



Clinical trial results:

A Phase 3, Randomized, Double-blind, Placebo-controlled, Two-period, Three-sequence, Partial Crossover Study to Evaluate the Efficacy and Safety of Subcutaneous Administration of 2000 IU of C1 Esterase Inhibitor [Human] Liquid for Injection for the Prevention of Angioedema Attacks in Adolescents and Adults With Hereditary Angioedema

Summary

EudraCT number	2015-002478-19
Trial protocol	DE HU ES
Global end of trial date	24 July 2017

Results information

Result version number	v1 (current)
This version publication date	02 March 2018
First version publication date	02 March 2018

Trial information

Trial identification

Sponsor protocol code	SHP616-300
-----------------------	------------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02584959
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Shire
Sponsor organisation address	300 Shire Way, Lexington, United States, MA 02421
Public contact	Study Physician, Shire, ClinicalTransparency@shire.com
Scientific contact	Study Physician, Shire, ClinicalTransparency@shire.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	24 July 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	24 July 2017
Global end of trial reached?	Yes
Global end of trial date	24 July 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 demonstrate superior efficacy of SC administration of 2000 IU C1 esterase inhibitor [human] liquid for injection for the prevention of angioedema attacks relative to placebo based on the normalized number of angioedema attacks (NNA) during a treatment period.

Protection of trial subjects:

This study was conducted in accordance with the International Council for Harmonisation (ICH) of Good Clinical Practice, and consistent with the principles protecting clinical trial subjects that have their origin in the Declaration of Helsinki, as well as other applicable local ethical and legal requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	08 January 2016
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	Hungary: 4
Country: Number of subjects enrolled	Spain: 7
Country: Number of subjects enrolled	Romania: 8
Country: Number of subjects enrolled	Germany: 2
Country: Number of subjects enrolled	Israel: 10
Country: Number of subjects enrolled	United States: 46
Country: Number of subjects enrolled	Canada: 4
Worldwide total number of subjects	81
EEA total number of subjects	21

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)	3
Adults (18-64 years)	74
From 65 to 84 years	4
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This was a multicenter study conducted at 33 sites/centers in 7 countries: Unites States, Canada, Germany, Hungary, Israel, Spain, and Romania.

Pre-assignment

Screening details:

Of the 81 subjects screened, 6 subjects failed to meet the randomization criteria and were not randomly assigned to a treatment sequence. All 75 randomly assigned subjects received at least 1 dose of the IP.

Pre-assignment period milestones

Number of subjects started	81
Number of subjects completed	75

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Failed to meet the randomization criteria: 6
----------------------------	--

Period 1

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

Blinding implementation details:

To maintain the blind, C1 esterase inhibitor [human] liquid for injection and placebo had an identical presentation, including its packaging and labeling, such that the contents of the glass vials within the prepackaged study kits were indistinguishable from each other. Independent external laboratory performing the PK/PD analyses kept the results in strict confidence until the study was unblinded. Some representatives of the sponsor were unblinded to review drug accountability.

Arms

Are arms mutually exclusive?	Yes
Arm title	Sequence A/B (SHP 616)

Arm description:

Subjects randomized to Sequence A/B received investigational product (SHP616) in treatment period 1.

Arm type	Experimental
Investigational medicinal product name	C1 esterase inhibitor [human] liquid
Investigational medicinal product code	SHP 616
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

2000 IU (4.0 ml) C1 esterase inhibitor [human] liquid was administered subcutaneously twice weekly (every 3 or 4 days) for 14 weeks.

Arm title	Sequence B/A (Placebo)
------------------	------------------------

Arm description:

Subjects randomized to Sequence B/A received Placebo in treatment period 1.

Arm type	Placebo
----------	---------

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use
Dosage and administration details:	
Placebo (4.0 ml) was administered subcutaneously twice weekly (every 3 or 4 days) for 14 weeks.	
Arm title	Sequence A/A (SHP 616)

Arm description:

Subjects randomized to Sequence A/A received investigational product (SHP616) in treatment period 1.

Arm type	Experimental
Investigational medicinal product name	C1 esterase inhibitor [human] liquid
Investigational medicinal product code	SHP 616
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

2000 IU (4.0 ml) C1 esterase inhibitor [human] liquid was administered subcutaneously twice weekly (every 3 or 4 days) for 14 weeks.

Number of subjects in period 1^[1]	Sequence A/B (SHP 616)	Sequence B/A (Placebo)	Sequence A/A (SHP 616)
Started	31	29	15
Completed	28	25	15
Not completed	3	4	0
Withdrew from study	3	4	-

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Of the 81 subjects screened, 6 subjects failed to meet the randomization criteria and were not randomly assigned to a treatment sequence. All 75 randomly assigned subjects received at least 1 dose of the investigational product.

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, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

To maintain the blind, C1 esterase inhibitor [human] liquid for injection and placebo had an identical presentation, including its packaging and labeling, such that the contents of the glass vials within the prepackaged study kits were indistinguishable from each other. Independent external laboratory performing the PK/PD analyses kept the results in strict confidence until the study was unblinded. Some representatives of the sponsor were unblinded to review drug accountability.

Arms

Are arms mutually exclusive?	Yes
------------------------------	-----

Arm title	Sequence A/B (Placebo)
Arm description: Subjects randomized to Sequence A/B received Placebo in treatment period 2.	
Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use
Dosage and administration details: Placebo (4.0 ml) was administered subcutaneously twice weekly (every 3 or 4 days) for 14 weeks.	
Arm title	Sequence B/A (SHP 616)
Arm description: Subjects randomized to Sequence B/A received investigational product (SHP616) in treatment period 2.	
Arm type	Experimental
Investigational medicinal product name	C1 esterase inhibitor [human] liquid
Investigational medicinal product code	SHP 616
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use
Dosage and administration details: 2000 IU (4.0 ml) C1 esterase inhibitor [human] liquid was administered subcutaneously twice weekly (every 3 or 4 days) for 14 weeks.	
Arm title	Sequence A/A (SHP 616)
Arm description: Subjects randomized to Sequence A/A received investigational product (SHP616) in treatment period 2.	
Arm type	Experimental
Investigational medicinal product name	C1 esterase inhibitor [human] liquid
Investigational medicinal product code	SHP 616
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use
Dosage and administration details: 2000 IU (4.0 ml) C1 esterase inhibitor [human] liquid was administered subcutaneously twice weekly (every 3 or 4 days) for 14 weeks.	

Number of subjects in period 2	Sequence A/B (Placebo)	Sequence B/A (SHP 616)	Sequence A/A (SHP 616)
Started	28	25	15
Completed	22	24	13
Not completed	6	1	2
Withdrew from study	6	1	2

Baseline characteristics

Reporting groups

Reporting group title	Sequence A/B (SHP 616)
Reporting group description:	
Subjects randomized to Sequence A/B received investigational product (SHP616) in treatment period 1.	
Reporting group title	Sequence B/A (Placebo)
Reporting group description:	
Subjects randomized to Sequence B/A received Placebo in treatment period 1.	
Reporting group title	Sequence A/A (SHP 616)
Reporting group description:	
Subjects randomized to Sequence A/A received investigational product (SHP616) in treatment period 1.	

Reporting group values	Sequence A/B (SHP 616)	Sequence B/A (Placebo)	Sequence A/A (SHP 616)
Number of subjects	31	29	15
Age categorical			
Units: Subjects			
< 18 years	0	2	1
18 to ≤ 64 years	30	25	13
≥ 65 years	1	2	1
Age continuous			
Units: years			
arithmetic mean	40.5	40.7	44.4
standard deviation	± 13.16	± 15.34	± 16.40
Gender categorical			
Units:			
Male	8	8	7
Female	23	21	8

Reporting group values	Total		
Number of subjects	75		
Age categorical			
Units: Subjects			
< 18 years	3		
18 to ≤ 64 years	68		
≥ 65 years	4		
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units:			
Male	23		
Female	52		

End points

End points reporting groups

Reporting group title	Sequence A/B (SHP 616)
Reporting group description:	
Subjects randomized to Sequence A/B received investigational product (SHP616) in treatment period 1.	
Reporting group title	Sequence B/A (Placebo)
Reporting group description:	
Subjects randomized to Sequence B/A received Placebo in treatment period 1.	
Reporting group title	Sequence A/A (SHP 616)
Reporting group description:	
Subjects randomized to Sequence A/A received investigational product (SHP616) in treatment period 1.	
Reporting group title	Sequence A/B (Placebo)
Reporting group description:	
Subjects randomized to Sequence A/B received Placebo in treatment period 2.	
Reporting group title	Sequence B/A (SHP 616)
Reporting group description:	
Subjects randomized to Sequence B/A received investigational product (SHP616) in treatment period 2.	
Reporting group title	Sequence A/A (SHP 616)
Reporting group description:	
Subjects randomized to Sequence A/A received investigational product (SHP616) in treatment period 2.	
Subject analysis set title	Safety set
Subject analysis set type	Safety analysis
Subject analysis set description:	
All subjects who received at least one dose of investigational product.	
Subject analysis set title	Treatment A (SHP 616) Overall
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
All subjects who received treatment A (SHP 616).	
Subject analysis set title	Treatment B (Placebo) Overall
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
All subjects who received treatment B (Placebo).	
Subject analysis set title	Full analysis set
Subject analysis set type	Full analysis
Subject analysis set description:	
All subjects in the safety set who received at least 1 postbaseline (eg, randomization) primary efficacy assessment.	

Primary: Time-Normalized Number of Attacks (NNA) for participants during a treatment period

End point title	Time-Normalized Number of Attacks (NNA) for participants during a treatment period ^[1]
End point description:	
Time-normalized number of angioedema attacks was expressed as the number of attacks per month (ie, 30.4 days) of exposure. $NNA = 30.4 \times (\text{number of attacks during treatment period}) / (\text{days of treatment period})$.	
End point type	Primary
End point timeframe:	
Weeks 1 to 14 for treatment period 1 and 2	

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Statistics are reported per overall treatment (SHP616 or Placebo) for this endpoint.

End point values	Sequence A/B (SHP 616)	Sequence A/B (Placebo)	Sequence B/A (Placebo)	Sequence B/A (SHP 616)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	31	28	29	25
Units: Number				
least squares mean (confidence interval 95%)	1.436 (0.821 to 2.052)	3.756 (3.125 to 4.387)	4.106 (3.469 to 4.744)	1.786 (1.127 to 2.446)

End point values	Treatment A (SHP 616) Overall	Treatment B (Placebo) Overall		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	56	57		
Units: Number				
least squares mean (confidence interval 95%)	1.611 (1.067 to 2.156)	3.931 (3.391 to 4.471)		

Statistical analyses

Statistical analysis title	Difference in LS means
----------------------------	------------------------

Statistical analysis description:

The LS means, 95% CIs, and p-values were based on a mixed effect linear model with period, sequence, use of prophylactic therapy with C1 INH at randomization, and treatment as fixed effects and subject nested within sequence as a random effect.

Comparison groups	Treatment A (SHP 616) Overall v Treatment B (Placebo) Overall
Number of subjects included in analysis	113
Analysis specification	Pre-specified
Analysis type	other ^[2]
P-value	< 0.0001 ^[3]
Method	Mixed models analysis
Parameter estimate	Difference in LS means
Point estimate	-2.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.895
upper limit	-1.744

Notes:

[2] - Due to the cross-over design of the study the overall number of unique subjects in this analysis is 60.

[3] - Sequence effect p-value=0.2997; Period effect p-value=0.8473; Prophylactic effect p-value=0.0009

Secondary: Proportion of subjects meeting the criterion of at least 50% reduction in the NNA during the experimental injection treatment period relative to the placebo

period

End point title	Proportion of subjects meeting the criterion of at least 50% reduction in the NNA during the experimental injection treatment period relative to the placebo period
-----------------	---

End point description:

Time-Normalized Number of Attacks was expressed as the number of attacks per month (ie, 30.4 days) of exposure. $NNA = 30.4 \times (\text{number of attacks during treatment period}) / (\text{days of treatment period})$. Subjects with 0 attacks in the placebo period were excluded because a percent reduction could not be calculated. Analysis was done on subjects who were dosed in both treatment periods.

End point type	Secondary
----------------	-----------

End point timeframe:

Weeks 1 to 14 for treatment period 1 and 2

End point values	Full analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	49			
Units: Number of subjects	38			

Statistical analyses

No statistical analyses for this end point

Secondary: The normalized number of attacks (NNA) during each treatment period excluding the first 2 weeks.

End point title	The normalized number of attacks (NNA) during each treatment period excluding the first 2 weeks. ^[4]
-----------------	---

End point description:

Time-Normalized Number of Attacks was expressed as the number of attacks per month (ie, 30.4 days) of exposure. $NNA = 30.4 \times (\text{number of attacks during treatment period}) / (\text{days of treatment period})$.

End point type	Secondary
----------------	-----------

End point timeframe:

Weeks 3 to 14 for treatment period 1 and 2

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Statistics are reported per overall treatment (SHP616 or Placebo) for this endpoint.

End point values	Sequence A/B (SHP 616)	Sequence A/B (Placebo)	Sequence B/A (Placebo)	Sequence B/A (SHP 616)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	30	27	28	25
Units: Number				
least squares mean (confidence interval 95%)	1.309 (0.611 to 2.006)	3.631 (2.917 to 4.346)	4.062 (3.339 to 4.785)	1.740 (0.997 to 2.482)

End point values	Treatment A	Treatment B		
-------------------------	-------------	-------------	--	--

	(SHP 616) Overall	(Placebo) Overall		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	55	55		
Units: Number				
least squares mean (confidence interval 95%)	1.524 (0.912 to 2.136)	3.847 (3.237 to 4.457)		

Statistical analyses

Statistical analysis title	Difference in LS means
Statistical analysis description:	
The LS means, 95% CIs, and p-values were based on a mixed effect linear model with period, sequence, use of prophylactic therapy with C1 INH at randomization, and treatment as fixed effects and subject nested within sequence as a random effect.	
Comparison groups	Treatment A (SHP 616) Overall v Treatment B (Placebo) Overall
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	other ^[5]
P-value	< 0.0001 ^[6]
Method	Mixed models analysis
Parameter estimate	Difference in LS means
Point estimate	-2.323
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.969
upper limit	-1.677

Notes:

[5] - Due to the cross-over design of the study the overall number of unique subjects in this analysis is 60.

[6] - Sequence effect p-value=0.2630; Period effect p-value=0.8792; Prophylactic effect p-value=0.0065

Secondary: Proportion of subjects meeting the criterion of at least 50% reduction in the NNA during the experimental injection treatment period relativ to the placebo period excluding the first 2 weeks of each treatment period

End point title	Proportion of subjects meeting the criterion of at least 50% reduction in the NNA during the experimental injection treatment period relativ to the placebo period excluding the first 2 weeks of each treatment period
End point description:	
Time-Normalized Number of Attacks was expressed as the number of attacks per month (ie, 30.4 days) of exposure. $NNA = 30.4 \times (\text{number of attacks during treatment period}) / (\text{days of treatment period})$. Subjects with 0 attacks in the placebo period were excluded because a percent reduction could not be calculated.	
End point type	Secondary
End point timeframe:	
Weeks 3 to 14 for treatment period 1 and 2	

End point values	Full analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	47			
Units: Number of subjects	36			

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of subjects meeting the criterion of at least 50% reduction in the NNA during the experimental injection treatment period relative to the pretreatment assessment.

End point title	Proportion of subjects meeting the criterion of at least 50% reduction in the NNA during the experimental injection treatment period relative to the pretreatment assessment.
End point description:	
Subjects with 0 attacks at baseline were excluded because a percent reduction could not be calculated.	
End point type	Secondary
End point timeframe:	
Weeks 1 to 14 for treatment period 1 and 2	

End point values	Treatment A (SHP 616) Overall	Treatment B (Placebo) Overall		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	53	55		
Units: Number of subjects	41	13		

Statistical analyses

No statistical analyses for this end point

Secondary: Cumulative attack severity

End point title	Cumulative attack severity ^[7]
End point description:	
Cumulative attack severity was defined as the summation of the maximum symptom severity recorded for each angioedema attack in a treatment period for each subject.	
End point type	Secondary
End point timeframe:	
Weeks 1 to 14 for treatment period 1 and 2	

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Statistics are reported per overall treatment (SHP616 or Placebo) for this endpoint.

End point values	Sequence A/B (SHP 616)	Sequence A/B (Placebo)	Sequence B/A (Placebo)	Sequence B/A (SHP 616)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	31	28	29	25
Units: Number				
least squares mean (confidence interval 95%)	2.682 (1.191 to 4.172)	7.563 (6.040 to 9.086)	8.518 (6.972 to 10.065)	3.637 (2.045 to 5.230)

End point values	Treatment A (SHP 616) Overall	Treatment B (Placebo) Overall		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	56	57		
Units: Number				
least squares mean (confidence interval 95%)	3.159 (1.856 to 4.463)	8.041 (6.746 to 9.336)		

Statistical analyses

Statistical analysis title	Difference in LS means
Statistical analysis description: The LS means, 95% CIs, and p-values were based on a mixed effect linear model with period, sequence, use of prophylactic therapy with C1 INH at randomization, and treatment as fixed effects and subject nested within sequence as a random effect. Cumulative attack severity was the summation of the maximum symptom severity recorded for each angioedema attack in a treatment period for each subject.	
Comparison groups	Treatment A (SHP 616) Overall v Treatment B (Placebo) Overall
Number of subjects included in analysis	113
Analysis specification	Pre-specified
Analysis type	other ^[8]
P-value	< 0.0001 ^[9]
Method	Mixed models analysis
Parameter estimate	Difference in LS means
Point estimate	-4.881
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.113
upper limit	-3.649

Notes:

[8] - Due to the cross-over design of the study the overall number of unique subjects in this analysis is 60.

[9] - Sequence effect p-value=0.2538; Period effect p-value=0.6213; Prophylactic effect p-value=0.

Secondary: Number of attack-free days

End point title	Number of attack-free days ^[10]
-----------------	--

End point description:

Attack-free days were normalized per month

End point type	Secondary
----------------	-----------

End point timeframe:

Weeks 1 to 14 for treatment period 1 and 2

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Statistics are reported per overall treatment (SHP616 or Placebo) for this endpoint.

End point values	Sequence A/B (SHP 616)	Sequence A/B (Placebo)	Sequence B/A (Placebo)	Sequence B/A (SHP 616)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	31	28	29	25
Units: Number				
least squares mean (confidence interval 95%)	27.406 (25.468 to 29.343)	21.971 (19.995 to 23.946)	20.736 (18.722 to 22.749)	26.171 (24.105 to 28.237)

End point values	Treatment A (SHP 616) Overall	Treatment B (Placebo) Overall		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	56	57		
Units: Number				
least squares mean (confidence interval 95%)	26.788 (25.106 to 28.470)	21.353 (19.681 to 23.025)		

Statistical analyses

Statistical analysis title	Difference in LS means
----------------------------	------------------------

Statistical analysis description:

The LS means, 95% CIs, and p-values were based on a mixed effect linear model with period, sequence, use of prophylactic therapy with C1 INH at randomization, and treatment as fixed effects and subject nested within sequence as a random effect.

Comparison groups	Treatment A (SHP 616) Overall v Treatment B (Placebo) Overall
-------------------	---

Number of subjects included in analysis	113
Analysis specification	Pre-specified
Analysis type	other ^[11]
P-value	< 0.0001 ^[12]
Method	Mixed models analysis
Parameter estimate	Difference in LS means
Point estimate	5.435
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.981
upper limit	6.889

Notes:

[11] - Due to the cross-over design of the study the overall number of unique subjects in this analysis is 60.

[12] - Sequence effect p-value=0.2629; Period effect p-value=0.2659, Prophylactic effect p-value=0.0487

Secondary: Number of angioedema attacks requiring acute treatment

End point title	Number of angioedema attacks requiring acute treatment ^[13]
End point description:	
Angioedema attacks were normalized per month	
End point type	Secondary
End point timeframe:	
Weeks 1 to 14 for treatment period 1 and 2	

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Statistics are reported per overall treatment (SHP616 or Placebo) for this endpoint.

End point values	Sequence A/B (SHP 616)	Sequence A/B (Placebo)	Sequence B/A (Placebo)	Sequence B/A (SHP 616)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	31	28	29	25
Units: Number				
least squares mean (confidence interval 95%)	1.301 (0.681 to 1.921)	3.476 (2.840 to 4.111)	3.781 (3.139 to 4.423)	1.607 (0.943 to 2.270)

End point values	Treatment A (SHP 616) Overall	Treatment B (Placebo) Overall		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	56	57		
Units: Number				
least squares mean (confidence interval 95%)	1.454 (0.906 to 2.002)	3.628 (3.085 to 4.172)		

Statistical analyses

Statistical analysis title	Difference in LS means
Statistical analysis description: The LS means, 95% CIs, and p-values were based on a mixed effect linear model with period, sequence, use of prophylactic therapy with C1 INH at randomization, and treatment as fixed effects and subject nested within sequence as a random effect.	
Comparison groups	Treatment A (SHP 616) Overall v Treatment B (Placebo) Overall
Number of subjects included in analysis	113
Analysis specification	Pre-specified
Analysis type	other ^[14]
P-value	< 0.0001 ^[15]
Method	Mixed models analysis
Parameter estimate	Difference in LS means
Point estimate	-2.175
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.75
upper limit	-1.599

Notes:

[14] - Due to the cross-over design of the study the overall number of unique subjects in this analysis is 60.

[15] - Sequence effect p-value=0.3687; Period effect p-value=0.8883; Prophylactic effect p-value=0.0009

Secondary: Safety and tolerability - Adverse Events, Injection Site Reactions and Immunogenicity

End point title	Safety and tolerability - Adverse Events, Injection Site Reactions and Immunogenicity
-----------------	---

End point description:

Treatment-emergent adverse events (TEAE) were counted by the treatment most recently taken when the event occurred. Subjects were counted once per category per treatment.

Injection site reactions (Erythema, Swelling, Cutaneous pain, Burning sensation, Itching/Pruritus, Warm sensation) were recorded on a designated eCRF page by the site personnel who monitored the local reaction for 1 hour after IP administration 5 times during each treatment period.

End point type	Secondary
----------------	-----------

End point timeframe:

From day of first dose in week 1 to week 15 for treatment period 1 and 2

End point values	Treatment A (SHP 616) Overall	Treatment B (Placebo) Overall		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	71	57		
Units: Number of subjects				
Any TEAE	42	32		
Serious TEAE	2	3		
Severe TEAE	4	3		
TEAE within 24 hours of IP administration	10	7		
Serious TEAE within 24 hours of IP administration	0	0		

Treatment-related TEAE within 24 hrs of IP admin.	3	2		
Treatment-related SAE within 24 hrs of IP admin.	0	0		
TEAE within 24hrs IP admin. leading to withdrawal	1	0		
Deaths due to TEAE	0	0		
Hospitalizations due to TEAE	2	3		
TEAE leading to withdrawal	1	2		
Treatment-related TEAE	5	4		
Treatment-related SAE	0	0		
Treatment-related severe TEAE	0	0		
Treatment-related TEAE leading to withdrawal	1	0		
Any injection site reaction	42	15		
Any severe injection site reaction	2	0		
Any mild injection site reaction	42	15		
Any moderate injection site reaction	14	1		
Positive anti-C1 INH antibodies prior treatment	0	0		
Positive anti-C1 INH antibodies developed	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: PK parameters: AUC (0-96) and AUC (0-t) for Functional C1 INH Binding Activity

End point title	PK parameters: AUC (0-96) and AUC (0-t) for Functional C1 INH Binding Activity
-----------------	--

End point description:

AUC(0-96)=area under the plasma concentration-time curve from time zero to last measurable concentration; AUC(0-t)=area under the plasma concentration-time curve from time zero extrapolated to the end of the dosing interval tau, where tau is approximately 84 hours (ie, average of every 3 or 4 days)

AUC(0-96) = AUC(0-tau)

End point type	Secondary
----------------	-----------

End point timeframe:

Within 15 min prior dosing at week 1, week 2, week 8, week 16, week 24, week 27/28 and 48 (± 3) hours after dose in week 27/28 in period 1 and 2. In addition 24 (±3) hours, 72 (±6) hours and 96 (±6) hours post dose in week 28 for period 2.

End point values	Treatment A (SHP 616) Overall	Treatment B (Placebo) Overall		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	6	3		
Units: mU*h/mL				
arithmetic mean (standard deviation)				

AUC (0-96)	31070 (± 17396)	13860 (± 7269.0)		
AUC (0-t)	31190 (± 17389)	13860 (± 7268.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: PK parameters: AUC (0-96) and AUC (0-t) for C1 INH Antigen Concentrations

End point title	PK parameters: AUC (0-96) and AUC (0-t) for C1 INH Antigen Concentrations
-----------------	---

End point description:

AUC(0-96)=area under the plasma concentration-time curve from time zero to last measurable concentration; AUC(0-t)=area under the plasma concentration-time curve from time zero extrapolated to the end of the dosing interval tau, where tau is approximately 84 hours (ie, average of every 3 or 4 days)

AUC(0-96) = AUC(0-tau)

End point type	Secondary
----------------	-----------

End point timeframe:

Within 15 min prior dosing at week 1, week 2, week 8, week 16, week 24, week 27/28 and 48 (± 3) hours after dose in week 27/28 in period 1 and 2. In addition 24 (±3) hours, 72 (±6) hours and 96 (±6) hours post dose in week 28 for period 2.

End point values	Treatment A (SHP 616) Overall	Treatment B (Placebo) Overall		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	6	3		
Units: µg*h/mL				
arithmetic mean (standard deviation)				
AUC (0-96)	6882 (± 4586.0)	1849 (± 426.36)		
AUC (0-t)	6902 (± 4574.0)	1849 (± 426.09)		

Statistical analyses

No statistical analyses for this end point

Secondary: PK parameters: AUC (0-96) and AUC (0-t) for Complement C4 Concentrations

End point title	PK parameters: AUC (0-96) and AUC (0-t) for Complement C4 Concentrations
-----------------	--

End point description:

AUC(0-96)=area under the plasma concentration-time curve from time zero to last measurable concentration; AUC(0-t)=area under the plasma concentration-time curve from time zero extrapolated to the end of the dosing interval tau, where tau is approximately 84 hours (ie, average of every 3 or 4

days)

AUC(0-96) = AUC(0-tau)

End point type	Secondary
----------------	-----------

End point timeframe:

Within 15 min prior dosing at week 1, week 2, week 8, week 16, week 24, week 27/28 and 48 (± 3) hours after dose in week 27/28 in period 1 and 2. In addition 24 (±3) hours, 72 (±6) hours and 96 (±6) hours post dose in week 28 for period 2.

End point values	Treatment A (SHP 616) Overall	Treatment B (Placebo) Overall		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	5	2 ^[16]		
Units: mg*h/L				
arithmetic mean (standard deviation)				
AUC (0-96)	16690 (± 803.60)	99999 (± 99999)		
AUC (0-t)	16780 (± 895.63)	99999 (± 99999)		

Notes:

[16] - not calculated, 99999 was entered

Statistical analyses

No statistical analyses for this end point

Secondary: PK Parameters: Cmax and Cmin for Functional C1 INH Binding Activity

End point title	PK Parameters: Cmax and Cmin for Functional C1 INH Binding Activity
-----------------	---

End point description:

Cmax=maximum observed plasma concentration and Cmin=minimum observed plasma concentration

End point type	Secondary
----------------	-----------

End point timeframe:

Within 15 min prior dosing at at week 1, week 2, week 8, week 16, week 24, week 27/28 and 48 (± 3) hours after dose in week 27/28 in period 1 and 2 and in addition 24 (±3) hours, 72 (±6) hours and 96 (±6) hours post dose in week 28 for period 2

End point values	Treatment A (SHP 616) Overall	Treatment B (Placebo) Overall		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	6	3		
Units: mU/mL				
arithmetic mean (standard deviation)				
Cmax	396.20 (± 273.013)	159.50 (± 82.982)		
Cmin	258.15 (± 138.232)	125.90 (± 62.329)		

Statistical analyses

No statistical analyses for this end point

Secondary: PK Parameters: Cmax and Cmin for C1 INH Antigen Concentrations

End point title	PK Parameters: Cmax and Cmin for C1 INH Antigen Concentrations
End point description: Cmax=maximum observed plasma concentration and Cmin=minimum observed plasma concentration	
End point type	Secondary
End point timeframe: Within 15 min prior dosing at at week 1, week 2, week 8, week 16, week 24, week 27/28 and 48 (± 3) hours after dose in week 27/28 in period 1 and 2 and in addition 24 (±3) hours, 72 (±6) hours and 96 (±6) hours post dose in week 28 for period 2	

End point values	Treatment A (SHP 616) Overall	Treatment B (Placebo) Overall		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	6	3		
Units: µg/mL				
arithmetic mean (standard deviation)				
Cmax	77.680 (± 52.4375)	21.257 (± 5.1647)		
Cmin	65.562 (± 45.9331)	17.913 (± 4.4316)		

Statistical analyses

No statistical analyses for this end point

Secondary: PK Parameters: Cmax and Cmin for Complement C4 Concentrations

End point title	PK Parameters: Cmax and Cmin for Complement C4 Concentrations
End point description: Cmax=maximum observed plasma concentration and Cmin=minimum observed plasma concentration	
End point type	Secondary
End point timeframe: Within 15 min prior dosing at at week 1, week 2, week 8, week 16, week 24, week 27/28 and 48 (± 3) hours after dose in week 27/28 in period 1 and 2 and in addition 24 (±3) hours, 72 (±6) hours and 96 (±6) hours post dose in week 28 for period 2	

End point values	Treatment A (SHP 616) Overall	Treatment B (Placebo) Overall		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	5	2 ^[17]		
Units: mg/L				
arithmetic mean (standard deviation)				
Cmax	200 (± 30.82)	99999 (± 99999)		
Cmin	158 (± 13.04)	99999 (± 99999)		

Notes:

[17] - not calculated, 99999 was entered

Statistical analyses

No statistical analyses for this end point

Secondary: PK Parameters: tmax

End point title	PK Parameters: tmax
-----------------	---------------------

End point description:

tmax=time of maximum observed plasma concentration

End point type	Secondary
----------------	-----------

End point timeframe:

Within 15 min prior dosing at at week 1, week 2, week 8, week 16, week 24, week 27/28 and 48 (± 3) hours after dose in week 27/28 in period 1 and 2 and in addition 24 (±3) hours, 72 (±6) hours and 96 (±6) hours post dose in week 28 for period 2

End point values	Treatment A (SHP 616) Overall	Treatment B (Placebo) Overall		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	6 ^[18]	3 ^[19]		
Units: hours				
arithmetic mean (standard deviation)				
Funtional C1 INH Binding Activity	31.597 (± 12.7038)	55.689 (± 49.4851)		
C1 INH Antigen Concentration	31.656 (± 24.6912)	47.578 (± 47.3106)		
Complement C4 Concentrations	33.417 (± 36.5183)	99999 (± 99999)		

Notes:

[18] - n=5 for Complement C4 Concentration

[19] - n=2 for Complement C4 Concentration (not calculated, 99999 was entered)

Statistical analyses

No statistical analyses for this end point

Secondary: Response to icatibant when administered for an acute attack

End point title	Response to icatibant when administered for an acute attack
-----------------	---

End point description:

End point type	Secondary
----------------	-----------

End point timeframe:

Weeks 1 to 14 for each treatment period

End point values	Treatment A (SHP 616) Overall	Treatment B (Placebo) Overall		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	71	57		
Units: Number of attacks				
requiring 1 injection	129	306		
requiring 2 injections	38	89		
requiring 3 injections	13	30		
requiring >= 4 injections	1	28		

Statistical analyses

No statistical analyses for this end point

Secondary: Assess disease activity as measured by the Angioedema Activity Score (AAS)

End point title	Assess disease activity as measured by the Angioedema Activity Score (AAS)
-----------------	--

End point description:

The Least Square means, 95% confidence intervals and p-values are based on mixed effect linear model with period, sequence, use of prophylactic therapy with C1 INH at randomization and treatment as fixed effects and subject nested within sequence as a random effect.

The normalized 98-day Angioedema Activity Score (AAS) per month for a subject is calculated by (the sum of daily AAS within a treatment period/the number of days that a subject has AAS records within the treatment period)*30.4.

End point type	Secondary
----------------	-----------

End point timeframe:

Weeks 1 to 14 for treatment period 1 and 2

End point values	Treatment A (SHP 616) Overall	Treatment B (Placebo) Overall		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	56	57		
Units: Angioedema Activity Score				
least squares mean (confidence interval 95%)	25.433 (11.204 to 39.662)	57.168 (43.010 to 71.326)		

Statistical analyses

Statistical analysis title	Difference in least square means
Statistical analysis description:	
The Least Square means, 95% confidence intervals and p-values are based on mixed effect linear model with period, sequence, use of prophylactic therapy with C1 INH at randomization and treatment as fixed effects and subject nested within sequence as a random effect. The normalized 98-day Angioedema Activity Score (AAS) per month for a subject is calculated by (the sum of daily AAS within a treatment period/the number of days that a subject has AAS records within the treatment period)*30.4.	
Comparison groups	Treatment A (SHP 616) Overall v Treatment B (Placebo) Overall
Number of subjects included in analysis	113
Analysis specification	Pre-specified
Analysis type	other ^[20]
P-value	< 0.0001 ^[21]
Method	Mixed models analysis
Parameter estimate	Difference in LS means
Point estimate	-31.735
Confidence interval	
level	95 %
sides	2-sided
lower limit	-42.696
upper limit	-20.773

Notes:

[20] - Due to the cross-over design of the study the overall number of unique subjects in this analysis is 60.

[21] - Sequence effect p-value=0.3723; Period effect p-value=0.8735; Prophylactic effect p-value=0.0543

Secondary: Subject experience with self-administration: Overall experience with the syringe

End point title	Subject experience with self-administration: Overall experience with the syringe
End point description:	
Self-administration survey was assessed in week 14 (visit 28 and 28b). Visit 28 summarizes treatment period 1 of treatment sequence A/A and both treatment periods 1 and 2 of treatment sequences A/B and B/A. Visit 28b summarizes treatment period 2 of treatment sequence A/A.	
End point type	Secondary
End point timeframe:	
Visit 28 (week 14) for period 1 and visit 28b (week 14) for period 2	

End point values	Treatment A (SHP 616) Overall	Treatment B (Placebo) Overall		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	59 ^[22]	40 ^[23]		
Units: Number of subjects				
Visit 28: Easy to use	48	36		
Visit 28: Somewhat difficult to use	11	4		
Visit 28: Difficult to use	0	0		
Visit 28a: Easy to use	11	99999		
Visit 28a: Somewhat difficult to use	1	99999		
Visit 28a: Difficult to use	0	99999		

Notes:

[22] - n=12 for Visit 28b

[23] - not applicable for Visit 28b, 99999 was entered

Statistical analyses

No statistical analyses for this end point

Secondary: Subject experience with self-administration: How many visit for confidence with self-administration

End point title	Subject experience with self-administration: How many visit for confidence with self-administration
-----------------	---

End point description:

Self-administration survey was assessed in week 14 (visit 28 and 28b).

Visit 28 summarizes treatment period 1 of treatment sequence A/A and both treatment periods 1 and 2 of treatment sequences A/B and B/A. Visit 28b summarizes treatment period 2 of treatment sequence A/A.

End point type	Secondary
----------------	-----------

End point timeframe:

Visit 28 (week 14) for period 1 and visit 28b (week 14) for period 2

End point values	Treatment A (SHP 616) Overall	Treatment B (Placebo) Overall		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	59 ^[24]	40 ^[25]		
Units: Number				
arithmetic mean (standard deviation)				
Visit 28	1.8 (± 1.70)	2.0 (± 2.49)		
Visit 28b	1.8 (± 1.22)	99999 (± 99999)		

Notes:

[24] - n=12 for Visit 28b

[25] - not applicable for Visit 28b, 99999 was entered

Statistical analyses

No statistical analyses for this end point

Secondary: Subject experience with self-administration: Better long-term option for

subject and preferred administration for subject

End point title	Subject experience with self-administration: Better long-term option for subject and preferred administration for subject
-----------------	---

End point description:

Self-administration survey was assessed in week 14 (visit 28 and 28b).

Visit 28 summarizes treatment period 1 of treatment sequence A/A and both treatment periods 1 and 2 of treatment sequences A/B and B/A. Visit 28b summarizes treatment period 2 of treatment sequence A/A.

End point type	Secondary
----------------	-----------

End point timeframe:

Visit 28 (week 14) for period 1 and visit 28b (week 14) for period 2

End point values	Treatment A (SHP 616) Overall	Treatment B (Placebo) Overall		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	59 ^[26]	40 ^[27]		
Units: Number of subjects				
Visit 28: SC better long term option for subject	57	39		
Visit 28: IV better long term option for subject	2	1		
Visit 28: SC preferred administration for subject	56	40		
Visit 28: IV preferred administration for subject	3	0		
Visit 28b: SC better long term option for subject	12	99999		
Visit 28b: IV better long term option for subject	0	99999		
Visit 28b: SC preferred administration for subject	11	99999		
Visit 28b: IV preferred administration for subject	1	99999		

Notes:

[26] - n=12 for Visit 28b

[27] - not applicable for Visit 28b, 99999 was entered

Statistical analyses

No statistical analyses for this end point

Secondary: Subject experience with self-administration: Subject's preference for administration

End point title	Subject experience with self-administration: Subject's preference for administration
-----------------	--

End point description:

Self-administration survey was assessed in week 14 (visit 28 and 28b).

Visit 28 summarizes treatment period 1 of treatment sequence A/A and both treatment periods 1 and 2 of treatment sequences A/B and B/A. Visit 28b summarizes treatment period 2 of treatment sequence A/A.

End point type	Secondary
----------------	-----------

End point timeframe:

Visit 28 (week 14) for period 1 and visit 28b (week 14) for period 2

End point values	Treatment A (SHP 616) Overall	Treatment B (Placebo) Overall		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	59 ^[28]	40 ^[29]		
Units: Number of subjects				
Visit 28: Very strong	47	33		
Visit 28: Fairly strong	12	6		
Visit 28: Not very strong	0	1		
Visit 28b: Very strong	11	99999		
Visit 28b: Fairly strong	0	99999		
Visit 28b: Not very strong	1	99999		

Notes:

[28] - n=12 for Visit 28b

[29] - not applicable for Visit 28b, 99999 was entered

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change in Angioedema Quality of Life Questionnaire Scores from baseline to week 13

End point title	Mean change in Angioedema Quality of Life Questionnaire Scores from baseline to week 13 ^[30]
-----------------	---

End point description:

Absolute change calculated as visit score minus baseline per period. Baseline was dosing Day 1 visit, prior to investigational product administration/placebo, for each specific study period. Visit 1a was the baseline for period 1 and Visit 1b was the baseline for period 2.

End point type	Secondary
----------------	-----------

End point timeframe:

baseline (visit 1) to week 13 (visit 25) for period 1 and baseline (visit 1b) to week 13 (visit 25b) for period 2

Notes:

[30] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only descriptive statistics were collected for this endpoint.

End point values	Sequence A/B (SHP 616)	Sequence A/B (Placebo)	Sequence B/A (Placebo)	Sequence B/A (SHP 616)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	31	28	29	25
Units: Mean change				
arithmetic mean (standard deviation)				
AE-QoL Total	-10.35 (± 17.75)	4.77 (± 12.14)	-6.86 (± 10.72)	-12.10 (± 9.83)
Functioning	-9.25 (± 21.29)	6.11 (± 20.62)	-10.56 (± 17.23)	-23.33 (± 19.45)
Fatigue/Mood	-8.40 (± 21.94)	2.44 (± 14.20)	-9.11 (± 10.16)	-10.10 (± 13.42)
Fear/Shame	-12.50 (± 21.46)	5.19 (± 12.06)	-1.67 (± 10.62)	-5.40 (± 10.67)

Nutrition	-11.00 ($\pm$ 22.45)	6.67 ($\pm$ 19.70)	-9.44 ($\pm$ 25.55)	-14.76 ($\pm$ 17.50)
-----------	-----------------------	---------------------	----------------------	-----------------------

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were recorded from the time the informed consent was signed through 7 days after the last dose of investigational product (week 1 to 15 for treatment period 1 and 2).

Assessment type	Non-systematic
-----------------	----------------

Dictionary used

Dictionary name	MedDRA
-----------------	--------

Dictionary version	19.0
--------------------	------

Reporting groups

Reporting group title	Treatment B (Placebo)
-----------------------	-----------------------

Reporting group description:

Treatment B (Placebo) Overall

Reporting group title	Treatment A (SHP 616)
-----------------------	-----------------------

Reporting group description:

Treatment A (SHP 616) Overall

Serious adverse events	Treatment B (Placebo)	Treatment A (SHP 616)	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 57 (5.26%)	2 / 71 (2.82%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Congenital, familial and genetic disorders			
Hereditary angioedema			
subjects affected / exposed	1 / 57 (1.75%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	1 / 57 (1.75%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	1 / 57 (1.75%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			

Appendicitis			
subjects affected / exposed	0 / 57 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal infection			
subjects affected / exposed	0 / 57 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Treatment B (Placebo)	Treatment A (SHP 616)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 57 (24.56%)	23 / 71 (32.39%)	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	3 / 57 (5.26%)	0 / 71 (0.00%)	
occurrences (all)	3	0	
Nervous system disorders			
Headache			
subjects affected / exposed	6 / 57 (10.53%)	6 / 71 (8.45%)	
occurrences (all)	7	10	
Infections and infestations			
Viral upper respiratory tract infection			
subjects affected / exposed	3 / 57 (5.26%)	11 / 71 (15.49%)	
occurrences (all)	3	11	
Upper respiratory tract infections			
subjects affected / exposed	4 / 57 (7.02%)	7 / 71 (9.86%)	
occurrences (all)	4	7	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 July 2015	Inclusion of final clinical data from Study SHP616-103 was added, which was relevant to subject safety and the study rationale. The baseline angioedema attack rate required for study inclusion was modified. Updates were made to some study procedures or requirements (eg, parent/legal guardian/caregiver performing and/or assisting an adolescent subject, photographs and measurements of injection site reactions, longitudinal follow-up to test for C1 INH antibody titers).
03 September 2015	The inclusion and exclusion criteria regarding the attack rate and baseline prophylactic therapy was modified. A new exclusion criterion was added to prevent any changes of dose in hormonal products/therapies prior to study enrollment. Self-administration was allowed in both treatment periods (1 and 2), under supervision and after receiving adequate training by the site or home health professional. Clarification was added for the subjects who continued to have breakthrough attacks on the blinded IP despite receiving on-demand treatment for the management of angioedema attacks during the study. Added a section to clarify nonpharmacologic treatments and procedures. Added overall severity and duration assessment for injection site reactions. Number of subjects randomly assigned in each of the 3 treatment sequences (A/B, B/A, A/A) was modified along with the statistical power calculations. Removed "achieving a NNA <2.0" as a secondary efficacy endpoint.
11 January 2016	Allowed subjects (adolescent or adult) the option to self-administer IP with or without supervision after receiving appropriate training by the investigator or designee. Adolescent subjects self-administering IP were supervised by a parent/legal guardian/caregiver (if home health professional and/or study site personnel was not present). Subjects who elected to self-administer IP were instructed on IP transport, storage, treatment compliance, and retention of all used and unused product vials for drug accountability purposes. Written instructions on IP and self-administration procedures were provided to subjects at the screening or first dosing visit. Revised schedule for assessment of SC injection site reactions during treatment periods 1 and 2; the assessments were to be less frequent and only occur when IP was administered at the investigative site. An overall assessment of the impact on daily living and duration of injection sites reaction occurred at the last visit of each treatment period. In order to prevent subjects from missing a scheduled dose of IP, additional guidance on the dosing interval was provided. For subjects without documented C1 INH antigen level and/or C1 INH functional activity as part of eligibility criteria to confirm HAE diagnosis, a blood sample was collected at screening and sent to a local or central laboratory (as appropriate).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported