



Clinical trial results:

An Open-Label Study to Evaluate the Long-Term Safety and Efficacy of Lanadelumab for Prevention Against Acute Attacks of Nonhistaminergic Angioedema with Normal C1-Inhibitor (C1-INH)

Summary

EudraCT number	2019-004823-20
Trial protocol	DE HU PL NL IT FR
Global end of trial date	05 May 2023

Results information

Result version number	v1 (current)
This version publication date	08 May 2024
First version publication date	08 May 2024

Trial information

Trial identification

Sponsor protocol code	TAK-743-3001
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04444895
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Takeda
Sponsor organisation address	95 Hayden Avenue, Lexington, United States, MA 02421
Public contact	Study Director, Takeda, TrialDisclosures@takeda.com
Scientific contact	Study Director, Takeda, TrialDisclosures@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	05 May 2023
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	05 May 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study was to check the safety and efficacy of lanadelumab for prevention of acute attacks of non-histaminergic angioedema with normal C1-inhibitor

Protection of trial subjects:

All study participants were required to read and sign an informed consent form.

Background therapy:

N/A

Evidence for comparator:

N/A

Actual start date of recruitment	05 February 2021
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: 7
Country: Number of subjects enrolled	Japan: 4
Country: Number of subjects enrolled	Netherlands: 3
Country: Number of subjects enrolled	Poland: 6
Country: Number of subjects enrolled	Spain: 3
Country: Number of subjects enrolled	United States: 39
Worldwide total number of subjects	73
EEA total number of subjects	25

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)	70
From 65 to 84 years	3
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 73 participants took part in the study at 34 investigative sites in Canada, France, Germany, Hungary, Italy, Japan, Netherlands, Poland, Spain, and the United States from 05 February 2021 to 05 May 2023.

Pre-assignment

Screening details:

Participants with a diagnosis of non-histaminergic angioedema rolled over from the study SHP643-303 (NCT04206605) to receive lanadelumab 300 mg every 2 weeks (Q2W) of whom 2 participants switched to lanadelumab 300 mg at a reduced frequency of every 4 weeks (Q4W) for some time during the study.

Period 1

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

Arms

Arm title	Lanadelumab 300 mg Q2W
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Arm description:

Participants received 300 milligrams (mg) lanadelumab subcutaneous (SC) injection, every 2 weeks (Q2W) for up to 26 weeks with an option to switch to lanadelumab 300 mg every 4 weeks (Q4W) if attacks were well-controlled based on the investigator's discretion and consultation with the sponsor's medical monitor.

Arm type	Experimental
Investigational medicinal product name	Lanadelumab 300 mg
Investigational medicinal product code	
Other name	DX-2930, SHP-643, TAK-743
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

300 mg (300 mg/2 mL), Subcutaneous (SC) injection

Number of subjects in period 1	Lanadelumab 300 mg Q2W
Started	73
Reduced-dose Safety Analysis Set (RD-SFAS)	2 ^[1]
Completed	64
Not completed	9
Consent withdrawn by subject	5
Adverse event, non-fatal	2
Lost to follow-up	2

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Reduced-dose Safety Analysis Set includes participants who switched to lanadelumab 300 mg at a reduced frequency of every 4 weeks (Q4W) for some time during the study.

Baseline characteristics

Reporting groups

Reporting group title	Lanadelumab 300 mg Q2W
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Reporting group description:

Participants received 300 milligrams (mg) lanadelumab subcutaneous (SC) injection, every 2 weeks (Q2W) for up to 26 weeks with an option to switch to lanadelumab 300 mg every 4 weeks (Q4W) if attacks were well-controlled based on the investigator's discretion and consultation with the sponsor's medical monitor.

Reporting group values	Lanadelumab 300 mg Q2W	Total	
Number of subjects	73	73	
Age Categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	43.7 ± 12.63	-	
Gender categorical Units: Subjects			
Female	59	59	
Male	14	14	
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	9	9	
Not Hispanic or Latino	63	63	
Unknown or Not Reported	1	1	
Region of enrolment Units: Subjects			
Canada Canada	5	5	
France France	1	1	
Germany Germany	3	3	
Hungary Hungary	2	2	
Italy Italy	7	7	
Japan Japan	4	4	
Netherlands Netherlands	3	3	
Poland Poland	6	6	
Spain Spain	3	3	
United States United States	39	39	
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	4	4	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	4	4	
White	64	64	
More than one race	0	0	

Unknown or Not Reported	1	1	
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Weight			
Units: kilograms (kg)			
arithmetic mean	81.52		
standard deviation	± 23.129	-	
Body Mass Index (BMI)			
BMI= weight(kg) / height(meter)^2			
Units: kilogram per square meter (kg/m^2)			
arithmetic mean	29.23		
standard deviation	± 7.972	-	
Height			
Units: centimeters (cm)			
arithmetic mean	166.75		
standard deviation	± 8.938	-	

Subject analysis sets

Subject analysis set title	Lanadelumab 300 mg Q4W
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants who received 300 mg lanadelumab, SC injection, Q4W as attacks were well-controlled based on the investigator's discretion and consultation with the sponsor's medical monitor at any point during the 26-week treatment period were included in this group.

Subject analysis set title	Lanadelumab 300 mg Q2W
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants who received 300 mg lanadelumab SC injection, Q2W, and switched to the Q4W regimen as attacks were well-controlled based on the investigator's discretion and consultation with the sponsor's medical monitor at any point during the 26-week treatment period were included in this group.

Reporting group values	Lanadelumab 300 mg Q4W	Lanadelumab 300 mg Q2W	
Number of subjects	2	2	
Age Categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean		0	
standard deviation	±	±	
Gender categorical			
Units: Subjects			
Female	2	0	
Male	0	0	
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino		0	
Not Hispanic or Latino	0	0	
Unknown or Not Reported	0	0	
Region of enrolment			

Units: Subjects			
Canada Canada	0	0	
France France	0	0	
Germany Germany	0	0	
Hungary Hungary	0	0	
Italy Italy	0	0	
Japan Japan	0	0	
Netherlands Netherlands	0	0	
Poland Poland	0	0	
Spain Spain	0	0	
United States United States	0	0	
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	0	0	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	0	0	
White	0	0	
More than one race	0	0	
Unknown or Not Reported	0	0	
Weight			
Units: kilograms (kg)			
arithmetic mean	84.40	0	
standard deviation	± 7.920	±	
Body Mass Index (BMI)			
BMI= weight(kg) / height(meter)^2			
Units: kilogram per square meter (kg/m^2)			
arithmetic mean	0	0	
standard deviation	±	±	
Height			
Units: centimeters (cm)			
arithmetic mean	163.0	0	
standard deviation	± 4.24	±	

End points

End points reporting groups

Reporting group title	Lanadelumab 300 mg Q2W
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Reporting group description:

Participants received 300 milligrams (mg) lanadelumab subcutaneous (SC) injection, every 2 weeks (Q2W) for up to 26 weeks with an option to switch to lanadelumab 300 mg every 4 weeks (Q4W) if attacks were well-controlled based on the investigator's discretion and consultation with the sponsor's medical monitor.

Subject analysis set title	Lanadelumab 300 mg Q4W
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Subject analysis set type	Sub-group analysis
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Subject analysis set description:

Participants who received 300 mg lanadelumab, SC injection, Q4W as attacks were well-controlled based on the investigator's discretion and consultation with the sponsor's medical monitor at any point during the 26-week treatment period were included in this group.

Subject analysis set title	Lanadelumab 300 mg Q2W
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Subject analysis set type	Sub-group analysis
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Subject analysis set description:

Participants who received 300 mg lanadelumab SC injection, Q2W, and switched to the Q4W regimen as attacks were well-controlled based on the investigator's discretion and consultation with the sponsor's medical monitor at any point during the 26-week treatment period were included in this group.

Primary: Number of Participants with Treatment Emergent Adverse Events (TEAEs) Including Adverse Events of Special Interest (AESI) and Serious Adverse Events (SAEs) During Treatment Period

End point title	Number of Participants with Treatment Emergent Adverse Events (TEAEs) Including Adverse Events of Special Interest (AESI) and Serious Adverse Events (SAEs) During Treatment Period ^[1]
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End point description:

TEAE: Any event emerging or manifesting at or after initiation of treatment with investigational product (IP) or medicinal product or any existing event that worsens in either intensity or frequency following exposure to IP or medicinal product including clinically meaningful findings in laboratory safety tests, vital signs, weight, and electrocardiogram (ECG) findings. SAE: Any untoward clinical manifestation of signs, symptoms or outcomes (whether considered related to IP 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. TEAEs were classified and reported as angioedema attack and non-angioedema attack adverse events in this outcome measure.

End point type	Primary
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End point timeframe:

From Day 0 up to Day 182

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only descriptive analyses were planned for this endpoint.

End point values	Lanadelumab 300 mg Q2W	Lanadelumab 300 mg Q4W		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	73	2		
Units: participants				
Any TEAEs: Non-Angioedema Attack	55	1		
Any TEAEs: Angioedema Attack	61	1		
AESI: Non-Angioedema Attack	1	0		
AESI: Angioedema Attack	0	0		

Any SAEs: Non-Angioedema Attack	5	1		
Any SAEs: Angioedema Attack	3	0		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants with Treatment Emergent Adverse Events (TEAEs) Including Adverse Events of Special Interest (AESI) and Serious Adverse Events (SAEs) During Follow-up

End point title	Number of Participants with Treatment Emergent Adverse Events (TEAEs) Including Adverse Events of Special Interest (AESI) and Serious Adverse Events (SAEs) During Follow-up ^[2]
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End point description:

TEAE: Any event emerging or manifesting at or after initiation of treatment with investigational product (IP) or medicinal product or any existing event that worsens in either intensity or frequency following exposure to IP or medicinal product including clinically meaningful findings in laboratory safety tests, vital signs, weight, and electrocardiogram (ECG) findings. SAE: Any untoward clinical manifestation of signs, symptoms or outcomes (whether considered related to IP 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. TEAEs were classified and reported as angioedema attack and non-angioedema attack adverse events in this outcome measure.

End point type	Primary
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End point timeframe:

From Day 183 up to Day 196

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only descriptive analyses were planned for this endpoint.

End point values	Lanadelumab 300 mg Q2W	Lanadelumab 300 mg Q4W		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	73	2		
Units: participants				
Any TEAEs: Non-Angioedema Attack	4	0		
Any TEAEs: Angioedema Attack	19	0		
AESI: Non-Angioedema Attack	0	0		
AESI: Angioedema Attack	0	0		
Any SAEs: Non-Angioedema Attack	0	0		
Any SAEs: Angioedema Attack	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: 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
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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 investigator-confirmed angioedema attacks during the treatment period of Day 0 through Day 182 was assessed. The SFAS included all participants who received any study drug after entering this study (i.e., any exposure to open-label lanadelumab). The data was partitioned by dosing regimen and reported accordingly to appropriately attribute to each dosing regimen.

End point type	Secondary
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End point timeframe:

From Day 0 up to Day 182

End point values	Lanadelumab 300 mg Q2W	Lanadelumab 300 mg Q4W		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	73	2		
Units: angioedema attacks				
number (not applicable)	595	2		

Statistical analyses

No statistical analyses for this end point

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

End point title	Number of Moderate or Severe Angioedema Attacks During the Treatment Period of Day 0 Through Day 182
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End point description:

The overall severity of angioedema attack was determined by the site using following definitions: mild (transient or mild discomfort), moderate (mild to moderate limitation in activity), severe (marked limitation in activity). Number of moderate or severe angioedema attacks during the treatment period of Day 0 through Day 182 was assessed. The SFAS included all participants who received any study drug after entering this study (i.e., any exposure to open-label lanadelumab). The data was partitioned by dosing regimen and reported accordingly to appropriately attribute to each dosing regimen.

End point type	Secondary
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End point timeframe:

From Day 0 up to Day 182

End point values	Lanadelumab 300 mg Q2W	Lanadelumab 300 mg Q4W		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	73	2		
Units: angioedema attacks				
number (not applicable)	391	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of High-Morbidity Angioedema Attacks During the Treatment Period of Day 0 Through Day 182

End point title	Number of High-Morbidity Angioedema Attacks During the Treatment Period of Day 0 Through Day 182
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End point description:

A high-morbidity angioedema attack was defined as any attack that has at least one of the following characteristics: severe, results in hospitalization (except hospitalization for observation <24 hours), hemodynamically significant (systolic blood pressure (BP) <90 millimetres of mercury (mmHg), requires intravenous hydration, or associated with syncope or near-syncope) or laryngeal. The SFAS included all participants who received any study drug after entering this study (i.e., any exposure to open-label lanadelumab). The data was partitioned by dosing regimen and reported accordingly to appropriately attribute to each dosing regimen.

End point type	Secondary
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End point timeframe:

From Day 0 up to Day 182

End point values	Lanadelumab 300 mg Q2W	Lanadelumab 300 mg Q4W		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	73	2		
Units: angioedema attacks				
number (not applicable)	232	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic (PK) Plasma Concentrations of Lanadelumab

End point title	Pharmacokinetic (PK) Plasma Concentrations of Lanadelumab
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End point description:

The data was partitioned by dosing regimen and reported accordingly to appropriately attribute to each dosing regimen. The Pharmacokinetic (PK) Set included all participants in the SFAS who had at least 1 evaluable postdose PK concentration value. Subjects analysed is the number of participants with data available for analyses. 'n' signifies number of participants analysed at specific time point. 9999 indicates that the standard deviation was not estimable as the values were below the lower limit of quantification. 999 indicates that the standard deviation was not estimable for a single participant.

End point type	Secondary
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End point timeframe:

Predose on Days 0, 84, and 140 and postdose on Day 182

End point values	Lanadelumab 300 mg Q2W	Lanadelumab 300 mg Q4W		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	68	2		
Units: nanograms per milliliter (ng/mL)				
arithmetic mean (standard deviation)				
Day 0 (n = 68, 2)	14419.068 (± 13208.1952)	0.000 (± 9999)		
Day 84 (n = 64, 1)	17021.002 (± 10116.5279)	7047.860 (± 999)		
Day 140 (n = 65, 1)	21138.057 (± 12076.9186)	4944.010 (± 999)		
Day 182 (n = 68, 1)	18799.596 (± 12054.1105)	14573.340 (± 999)		

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) with factor XIIa activation level to assess the pharmacodynamics of lanadelumab. The data was partitioned by dosing regimen and reported accordingly to appropriately attribute to each dosing regimen. The Pharmacodynamic (PD) Set included all participants in the SFAS who had at least 1 evaluable postdose PD concentration value. Subjects analysed is the number of participants with data available for analyses. 'n' signifies number of subjects analyzed at specific time point. 9999 indicates that the standard deviation was not estimable as the values were below the lower limit of quantification. 999 indicates that the standard deviation was not estimable for a single participant.

End point type | Secondary

End point timeframe:

Predose on Days 0, 84, and 140 and postdose on Day 182

End point values	Lanadelumab 300 mg Q2W	Lanadelumab 300 mg Q4W		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	67	2		
Units: percentage of cHMWK				
arithmetic mean (standard deviation)				
Day 0 (n = 67, 2)	15.306 (± 15.2413)	13.450 (± 9999)		
Day 84 (n = 63, 1)	17.586 (± 9.2437)	21.600 (± 999)		

Day 140 (n = 64, 1)	17.238 (\pm 9.1590)	44.700 (\pm 999)		
Day 182 (n = 67, 1)	15.515 (\pm 9.2074)	37.100 (\pm 999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Neutralizing Antidrug Antibodies (ADA) in Plasma

End point title	Number of Participants With Neutralizing Antidrug Antibodies (ADA) in Plasma
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End point description:

Number of participants with positive ADA including evaluation of neutralizing antibodies in plasma was assessed. As pre-specified in the statistical analysis plan (SAP), data for this outcome measure was collected and analyzed as a single group irrespective of dosing regimen. The SFAS included all participants who received any study drug after entering this study (i.e., any exposure to open-label lanadelumab). Subjects analysed is the number of participants with data available for analyses. 'n' signifies number of subjects analyzed at specific time point.

End point type	Secondary
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End point timeframe:

Predose on Days 0, 84, and 140 and postdose on Day 182

End point values	Lanadelumab 300 mg Q2W			
Subject group type	Reporting group			
Number of subjects analysed	72			
Units: participants				
Day 0 (n=72)	2			
Day 84 (n=65)	2			
Day 140 (n=66)	3			
Day 182 (n=69)	4			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Total Angioedema Quality of life (AE-QoL) Questionnaire Total Score at End of Treatment Period

End point title	Change From Baseline in Total Angioedema Quality of life (AE-QoL) Questionnaire Total Score at End of Treatment Period
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End point description:

The AE-QoL questionnaire is self-administered validated instrument to assess health related (HR)QoL among participants with recurrent angioedema(including hereditary angioedema[HAE]). It consists of 17 disease-specific QOL items, to produce total AE-QoL score & 4 domain scores(functioning,fatigue/mood,fear/shame,nutrition) each of 17 items had 5-point response scale ranging from 1(Never) to 5(Very Often). It was scored according to developers' guidelines to produce 4

score. The raw total score(mean of all item scores) was rescaled using linear transformations into final percentage scores ranging 0-100, based on maximum possible score, where higher score, greater QoL impairment. Negative change from Baseline indicates better QoL. Baseline: Last non-missing value prior to first exposure to study drug(based on date or date/time). As pre-specified in SAP, data for this outcome measure was collected and analyzed as single group irrespective of dosing regimen.

End point type	Secondary
End point timeframe:	
Baseline (Day 0) up to end of treatment period (Day 182)	

End point values	Lanadelumab 300 mg Q2W			
Subject group type	Reporting group			
Number of subjects analysed	66			
Units: score on a scale				
arithmetic mean (standard deviation)				
(n=66)	-12.73 (\pm 20.696)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Any Pause During Injection

End point title	Number of Participants with Any Pause During Injection
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End point description:

An injection report was completed by the participant (or parent/caregiver following each dose administration of lanadelumab injection used during the treatment period and any kind of pause during injection was captured. Categories with at least one participant with event are reported. The SFAS included all participants who received any study drug after entering this study (i.e., any exposure to open-label lanadelumab). 'n' signifies number of participants analysed at specific time point. The data was partitioned by dosing regimen and reported accordingly to appropriately attribute to each dosing regimen.

End point type	Secondary
End point timeframe:	
Days 0, 14, 28, 42, 56, 70, 84, 98, 112, 126, 140, 154, and 168	

End point values	Lanadelumab 300 mg Q2W	Lanadelumab 300 mg Q4W		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	73	2		
Units: participants				
Day 0 (n= 72, 1)	3	0		
Day 14 (n= 72, 1)	5	0		
Day 28 (n= 72, 1)	5	0		
Day 42 (n= 72, 1)	3	0		
Day 56 (n= 72, 1)	3	0		
Day 70 (n= 72, 1)	4	0		

Day 84 (n= 72, 1)	4	0		
Day 98 (n= 72, 1)	1	0		
Day 112 (n= 72, 1)	2	1		
Day 126 (n= 72, 1)	2	0		
Day 140 (n= 72, 1)	3	0		
Day 154 (n= 72, 1)	2	0		
Day 168 (n= 72, 1)	1	0		

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) in Participants who Switched Dosing Regimen

End point title	Number of Participants with Treatment Emergent Adverse Events (TEAEs) Including Adverse Events of Special Interest (AESI) and Serious Adverse Events (SAEs) in Participants who Switched Dosing Regimen
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End point description:

TEAE: Any event emerging or manifesting at or after initiation of treatment with investigational product (IP) or medicinal product or any existing event that worsens in either intensity or frequency following exposure to IP or medicinal product including clinically meaningful findings in laboratory safety tests, vital signs, weight, and electrocardiogram (ECG) findings. SAE: Any untoward clinical manifestation of signs, symptoms or outcomes (whether considered related to IP 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. TEAEs were classified and reported as angioedema attack and non-angioedema attack adverse events in this outcome measure.

End point type	Secondary
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End point timeframe:

From Day 0 up to Day 196

End point values	Lanadelumab 300 mg Q4W	Lanadelumab 300 mg Q2W		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	2	2		
Units: participants				
Non-Angioedema Attack Reported TEAEs	1	2		
Angioedema Attack Reported TEAEs	1	0		
Non-Angioedema Attack Reported AESI	0	0		
Angioedema Attack Reported AESI	0	0		
Non-Angioedema Attack Reported Serious TEAEs	1	0		
Angioedema Attack Reported Serious TEAEs	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Investigator-Confirmed Angioedema Attacks During the Treatment Period of Day 0 Through Day 182 in Participants who Switched Dosing Regimen

End point title	Number of Investigator-Confirmed Angioedema Attacks During the Treatment Period of Day 0 Through Day 182 in Participants who Switched Dosing Regimen
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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 investigator-confirmed angioedema attacks during the treatment period of Day 0 through Day 182 was assessed. The RD-SFAS Set was a subset of the SFAS Set and included participants who switched from lanadelumab 300 mg Q2W to a lanadelumab 300 mg Q4W dosing regimen as recorded on the Dose Frequency Modification electronic case report form. The data was partitioned by dosing regimen and reported accordingly to appropriately attribute to each dosing regimen.

End point type	Secondary
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End point timeframe:

From Day 0 up to Day 182

End point values	Lanadelumab 300 mg Q4W	Lanadelumab 300 mg Q2W		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	2	2		
Units: angioedema attacks				
number (not applicable)	2	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Moderate or Severe Angioedema Attacks During the Treatment Period of Day 0 Through Day 182 in Participants who Switched Dosing Regimen

End point title	Number of Moderate or Severe Angioedema Attacks During the Treatment Period of Day 0 Through Day 182 in Participants who Switched Dosing Regimen
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End point description:

The overall severity of angioedema attack was determined by the site using following definitions: mild (transient or mild discomfort), moderate (mild to moderate limitation in activity), severe (marked limitation in activity). Number of moderate or severe angioedema attacks during the treatment period of Day 0 through Day 182 was assessed. The RD-SFAS Set was a subset of the SFAS Set and included participants who switched from lanadelumab 300 mg Q2W to a lanadelumab 300 mg Q4W dosing regimen as recorded on the Dose Frequency Modification electronic case report form. The data was partitioned by dosing regimen and reported accordingly to appropriately attribute to each dosing regimen.

End point type	Secondary
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End point timeframe:
From Day 0 up to Day 182

End point values	Lanadelumab 300 mg Q4W	Lanadelumab 300 mg Q2W		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	2	2		
Units: angioedema attacks				
number (not applicable)	2	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of High-Morbidity Angioedema Attacks During the Treatment Period of Day 0 through Day 182 in Participants who Switched Dosing Regimen

End point title	Number of High-Morbidity Angioedema Attacks During the Treatment Period of Day 0 through Day 182 in Participants who Switched Dosing Regimen			
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End point description:

A high-morbidity angioedema attack was defined as any attack that has at least one of the following characteristics: severe, results in hospitalization (except hospitalization for observation <24 hours), hemodynamically significant (systolic BP <90 mmHg, requires intravenous hydration, or associated with syncope or near-syncope) or laryngeal. The RD-SFAS Set was a subset of the SFAS Set and included participants who switched from lanadelumab 300 mg Q2W to a lanadelumab 300 mg Q4W dosing regimen as recorded on the Dose Frequency Modification electronic case report form. The data was partitioned by dosing regimen and reported accordingly to appropriately attribute to each dosing regimen.

End point type	Secondary			
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End point timeframe:
From Day 0 up to Day 182

End point values	Lanadelumab 300 mg Q4W	Lanadelumab 300 mg Q2W		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	2	2		
Units: angioedema attacks				
number (not applicable)	1	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

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

Adverse event reporting additional description:

The SFAS included all participants who received any study drug after entering this study (i.e., any exposure to open-label lanadelumab). The data was partitioned by dosing regimen and reported accordingly to appropriately attribute to each dosing regimen.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	26
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Reporting groups

Reporting group title	Lanadelumab 300 mg Every 4 Weeks
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Reporting group description:

Participants who received 300 mg lanadelumab, SC injection, Q4W as attacks were well-controlled based on the investigator's discretion and consultation with the sponsor's medical monitor at any point during the 26-week treatment period were included in this group.

Reporting group title	Lanadelumab 300 mg Every 2 Weeks
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Reporting group description:

Participants received 300 mg lanadelumab SC injection, Q2W for up to 26 weeks with an option to switch to lanadelumab 300 mg Q4W if attacks were well-controlled based on the investigator's discretion and consultation with the sponsor's medical monitor.

Serious adverse events	Lanadelumab 300 mg Every 4 Weeks	Lanadelumab 300 mg Every 2 Weeks	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 2 (50.00%)	7 / 73 (9.59%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 2 (0.00%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 2 (0.00%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain upper			

subjects affected / exposed	1 / 2 (50.00%)	0 / 73 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	0 / 2 (0.00%)	3 / 73 (4.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Suicide attempt			
subjects affected / exposed	0 / 2 (0.00%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Arthritis viral			
subjects affected / exposed	0 / 2 (0.00%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 2 (0.00%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related sepsis			
subjects affected / exposed	0 / 2 (0.00%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Lactic acidosis			
subjects affected / exposed	0 / 2 (0.00%)	1 / 73 (1.37%)	
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	Lanadelumab 300 mg Every 4 Weeks	Lanadelumab 300 mg Every 2 Weeks	
Total subjects affected by non-serious adverse events subjects affected / exposed	1 / 2 (50.00%)	65 / 73 (89.04%)	
Injury, poisoning and procedural complications Ligament sprain subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0	4 / 73 (5.48%) 5	
Nervous system disorders Headache subjects affected / exposed occurrences (all)	1 / 2 (50.00%) 1	10 / 73 (13.70%) 22	
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all) Injection site pain subjects affected / exposed occurrences (all) Malaise subjects affected / exposed occurrences (all)	1 / 2 (50.00%) 1 0 / 2 (0.00%) 0 1 / 2 (50.00%) 1	1 / 73 (1.37%) 4 8 / 73 (10.96%) 48 1 / 73 (1.37%) 1	
Eye disorders Eye swelling subjects affected / exposed occurrences (all)	1 / 2 (50.00%) 1	0 / 73 (0.00%) 0	
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0	6 / 73 (8.22%) 8	
Skin and subcutaneous tissue disorders Angioedema subjects affected / exposed occurrences (all) Urticaria subjects affected / exposed occurrences (all)	1 / 2 (50.00%) 2 0 / 2 (0.00%) 0	61 / 73 (83.56%) 646 4 / 73 (5.48%) 4	
Musculoskeletal and connective tissue			

disorders			
Arthralgia			
subjects affected / exposed	0 / 2 (0.00%)	7 / 73 (9.59%)	
occurrences (all)	0	9	
Infections and infestations			
COVID-19			
subjects affected / exposed	0 / 2 (0.00%)	17 / 73 (23.29%)	
occurrences (all)	0	17	
Upper respiratory tract infection			
subjects affected / exposed	0 / 2 (0.00%)	6 / 73 (8.22%)	
occurrences (all)	0	7	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 September 2020	The following changes were made as per Amendment 1: 1. Included Takeda appropriate forms for AEs and pregnancy. 2. Removed specificity to European Union and Israel 3. Removed references to acquired angioedema due to C1-INH. 4. Removed exclusion criteria 5. Corrected errors referring to treatment period. 6. PK and PD analysis sets were added and "concentration" was removed in regard to plasma cHMWK and pKal levels. 7. Revised exploratory biomarkers to state "...angioedema-disease state bioactivity, including pKal activity." 8. Visits 5 and 9 were revised to subject-elected off-site visits. 9. Timing of site check-in calls was added. 10. Added study procedure modifications due to coronavirus disease (COVID) pandemic. 11. Secondary objective with regard to prefilled syringe was revised to state "to evaluate subject experience of injection. 12. Added section on collection of angioedema attack data. 13. Revised HAE attack to angioedema attack.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

N/A

Notes: