



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 |
|-----------------------|--------------|

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 |
|------------------|------------------------|

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 |
|-----------------------|------------------------|

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 | 43.7 | | |
| standard deviation | ± 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 | |
|-------------------------|---|---|--|

| | | | |
|---|----------|---|--|
| 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 |
| 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 |
| 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. | |

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] |
| 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 |
| 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] |
|-----------------|---|

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 |
|----------------|---------|

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 |
| 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 |
| 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 |
| 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 |
| 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 |
|-----------------|--|

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 |
|----------------|-----------|

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 |
|-----------------|---|

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 |
|----------------|-----------|

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 |
|-----------------|--|

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 |
|----------------|-----------|

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 |
|-----------------|--|

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 (± 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 |
|-----------------|--|

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 |
|-----------------|---|

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 |
|----------------|-----------|

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 |
|-----------------|--|

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 |
|----------------|-----------|

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 |
|-----------------|--|

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 |
|----------------|-----------|

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 |
|-----------------|--|

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 |
|----------------|-----------|

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 |
|-----------------|------------|

Dictionary used

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

| | |
|--------------------|----|
| Dictionary version | 26 |
|--------------------|----|

Reporting groups

| | |
|-----------------------|----------------------------------|
| Reporting group title | Lanadelumab 300 mg Every 4 Weeks |
|-----------------------|----------------------------------|

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 |
|-----------------------|----------------------------------|

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: