Clinical trial results:
A Phase 3, Multicenter, Randomized, Single-Blind, Dose-Ranging, Crossover Study to Evaluate the Safety and Efficacy of Intravenous Administration of CINRYZE® (C1 Esterase Inhibitor [Human]) for the Prevention of Angioedema Attacks in Children 6 to 11 Years of Age with Hereditary Angioedema

Summary

EudraCT number	2013-002453-29
Trial protocol	GB DE IT RO
Global end of trial date	04 May 2017

Results information

Result version number	v1 (current)
This version publication date	19 November 2017
First version publication date	19 November 2017

Trial information

Trial identification

Sponsor protocol code	0624-301

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02052141
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Shire
Sponsor organisation address	300 Shire Way, Lexington, MA, United States, 02421
Public contact	Study Physician, Shire, 1 866-842-5335,
Scientific contact	Study Physician, Shire, 1 866-842-5335,

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000568-PIP01-09
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	08 September 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	04 May 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to assess the relative efficacy of 2 dose levels of CINRYZE (500 units (U) and 1000 U) administered by intravenous (IV) injection every 3 or 4 days to prevent angioedema attacks in children 6 to 11 years of age.

Protection of trial subjects:

This study was conducted in accordance with current applicable regulations, International Council for Harmonisation (ICH) of Good Clinical Practice, the principles of the Declaration of Helsinki, as well as other applicable local ethical and legal requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 March 2014
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: 5
Country: Number of subjects enrolled	Germany: 3
Country: Number of subjects enrolled	Mexico: 3
Country: Number of subjects enrolled	Romania: 1
Worldwide total number of subjects	12
EEA total number of subjects	4

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)	12
Adolescents (12-17 years)	0
Adults (18-64 years)	0

From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted in 10 study centers in the United States, European Union, Mexico, and Israel between 20 March 2014 (first subject first visit) and 04 May 2017 (last subject last visit).

Pre-assignment

Screening details:

A total of 16 subjects were screened and of them, 12 were enrolled into the baseline observational period (12 weeks) and were randomized to receive the treatment in sequence A-B and B-A during this crossover study without a washout period.

Period 1

Period 1 title	Intervention Period 1
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Treatment A-B (500 U/1000 U CINRYZE)

Arm description:

Subjects received 500 U of CINRYZE IV injection twice weekly (every 3 or 4 days) for 12 weeks (Treatment A) during intervention period 1 followed by 1000 U CINRYZE IV injection twice weekly (every 3 or 4 days) for 12 weeks (Treatment B) during intervention period 2. There was no washout period between the two intervention periods.

Arm type	Experimental
Investigational medicinal product name	CINRYZE
Investigational medicinal product code	SHP616
Other name	C1 Esterase Inhibitor (Human)
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received CINRYZE intravenous (IV) injection twice weekly (every 3 or 4 days) for 12 weeks during each intervention period.

Arm title	Treatment B-A (1000 U/500 U CINRYZE)

Arm description:

Subjects received 1000 U CINRYZE IV injection twice weekly (every 3 or 4 days) for 12 weeks (Treatment B) during intervention period 1 followed by 500 U CINRYZE IV injection twice weekly (every 3 or 4 days) for 12 weeks (Treatment A) during intervention period 2. There was no washout period between the two intervention periods.

Arm type	Experimental
Investigational medicinal product name	CINRYZE
Investigational medicinal product code	SHP616
Other name	C1 Esterase Inhibitor (Human)
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received CINRYZE intravenous (IV) injection twice weekly (every 3 or 4 days) for 12 weeks during each intervention period.

Number of subjects in period 1	Treatment A-B (500 U/1000 U CINRYZE)	Treatment B-A (1000 U/500 U CINRYZE)
Started	5	7
Completed	5	7

Period 2

Period 2 title	Intervention Period 2
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Treatment A-B (500 U/1000 U CINRYZE)

Arm description:

Subjects received 500 U of CINRYZE IV injection twice weekly (every 3 or 4 days) for 12 weeks (Treatment A) during intervention period 1 followed by 1000 U CINRYZE IV injection twice weekly (every 3 or 4 days) for 12 weeks (Treatment B) during intervention period 2. There was no washout period between the two intervention periods.

Arm type	Experimental
Investigational medicinal product name	CINRYZE
Investigational medicinal product code	SHP616
Other name	C1 Esterase Inhibitor (Human)
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received CINRYZE intravenous (IV) injection twice weekly (every 3 or 4 days) for 12 weeks during each intervention period.

Arm title	Treatment B-A (1000 U/500 U CINRYZE)

Arm description:

Subjects received 1000 U CINRYZE IV injection twice weekly (every 3 or 4 days) for 12 weeks (Treatment B) during intervention period 1 followed by 500 U CINRYZE IV injection twice weekly (every 3 or 4 days) for 12 weeks (Treatment A) during intervention period 2. There was no washout period between the two intervention periods.

Arm type	Experimental
Investigational medicinal product name	CINRYZE
Investigational medicinal product code	SHP616
Other name	C1 Esterase Inhibitor (Human)
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received CINRYZE intravenous (IV) injection twice weekly (every 3 or 4 days) for 12 weeks during each intervention period.

Number of subjects in period 2	Treatment A-B (500 U/1000 U CINRYZE)	Treatment B-A (1000 U/500 U CINRYZE)
Started	5	7
Completed	5	7

Baseline characteristics

Reporting groups	
Reporting group title	Treatment A-B (500 U/1000 U CINRYZE)
Reporting group description:	
Subjects received 500 U of CINRYZE IV injection twice weekly (every 3 or 4 days) for 12 weeks (Treatment A) during intervention period 1 followed by 1000 U CINRYZE IV injection twice weekly (every 3 or 4 days) for 12 weeks (Treatment B) during intervention period 2. There was no washout period between the two intervention periods.	
Reporting group title	Treatment B-A (1000 U/500 U CINRYZE)
Reporting group description:	
Subjects received 1000 U CINRYZE IV injection twice weekly (every 3 or 4 days) for 12 weeks (Treatment B) during intervention period 1 followed by 500 U CINRYZE IV injection twice weekly (every 3 or 4 days) for 12 weeks (Treatment A) during intervention period 2. There was no washout period between the two intervention periods.	

Reporting group values	Treatment A-B (500 U/1000 U CINRYZE)	Treatment B-A (1000 U/500 U CINRYZE)	Total
Number of subjects	5	7	12
Age categorical Units: Subjects			
Age continuous			
Age was calculated as the difference between date of birth and date of informed consent, truncated to years.			
Units: years arithmetic mean standard deviation	 10.2 ± 0.84	 9.4 ± 1.51	 -
Gender categorical Units: Subjects			
Female	2	5	7
Male	3	2	5
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	2	2	4
Not Hispanic or Latino	3	5	8
Unknown or Not Reported	0	0	0

End points

End points reporting groups

Reporting group title	Treatment A-B (500 U/1000 U CINRYZE)

Reporting group description:

Subjects received 500 U of CINRYZE IV injection twice weekly (every 3 or 4 days) for 12 weeks (Treatment A) during intervention period 1 followed by 1000 U CINRYZE IV injection twice weekly (every 3 or 4 days) for 12 weeks (Treatment B) during intervention period 2. There was no washout period between the two intervention periods.

Reporting group title	Treatment B-A (1000 U/500 U CINRYZE)

Reporting group description:

Subjects received 1000 U CINRYZE IV injection twice weekly (every 3 or 4 days) for 12 weeks (Treatment B) during intervention period 1 followed by 500 U CINRYZE IV injection twice weekly (every 3 or 4 days) for 12 weeks (Treatment A) during intervention period 2. There was no washout period between the two intervention periods.

Reporting group title	Treatment A-B (500 U/1000 U CINRYZE)

Reporting group description:

Subjects received 500 U of CINRYZE IV injection twice weekly (every 3 or 4 days) for 12 weeks (Treatment A) during intervention period 1 followed by 1000 U CINRYZE IV injection twice weekly (every 3 or 4 days) for 12 weeks (Treatment B) during intervention period 2. There was no washout period between the two intervention periods.

Reporting group title	Treatment B-A (1000 U/500 U CINRYZE)

Reporting group description:

Subjects received 1000 U CINRYZE IV injection twice weekly (every 3 or 4 days) for 12 weeks (Treatment B) during intervention period 1 followed by 500 U CINRYZE IV injection twice weekly (every 3 or 4 days) for 12 weeks (Treatment A) during intervention period 2. There was no washout period between the two intervention periods.

Subject analysis set title	Treatment A (500 U CINRYZE)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects received 500 U CINRYZE IV injection twice weekly (every 3 or 4 days) for 24 weeks (Intervention period 1 in sequence A-B and ntervention period 2 in sequence B-A). Each intervention period was of 12 weeks.

Subject analysis set title	Treatment B (1000 U CINRYZE)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects received 1000 U CINRYZE IV injection twice weekly (every 3 or 4 days) for 24 weeks (Intervention period 2 in sequence A-B and ntervention period 1 in sequence B-A). Each intervention period was of 12 weeks.

Primary: Normalized Number of Angioedema Attacks Per Month in a Treatment Period

End point title	Normalized Number of Angioedema Attacks Per Month in a Treatment Period

End point description:

Angioedema attack was defined as the subject-reported indication of symptoms or signs such as swelling or pain at any location following a report of no swelling or pain on the previous day. Manifestations of an attack that progress from one site to another, prior to complete resolution, was considered a single attack. Attacks that began to regress and then worsened before complete resolution was also considered one attack. Attacks that began then appeared to resolve and then reappeared without a symptom-free calendar day reported after the appearance of resolution were considered 1 attack. Any events of swelling due to trauma or symmetrical nonpainful swelling of the lower extremities were not considered an angioedema attack. The number of attacks was normalized for the number of days subjects participated in a given period and expressed as the monthly frequency.

End point type	Primary

End point timeframe:

From start of treatment up to 12 weeks during each treatment period

End point values	Treatment A (500 U CINRYZE)	Treatment B (1000 U CINRYZE)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	12	12		
Units: Angioedema attacks				
arithmetic mean (standard deviation)				
Angioedema attacks	1.2 (± 1.53)	0.7 (± 1.35)		

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Database auto-calculate number of subjects analysed, but the actual number of subjects analysed was 12.

Comparison groups	Treatment A (500 U CINRYZE) v Treatment B (1000 U CINRYZE)
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.03
Method	Paired t-test
Parameter estimate	Mean difference
Point estimate	-0.4
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.71
upper limit	-0.1
Variability estimate	Standard deviation
Dispersion value	0.58

Secondary: Cumulative Attack-severity of Angioedema Attacks Normalized Per Month in a Treatment Period

End point title	Cumulative Attack-severity of Angioedema Attacks Normalized Per Month in a Treatment Period

End point description:

Severity of the angioedema attack sign/symptom at each location was characterized as None: no symptom; Mild: noticeable symptom but easily tolerated by the subject and did not interfere with routine activities; Moderate: symptom interfered with the subject's ability to attend school or participate in family life and social/recreational activities; Severe: symptom significantly limited the subject's ability to attend school or participate in family life and social/recreational activities. Cumulative attack severity score was the sum of the maximum symptom severity recorded for each angioedema attack in a treatment period. Cumulative attack-severity score normalized per month was reported here.

End point type	Secondary

End point timeframe:

From start of treatment up to 12 weeks during each treatment period

End point values	Treatment A (500 U CINRYZE)	Treatment B (1000 U CINRYZE)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	12	12		
Units: Score on a scale				
arithmetic mean (standard deviation)				
Score on a scale	2.0 (± 2.91)	1.4 (± 2.68)		

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Database auto-calculate number of subjects analysed, but the actual number of subjects analysed was 12.

Comparison groups	Treatment A (500 U CINRYZE) v Treatment B (1000 U CINRYZE)
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.05
Method	Paired t-test
Parameter estimate	Mean difference
Point estimate	-0.7
Confidence interval	
level	90 %
sides	2-sided
lower limit	-1.2
upper limit	-0.11
Variability estimate	Standard deviation
Dispersion value	1.06

Secondary: Cumulative Daily-severity of Angioedema Attacks Normalized Per Month in a Treatment Period

End point title	Cumulative Daily-severity of Angioedema Attacks Normalized Per Month in a Treatment Period

End point description:

Severity of the angioedema attack sign/symptom at each location was characterized as None: no symptom; Mild: noticeable but easily tolerated by the subject and did not interfere with routine activities; Moderate: interfered with the subject's ability to attend school or participate in family life and social/recreational activities; Severe: significantly limited the subject's ability to attend school or participate in family life and social/recreational activities. Cumulative daily-severity score was the sum of the severity scores recorded for every day of reported symptoms in a treatment period. Cumulative daily-severity score normalized per month was reported here.

End point type	Secondary

End point timeframe:

From start of treatment up to 12 weeks during each intervention period

End point values	Treatment A (500 U CINRYZE)	Treatment B (1000 U CINRYZE)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	12	12		
Units: Score on a scale				
arithmetic mean (standard deviation)				
Score on a scale	4.1 (± 5.01)	2.2 (± 3.50)		

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Database auto-calculate number of subjects analysed, but the actual number of subjects analysed was 12.

Comparison groups	Treatment B (1000 U CINRYZE) v Treatment A (500 U CINRYZE)
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.04
Method	Paired t-test
Parameter estimate	Mean difference
Point estimate	-1.9
Confidence interval	
level	90 %
sides	2-sided
lower limit	-3.31
upper limit	-0.38
Variability estimate	Standard deviation
Dispersion value	2.82

Secondary: Normalized Number of Angioedema Attacks Per Month Requiring Acute Treatment in a Treatment Period

End point title	Normalized Number of Angioedema Attacks Per Month Requiring Acute Treatment in a Treatment Period

End point description:

Angioedema attack was defined as the subject-reported indication of symptoms or signs such as swelling or pain at any location following a report of no swelling or pain on the previous day. Manifestations of an attack that progress from one site to another, prior to complete resolution, was considered a single attack. Attacks that began to regress and then worsened before complete resolution was also considered one attack. Attacks that began then appeared to resolve and then reappeared without a symptom-free calendar day reported after the appearance of resolution were considered 1

attack. Any events of swelling due to trauma or symmetrical nonpainful swelling of the lower extremities were not considered an angioedema attack. The number of attacks requiring acute treatment was normalized for the number of days subjects participated in a given period and expressed as the monthly frequency.

End point type	Secondary

End point timeframe:

From start of treatment up to 12 weeks during each intervention period

End point values	Treatment A (500 U CINRYZE)	Treatment B (1000 U CINRYZE)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	12	12		
Units: Angioedema attacks				
arithmetic mean (standard deviation)				
Angioedema attacks	0.7 (± 1.5)	0.4 (± 1.27)		

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Database auto-calculate number of subjects analysed, but the actual number of subjects analysed was 12.

Comparison groups	Treatment A (500 U CINRYZE) v Treatment B (1000 U CINRYZE)
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.07
Method	Paired t-test
Parameter estimate	Mean difference
Point estimate	-0.2
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.41
upper limit	-0.03
Variability estimate	Standard deviation
Dispersion value	0.37

Secondary: Number of Subjects With Treatment-emergent Adverse Events (TEAEs) by Dose Group

End point title	Number of Subjects With Treatment-emergent Adverse Events (TEAEs) by Dose Group

End point description:

An adverse event (AE) was any untoward, undesired, unplanned clinical event in the form of signs, symptoms, disease, or laboratory or physiological observations occurring in a subject participating in a

clinical study with the sponsor's product, regardless of causal relationship. TEAEs were defined as events that started or worsened on or after the date and time of the first dose of investigational product and up to 7 days after the last dose of investigational product.

End point type	Secondary

End point timeframe:

From start of study treatment up to 25 weeks

End point values	Treatment A (500 U CINRYZE)	Treatment B (1000 U CINRYZE)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	12	12		
Units: Subject				
Subjects	10	11		

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentration of C1 Esterase Inhibitor (C1 INH) Antigen

End point title	Plasma Concentration of C1 Esterase Inhibitor (C1 INH) Antigen

End point description:

C1 INH antigen concentration in plasma was determined using an automated nephelometric assay.

End point type	Secondary

End point timeframe:

Pre-dose and 1 hour (h) post-dose at Week 1 (Dose 1) and Week 6 (Dose 12); Pre-dose, 1, 2, 4 and 8 h post-dose at Week 12 (Dose 24) of each intervention period

End point values	Treatment A (500 U CINRYZE)	Treatment B (1000 U CINRYZE)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	12	12		
Units: Gram per liter (g/L)				
arithmetic mean (standard deviation)				
Week 1: Pre-dose 1 (n=12,11)	0.0945 (± 0.03294)	0.0736 (± 0.02885)		
Week 1: 1 h post-dose 1 (n=11,11)	0.1819 (± 0.04331)	0.2084 (± 0.08757)		
Week 6: Pre-dose 12 (n=12,12)	0.0965 (± 0.03129)	0.1068 (± 0.03098)		
Week 6: 1 h post-dose 12 (n=10,11)	0.1631 (± 0.04188)	0.2543 (± 0.05499)		
Week 12: Pre-dose 24 (n=12,11)	0.0823 (± 0.02758)	0.1002 (± 0.04420)		
Week 12: 1 h post-dose 24 (n=12,10)	0.1621 (± 0.02990)	0.2396 (± 0.04511)		

Week 12: 2 h post-dose 24 (n=3,2)	0.1440 (± 0.00400)	0.2070 (± 0.01838)		
Week 12: 4 h post-dose 24 (n=2,2)	0.1440 (± 0.01131)	0.1770 (± 0.02970)		
Week 12: 8 h post-dose 24 (n=2,3)	0.1280 (± 0.00990)	0.1790 (± 0.03100)		

Statistical analyses

No statistical analyses for this end point

Secondary: C1 Esterase Inhibitor (C1 INH) Functional Activity in Plasma

End point title	C1 Esterase Inhibitor (C1 INH) Functional Activity in Plasma

End point description:

The functional activity of C1 INH in plasma samples was determined by a chromogenic assay.

End point type	Secondary

End point timeframe:

Pre-dose and 1 h post-dose at Week 1 (Dose 1) and Week 6 (Dose 12); Pre-dose, 1, 2, 4 and 8 h post-dose at Week 12 (Dose 24) of each intervention period

End point values	Treatment A (500 U CINRYZE)	Treatment B (1000 U CINRYZE)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	12	12		
Units: Units per milliliter (U/mL)				
arithmetic mean (standard deviation)				
Week 1: Pre-dose 1 (n=12,11)	0.290 (± 0.0914)	0.210 (± 0.1282)		
Week 1: 1 h post-dose 1 (n=12,11)	0.575 (± 0.1358)	0.725 (± 0.3100)		
Week 6: Pre-dose 12 (n=12,12)	0.297 (± 0.1375)	0.336 (± 0.0933)		
Week 6: 1 h post-dose 12 (n=11,11)	0.570 (± 0.1190)	0.865 (± 0.1550)		
Week 12: Pre-dose 24 (n=12,11)	0.255 (± 0.1108)	0.362 (± 0.1897)		
Week 12: 1 h post-dose 24 (n=12,10)	0.531 (± 0.1330)	0.803 (± 0.1906)		
Week 12: 2 h post-dose 24 (n=3,3)	0.497 (± 0.0635)	0.613 (± 0.2601)		
Week 12: 4 h post-dose 24 (n=3,3)	0.497 (± 0.0058)	0.590 (± 0.1803)		
Week 12: 8 h post-dose 24 (n=3,3)	0.430 (± 0.0458)	0.643 (± 0.0723)		

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentration of Complement C4

End point title	Plasma Concentration of Complement C4

End point description:

Concentration of Complement C4 in plasma was determined using an automated nephelometric assay.

End point type	Secondary

End point timeframe:

Pre-dose and 1 h post-dose at Week 1 (Dose 1) and Week 6 (Dose 12); Pre-dose, 1, 2, 4 and 8 h post-dose at Week 12 (Dose 24) of each intervention period

End point values	Treatment A (500 U CINRYZE)	Treatment B (1000 U CINRYZE)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	12	12		
Units: Milligram per liter (mg/L)				
arithmetic mean (standard deviation)				
Week 1: Pre-dose 1 (n=12,11)	105.1 (± 39.38)	71.2 (± 29.63)		
Week 1: 1 h post-dose 1 (n=12,11)	99.7 (± 36.73)	71.4 (± 33.20)		
Week 6: Pre-dose 12 (n=12,12)	97.3 (± 37.26)	121.3 (± 41.50)		
Week 6: 1 h post-dose 12 (n=11,11)	88.0 (± 27.75)	111.7 (± 41.75)		
Week 12: Pre-dose 24 (n=12,11)	83.3 (± 21.63)	111.6 (± 50.28)		
Week 12: 1 h post-dose 24 (n=12,10)	79.2 (± 20.21)	90.7 (± 27.72)		
Week 12: 2 h post-dose 24 (n=3,3)	86.7 (± 4.93)	94.3 (± 32.04)		
Week 12: 4 h post-dose 24 (n=3,3)	89.3 (± 12.66)	103.7 (± 32.35)		
Week 12: 8 h post-dose 24 (n=3,3)	99.3 (± 11.02)	114.7 (± 30.75)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with C1 Esterase Inhibitor (C1 INH) Antibodies in Plasma

End point title	Number of Subjects with C1 Esterase Inhibitor (C1 INH) Antibodies in Plasma

End point description:

The presence of C1 INH antibodies in plasma samples was determined using a proprietary enzyme-linked-immunosorbent-assay. Number of subjects with C1 INH Antibodies was reported here.

End point type	Secondary

End point timeframe:

Pre-dose, 1 week post treatment (Week 13, Week 25) and 1 month post treatment follow-up (Week 28)

End point values	Treatment A (500 U CINRYZE)	Treatment B (1000 U CINRYZE)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	5	7		
Units: Subject				
Subjects	0	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From start of study drug administration up to Week 25	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups	
Reporting group title	Treatment B (1000 U CINRYZE)
Reporting group description:	
Subjects received 1000 U CINRYZE IV injection twice weekly (every 3 or 4 days) for 24 weeks (Intervention period 2 in sequence A-B and ntervention period 1 in sequence B-A). Each intervention period was of 12 weeks.	
Reporting group title	Treatment A (500 U CINRYZE)
Reporting group description:	
Subjects received 500 U CINRYZE IV injection twice weekly (every 3 or 4 days) for 24 weeks (Intervention period 1 in sequence A-B and ntervention period 2 in sequence B-A). Each intervention period was of 12 weeks.	

Serious adverse events	Treatment B (1000 U CINRYZE)	Treatment A (500 U CINRYZE)	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	Treatment B (1000 U CINRYZE)	Treatment A (500 U CINRYZE)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 12 (91.67%)	10 / 12 (83.33%)	
Vascular disorders			
Vascular pain			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Facial pain			

subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Fatigue			
subjects affected / exposed	1 / 12 (8.33%)	1 / 12 (8.33%)	
occurrences (all)	9	9	
Infusion site pain			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	19	
Pyrexia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 12 (0.00%)	2 / 12 (16.67%)	
occurrences (all)	0	2	
Epistaxis			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Oropharyngeal pain			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Rhinitis allergic			
subjects affected / exposed	2 / 12 (16.67%)	0 / 12 (0.00%)	
occurrences (all)	2	0	
Psychiatric disorders			
Irritability			
subjects affected / exposed	1 / 12 (8.33%)	1 / 12 (8.33%)	
occurrences (all)	7	7	
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Excoriation			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Face injury			

subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Fall			
subjects affected / exposed	1 / 12 (8.33%)	1 / 12 (8.33%)	
occurrences (all)	1	1	
Head injury			
subjects affected / exposed	1 / 12 (8.33%)	1 / 12 (8.33%)	
occurrences (all)	1	1	
Joint injury			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Lip injury			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Multiple injuries			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Post-Traumatic neck syndrome			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Skin abrasion			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Sunburn			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Congenital, familial and genetic disorders			
Hereditary angioedema			
subjects affected / exposed	8 / 12 (66.67%)	9 / 12 (75.00%)	
occurrences (all)	25	41	
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Headache			

subjects affected / exposed	2 / 12 (16.67%)	1 / 12 (8.33%)	
occurrences (all)	5	1	
Eye disorders			
Eye pain			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Abdominal pain			
subjects affected / exposed	2 / 12 (16.67%)	1 / 12 (8.33%)	
occurrences (all)	2	2	
Constipation			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Dental caries			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Diarrhoea			
subjects affected / exposed	1 / 12 (8.33%)	1 / 12 (8.33%)	
occurrences (all)	1	2	
Nausea			
subjects affected / exposed	2 / 12 (16.67%)	1 / 12 (8.33%)	
occurrences (all)	2	2	
Toothache			
subjects affected / exposed	1 / 12 (8.33%)	1 / 12 (8.33%)	
occurrences (all)	4	1	
Vomiting			
subjects affected / exposed	1 / 12 (8.33%)	1 / 12 (8.33%)	
occurrences (all)	1	1	
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Erythema			

subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Erythema marginatum			
subjects affected / exposed	2 / 12 (16.67%)	2 / 12 (16.67%)	
occurrences (all)	12	12	
Prurigo			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Pruritus			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Coccydynia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Myalgia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Pain in extremity			
subjects affected / exposed	1 / 12 (8.33%)	1 / 12 (8.33%)	
occurrences (all)	1	2	
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Gingivitis			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
H1n1 influenza			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Hordeolum			

subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Nasopharyngitis			
subjects affected / exposed	2 / 12 (16.67%)	1 / 12 (8.33%)	
occurrences (all)	3	1	
Paronychia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Sinusitis			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Tinea pedis			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Tonsillitis			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Upper respiratory tract infection			
subjects affected / exposed	2 / 12 (16.67%)	1 / 12 (8.33%)	
occurrences (all)	4	1	
Viral pharyngitis			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Viral upper respiratory tract infection			
subjects affected / exposed	6 / 12 (50.00%)	2 / 12 (16.67%)	
occurrences (all)	8	3	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 October 2013	Blood sample collection for post-treatment immunogenicity assessments, the post-dose time point was changed to Dose 12.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported