Clinical trial results:
A Phase 3, Multicenter, Randomized, Placebo-controlled, Double-blind Study to Evaluate the Efficacy and Safety of Lanadelumab for Prevention Against Acute Attacks of Non-histaminergic Angioedema with Normal C1-Inhibitor (C1-INH) and Acquired Angioedema (AAE) Due to C1-INH Deficiency

Summary

EudraCT number	2019-001703-20
Trial protocol	GB DE HU PL IT FR
Global end of trial date	20 October 2022

Results information

Result version number	v1 (current)
This version publication date	03 November 2023
First version publication date	03 November 2023

Trial information

Trial identification

Sponsor protocol code	SHP643-303

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04206605
WHO universal trial number (UTN)	-
Other trial identifiers	IND: 116647

Notes:

Sponsors

Sponsor organisation name	Takeda
Sponsor organisation address	95 Hayden Avenue, Lexington, United States, MA 02421
Public contact	Study Director, Takeda, ClinicalTransparency@takeda.com
Scientific contact	Study Director, Takeda, ClinicalTransparency@takeda.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	20 October 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	20 October 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main aim of this study is to check if repeated subcutaneous (SC) injections of lanadelumab can prevent angioedema attacks in teenagers and adults with non-histaminergic angioedema with normal C1-INH. Another aim is to check if they tolerate the repeated SC injections. Participants will receive a SC injection of lanadelumab every two weeks for 26 weeks. The first two doses of lanadelumab will be given at the study clinic. Once a participant (and/or parent/caregiver) has been appropriately trained, lanadelumab can be self-injected. Visits to the study clinic are planned for the first, third and fourth week and then every 4 weeks.

Protection of trial subjects:

Each subject signed an informed consent form before participating in the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	04 May 2020
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	Canada: 5
Country: Number of subjects enrolled	France: 1
Country: Number of subjects enrolled	Germany: 3
Country: Number of subjects enrolled	Hungary: 2
Country: Number of subjects enrolled	Italy: 9
Country: Number of subjects enrolled	Japan: 4
Country: Number of subjects enrolled	Netherlands: 4
Country: Number of subjects enrolled	Poland: 6
Country: Number of subjects enrolled	Spain: 3
Country: Number of subjects enrolled	United States: 40
Worldwide total number of subjects	77
EEA total number of subjects	28

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

Subject disposition

Recruitment

Recruitment details:

Participants took part in the study at 34 investigative sites in Canada, United States, Germany, Hungary, Italy, Spain, France, Japan, Netherlands, and Poland from 04 May 2020 to 20 October 2022.

Pre-assignment

Screening details:

Participants with a diagnosis of non-histaminergic angioedema were randomized in a 2:1 ratio to receive lanadelumab or placebo.

Period 1

Period 1 title	Overall Period (overall period)
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
Arm title	Placebo

Arm description:

Participants received placebo-matching lanadelumab subcutaneous (SC) injection once every 2 weeks (q2w) for up to 26 weeks.

Arm type	Placebo
Investigational medicinal product name	Matching-placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Matching placebo, SC injection, once Q2W.

Arm title	Lanadelumab 300 mg

Arm description:

Participants received 300 mg of lanadelumab solution in a prefilled syringe (PFS) as SC injection once q2w for up to 26 weeks.

Arm type	Experimental
Investigational medicinal product name	Lanadelumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Lanadelumab 300 mg, SC injection, once Q2W.

Number of subjects in period 1	Placebo	Lanadelumab 300 mg
Started	27	50
Completed	26	49
Not completed	1	1
Adverse event, non-fatal	-	1
Withdrawal by Subject	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Participants received placebo-matching lanadelumab subcutaneous (SC) injection once every 2 weeks (q2w) for up to 26 weeks.	
Reporting group title	Lanadelumab 300 mg
Reporting group description:	
Participants received 300 mg of lanadelumab solution in a prefilled syringe (PFS) as SC injection once q2w for up to 26 weeks.	

Reporting group values	Placebo	Lanadelumab 300 mg	Total
Number of subjects	27	50	77
Age categorical Units: Subjects			
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age (2 to 6 years)			0
Age continuous Units: years			
arithmetic mean	43.8	42.3	
standard deviation	± 10.77	± 14.06	-
Gender categorical Units: Subjects			
Male	8	7	15
Female	19	43	62
Ethnicity Units: Subjects			
Hispanic or Latino	2	7	9
Not Hispanic or Latino	24	43	67
Unknown or Not Reported	1	0	1
Race Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	2	2	4
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	4	4
White	24	44	68
More Than one Race	0	0	0
Unknown or Not Reported	1	0	1

Height			
Units: centimeter			
arithmetic mean	168.32	166.09	
standard deviation	± 9.779	± 8.232	-
Weight			
Units: kilogram			
arithmetic mean	82.09	82.04	
standard deviation	± 22.701	± 25.217	-
Body Mass Index (BMI)			
BMI is calculated as [weight(kg)/height(m^2)].			
Units: kilogram per squared meter			
arithmetic mean	28.88	29.75	
standard deviation	± 7.413	± 9.127	-

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Participants received placebo-matching lanadelumab subcutaneous (SC) injection once every 2 weeks (q2w) for up to 26 weeks.	
Reporting group title	Lanadelumab 300 mg
Reporting group description:	
Participants received 300 mg of lanadelumab solution in a prefilled syringe (PFS) as SC injection once q2w for up to 26 weeks.	

Primary: Number of Investigator-Confirmed Angioedema Attacks During the Treatment Period of Day 0 Through Day 182

End point title	Number of Investigator-Confirmed Angioedema Attacks During the Treatment Period of Day 0 Through Day 182
End point description:	
An angioedema attack was defined as symptoms or signs consistent with an attack in at least 1 of following locations: peripheral angioedema (cutaneous swelling involving an extremity, the face, neck, torso, and/or genitourinary region), abdominal angioedema (abdominal pain, with/without abdominal distention, nausea, vomiting, or diarrhea), laryngeal angioedema (stridor, dyspnea, difficulty speaking, difficulty swallowing, throat tightening, or swelling of the tongue, palate, uvula, or larynx). Attack rate=number of attacks occurring during specified period divided by number of days participant contributed to specified period multiplied by 28 days. Number of investigator-confirmed angioedema attacks during treatment period of Day 0 through Day 182 were assessed. Full Analysis Set (FAS) included all randomized participants who received any exposure to the investigational product (IP) during the treatment period (Day 0 through Day 182).	
End point type	Primary
End point timeframe:	
Day 0 through Day 182	

End point values	Placebo	Lanadelumab 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	50		
Units: attacks/month				
arithmetic mean (standard deviation)	1.63 (± 1.357)	2.17 (± 2.062)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Lanadelumab 300 mg

Number of subjects included in analysis	77
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.899 [1]
Method	Chi-squared
Parameter estimate	Rate Ratio
Point estimate	1.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.71
upper limit	1.47

Notes:

[1] - P-value was from Wald-based chi-square test; unadjusted for multiple testing.

Secondary: Number of Participants Achieving Attack-Free Status During the Treatment Period of Day 0 Through Day 182

End point title	Number of Participants Achieving Attack-Free Status During the Treatment Period of Day 0 Through Day 182

End point description:

An angioedema attack=symptoms/signs consistent with an attack in at least 1 of following: peripheral angioedema (cutaneous swelling involving an extremity, face, neck, torso, and/or genitourinary region), abdominal angioedema (abdominal pain, with/without abdominal distention, nausea, vomiting, or diarrhea), laryngeal angioedema (stridor, dyspnea, difficulty speaking, difficulty swallowing, throat tightening, or swelling of tongue, palate, uvula, or larynx). Participant was considered attack free if has no investigator-confirmed angioedema attacks during that time period. For participants who discontinued study prior to completion of analysis period, were classified as attack-free or not based on observed contribution to analysis period. Number of participants achieving attack-free status during treatment period of day 0 through day 182 was assessed. FAS included all randomized participants who receive any exposure to the IP during the treatment period (Day 0 through Day 182).

End point type	Secondary

End point timeframe:

Day 0 through Day 182

End point values	Placebo	Lanadelumab 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	50		
Units: participants	1	2		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Lanadelumab 300 mg

Number of subjects included in analysis	77
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1 [2]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Risk Difference (RD)
Point estimate	0.003
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.153
upper limit	0.114

Notes:

[2] - P-value was from the corresponding Mantel-Haenszel estimate for the common risk difference from Cochran-Mantel-Haenszel (CMH) test; unadjusted for multiple testing.

Secondary: Number of Investigator-Confirmed Moderate or Severe Angioedema Attacks During the Treatment Period of Day 0 Through Day 182

End point title	Number of Investigator-Confirmed Moderate or Severe Angioedema Attacks During the Treatment Period of Day 0 Through Day 182

End point description:

An angioedema attack was defined as symptoms or signs consistent with an attack in at least 1 of the following locations: peripheral angioedema (cutaneous swelling involving an extremity, face, neck, torso, and/or genitourinary region), abdominal angioedema (abdominal pain, with or without abdominal distention, nausea, vomiting, or diarrhea), laryngeal angioedema (stridor, dyspnea, difficulty speaking, difficulty swallowing, throat tightening, or swelling of tongue, palate, uvula, or larynx). Attack rate=number of attacks occurring during the specified period divided by number of days the participant contributed to specified period multiplied by 28 days. Number of investigator-confirmed angioedema attacks during treatment period of Day 0 through Day 182 were assessed. FAS included all randomized participants who received any exposure to the IP during the treatment period (Day 0 through Day 182).

End point type	Secondary

End point timeframe:

Day 0 Through Day 182

End point values	Placebo	Lanadelumab 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	50		
Units: attacks/month				
arithmetic mean (standard deviation)	1.10 (± 0.984)	1.45 (± 1.711)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Lanadelumab 300 mg

Number of subjects included in analysis	77
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.852 [3]
Method	Chi-squared
Parameter estimate	Rate Ratio
Point estimate	0.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.62
upper limit	1.48

Notes:

[3] - P-value was from Wald-based chi-square test; unadjusted for multiple testing.

Secondary: Number of Investigator-Confirmed Angioedema Attacks During the Presumed Steady State Period of Day 70 Through Day 182

End point title	Number of Investigator-Confirmed Angioedema Attacks During the Presumed Steady State Period of Day 70 Through Day 182

End point description:

Angioedema attack=symptoms or signs consistent with an attack in at least 1 of following: peripheral angioedema (cutaneous swelling involving an extremity, face, neck, torso, and/or genitourinary region), abdominal angioedema (abdominal pain, with/without abdominal distention, nausea, vomiting, or diarrhea), laryngeal angioedema (stridor, dyspnea, difficulty speaking, difficulty swallowing, throat tightening, or swelling of tongue, palate, uvula, or larynx). Number of investigator-confirmed angioedema attacks during presumed steady state period of day 70 through day 182 were assessed. Attack rate =number of attacks occurring during the specified period divided by the number of days the participant contributed to the specified period multiplied by 28 days. Steady State (SS)-FAS included all randomized participants who received any exposure to the investigational product during the presumed steady state period (Day 70 through Day 182).

End point type	Secondary

End point timeframe:

Day 70 through Day 182

End point values	Placebo	Lanadelumab 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	49		
Units: attacks/month				
arithmetic mean (standard deviation)	1.37 (± 1.231)	2.05 (± 2.211)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Lanadelumab 300 mg

Number of subjects included in analysis	76
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.66 [4]
Method	Chi-squared
Parameter estimate	Rate Ratio
Point estimate	1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.72
upper limit	1.7

Notes:

[4] - P-value was from Wald-based chi-square test; unadjusted for multiple testing.

Secondary: Number of Participants Achieving Attack-Free Status During the Presumed Steady State Period of Day 70

End point title	Number of Participants Achieving Attack-Free Status During the Presumed Steady State Period of Day 70

End point description:

Angioedema attack=symptoms/signs consistent with an attack in at least 1 of following: peripheral angioedema (cutaneous swelling involving an extremity, face, neck, torso, and/or genitourinary region), abdominal angioedema (abdominal pain, with/without abdominal distention, nausea, vomiting, or diarrhea), laryngeal angioedema (stridor, dyspnea, difficulty speaking, difficulty swallowing, throat tightening, or swelling of tongue, palate, uvula, or larynx). Participant was considered as attack free if participant has no investigator-confirmed angioedema attacks during that time period. Participants who discontinue study prior to completion of analysis period, were classified as attack-free. Number of participants achieving attack-free status during the presumed steady state period of day 70 through 182 was assessed. SS-FAS included all randomized participants who received any exposure to the investigational product during the presumed steady state period (Day 70 through Day 182).

End point type	Secondary

End point timeframe:

Day 70 through Day 182

End point values	Placebo	Lanadelumab 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	49		
Units: Participants	4	3		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Lanadelumab 300 mg

Number of subjects included in analysis	76
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.25 [5]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Risk Difference (RD)
Point estimate	-0.087
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.28
upper limit	0.063

Notes:

[5] - P-value was from the corresponding Mantel-Haenszel estimate for the common risk difference from CMH test; unadjusted for multiple testing.

Secondary: Number of Participants With Maximum Attack Severity During Treatment Period of Day 0 Through Day 182

End point title	Number of Participants With Maximum Attack Severity During Treatment Period of Day 0 Through Day 182

End point description:

An angioedema attack was defined as the symptoms or signs consistent with an attack in at least 1 of the following locations: peripheral angioedema (cutaneous swelling involving an extremity, the face, neck, torso, and/or genitourinary region), abdominal angioedema (abdominal pain, with or without abdominal distention, nausea, vomiting, or diarrhea), laryngeal angioedema (stridor, dyspnea, difficulty speaking, difficulty swallowing, throat tightening, or swelling of the tongue, palate, uvula, or larynx). Number of participants with maximum attack severity during treatment period of day 0 through day 182 was assessed. Angioedema attack severity was calculated per participant based on the severity categories as follows: No attack, Mild, Moderate, and Severe. FAS included all randomized participants who receive any exposure to the IP during the treatment period (Day 0 through Day 182).

End point type	Secondary

End point timeframe:

Day 0 through Day 182

End point values	Placebo	Lanadelumab 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	50		
Units: participants				
No Attack	1	2		
Mild	2	4		
Moderate	17	17		
Severe	7	27		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Investigator-Confirmed Moderate or Severe Angioedema Attacks During the Presumed Steady State Period of Day 70 Through Day 182

End point title	Number of Investigator-Confirmed Moderate or Severe Angioedema Attacks During the Presumed Steady State Period of Day 70 Through Day 182

End point description:

Angioedema attack was defined as symptoms or signs consistent with an attack in at least 1 of following: peripheral angioedema (cutaneous swelling involving an extremity, face, neck, torso, and/or genitourinary region), abdominal angioedema (abdominal pain, with/without abdominal distention, nausea, vomiting, or diarrhea), laryngeal angioedema (stridor, dyspnea, difficulty speaking, difficulty swallowing, throat tightening, or swelling of tongue, palate, uvula, or larynx). Attack rate=number of attacks occurring during the specified period divided by number of days participant contributed to specified period multiplied by 28 days. Number of investigator-confirmed moderate or severe angioedema attacks during presumed steady state period of day 70 through day 182 were assessed. SS-FAS included all randomized participants who received any exposure to the investigational product during the presumed steady state period (Day 70 through Day 182).

End point type	Secondary

End point timeframe:

Day 70 through Day 182

End point values	Placebo	Lanadelumab 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	49		
Units: attacks/month				
arithmetic mean (standard deviation)	0.97 (± 1.013)	1.35 (± 1.764)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Lanadelumab 300 mg
Number of subjects included in analysis	76
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.896 [6]
Method	Chi-squared
Parameter estimate	Rate Ratio
Point estimate	0.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.58
upper limit	1.61

Notes:

[6] - P-value was from Wald-based chi-square test; unadjusted for multiple testing.

Secondary: Number of Participants With Maximum Attack Severity During Presumed Steady State Period of Day 70 Through Day 182

End point title	Number of Participants With Maximum Attack Severity During Presumed Steady State Period of Day 70 Through Day 182

End point description:

An angioedema attack was defined as the symptoms or signs consistent with an attack in at least 1 of

the following locations: peripheral angioedema (cutaneous swelling involving an extremity, the face, neck, torso, and/or genitourinary region), abdominal angioedema (abdominal pain, with or without abdominal distention, nausea, vomiting, or diarrhea), laryngeal angioedema (stridor, dyspnea, difficulty speaking, difficulty swallowing, throat tightening, or swelling of the tongue, palate, uvula, or larynx). Number of participants with maximum attack severity during the presumed steady state period of day 70 through day 182 was assessed. Angioedema attack severity was calculated per participant based on the severity categories as follows: No attack, Mild, Moderate, and Severe. SS-FAS included all randomized participants who received any exposure to the investigational product during the presumed steady state period (Day 70 through Day 182).

End point type	Secondary

End point timeframe:

Day 70 through Day 182

End point values	Placebo	Lanadelumab 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	49		
Units: participants				
No Attack	4	3		
Mild	5	5		
Moderate	12	23		
Severe	6	18		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to First Angioedema Attack After Day 0 Through Day 182

End point title	Time to First Angioedema Attack After Day 0 Through Day 182

End point description:

The time to the first angioedema attack (days) after Day 0 for the efficacy evaluation period of Day 0 through Day 182 was calculated from the date and time of the first dose of lanadelumab for the efficacy evaluation period (Day 0 through Day 182) to the date and time of the first in angioedema attack after the first dose for the efficacy evaluation period of Day 0 through Day 182. The data is reported for angioedema attack rate groups i.e. 1 to < 2 Attacks/Month and >=2 Attacks/Month. FAS included all randomized participants who receive any exposure to the IP during the treatment period (Day 0 through Day 182).

End point type	Secondary

End point timeframe:

Day 0 Through Day 182

End point values	Placebo	Lanadelumab 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	50		
Units: days				
median (confidence interval 95%)				

1 to <2 Attacks/Month	10.5 (6.6 to 9999)	81.0 (6.4 to 9999)		
>=2 Attacks/Month	6.8 (1.4 to 11.6)	5.9 (3.7 to 11.6)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Lanadelumab 300 mg
Number of subjects included in analysis	77
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.498 [7]
Method	Logrank

Notes:

[7] - P-value comparing lanadelumab to placebo was from a log rank test stratified by baseline strata.

Secondary: Time to First Angioedema Attack After Day 70 Through Day 182

End point title	Time to First Angioedema Attack After Day 70 Through Day 182

End point description:

The time to the first angioedema attack (days) after Day 0 for the efficacy evaluation period of Day 70 through Day 182 was calculated from the date and time of the first dose of lanadelumab for the efficacy evaluation period (Day 70 through Day 182) to the date and time of the first in angioedema attack after the first dose for the efficacy evaluation period of Day 70 through Day 182. The data is reported for angioedema attack rate groups i.e. 1 to < 2 Attacks/Month and >=2 Attacks/Month. SS-FAS included all randomized participants who received any exposure to the investigational product during the presumed steady state period (Day 70 through Day 182). '9999' indicates Upper limit of CI was not estimable due to censoring of participants who discontinued or completed the study before having an attack.

End point type	Secondary

End point timeframe:

Day 70 through Day 182

End point values	Placebo	Lanadelumab 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	49		
Units: days				
median (confidence interval 95%)				
1 to <2 Attacks/Month	12.3 (10.3 to 9999)	40.8 (3.4 to 9999)		
>=2 Attacks/Month	16.9 (6.7 to 32.5)	10.6 (5.0 to 15.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Achieving at Least 50 %, 70%, 90% and 100% Reduction in the Investigator-Confirmed Normalized Number of Attacks (NNA) Per 4 Weeks During Each of the Efficacy Evaluation Periods Relative to the Observation Period NNA

End point title	Number of Participants Achieving at Least 50 %, 70%, 90% and 100% Reduction in the Investigator-Confirmed Normalized Number of Attacks (NNA) Per 4 Weeks During Each of the Efficacy Evaluation Periods Relative to the Observation Period NNA

End point description:

Normalized number of investigator-confirmed angioedema attacks (NNA) during each efficacy evaluation period was expressed as a monthly (28 days) angioedema attack rate. Attack rate=number of attacks occurring during specified period divided by number of days participants contributed to specified period multiplied by 28 days. Number of participants achieving at least 50 %, 70%, 90% and 100% reduction in investigator-confirmed normalized number of attacks per 4 weeks during each of efficacy evaluation periods relative to the observation period NNA was assessed. Percentage reduction groups are not mutually exclusive, participants may appear in more than one group as applicable based on their percentage reduction. FAS included all randomized participants who receive any exposure to IP during treatment period (Day 0 through Day 182). Overall number of participants analyzed=number of participants achieving at Least 50 %, 70%, 90% and 100% reduction in investigator-confirmed normalized.

End point type	Secondary

End point timeframe:

Day 0 Through Day 182

End point values	Placebo	Lanadelumab 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	48		
Units: participants				
>=50% Reduction	13	28		
>=70% Reduction	9	12		
>=90% Reduction	3	6		
100% Reduction	1	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Achieving Normalized Number of Attacks (NNA) Less Than (<)1.0 Per 4 Weeks During Each of the Efficacy Evaluation Periods

End point title	Number of Participants Achieving Normalized Number of Attacks (NNA) Less Than (<)1.0 Per 4 Weeks During Each of the Efficacy Evaluation Periods

End point description:

The normalized number of investigator-confirmed angioedema attacks (NNA) during each efficacy evaluation period was expressed as a monthly (28 days) angioedema attack rate. Attack rate was calculated for each participant as the number of attacks occurring during the specified period divided by the number of days the participant contributed to the specified period multiplied by 28 days. Number of participants achieving normalized number of attacks < 1.0 per 4 weeks during each of the efficacy evaluation periods was assessed. The percentage reduction groups are not mutually exclusive, participants may appear in more than one group as applicable based on their percentage reduction. SS-FAS included all randomized participants who received any exposure to the investigational product during the presumed steady state period (Day 70 through Day 182).

End point type	Secondary

End point timeframe:

Day 0 through Day 182, Day 70 through Day 182

End point values	Placebo	Lanadelumab 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	49		
Units: participants				
>=50% Reduction	14	31		
>=70% Reduction	12	18		
>=90% Reduction	5	5		
100% Reduction	4	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Treatment Emergent Adverse Events (TEAEs) Including Adverse Events of Special Interest (AESI) and Serious Adverse Events (SAEs)

End point title	Number of Participants With Treatment Emergent Adverse Events (TEAEs) Including Adverse Events of Special Interest (AESI) and Serious Adverse Events (SAEs)

End point description:

TEAE=as any event emerging or manifesting at or after the initiation of treatment with an IP or medicinal product or any existing event that worsens in either intensity or frequency following exposure to the IP or medicinal product. SAE=untoward clinical manifestation of signs, symptoms or outcomes (whether considered related to investigational product or not and at any dose: results in death, is life-threatening, requires inpatient hospitalization or prolongation of hospitalization, results in persistent or significant disability/incapacity, congenital abnormality/birth defect, an important medical event. AESI included hypersensitivity reactions, events of disordered coagulation such as bleeding AESI, hypercoagulable AESI. Number of participants with TEAEs including AESI and SAE was assessed.

End point type	Secondary

End point timeframe:

From the first study drug administration up to follow-up (Day 196)

End point values	Placebo	Lanadelumab 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	50		
Units: participants				
Any TEAE	23	46		
AESI	0	1		
SAE	1	7		

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentrations of Lanadelumab

End point title	Plasma Concentrations of Lanadelumab

End point description:

Pharmacokinetic Set (PK Set) included all participants in the SAS who had at least 1 evaluable postdose PK concentration value. Overall number of participants analyzed is the number of participants available with data for analyses. Number analyzed is the number of participants available for analyses at the given timepoint. 'n' indicates number of participants analysed are the participants available for analysis at the given timepoint. '9999' indicates the standard deviation (SD) was not estimable for a single participant.

End point type	Secondary

End point timeframe:

Pre-dose and post-dose at Days 0, 4, 14, 28, 56, 84, 112, 140, 168 and 182

End point values	Placebo	Lanadelumab 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	49		
Units: nanogram/milliliter (ng/mL)				
arithmetic mean (standard deviation)				
Baseline (n=22,45)	661.573 (± 2991.1363)	1.665 (± 7.8812)		
Day 0 (n=0,1)	0 (± 0)	0.000 (± 9999)		
Day 4 (n=7,7)	42.749 (± 113.1021)	16895.996 (± 8136.5164)		
Day 14 (n=16,32)	5.366 (± 21.4650)	11030.519 (± 4632.9383)		
Day 28 (n=26,46)	6.188 (± 17.9944)	15969.813 (± 7210.5963)		
Day 56 (n=27,46)	16.820 (± 61.3021)	20722.131 (± 8396.5980)		
Day 84 (n=26,49)	7.335 (± 30.0848)	22698.616 (± 8953.3488)		
Day 112 (n=25,48)	5.604 (± 22.1843)	22938.312 (± 10021.8340)		
Day 140 (n=26,46)	3.200 (± 16.3188)	22778.286 (± 9680.4686)		
Day 168 (n=24,48)	9.260 (± 23.0763)	21369.818 (± 11072.0806)		
Day 182 (n=26,49)	4.733 (± 18.7014)	20496.158 (± 10774.2169)		

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Kallikrein (pKal) Activity

End point title	Plasma Kallikrein (pKal) Activity

End point description:

Plasma Kallikrein activity was measured by biomarker cleaved high molecular weight kininogen (cHMWK) level to assess pharmacodynamics of lanadelumab. The Pharmacodynamic Set (PD Set) included all participants in the SAS who had at least 1 evaluable PD concentration value. Overall number of participants analyzed are the number of participants with data available for analyses. Number analyzed is the number of participants available for analyses at the given timepoint.

End point type	Secondary

End point timeframe:

Pre-dose and post-dose at Days 4, 14, 28, 56, 84, 112, 140, 168 and 182

End point values	Placebo	Lanadelumab 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	50		
Units: % cHMWK				
arithmetic mean (standard deviation)				
Baseline (n=25,50)	20.30 (± 14.927)	18.69 (± 11.854)		
Day 4 (n=7,7)	25.94 (± 33.285)	20.20 (± 20.333)		
Day 14 (n=16,31)	17.23 (± 9.801)	12.83 (± 13.136)		
Day 28 (n=27,47)	16.16 (± 12.458)	14.24 (± 13.472)		
Day 56 (n=27,46)	17.83 (± 12.169)	15.88 (± 15.618)		
Day 84 (n=27, 46)	17.00 (± 15.508)	16.76 (± 15.941)		
Day 112 (n=25,48)	15.88 (± 11.109)	16.12 (± 17.242)		
Day 140 (n=27,47)	17.40 (± 15.413)	14.91 (± 14.656)		
Day 168 (n=25,47)	20.90 (± 16.588)	15.07 (± 15.061)		
Day 182 (n=27,50)	18.08 (± 20.384)	15.39 (± 15.333)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Neutralizing or Non-neutralizing Antidrug Antibodies (ADA) in Plasma

End point title	Number of Participants With Neutralizing or Non-neutralizing Antidrug Antibodies (ADA) in Plasma

End point description:

Number of participants with neutralizing or non-neutralizing antidrug antibodies in plasma was assessed. FAS included all randomized participants who receive any exposure to the IP during the treatment period (Day 0 through Day 182). Number analyzed is the number of participants available for analyses at the given timepoint.

End point type	Secondary

End point timeframe:

Pre-dose and post-dose at Days 28, 56, 84, 112, 140, 168 and 182

End point values	Placebo	Lanadelumab 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	50		
Units: participants				
Baseline (n=22,46)	0	0		
Day 28 (n=26,46)	0	0		
Day 56 (n=27,47)	0	0		
Day 84 (n=26,50)	0	0		
Day 112 (n=25,48)	0	1		
Day 140 (n=26,46)	0	1		
Day 168 (n=24,48)	0	0		
Day 182 (n=26,50)	0	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Change in Total Angioedema Quality of Life (AE-QoL) Questionnaire Score During the Treatment Period of Day 0 Through Day 182

End point title	Number of Participants With Change in Total Angioedema Quality of Life (AE-QoL) Questionnaire Score During the Treatment Period of Day 0 Through Day 182

End point description:

The AE-QoL questionnaire was a self-administered validated instrument to assess health related (HR) QoL among participants with recurrent angioedema. The AE-QoL consisted of 17 disease-specific quality-of-life items, to produce a total AEQoL score and 4 domain scores (functioning, fatigue/mood, fear/shame, and nutrition) and each of the 17 items has a five point response scale ranging from 0 (Never) to 4 (Very Often). Taw total score (mean of all item scores) was rescaled using linear transformations into final percentage scores ranging 0 to 100. SAS:all participants who receive any exposure to the IP. Overall number of participants analyzed are number of participants with data available for analyses. 'n' indicates number analyzed is the number of participants available for analyses in the specific category. Occassionally (O); Very Often (VO); Food or Beverages (F/B); Swelling Episodes (SE); Negative effects (NE). basline (n) = 26, 49 and Day 189 (n) = 26, 50.

End point type	Secondary

End point timeframe:

Baseline through Day 182

End point values	Placebo	Lanadelumab 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	50		
Units: participants				
Baseline: Work - Never	7	6		
Baseline: Work - Rarely	4	8		
Baseline: Work - O	6	14		
Baseline: Work - Often	7	10		
Baseline: Work - VO	2	10		
Baseline: Physical activity - Never	1	4		
Baseline: Physical activity - Rarely	1	7		
Baseline: Physical activity - O	16	15		
Baseline: Physical activity - Often	4	12		
Baseline: Physical activity - VO	4	11		
Baseline: Leisure time - Never	1	4		
Baseline: Leisure time - Rarely	5	9		
Baseline: Leisure time - O	12	17		
Baseline: Leisure time - Often	5	15		
Baseline: Leisure time - VO	3	4		
Baseline: Social relations - Never	2	4		
Baseline: Social relations - Rarely	4	9		
Baseline: Social relations - O	12	16		
Baseline: Social relations - Often	7	16		
Baseline: Social relations - VO	1	4		
Baseline: Eating and drinking - Never	3	8		
Baseline: Eating and drinking - Rarely	6	10		
Baseline: Eating and drinking - O	9	16		
Baseline: Eating and drinking - Often	6	13		
Baseline: Eating and drinking - VO	2	2		
Baseline: Difficulty falling asleep - Never	3	7		
Baseline: Difficulty falling asleep - Rarely	11	17		
Baseline: Difficulty falling asleep - O	5	8		
Baseline: Difficulty falling asleep - Often	4	10		
Baseline: Difficulty falling asleep - VO	2	2		
Baseline: Wake up during the night - Never	7	11		
Baseline: Wake up during the night - Rarely	5	12		
Baseline: Wake up during the night - O	6	10		
Baseline: Wake up during the night - Often	6	10		
Baseline: Wake up during the night - VO	6	14		
Baseline: Tired during the day - Never	1	3		
Baseline: Tired during the day - Rarely	7	8		
Baseline: Tired during the day - O	6	16		
Baseline: Tired during the day - Often	7	9		
Baseline: Tired during the day - VO	5	13		
Baseline: Trouble concentrating - Never	2	3		
Baseline: Trouble concentrating - Rarely	8	14		
Baseline: Trouble concentrating - O	10	14		
Baseline: Trouble concentrating - Often	4	10		

Baseline: Trouble concentrating - VO	2	8		
Baseline: Feel depressed - Never	9	10		
Baseline: Feel depressed - Rarely	5	18		
Baseline: Feel depressed - O	5	11		
Baseline: Feel depressed - VO	1	3		
Baseline: Limit your choices of F/B: Never	10	17		
Baseline: Limit your choices of F/B: Rarely	1	4		
Baseline: Limit your choices of F/B: O	2	13		
Baseline: Limit your choices of F/B: Often	8	7		
Baseline: Limit your choices of F/B: VO	5	8		
Baseline: SE place a burden on you: Never	1	1		
Baseline: SE place a burden on you: Rarely	1	0		
Baseline: SE place a burden on you: O	7	8		
Baseline: SE place a burden on you: Often	10	24		
Baseline: SE place a burden on you: VO	7	16		
Baseline: SE could occur suddenly - Never	1	2		
Baseline: SE could occur suddenly - Rarely	4	1		
Baseline: SE could occur suddenly - O	4	12		
Baseline: SE could occur suddenly - Often	6	16		
Baseline: SE could occur suddenly - VO	11	18		
Baseline: Freq of SE might increase - Never	2	1		
Baseline: Freq of SE might increase - Rarely	3	3		
Baseline: Freq of SE might increase - O	5	7		
Baseline: Freq of SE might increase - Often	8	21		
Baseline: Freq of SE might increase - VO	8	17		
Baseline: Ashamed to go out due to SE - Never	6	10		
Baseline: Ashamed to go out due to SE - Rarely	1	7		
Baseline: Ashamed to go out due to SE - O	8	10		
Baseline: Ashamed to go out due to SE - Often	4	11		
Baseline: Ashamed to go out due to SE - VO	7	11		
Baseline: SE make you embarrassed - Never	5	9		
Baseline: SE make you embarrassed - Rarely	4	5		
Baseline: SE make you embarrassed - O	6	13		
Baseline: SE make you embarrassed - Often	3	8		
Baseline: SE make you embarrassed - VO	8	14		
Baseline: Afraid of long term NE - Never	3	9		

Baseline: Afraid of long term NE - Rarely	6	15		
Baseline: Afraid of long term NE - O	6	4		
Baseline: Afraid of long term NE - Often	6	12		
Baseline: Afraid of long term NE - VO	5	9		
Day 182: Work - Never	3	17		
Day 182: Work - Rarely	10	8		
Day 182: Work - O	8	12		
Day 182: Work - Often	4	10		
Day 182: Work - VO	1	3		
Day 182: Physical activity - Never	3	13		
Day 182: Physical activity - Rarely	10	12		
Day 182: Physical activity - O	8	13		
Day 182: Physical activity - Often	4	8		
Day 182: Physical activity - VO	1	4		
Day 182: Leisure time - Never	3	14		
Day 182: Leisure time - Rarely	12	15		
Day 182: Leisure time - O	7	10		
Day 182: Leisure time - Often	3	7		
Day 182: Leisure time - VO	1	4		
Day 182: Social relations - Never	4	15		
Day 182: Social relations - Rarely	8	11		
Day 182: Social relations - O	9	13		
Day 182: Social relations - Often	2	6		
Day 182: Social relations - VO	3	5		
Day 182: Eating and drinking - Never	5	18		
Day 182: Eating and drinking - Rarely	8	8		
Day 182: Eating and drinking - O	8	9		
Day 182: Eating and drinking - Often	4	14		
Day 182: Eating and drinking - VO	1	1		
Day 182: Difficulty falling asleep - Never	4	9		
Day 182: Difficulty falling asleep - Rarely	7	15		
Day 182: Difficulty falling asleep - O	8	12		
Day 182: Difficulty falling asleep - Often	6	9		
Day 182: Difficulty falling asleep - VO	1	5		
Day 182: Wake up during the night - Never	1	9		
Day 182: Wake up during the night - Rarely	7	10		
Day 182: Wake up during the night - O	8	15		
Day 182: Wake up during the night - Often	7	9		
Day 182: Wake up during the night - VO	3	7		
Day 182: Tired during the day - Never	2	9		
Day 182: Tired during the day - Rarely	6	15		
Day 182: Tired during the day - O	11	12		
Day 182: Tired during the day - Often	6	9		
Day 182: Tired during the day - VO	1	5		
Day 182: Trouble concentrating - Never	2	13		
Day 182: Trouble concentrating - Rarely	17	10		
Day 182: Trouble concentrating - O	5	14		
Day 182: Trouble concentrating - Often	1	10		

Day 182: Trouble concentrating - VO	1	3		
Day 182: Feel depressed - Never	8	8		
Day 182: Feel depressed - Rarely	8	18		
Day 182: Feel depressed - O	5	7		
Day 182: Feel depressed - Often	4	5		
Day 182: Feel depressed - VO	1	2		
Day 182: Limit your choices of F/B - Never	7	19		
Day 182: Limit your choices of F/B - Rarely	6	8		
Day 182: Limit your choices of F/B - O	6	10		
Day 182: Limit your choices of F/B - Often	5	8		
Day 182: Limit your choices of F/B - VO	2	5		
Day 182: SE place a burden on you - Never	2	6		
Day 182: SE place a burden on you - Rarely	7	9		
Day 182: SE place a burden on you - O	8	17		
Day 182: SE place a burden on you - Often	7	7		
Day 182: SE place a burden on you - VO	2	11		
Day 182: SE could occur suddenly - Never	2	7		
Day 182: SE could occur suddenly - Rarely	6	14		
Day 182: SE could occur suddenly - O	9	10		
Day 182: SE could occur suddenly - Often	5	7		
Day 182: SE could occur suddenly - VO	4	12		
Day 182: Freq of SE might increase - Never	2	7		
Day 182: Freq of SE might increase - Rarely	7	12		
Day 182: Freq of SE might increase - O	9	13		
Day 182: Freq of SE might increase - Often	5	6		
Day 182: Freq of SE might increase - VO	3	12		
Day 182: Ashamed to go out due to SE - Never	5	15		
Day 182: Ashamed to go out due to SE - Rarely	8	11		
Day 182: Ashamed to go out due to SE - O	4	10		
Day 182: Ashamed to go out due to SE - Often	7	8		
Day 182: Ashamed to go out due to SE - VO	2	6		
Day 182: SE make you embarrassed - Never	7	14		
Day 182: SE make you embarrassed - Rarely	5	10		
Day 182: SE make you embarrassed - O	6	10		
Day 182: SE make you embarrassed - Often	6	8		
Day 182: SE make you embarrassed - VO	2	8		
Day 182: Afraid of long term NE - Never	4	15		

Day 182: Afraid of long term NE - Rarely	10	13		
Day 182: Afraid of long term NE - O	7	11		
Day 182: Afraid of long term NE - Often	1	3		
Day 182: Afraid of long term NE - VO	4	8		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From start of the study up to follow up (Day 196)	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	25.0

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Participants received placebo-matching lanadelumab subcutaneous (SC) injection once every 2 weeks (q2w) for up to 26 weeks.	
Reporting group title	Lanadelumab 300 mg
Reporting group description:	
Participants received 300 mg of lanadelumab solution in a prefilled syringe (PFS) as SC injection once q2w for up to 26 weeks.	

Serious adverse events	Placebo	Lanadelumab 300 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 27 (3.70%)	7 / 50 (14.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Vascular disorders			
Lymphoedema			
subjects affected / exposed	0 / 27 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	1 / 27 (3.70%)	6 / 50 (12.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Cellulitis staphylococcal			
subjects affected / exposed	0 / 27 (0.00%)	1 / 50 (2.00%)	
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	Placebo	Lanadelumab 300 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	27 / 27 (100.00%)	49 / 50 (98.00%)	
Injury, poisoning and procedural complications			
Ligament sprain			
subjects affected / exposed	2 / 27 (7.41%)	0 / 50 (0.00%)	
occurrences (all)	2	0	
Nervous system disorders			
Headache			
subjects affected / exposed	6 / 27 (22.22%)	6 / 50 (12.00%)	
occurrences (all)	13	13	
Migraine			
subjects affected / exposed	1 / 27 (3.70%)	3 / 50 (6.00%)	
occurrences (all)	1	3	
Blood and lymphatic system disorders			
Lymphadenopathy			
subjects affected / exposed	2 / 27 (7.41%)	1 / 50 (2.00%)	
occurrences (all)	2	1	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 27 (7.41%)	4 / 50 (8.00%)	
occurrences (all)	9	13	
Injection site erythema			
subjects affected / exposed	3 / 27 (11.11%)	3 / 50 (6.00%)	
occurrences (all)	6	22	
Injection site pain			
subjects affected / exposed	7 / 27 (25.93%)	15 / 50 (30.00%)	
occurrences (all)	9	61	
Pyrexia			
subjects affected / exposed	2 / 27 (7.41%)	3 / 50 (6.00%)	
occurrences (all)	2	3	
Gastrointestinal disorders			
Constipation			

subjects affected / exposed	2 / 27 (7.41%)	1 / 50 (2.00%)	
occurrences (all)	3	1	
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 27 (0.00%)	3 / 50 (6.00%)	
occurrences (all)	0	3	
Nausea			
subjects affected / exposed	3 / 27 (11.11%)	4 / 50 (8.00%)	
occurrences (all)	8	4	
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	0 / 27 (0.00%)	3 / 50 (6.00%)	
occurrences (all)	0	3	
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	26 / 27 (96.30%)	48 / 50 (96.00%)	
occurrences (all)	305	740	
Urticaria			
subjects affected / exposed	0 / 27 (0.00%)	3 / 50 (6.00%)	
occurrences (all)	0	5	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	3 / 27 (11.11%)	1 / 50 (2.00%)	
occurrences (all)	3	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 27 (7.41%)	7 / 50 (14.00%)	
occurrences (all)	2	8	
Back pain			
subjects affected / exposed	2 / 27 (7.41%)	0 / 50 (0.00%)	
occurrences (all)	2	0	
Myalgia			
subjects affected / exposed	1 / 27 (3.70%)	4 / 50 (8.00%)	
occurrences (all)	2	4	
Infections and infestations			
COVID-19			

subjects affected / exposed	4 / 27 (14.81%)	3 / 50 (6.00%)	
occurrences (all)	4	3	
Nasopharyngitis			
subjects affected / exposed	2 / 27 (7.41%)	3 / 50 (6.00%)	
occurrences (all)	2	5	
Upper respiratory tract infection			
subjects affected / exposed	3 / 27 (11.11%)	3 / 50 (6.00%)	
occurrences (all)	3	5	
Urinary tract infection			
subjects affected / exposed	1 / 27 (3.70%)	4 / 50 (8.00%)	
occurrences (all)	1	6	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 April 2021	Amendment 3 changes: • Sponsor was revised from Shire to Takeda Development Centers Americas, Inc. (TDCA)/Takeda. • Removed IQVIA medical monitor contact information and added reference to the study specific contact list. The contact list contains the most accurate and up-to-date contact information. • Revised to include appropriate Takeda forms for reporting AEs and pregnancy. • Revised footnote to clarify that participants <18 years of age were only enrolled if allowed based on local site and/or country regulations. • Revised inclusion criterion #3 to clarify that participants with C4 level not below the normal range should be enrolled. • Revised footnote f for Table 1 (Table 1 Schedule of Activities - Screening and Observation Period) to clarify that an additional confirmatory test may be performed during the observation period if C1-INH therapy washout was not completed during the screening period. • Revised footnote g for Table 1 (Table 1 Schedule of Activities - Screening and Observation Period) to clarify that the 2-week washout period was completed in the screening period only for participants where it was deemed safe to complete. • Timeframe for male contraception was revised to align with female contraception (for the duration of the study and 70 days after the last dose of investigational product [IP]). • Specific quantitative stopping criteria, particularly in regard to liver values were added. • Added language to clarify that sample collection for genotype testing during the screening period was required; an additional sample for exploratory genetic analyses was optional.
18 August 2022	Amendment 2 changes: • Shire Global Drug Safety was updated to Takeda Global Patient Safety Evaluation (GPSE) Group. • The study population was revised to remove participants with acquired angioedema due to C1-INH deficiency. • For study site regions, removed specific countries in Europe and added Japan. • The study number for the open-label extension study was added (Study TAK-743-3001). • An additional visit prior to the start of the observation period was added. This visit would allow for an eligibility review, angioedema attack and adverse event (AE) monitoring, and distribution of icatibant and antihistamine treatment. • Removed plasma pharmacokinetic (PK) and pharmacodynamic (PD) sample from Visit 2 to Visit 3. Visit 2 was now an off-site visit. Reference to collecting samples predose on Study Day 4 was removed. • Provided clarification that participants were to begin Visit 1 in the treatment period within 7 days of the observation period. Any delay to the start of the treatment period should be discussed with the sponsor. • Added angioedema attack monitoring. • Revised physical examinations to include body weight as part of all examinations. • Revised exploratory endpoints to exploratory efficacy endpoints and added text indicating that exploratory efficacy endpoints would be defined in the statistical analysis plan (SAP).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported