population consisted of all subjects who provided informed consent / assent, were randomized, and received at least 1 dose (or partial dose) of investigational product.

Primary: Time-normalized number of hereditary angioedema attacks

End point title	Time-normalized number of hereditary angioedema attacks
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End point description:

The time normalized number of HAE attacks as reported by the investigator per subject was calculated as:

- The total number of HAE attacks per subject and per treatment period / length of stay of subject in treatment period (days),

Where length of stay of subject in treatment period was calculated as:

- Date of last day of subject in treatment period – date of first day of Week 3 of subject in treatment period + 1.

End point type	Primary
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End point timeframe:

During the treatment phase, up to 28 weeks

End point values	CSL830 (40) - ITT	CSL830 (60) - ITT	Placebo high - ITT	Placebo Low - ITT
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	43	43	44	42
Units: Number/day				
least squares mean (standard error)	0.04 (± 0.011)	0.02 (± 0.009)	0.12 (± 0.011)	0.13 (± 0.009)

Statistical analyses

Statistical analysis title	Within-subject analysis - Placebo Low /CSL830 (60)
Comparison groups	Placebo Low - ITT v CSL830 (60) - ITT
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	other ^[1]
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.14
upper limit	-0.09

Notes:

[1] - Because of the crossover design, each subject was randomized to receive both the 60 IU/kg CSL830 and Placebo Low Volume treatments in consecutive treatment periods. Therefore, the subjects in each treatment period are the same subjects and data for all 45 subjects in the ITT population are included in this mixed model analysis.

Statistical analysis title	Within-subject analysis - CSL830 (40)/Placebo High
Comparison groups	CSL830 (40) - ITT v Placebo high - ITT
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	other ^[2]
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.11
upper limit	-0.05

Notes:

[2] - Because of the crossover design, each subject was randomized to receive both the 40 IU/kg CSL830 and Placebo High Volume treatments in consecutive treatment periods. Therefore, the subjects in each treatment period are the same subjects and data for all 45 subjects in the ITT population are included in this mixed model analysis.

Statistical analysis title	Between-subject analysis - CSL830 (40)/CSL830 (60)
Comparison groups	CSL830 (40) - ITT v CSL830 (60) - ITT

Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	other ^[3]
P-value	= 0.114
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.05
upper limit	0.01

Notes:

[3] - Because of the crossover design, each subject was randomized to receive both CSL830 and Placebo treatments in consecutive treatment periods. Therefore, the subjects in each treatment period are the same subjects and data for all 90 subjects in the ITT population are included in this mixed model analysis.

Secondary: Percentage of subjects with a $\geq 50\%$ reduction in the number of hereditary angioedema attacks

End point title	Percentage of subjects with a $\geq 50\%$ reduction in the number of hereditary angioedema attacks
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End point description:

The percentage reduction (%) in the time normalized number of HAE attacks was calculated as:
 $\bullet 100 \times [1 - (\text{the time normalized number of HAE attacks when treated with CSL830}) / (\text{the time normalized number of HAE attacks when treated with placebo})]$.

End point type	Secondary
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End point timeframe:

During the treatment phase, up to 28 weeks

End point values	CSL830 (40) - ITT	CSL830 (60) - ITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	42	40		
Units: Percent of subjects				
number (confidence interval 95%)	76.2 (61.5 to 86.5)	90 (76.9 to 96)		

Statistical analyses

Statistical analysis title	Between-subject analysis - CSL830 (40)/CSL830 (60)
Comparison groups	CSL830 (60) - ITT v CSL830 (40) - ITT
Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	other
Method	Wilson CI - calculation of percentages
Parameter estimate	difference in the percentages
Point estimate	13.8

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.8
upper limit	29.7

Secondary: Time-Normalized Number of Uses of Rescue Medication

End point title	Time-Normalized Number of Uses of Rescue Medication
End point description:	
End point type	Secondary
End point timeframe:	
During the treatment phase, up to 28 weeks	

End point values	CSL830 (40) - ITT	CSL830 (60) - ITT	Placebo high - ITT	Placebo Low - ITT
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	43	43	44	42
Units: Number/day				
least squares mean (standard error)	0.04 (± 0.042)	0.01 (± 0.011)	0.18 (± 0.04)	0.13 (± 0.011)

Statistical analyses

Statistical analysis title	Within-subject analysis - Placebo Low/CSL830 (60)
Comparison groups	CSL830 (60) - ITT v Placebo Low - ITT
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	other ^[4]
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.15
upper limit	-0.09

Notes:

[4] - Because of the crossover design, each subject was randomized to receive both the 60 IU/kg CSL830 and Placebo Low Volume treatments in consecutive treatment periods. Therefore, the subjects in each treatment period are the same subjects and data for all 45 subjects in the ITT population are included in this mixed model analysis.

Statistical analysis title	Within-subject analysis - CSL830 (40)/Placebo High
Comparison groups	CSL830 (40) - ITT v Placebo high - ITT

Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	other ^[5]
P-value	= 0.018
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.26
upper limit	-0.03

Notes:

[5] - Because of the crossover design, each subject was randomized to receive both the 40 IU/kg CSL830 and Placebo High Volume treatments in consecutive treatment periods. Therefore, the subjects in each treatment period are the same subjects and data for all 45 subjects in the ITT population are included in this mixed model analysis.

Statistical analysis title	Between-subject analysis - CSL830 (40)/CSL830 (60)
Comparison groups	CSL830 (40) - ITT v CSL830 (60) - ITT
Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	other ^[6]
P-value	= 0.31
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.07
upper limit	0.02

Notes:

[6] - Because of the crossover design, each subject was randomized to receive both CSL830 and Placebo treatments in consecutive treatment periods. Therefore, the subjects in each treatment period are the same subjects and data for all 90 subjects in the ITT population are included in this mixed model analysis.

Secondary: Percentage of subjects with adverse events (AEs) within 24 hours of C1-esterase inhibitor or placebo administration

End point title	Percentage of subjects with adverse events (AEs) within 24 hours of C1-esterase inhibitor or placebo administration
End point description:	
End point type	Secondary
End point timeframe:	
Within 24 hours of C1-esterase inhibitor or placebo administration	

End point values	CSL830 (40) - Safety	CSL830 (60) - Safety	Placebo high - Safety	Placebo low - Safety
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	43	43	44	42
Units: Percent of subjects				
number (not applicable)	58.1	60.5	45.5	54.8

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects with AEs or other specified safety events

End point title	Percentage of subjects with AEs or other specified safety events
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End point description:

The percentage of subjects experiencing the following during treatment with CSL830 and placebo: unsolicited AEs, serious AEs, suspected adverse drug reactions, increased risk scores for deep vein thrombosis and pulmonary embolism, thromboembolic events, inhibitory anti C1 INH antibodies, or clinically significant abnormalities in laboratory assessments.

End point type	Secondary
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End point timeframe:

During the treatment phase, up to 32 weeks

End point values	CSL830 (40) - Safety	CSL830 (60) - Safety	Placebo high - Safety	Placebo low - Safety
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	43	43	44	42
Units: Percent of subjects				
number (not applicable)	67.4	69.8	61.4	71.4

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects experiencing solicited local AEs (Injection site reactions)

End point title	Percentage of subjects experiencing solicited local AEs (Injection site reactions)
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End point description:

The percentage of subjects experiencing solicited local AEs (discomfort [eg, pain, burning], swelling, bruising, or itching at the investigational product injection site) during treatment with CSL830 and placebo.

End point type	Secondary
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End point timeframe:

During the treatment phase, up to 32 weeks

End point values	CSL830 (40) - Safety	CSL830 (60) - Safety	Placebo high - Safety	Placebo low - Safety
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	43	43	44	42
Units: Percent of subjects				
number (not applicable)	27.9	34.9	22.7	26.2

Statistical analyses

No statistical analyses for this end point

Secondary: Investigational product injections resulting in solicited local AEs (Injection site reactions)

End point title	Investigational product injections resulting in solicited local AEs (Injection site reactions)
End point description: The rate/injection of injections of C1-esterase inhibitor or placebo that were followed by solicited local AEs (discomfort [eg, pain, burning], swelling, bruising, or itching at the investigational product injection site) during treatment with CSL830 and placebo. Rate/Injection = Number of events/number of injections.	
End point type	Secondary
End point timeframe: During the treatment phase, up to 32 weeks	

End point values	CSL830 (40) - Safety	CSL830 (60) - Safety	Placebo high - Safety	Placebo low - Safety
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	43 ^[7]	43 ^[8]	44 ^[9]	42 ^[10]
Units: injection site reactions/injection				
number (not applicable)	0.21	0.08	0.12	0.05

Notes:

[7] - 1307 total number of injections within treatment

[8] - 1320 total number of injections within treatment

[9] - 1290 total number of injections within treatment

[10] - 1164 total number of injections within treatment

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

During the treatment phase, up to 32 weeks.

Adverse event reporting additional description:

The Safety Population consisted of all subjects who provided informed consent / assent, were randomized, and received at least 1 dose (or partial dose) of investigational product.

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: -

Reporting group title	CSL830 (60)
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Reporting group description: -

Reporting group title	Placebo high
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Reporting group description: -

Reporting group title	Placebo low
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Reporting group description: -

Serious adverse events	CSL830 (40)	CSL830 (60)	Placebo high
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 43 (2.33%)	0 / 43 (0.00%)	1 / 44 (2.27%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Congenital, familial and genetic disorders			
Hereditary angioedema			
subjects affected / exposed	0 / 43 (0.00%)	0 / 43 (0.00%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Syncope			
subjects affected / exposed	0 / 43 (0.00%)	0 / 43 (0.00%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			

subjects affected / exposed	0 / 43 (0.00%)	0 / 43 (0.00%)	1 / 44 (2.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Urosepsis			
subjects affected / exposed	1 / 43 (2.33%)	0 / 43 (0.00%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Placebo low		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 42 (2.38%)		
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 / 42 (2.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Syncope			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Urosepsis			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	CSL830 (40)	CSL830 (60)	Placebo high
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 43 (23.26%)	17 / 43 (39.53%)	12 / 44 (27.27%)
Nervous system disorders			
Dizziness			
subjects affected / exposed	4 / 43 (9.30%)	0 / 43 (0.00%)	0 / 44 (0.00%)
occurrences (all)	5	0	0
General disorders and administration site conditions			
Injection site erythema			
subjects affected / exposed	7 / 43 (16.28%)	9 / 43 (20.93%)	6 / 44 (13.64%)
occurrences (all)	86	20	36
Injection site pain			
subjects affected / exposed	7 / 43 (16.28%)	7 / 43 (16.28%)	5 / 44 (11.36%)
occurrences (all)	90	19	34
Injection site bruising			
subjects affected / exposed	2 / 43 (4.65%)	4 / 43 (9.30%)	2 / 44 (4.55%)
occurrences (all)	5	5	2
Injection site swelling			
subjects affected / exposed	1 / 43 (2.33%)	4 / 43 (9.30%)	2 / 44 (4.55%)
occurrences (all)	1	39	6
Injection site induration			
subjects affected / exposed	3 / 43 (6.98%)	4 / 43 (9.30%)	1 / 44 (2.27%)
occurrences (all)	8	6	2
Fatigue			
subjects affected / exposed	1 / 43 (2.33%)	1 / 43 (2.33%)	3 / 44 (6.82%)
occurrences (all)	1	1	3
Injection site oedema			
subjects affected / exposed	5 / 43 (11.63%)	0 / 43 (0.00%)	2 / 44 (4.55%)
occurrences (all)	60	0	62
Injection site haemorrhage			
subjects affected / exposed	3 / 43 (6.98%)	1 / 43 (2.33%)	4 / 44 (9.09%)
occurrences (all)	8	1	4
Musculoskeletal and connective tissue disorders			

Back pain subjects affected / exposed occurrences (all)	1 / 43 (2.33%) 1	1 / 43 (2.33%) 1	3 / 44 (6.82%) 4
Infections and infestations			
Nasopharyngitis subjects affected / exposed occurrences (all)	1 / 43 (2.33%) 1	8 / 43 (18.60%) 9	3 / 44 (6.82%) 3
Upper respiratory tract infection subjects affected / exposed occurrences (all)	3 / 43 (6.98%) 3	3 / 43 (6.98%) 3	3 / 44 (6.82%) 3

Non-serious adverse events	Placebo low		
Total subjects affected by non-serious adverse events subjects affected / exposed	12 / 42 (28.57%)		
Nervous system disorders			
Dizziness subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 1		
General disorders and administration site conditions			
Injection site erythema subjects affected / exposed occurrences (all)	7 / 42 (16.67%) 28		
Injection site pain subjects affected / exposed occurrences (all)	4 / 42 (9.52%) 9		
Injection site bruising subjects affected / exposed occurrences (all)	3 / 42 (7.14%) 5		
Injection site swelling subjects affected / exposed occurrences (all)	2 / 42 (4.76%) 18		
Injection site induration subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 2		
Fatigue subjects affected / exposed occurrences (all)	3 / 42 (7.14%) 3		

Injection site oedema subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 1		
Injection site haemorrhage subjects affected / exposed occurrences (all)	0 / 42 (0.00%) 0		
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	2 / 42 (4.76%) 4		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	3 / 42 (7.14%) 3		
Upper respiratory tract infection subjects affected / exposed occurrences (all)	3 / 42 (7.14%) 3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 February 2014	<p>The study design has been revised so that subjects are not required to discontinue use of their medication for hereditary angioedema (HAE) prophylaxis at entry into the Run-in Period.</p> <p>The inclusion criteria have been revised to permit the inclusion of subjects who have used a stable regimen of oral medication for prophylaxis against HAE attacks (ie, androgens, tranexamic acid, progestins) within 3 months of the Screening Visit and who do not plan to change that regimen during the study.</p> <p>The exclusion criteria have been revised to exclude:</p> <ul style="list-style-type: none">a. Subjects with body weight < 40 kilogramsb. Subjects who have used intravenous C1-esterase inhibitor (C1-INH) for routine prophylaxis against HAE attacks (ie, administered every 3 or 4 days) within 3 months of the Screening Visit or who plan to use intravenous C1-INH for routine prophylaxis against HAE attacks during the study.c. Subjects who are unable to have their HAE adequately managed pharmacologically with on demand treatment, administered either independently or with assistance. <p>Secondary safety and tolerability endpoints have been added.</p> <p>The planned statistical analyses have been revised:</p> <ul style="list-style-type: none">a. New sub-group analyses have been included.b. A description of missing data handling has been added.c. The lower bound of the 95% confidence interval for the responder rate of the combined active treatment group has been added. The lower bound is 33%.d. Additional details have been included to support statistical analyses. <p>The list of permitted on-study medications has been revised to allow the use of medications (eg, intravenous C1-INH) for the pre-procedure prevention of acute HAE attacks during the study.</p>
11 December 2014	<p>The protocol has undergone administrative revisions to more clearly convey the joint intent of the Steering Committee, the Data Safety Monitoring Board, and CSL Behring regarding study conduct as pertains to the stopping, restarting, and termination rules.</p>

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported