Clinical trial results:
SPRING STUDY: An Open-Label, Multicenter, Phase 3 Study to Evaluate the Safety, Pharmacokinetics, and Pharmacodynamics of Lanadelumab for Prevention Against Acute Attacks of Hereditary Angioedema (HAE) in Pediatric Subjects 2 to <12 Years of Age

Summary

EudraCT number	2018-002093-42
Trial protocol	DE HU ES Outside EU/EEA
Global end of trial date	30 October 2021

Results information

Result version number	v1 (current)
This version publication date	15 May 2022
First version publication date	15 May 2022

Trial information

Trial identification

Sponsor protocol code	SHP643-301

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04070326
WHO universal trial number (UTN)	-
Other trial identifiers	IND Number: 116647

Notes:

Sponsors

Sponsor organisation name	Shire
Sponsor organisation address	300 Shire Way, Lexington, United States, MA 02421
Public contact	Study Director, Shire, ClinicalTransparenc@takeda.com
Scientific contact	Study Director, Shire, ClinicalTransparenc@takeda.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001864-PIP01-15
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	30 October 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 October 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to evaluate the safety and pharmacokinetics (PK) of lanadelumab in children (2 to <12 years of age) with HAE.

Protection of trial subjects:

All study participants were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	19 August 2019
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	Spain: 1
Country: Number of subjects enrolled	Germany: 4
Country: Number of subjects enrolled	Hungary: 1
Country: Number of subjects enrolled	United States: 13
Country: Number of subjects enrolled	Canada: 2
Worldwide total number of subjects	21
EEA total number of subjects	6

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)	21
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Total 24 participants were screened and 21 participants were enrolled in the study at 15 investigative sites in the US, Canada, Spain, Hungary, and Germany from 19 August 2019 to 30 October 2021.

Pre-assignment

Screening details:

Participants were observed in 12-week Baseline Observation Period. Participants experiencing ≥1.0 angioedema attacks/3 months during 12-week Baseline Observation Period,who remained eligible per inclusion criteria entered treatment period(TP).Participants aged 2 to <12 years received lanadelumab SC Injection over 52-week Treatment Period.

Period 1

Period 1 title	Baseline Observation-12 Weeks Before TP
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Lanadelumab 150 mg: Age 2 to <6 Years

Arm description:

Participants aged 2 to <6 years received lanadelumab subcutaneous (SC) injection at a dose of 150 milligrams (mg) for every 4 weeks (q4wks) over 52-week Treatment Period (26-week Treatment Period A and 26-week Treatment Period B).

Arm type	Experimental
Investigational medicinal product name	Lanadelumab
Investigational medicinal product code	
Other name	TAK-743, DX-2930, SHP643
Pharmaceutical forms	Intravesical solution/solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Participants received 150 mg dose of lanadelumab every 2 or 4 weeks, depending on the participants age, over the 52-week Treatment Period.

Arm title	Lanadelumab 150 mg: Age 6 to <12 Years

Arm description:

Participants aged 6 to <12 years received lanadelumab SC injection at a dose of 150 mg for every 2 weeks (q2wks) 52-week Treatment Period (26-week Treatment Period A and 26-week Treatment Period B). Participants could switch to a dosing regimen of 150 mg q4wks in Treatment Period B at the investigator’s discretion and sponsor’s medical monitor approval, if they were well controlled (e.g., attack free) for 26 weeks with lanadelumab treatment in this study.Participants aged 6 to <12 years received lanadelumab SC injection at a dose of 150 mg for every 2 weeks (q2wks) over 52-week Treatment Period (26-week Treatment Period A and 26-week Treatment Period B). Participants could switch to a dosing regimen of 150 mg q4wks in Treatment Period B at the investigator’s discretion and sponsor’s medical monitor approval, if they were well controlled (e.g., attack free) for 26 weeks with lanadelumab treatment in this study.

Arm type	Experimental
Investigational medicinal product name	Lanadelumab
Investigational medicinal product code	
Other name	TAK-743, DX-2930, SHP643
Pharmaceutical forms	Intravesical solution/solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Participants received 150 mg dose of lanadelumab every 2 or 4 weeks, depending on the participants

age, over the 52-week Treatment Period.

Number of subjects in period 1	Lanadelumab 150 mg: Age 2 to <6 Years	Lanadelumab 150 mg: Age 6 to <12 Years
Started	4	17
Completed	4	17

Period 2	
Period 2 title	Treatment Period A (Weeks 1 to 26)
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms	
Are arms mutually exclusive?	Yes
Arm title	Lanadelumab 150 mg: Age 2 to <6 Years

Arm description:

Participants aged 2 to <6 years received lanadelumab SC injection at a dose of 150 mg for q4wks over 52-week Treatment Period (26-week Treatment Period A and 26-week Treatment Period B).

Arm type	Experimental
Investigational medicinal product name	Lanadelumab
Investigational medicinal product code	
Other name	TAK-743, DX-2930, SHP643
Pharmaceutical forms	Intravesical solution/solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Participants received 150 mg dose of lanadelumab every 2 or 4 weeks, depending on the participants age, over the 52-week Treatment Period.

Arm title	Lanadelumab 150 mg: Age 6 to <12 Years

Arm description:

Participants aged 6 to <12 years received lanadelumab SC injection at a dose of 150 mg for q2wks over 52-week Treatment Period (26-week Treatment Period A and 26-week Treatment Period B). Participants could switch to a dosing regimen of 150 mg q4wks in Treatment Period B at the investigator’s discretion and sponsor’s medical monitor approval, if they were well controlled (e.g., attack free) for 26 weeks with lanadelumab treatment in this study.

Arm type	Experimental

Investigational medicinal product name	Lanadelumab
Investigational medicinal product code	
Other name	TAK-743, DX-2930, SHP643
Pharmaceutical forms	Intravesical solution/solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Participants received 150 mg dose of lanadelumab every 2 or 4 weeks, depending on the participants age, over the 52-week Treatment Period.

Number of subjects in period 2	Lanadelumab 150 mg: Age 2 to <6 Years	Lanadelumab 150 mg: Age 6 to <12 Years
Started	4	17
Completed	3	17
Not completed	1	0
Withdrawal by Parent/Guardian	1	-

Period 3

Period 3 title	Treatment Period B (Weeks 27 to 52)
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Lanadelumab 150 mg: Age 2 to <6 Years

Arm description:

Participants aged 2 to <6 years received lanadelumab SC injection at a dose of 150 mg for q4wks over 52-week Treatment Period (26-week Treatment Period A and 26-week Treatment Period B).

Arm type	Experimental
Investigational medicinal product name	Lanadelumab
Investigational medicinal product code	
Other name	TAK-743, DX-2930, SHP643
Pharmaceutical forms	Intravesical solution/solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Participants received 150 mg dose of lanadelumab every 2 or 4 weeks, depending on the participants age, over the 52-week Treatment Period.

Arm title	Lanadelumab 150 mg: Age 6 to <12 Years

Arm description:

Participants aged 6 to <12 years received lanadelumab SC injection at a dose of 150 mg for q2wks over 52-week Treatment Period (26-week Treatment Period A and 26-week Treatment Period B). Participants could switch to a dosing regimen of 150 mg q4wks in Treatment Period B at the investigator’s discretion and sponsor’s medical monitor approval, if they were well controlled (e.g., attack free) for 26 weeks with lanadelumab treatment in this study.

Arm type	Experimental

Investigational medicinal product name	Lanadelumab
Investigational medicinal product code	
Other name	TAK-743, DX-2930, SHP643
Pharmaceutical forms	Intravesical solution/solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Participants received 150 mg dose of lanadelumab every 2 or 4 weeks, depending on the participants age, over the 52-week Treatment Period.

Number of subjects in period 3	Lanadelumab 150 mg: Age 2 to <6 Years	Lanadelumab 150 mg: Age 6 to <12 Years
Started	3	17
Completed	3	17

Baseline characteristics

Reporting groups	
Reporting group title	Lanadelumab 150 mg: Age 2 to <6 Years
Reporting group description:	
Participants aged 2 to <6 years received lanadelumab subcutaneous (SC) injection at a dose of 150 milligrams (mg) for every 4 weeks (q4wks) over 52-week Treatment Period (26-week Treatment Period A and 26-week Treatment Period B).	
Reporting group title	Lanadelumab 150 mg: Age 6 to <12 Years
Reporting group description:	
Participants aged 6 to <12 years received lanadelumab SC injection at a dose of 150 mg for every 2 weeks (q2wks) 52-week Treatment Period (26-week Treatment Period A and 26-week Treatment Period B). Participants could switch to a dosing regimen of 150 mg q4wks in Treatment Period B at the investigator's discretion and sponsor's medical monitor approval, if they were well controlled (e.g., attack free) for 26 weeks with lanadelumab treatment in this study.Participants aged 6 to <12 years received lanadelumab SC injection at a dose of 150 mg for every 2 weeks (q2wks) over 52-week Treatment Period (26-week Treatment Period A and 26-week Treatment Period B). Participants could switch to a dosing regimen of 150 mg q4wks in Treatment Period B at the investigator's discretion and sponsor's medical monitor approval, if they were well controlled (e.g., attack free) for 26 weeks with lanadelumab treatment in this study.	

Reporting group values	Lanadelumab 150 mg: Age 2 to <6 Years	Lanadelumab 150 mg: Age 6 to <12 Years	Total
Number of subjects	4	17	21
Age categorical Units: Subjects			
Children (2-11 years)	4	17	21
Age continuous Units: years			
arithmetic mean	4.45	8.68	
standard deviation	± 0.843	± 1.391	-
Gender categorical Units: Subjects			
Female	2	10	12
Male	2	7	9
Race Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	1	1
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	4	16	20
More than one race	0	0	0
Unknown or Not Reported	0	0	0
Ethnicity Units: Subjects			
Hispanic or Latino	0	2	2
Not Hispanic or Latino	4	15	19
Unknown or Not Reported	0	0	0

End points

End points reporting groups

Reporting group title	Lanadelumab 150 mg: Age 2 to <6 Years
Reporting group description:	
Participants aged 2 to <6 years received lanadelumab subcutaneous (SC) injection at a dose of 150 milligrams (mg) for every 4 weeks (q4wks) over 52-week Treatment Period (26-week Treatment Period A and 26-week Treatment Period B).	
Reporting group title	Lanadelumab 150 mg: Age 6 to <12 Years
Reporting group description:	
Participants aged 6 to <12 years received lanadelumab SC injection at a dose of 150 mg for every 2 weeks (q2wks) 52-week Treatment Period (26-week Treatment Period A and 26-week Treatment Period B). Participants could switch to a dosing regimen of 150 mg q4wks in Treatment Period B at the investigator's discretion and sponsor's medical monitor approval, if they were well controlled (e.g., attack free) for 26 weeks with lanadelumab treatment in this study.Participants aged 6 to <12 years received lanadelumab SC injection at a dose of 150 mg for every 2 weeks (q2wks) over 52-week Treatment Period (26-week Treatment Period A and 26-week Treatment Period B). Participants could switch to a dosing regimen of 150 mg q4wks in Treatment Period B at the investigator's discretion and sponsor's medical monitor approval, if they were well controlled (e.g., attack free) for 26 weeks with lanadelumab treatment in this study.	
Reporting group title	Lanadelumab 150 mg: Age 2 to <6 Years
Reporting group description:	
Participants aged 2 to <6 years received lanadelumab SC injection at a dose of 150 mg for q4wks over 52-week Treatment Period (26-week Treatment Period A and 26-week Treatment Period B).	
Reporting group title	Lanadelumab 150 mg: Age 6 to <12 Years
Reporting group description:	
Participants aged 6 to <12 years received lanadelumab SC injection at a dose of 150 mg for q2wks over 52-week Treatment Period (26-week Treatment Period A and 26-week Treatment Period B). Participants could switch to a dosing regimen of 150 mg q4wks in Treatment Period B at the investigator's discretion and sponsor's medical monitor approval, if they were well controlled (e.g., attack free) for 26 weeks with lanadelumab treatment in this study.	
Reporting group title	Lanadelumab 150 mg: Age 2 to <6 Years
Reporting group description:	
Participants aged 2 to <6 years received lanadelumab SC injection at a dose of 150 mg for q4wks over 52-week Treatment Period (26-week Treatment Period A and 26-week Treatment Period B).	
Reporting group title	Lanadelumab 150 mg: Age 6 to <12 Years
Reporting group description:	
Participants aged 6 to <12 years received lanadelumab SC injection at a dose of 150 mg for q2wks over 52-week Treatment Period (26-week Treatment Period A and 26-week Treatment Period B). Participants could switch to a dosing regimen of 150 mg q4wks in Treatment Period B at the investigator's discretion and sponsor's medical monitor approval, if they were well controlled (e.g., attack free) for 26 weeks with lanadelumab treatment in this study.	
Subject analysis set title	Lanadelumab 150 mg, q4wks
Subject analysis set type	Safety analysis
Subject analysis set description:	
Participants received lanadelumab SC injection at a dose of 150 mg for q4wks with over 52-week Treatment Period (26-week Treatment Period A and 26-week Treatment Period B).	
Subject analysis set title	Lanadelumab 150 mg, q2wks
Subject analysis set type	Safety analysis
Subject analysis set description:	
Participants received lanadelumab SC injection at a dose of 150 mg for q2wks over 52-week Treatment Period (26-week Treatment Period A and 26-week Treatment Period B).	

Primary: Number of Participants with Adverse Events Including Serious Adverse Events (SAEs) and Adverse Events of Special Interest (AESIs)

End point title	Number of Participants with Adverse Events Including Serious Adverse Events (SAEs) and Adverse Events of Special Interest (AESIs)[1]

End point description:

Adverse event(AE):any untoward medical occurrence in a clinical investigation participant administered a pharmaceutical product and that does not necessarily have a causal relationship with investigational product or medicinal product.SAE:any untoward clinical manifestation of signs,symptoms or outcomes(whether considered related to investigational product or not and at any dose which results in death,is life-threatening,requires inpatient hospitalization or prolongation of hospitalization,results in persistent or significant disability/incapacity,results in congenital abnormality/birth defect,is important medical event.AEs of special interest(AESIs):are hypersensitivity reactions and disordered coagulation(hypercoagulability events and bleeding events).Safety Analysis Set:all participants who received study drug.'n'=participants presented by actual treatment regimen.Due to dose modifications,some participants treated with both dosing regimens were counted in both treatment

End point type	Primary

End point timeframe:

Up to approximately 115 weeks

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 summary statistics was planned for this outcome measure.

End point values	Lanadelumab 150 mg, q4wks	Lanadelumab 150 mg, q2wks		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	11	18		
Units: participants				
SAEs	0	0		
AESIs	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants With Clinically Significant Laboratory Assessment Abnormalities

End point title	Number of Participants With Clinically Significant Laboratory Assessment Abnormalities[2]

End point description:

Laboratory values (chemistry, hematology, and coagulation) were to be considered clinically significant based on investigator's discretion. The Safety Analysis Set consisted of all participants who received study drug.

End point type	Primary

End point timeframe:

Up to approximately 115 weeks

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 summary statistics was planned for this outcome measure.

End point values	Lanadelumab 150 mg: Age 2 to <6 Years	Lanadelumab 150 mg: Age 6 to <12 Years		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	17		
Units: participants	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants With Clinically Significant Vital Signs Measurements

End point title	Number of Participants With Clinically Significant Vital Signs Measurements[3]

End point description:

Vital signs included blood pressure, heart rate, body temperature, and respiratory rate. The Safety Analysis Set consisted of all participants who received study drug.

End point type	Primary

End point timeframe:

Up to approximately 115 weeks

Notes:

[3] - 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 summary statistics was planned for this outcome measure.

End point values	Lanadelumab 150 mg: Age 2 to <6 Years	Lanadelumab 150 mg: Age 6 to <12 Years		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	17		
Units: participants	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Plasma Concentrations of Lanadelumab Over The Treatment Period

End point title	Plasma Concentrations of Lanadelumab Over The Treatment Period[4]

End point description:

The plasma concentration of lanadelumab over treatment period was assessed. The Pharmacokinetic (PK) Set included all participants in the Safety Analysis Set who have at least 1 evaluable post dose PK concentration value.

End point type	Primary

End point timeframe:

Day 0 (Pre-dose), Day 4, 14, 28, 56, 84, 112, 140, 168, 182 196, 252, 308, 364 and 392

Notes:

[4] - 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 summary statistics was planned for this outcome measure.

End point values	Lanadelumab 150 mg: Age 2 to <6 Years	Lanadelumab 150 mg: Age 6 to <12 Years		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	17		
Units: nanograms per milliliter (ng/mL)				
arithmetic mean (standard deviation)				
Visit 1 Day 0 (n=4,17)	0.000 (± 0.0000)	11.735 (± 39.2984)		
Visit 2 Day 4 (n=3,14)	32407.215 (± 9785.4332)	20349.609 (± 12587.7085)		
Visit 3 Day 14 (n=4,17)	20443.818 (± 7800.4019)	14589.883 (± 4734.4461)		
Visit 4 Day 28 (n=4,14)	10636.682 (± 6168.5347)	21198.858 (± 8378.3961)		
Visit 8 Day 56 (n=3,14)	10433.382 (± 3345.1718)	27751.659 (± 10048.7527)		
Visit 12 Day 84 (n=3,14)	14758.407 (± 8392.8620)	24895.121 (± 11852.7671)		
Visit 16 Day 112 (n=3,10)	15020.780 (± 5730.4397)	31053.260 (± 14012.6464)		
Visit 20 Day 140 (n=3,12)	13318.715 (± 4432.0728)	26534.885 (± 11234.6051)		
Visit 24 Day 168 (3,12)	12189.214 (± 11367.4241)	26166.340 (± 11070.0337)		
Visit 26 Day 182 (n=3,11)	25630.909 (± 11054.3701)	25372.349 (± 8242.4858)		
Visit 28 Day 196 (n=3,14)	14293.013 (± 6014.0384)	25238.600 (± 9921.4264)		
Visit 36 Day 252 (n=3,16)	23110.526 (± 18241.5743)	19058.886 (± 12079.1976)		
Visit 44 Day 308 (n=3,16)	22687.442 (± 20911.9442)	15774.463 (± 12043.0984)		
Visit 52 Day 364 (n=3,15)	27178.967 (± 24111.9243)	17239.653 (± 11975.4861)		
Visit 56 Day 392 (End of Study Visit) (n=2,14)	32400.148 (± 24303.4128)	15689.458 (± 11811.7412)		

Statistical analyses

No statistical analyses for this end point

Primary: Maximum Observed Concentration at Steady State (Cmax,ss) of Lanadelumab in Plasma

End point title	Maximum Observed Concentration at Steady State (Cmax,ss) of Lanadelumab in Plasma[5]

End point description:

The PK Set included all participants in the Safety Analysis Set who have at least 1 evaluable post dose PK concentration value.

End point type	Primary

End point timeframe:

Day 0 (Pre-dose), at any time pre-dose on Day 4, 14, 28, 56, 84, 112, 140, 168, 182 196, 252, 308, 364 and 392

Notes:

[5] - 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 summary statistics was planned for this outcome measure.

End point values	Lanadelumab 150 mg: Age 2 to <6 Years	Lanadelumab 150 mg: Age 6 to <12 Years		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	17		
Units: micrograms per mL (µg/mL)				
geometric mean (geometric coefficient of variation)	37.7 (± 30.1)	39.0 (± 39.2)		

Statistical analyses

No statistical analyses for this end point

Primary: Average Concentration Over Dosing Interval at Steady State (Cavg,ss) of Lanadelumab in Plasma

End point title	Average Concentration Over Dosing Interval at Steady State (Cavg,ss) of Lanadelumab in Plasma[6]

End point description:

The PK Set included all participants in the Safety Analysis Set who have at least 1 evaluable post dose PK concentration value.

End point type	Primary

End point timeframe:

Day 0 (Pre-dose), at any time pre-dose on Day 4, 14, 28, 56, 84, 112, 140, 168, 182 196, 252, 308, 364 and 392

Notes:

[6] - 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 summary statistics was planned for this outcome measure.

End point values	Lanadelumab 150 mg: Age 2 to <6 Years	Lanadelumab 150 mg: Age 6 to <12 Years		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	17		
Units: µg/mL				
geometric mean (geometric coefficient of variation)	24.6 (± 34.0)	33.2 (± 37.7)		

Statistical analyses

No statistical analyses for this end point

Primary: Minimum Concentration at Steady State (Cmin,ss) of Lanadelumab in

Plasma

End point title	Minimum Concentration at Steady State (Cmin,ss) of Lanadelumab in Plasma[7]

End point description:

The PK Set included all participants in the Safety Analysis Set who have at least 1 evaluable post dose PK concentration value.

End point type	Primary

End point timeframe:

Day 0 (Pre-dose), at any time pre-dose on Day 4, 14, 28, 56, 84, 112, 140, 168, 182 196, 252, 308, 364 and 392

Notes:

[7] - 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 summary statistics was planned for this outcome measure.

End point values	Lanadelumab 150 mg: Age 2 to <6 Years	Lanadelumab 150 mg: Age 6 to <12 Years		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	17		
Units: µg/mL				
geometric mean (geometric coefficient of variation)	11.1 (± 46.5)	24.8 (± 37.3)		

Statistical analyses

No statistical analyses for this end point

Primary: Time to Reach Maximum Observed Concentration (Cmax) [tmax] of Lanadelumab in Plasma

End point title	Time to Reach Maximum Observed Concentration (Cmax) [tmax] of Lanadelumab in Plasma[8]

End point description:

The PK Set included all participants in the Safety Analysis Set who have at least 1 evaluable post dose PK concentration value.

End point type	Primary

End point timeframe:

Day 0 (Pre-dose), at any time pre-dose on Day 4, 14, 28, 56, 84, 112, 140, 168, 182 196, 252, 308, 364 and 392

Notes:

[8] - 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 summary statistics was planned for this outcome measure.

End point values	Lanadelumab 150 mg: Age 2 to <6 Years	Lanadelumab 150 mg: Age 6 to <12 Years		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	17		
Units: hours (h)				
median (full range (min-max))	122 (108 to 135)	86.0 (66.0 to 137)		

Statistical analyses

No statistical analyses for this end point

Primary: Area Under the Concentration-Time Curve Over the Dosing Interval at Steady State (AUCtau,ss) of Lanadelumab in Plasma

End point title	Area Under the Concentration-Time Curve Over the Dosing Interval at Steady State (AUCtau,ss) of Lanadelumab in Plasma[9]

End point description:

The PK Set included all participants in the Safety Analysis Set who have at least 1 evaluable post dose PK concentration value.

End point type	Primary

End point timeframe:

Day 0 (Pre-dose), at any time pre-dose on Day 4, 14, 28, 56, 84, 112, 140, 168, 182 196, 252, 308, 364 and 392

Notes:

[9] - 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 summary statistics was planned for this outcome measure.

End point values	Lanadelumab 150 mg: Age 2 to <6 Years	Lanadelumab 150 mg: Age 6 to <12 Years		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	17		
Units: µg.day/mL				
geometric mean (geometric coefficient of variation)	690 (± 34.0)	464 (± 37.7)		

Statistical analyses

No statistical analyses for this end point

Primary: Terminal half-life (t1/2) of Lanadelumab in Plasma

End point title	Terminal half-life (t1/2) of Lanadelumab in Plasma[10]

End point description:

The PK Set included all participants in the Safety Analysis Set who have at least 1 evaluable post dose PK concentration value.

End point type	Primary

End point timeframe:

Day 0 (Pre-dose), at any time pre-dose on Day 4, 14, 28, 56, 84, 112, 140, 168, 182 196, 252, 308, 364 and 392

Notes:

[10] - 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 summary statistics was planned for this outcome measure.

End point values	Lanadelumab 150 mg: Age 2 to <6 Years	Lanadelumab 150 mg: Age 6 to <12 Years		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	17		
Units: days				
median (full range (min-max))	11.7 (10.2 to 13.9)	12.6 (9.59 to 27.3)		

Statistical analyses

No statistical analyses for this end point

Primary: Apparent clearance (CL/F) of Lanadelumab

End point title	Apparent clearance (CL/F) of Lanadelumab[11]

End point description:

The PK Set included all participants in the Safety Analysis Set who have at least 1 evaluable post dose PK concentration value.

End point type	Primary

End point timeframe:

Day 0 (Pre-dose), at any time pre-dose on Day 4, 14, 28, 56, 84, 112, 140, 168, 182 196, 252, 308, 364 and 392

Notes:

[11] - 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 summary statistics was planned for this outcome measure.

End point values	Lanadelumab 150 mg: Age 2 to <6 Years	Lanadelumab 150 mg: Age 6 to <12 Years		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	17		
Units: L/h				
geometric mean (geometric coefficient of variation)	0.00906 (± 34.0)	0.0135 (± 37.8)		

Statistical analyses

No statistical analyses for this end point

Primary: Apparent Volume of Distribution (V/F) of Lanadelumab

End point title	Apparent Volume of Distribution (V/F) of Lanadelumab[12]

End point description:

The PK Set included all participants in the Safety Analysis Set who have at least 1 evaluable post dose PK concentration value.

End point type	Primary

End point timeframe:

Day 0 (Pre-dose), at any time pre-dose on Day 4, 14, 28, 56, 84, 112, 140, 168, 182 196, 252, 308, 364 and 392

Notes:

[12] - 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 summary statistics was planned for this outcome measure.

End point values	Lanadelumab 150 mg: Age 2 to <6 Years	Lanadelumab 150 mg: Age 6 to <12 Years		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	17		
Units: Litres				
geometric mean (geometric coefficient of variation)	3.63 (± 25.9)	5.59 (± 39.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Normalized Number of Investigator-Confirmed Hereditary Angioedema (HAE) Attacks During Overall Treatment Period

End point title	Normalized Number of Investigator-Confirmed Hereditary Angioedema (HAE) Attacks During Overall Treatment Period

End point description:

Normalized number of investigator-confirmed HAE attacks during overall period are expressed as monthly HAE attack rate.Investigator-confirmed HAE attack rate calculated for each participant as number of investigator-confirmed HAE attacks occurring during given study period divided by number of days participant contributed to period multiplied by 28days.HAE attack:symptoms/signs consistent with attack in>=1of following locations:peripheral angioedema(cutaneous swelling involving extremity,face,neck,torso,and/or genitourinary region),abdominal angioedema(abdominal pain,with/without abdominal distention,nausea,vomiting,/diarrhea),laryngeal angioedema(stridor,dyspnea,difficulty speaking,difficulty swallowing,throat tightening,/swelling of tongue,palate,uvula,/larynx).Safety Analysis Set: participants who received study drug.n=participants presented by actual treatment regimen;due to dose modifications,some them were treated with both

End point type	Secondary

End point timeframe:

Day 0 (after start of study drug administration) through Day 364 (Week 52)

End point values	Lanadelumab 150 mg, q4wks	Lanadelumab 150 mg, q2wks		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	11	18		
Units: HAE attacks per month				
arithmetic mean (standard deviation)	0.07 (± 0.219)	0.08 (± 0.157)		

Statistical analyses

No statistical analyses for this end point

Secondary: Normalized Number of Investigator-Confirmed HAE Attacks For Each Efficacy Evaluation Period Other Than the Overall Treatment Period

End point title	Normalized Number of Investigator-Confirmed HAE Attacks For Each Efficacy Evaluation Period Other Than the Overall Treatment Period

End point description:

Normalized number of investigator-confirmed HAE attacks in each efficacy evaluation period except overall treatment period are expressed as monthly HAE attack rate and is calculated for each participant as number of investigator-confirmed HAE attacks occurring during given study period divided by number of days participant contributed to period multiplied by 28days.HAE attack:symptoms/signs consistent with attack in>=1of following locations:peripheral angioedema(cutaneous swelling involving extremity,face,neck,torso,and/or genitourinary region),abdominal angioedema(abdominal pain,with/without abdominal distention,nausea,vomiting,/diarrhea),laryngeal angioedema(stridor,dyspnea,difficulty speaking,difficulty swallowing,throat tightening,/swelling of tongue,palate,uvula,/larynx).Safety Analysis Set:participants who received study drug.n=participants presented by actual treatment;due to dose modifications,some of them were treated with both doses

End point type	Secondary

End point timeframe:

Day 0 through Day 182, Day 70 through Day 182, Day 183 through Day 364, Day 70 through Day 364

End point values	Lanadelumab 150 mg, q4wks	Lanadelumab 150 mg, q2wks		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	11	18		
Units: HAE attacks per month				
arithmetic mean (standard deviation)				
Overall Presumed Steady-state Period(n=10,18)	0.09 (± 0.288)	0.07 (± 0.143)		
Treatment Period A(n=4,17)	0.15 (± 0.308)	0.08 (± 0.207)		
Presumed Steady-state Period for TP-A(n=3,17)	0.25 (± 0.433)	0.06 (± 0.192)		
Treatment Period B(n=10,18)	0.28 (± 0.878)	0.08 (± 0.142)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to the First Investigator-Confirmed HAE Attack for Each Evaluation Period

End point title	Time to the First Investigator-Confirmed HAE Attack for Each Evaluation Period

End point description:

Time to first investigator-confirmed HAE attack for each efficacy evaluation period,was calculated from date and time of first dose to date and time of first investigator-confirmed HAE attack after first open-label dose for that efficacy evaluation period.HAE attack:symptoms/signs consistent with an attack in>=1of following locations:peripheral angioedema(cutaneous swelling involving extremity,face,neck,torso,and/or genitourinary region),abdominal angioedema(abdominal pain,with/without abdominal distention,nausea,vomiting,/diarrhea),laryngeal angioedema(stridor,dyspnea,difficulty speaking,difficulty swallowing,throat tightening,/swelling of

analysis.Safety Analysis Set:participants who received study drug.n=participants presented by actual treatment;due to dose modifications,some of them treated with both doses,counted in both treatment groups.99999:Median,95%CI not evaluable due to low number of events.

End point type	Secondary

End point timeframe:

Day 0 through Day 364, Day 0 through Day 182, Day 70 through Day 182, Day 183 through Day 364, Day 70 through Day 364

End point values	Lanadelumab 150 mg, q4wks	Lanadelumab 150 mg, q2wks		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	11	18		
Units: days				
median (full range (min-max))				
Treatment Period A(n=10,18)	99999 (99999 to 99999)	99999 (99999 to 99999)		
Presumed Steady-state Period for TP-A(n=3,17)	99999 (99999 to 99999)	99999 (99999 to 99999)		
Treatment Period B (n=10,18)	99999 (99999 to 99999)	99999 (99999 to 99999)		
Overall Treatment Period (n=11,18)	99999 (99999 to 99999)	99999 (99999 to 99999)		
Overall Presumed Steady-state Period(n=10,18)	99999 (99999 to 99999)	99999 (99999 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Normalized Number of HAE Attacks Requiring Acute Treatment for Each Efficacy Evaluation Period

End point title	Normalized Number of HAE Attacks Requiring Acute Treatment for Each Efficacy Evaluation Period

End point description:

Normalized number of investigator-confirmed HAE attacks requiring acute treatment during each efficacy evaluation period are expressed as monthly HAE attack rate and is calculated for each participant as number of investigator-confirmed HAE attacks occurring during given study period divided by number of days participant contributed to period multiplied by 28days.HAE attack:symptoms/signs consistent with attack in>=1of following locations:peripheral angioedema(cutaneous swelling involving extremity,face,neck,torso,and/or genitourinary region),abdominal angioedema(abdominal pain,with/without abdominal distention,nausea,vomiting,/diarrhea),laryngeal angioedema(stridor,dyspnea,difficulty speaking,difficulty swallowing,throat tightening,/swelling of tongue,palate,uvula,/larynx).Safety Analysis Set:participants who received study drug.n=participants presented by actual treatment;due to dose modifications,some of them were treated with both doses

End point type	Secondary

End point timeframe:

Day 0 through Day 364, Day 0 through Day 182, Day 70 through Day 182, Day 183 through Day 364, Day 70 through Day 364

End point values	Lanadelumab 150 mg, q4wks	Lanadelumab 150 mg, q2wks		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	11	18		
Units: HAE attacks per month				
arithmetic mean (standard deviation)				
Overall Treatment Period(n=11,18)	0.07 (± 0.219)	0.07 (± 0.140)		
Overall Presumed Steady-state Period(n=10,18)	0.09 (± 0.288)	0.06 (± 0.126)		
Treatment Period A(n=4,17)	0.15 (± 0.308)	0.07 (± 0.175)		
Presumed Steady-state Period for TP-A(n=3,17)	0.25 (± 0.433)	0.04 (± 0.135)		
Treatment Period B(n=10,18)	0.28 (± 0.878)	0.06 (± 0.132)		

Statistical analyses

No statistical analyses for this end point

Secondary: Normalized Number of Moderate or Severe Investigator-Confirmed HAE Attacks for Each Efficacy Evaluation Period

End point title	Normalized Number of Moderate or Severe Investigator-Confirmed HAE Attacks for Each Efficacy Evaluation Period

End point description:

Normalized number of moderate/severe investigator-confirmed HAE attacks requiring acute treatment during each efficacy evaluation period are expressed as monthly HAE attack rate,is calculated for each participant as number of investigator-confirmed HAE attacks occurring during given study period divided by number of days participant contributed to period multiplied by 28days.HAE attack:symptoms/signs consistent with attack in>=1of following locations:peripheral angioedema(cutaneous swelling involving extremity,face,neck,torso,and/or genitourinary region),abdominal angioedema(abdominal pain,with/without abdominal distention,nausea,vomiting,/diarrhea),laryngeal angioedema(stridor,dyspnea,difficulty speaking,difficulty swallowing,throat tightening,/swelling of tongue,palate,uvula,/larynx).Safety Analysis Set:participants received study drug.n=participants presented by actual treatment;due to dose modifications,some of them treated with both doses are

End point type	Secondary

End point timeframe:

Day 0 through Day 364, Day 0 through Day 182, Day 70 through Day 182, Day 183 through Day 364, Day 70 through Day 364

End point values	Lanadelumab 150 mg, q4wks	Lanadelumab 150 mg, q2wks		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	11	18		
Units: HAE attacks per month				
arithmetic mean (standard deviation)				
Overall Treatment Period(n=11,18)	0.07 (± 0.219)	0.07 (± 0.144)		
Overall Presumed Steady-state Period(n=10,18)	0.09 (± 0.288)	0.06 (± 0.125)		
Treatment Period A(n=4,17)	0.15 (± 0.308)	0.07 (± 0.175)		
Steady-state Period for TP-A(n=3,17)	0.25 (± 0.433)	0.04 (± 0.135)		
Treatment Period B(n=10,18)	0.3 (± 0.88)	0.1 (± 0.13)		

Statistical analyses

No statistical analyses for this end point

Secondary: Normalized Number of High Morbidity Investigator-Confirmed HAE Attacks for Each Efficacy Evaluation Period

End point title	Normalized Number of High Morbidity Investigator-Confirmed HAE Attacks for Each Efficacy Evaluation Period

End point description:

Normalized number of high morbidity investigator-confirmed HAE attacks requiring acute treatment during each efficacy evaluation period are expressed as monthly HAE attack rate,is calculated for each participant as number of investigator-confirmed HAE attacks occurring during given study period divided by number of days participant contributed to period multiplied by 28days.HAE attack:symptoms/signs consistent with attack in>=1of following locations:peripheral angioedema(cutaneous swelling involving extremity,face,neck,torso,and/or genitourinary region),abdominal angioedema(abdominal pain,with/without abdominal distention,nausea,vomiting,/diarrhea),laryngeal angioedema(stridor,dyspnea,difficulty speaking,difficulty swallowing,throat tightening,/swelling of tongue,palate,uvula,/larynx).Safety Analysis Set:participants received study drug.n=participants presented by actual treatment;due to dose modifications,some of them treated with both doses are

End point type	Secondary

End point timeframe:

Day 0 through Day 364, Day 0 through Day 182, Day 70 through Day 182, Day 183 through Day 364, Day 70 through Day 364

End point values	Lanadelumab 150 mg, q4wks	Lanadelumab 150 mg, q2wks		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	11	18		
Units: HAE attacks per month				
arithmetic mean (standard deviation)				
Overall Treatment Period(n=11,18)	0.01 (± 0.044)	0.01 (± 0.039)		
Overall Presumed Steady-state Period(n=10,18)	0.02 (± 0.072)	0.01 (± 0.039)		
Treatment Period A(n=4,17)	0.04 (± 0.077)	0.00 (± 0.000)		
Presumed Steady-state Period for TP-A(n=3,17)	0.08 (± 0.144)	0.00 (± 0.000)		
Treatment Period B(n=10,18)	0.00 (± 0.000)	0.01 (± 0.039)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Characteristics of Investigator-Confirmed HAE Attacks for Each Efficacy Evaluation Period

End point title	Number of Participants with Characteristics of Investigator-Confirmed HAE Attacks for Each Efficacy Evaluation Period

End point description:

Characteristics of investigator-confirmed HAE attacks for each efficacy evaluation period included duration,severity,attack location,and rescue medication use.HAE attack:symptoms or signs consistent with an attack in >=1 of 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).Safety Analysis Set:all participants who received study drug.Overall number analyzed:participants presented by actual treatment regimen. Because of dose modifications,some participants were treated with both dosing regimens and were counted in both treatment groups.Only categories with data are reported.TP:Treatment Period;PSSP:presumed steady

End point type	Secondary

End point timeframe:

Day 0 through Day 364, Day 0 through Day 182, Day 70 through Day 182, Day 183 through Day 364, Day 70 through Day 364

End point values	Lanadelumab 150 mg, q4wks	Lanadelumab 150 mg, q2wks		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	11	18		
Units: participants				
TP-A:Mean attack duration:0 hour[h],n=4,17	3	14		
TP-A:Mean attack duration:<12h,n=4,17	1	2		
TP-A:Mean attack duration:>24-48h,n=4,17	0	1		
TP-A:Max. attack severity:No attack,n=4,17	3	14		
TP-A:Max. attack severity:Moderate,n=4,17	0	3		
TP-A:Max. attack severity:Severe,n=4,17	1	0		
PSSP(TP-A):Mean attack duration: 0 h,n=3,17	2	15		
PSSP(TP-A):Mean attack duration:<12h,n=3,17	1	1		
PSSP(TP-A):Mean attack duration:>24-48h,n=3,17	0	1		
PSSP(TP-A):Max. attack severity:No attack,n=3,17	2	15		
PSSP(TP-A):Max. attack severity:Moderate,n=3,17	0	2		
PSSP(TP-A):Max. attack severity: Severe,n=3,17	1	0		
TP-B:Mean attack duration: 0 h,n=10,18	9	13		
TP-B:Mean attack duration:>0-<12h,n=10,18	1	3		
TP-B:Mean attack duration:12-24h,n=10,18	0	1		
TP-B:Mean attack duration:>48h,n=10,18	0	1		
TP-B:Max. attack severity:No attack,n=10,18	9	13		

TP-B:Max. attack severity:Moderate,n=10,18	1	4		
TP-B:Max. attack severity:Severe,n=10,18	0	1		
Overall TP:Mean attack duration:0 h,n=11,18	10	13		
Overall TP:Mean attack duration:>0-<12h,n=11,18	1	4		
Overall TP:Mean attack duration:>24-48h,n=11,18	0	1		
Overall TP:Max. attack severity:No attack,n=11,18	10	13		
Overall TP:Max. attack severity:Moderate,n=11,18	0	4		
Overall TP:Max. attack severity:Severe,n=11,18	1	1		
Overall PSSP:Mean attack duration:0h,n=10,18	9	13		
Overall PSSP:Mean attack duration:>0-<12h,n=10,18	1	4		
Overall PSSP:Mean attack duration:>48h,n=10,18	0	1		
Overall PSSP:Max.attack severity:No attack,n=10,18	9	13		
Overall PSSP:Max.attack severity:Moderate,n=10,18	0	4		
Overall PSSP:Max. attack severity:Severe,n=10,18	1	1		
TP-A:Primary Attack Location:Peripheral,n=4,17	1	2		
TP-A:Primary Attack Location:Abdominal,n=4,17	1	1		
TP-A:Attack Derived Location:Peripheral,n=4,17	1	2		
TP-A:Attack Derived Location:Abdominal,n=4,17	1	1		
TP-A:Rescue Medication(RM):No Use,n=4,17	0	1		
TP-A:RM:Icatibant,n=4,17	0	1		
TP-A:RM:Nano-filtered C1-INH,n=4,17	0	1		
TP-A:RM:Plasma-derivedC1-INH,n=4,17	1	1		
PSSP,TPA:Primary Attack Location:Peripheral,n=3,17	0	2		
PSSP,TPA:Primary Attack Location:Abdominal,n=3,17	1	0		
PSSP,TPA:Attack Derived Location:Peripheral,n=3,17	0	2		
PSSP,TPA:Attack Derived Location:Abdominal,n=3,17	1	0		
PSSP,TPA:Rescue Medication(RM):No Use,n=3,17	0	1		
PSSP,TPA:RM:Icatibant,n=3,17	0	1		
PSSP,TPA:RM:Plasma-derivedC1-INH,n=3,17	1	1		
TP-B:Primary Attack Location:Peripheral,n=10,18	0	3		
TP-B:Primary Attack Location:Abdominal,n=10,18	1	4		
TP-B:Attack Derived Location:Peripheral,n=10,18	0	3		

TP-B:Attack Derived Location:Abdominal,n=10,18	1	4		
TP-B:RM:No Use,n=10,18	0	2		
TP-B:RM:Icatibant,n=10,18	0	2		
TP-B:RM:Plasma-derivedC1-INH,n=10,18	1	2		
Overall TP:Pri.Attack Location:Peripheral,n=11,18	1	3		
Overall TP:Pri.Attack Location:Abdominal,n=11,18	1	4		
Overall TP:Attack Der.Location:Peripheral,n=11,18	1	3		
Overall TP:Attack Der.Location:Abdominal,n=11,18	1	4		
Overall TP:RM:No Use,n=11,18	0	3		
Overall TP:RM:Icatibant,n=11,18	0	2		
Overall TP:RM:Nano-filteredC1-INH,n=11,18	0	1		
Overall TP:RM:Plasma-derivedC1-INH,n=11,18	1	2		
OverallPSSP:Pri.Attack Location:Peripheral,n=10,18	0	3		
OverallPSSP:Pri.Attack Location:Abdominal,n=10,18	1	4		
OverallPSSP:Der.Attack Location:Peripheral,n=10,18	0	3		
Overall PSSP:Der.Attack Location:Abdominal,n=10,18	1	4		
Overall PSSP:RM:No Use,n=10,18	0	3		
Overall PSSP:RM:Icatibant,n=10,18	0	2		
Overall PSSP:RM:Plasma-derivedC1-INH,n=10,18	1	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with HAE Attack-Free Status for Each Evaluation Period

End point title	Number of Participants with HAE Attack-Free Status for Each Evaluation Period

End point description:

A HAE attack is 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). The Safety Analysis Set consists of all participants who received study drug. Overall number analyzed are participants presented by the actual treatment regimen. Because of dose modifications, some participants were treated with both dosing regimens and were counted in both treatment groups.

End point type	Secondary

End point timeframe:

Day 0 through Day 364, Day 0 through Day 182, Day 70 through Day 182, Day 183 through Day 364, Day 70 through Day 364

End point values	Lanadelumab 150 mg, q4wks	Lanadelumab 150 mg, q2wks		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	11	18		
Units: participants				
Treatment Period A(n=4,17)	3	14		
Presumed Steady-state Period for TP-A(n=10,18)	2	15		
Treatment Period B(n=10,18)	9	13		
Overall Treatment Period(n=11,18)	10	13		
Overall Presumed Steady-state Period(n=10,18)	9	13		

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Kallikrein (pKal) Activity

End point title	Plasma Kallikrein (pKal) Activity

End point description:

pKal activity was measured by biomarker cleaved high molecular weight kininogen (cHMWK) level to assess pharmacodynamics of lanadelumab. The Pharmacodynamic (PD) Set included all participants in the Safety Analysis Set who have at least 1 evaluable post dose PD value. Number analyzed is the number of participants with data available for analysis at the given timepoint.

End point type	Secondary

End point timeframe:

Day 0 (Pre-dose), at any time on Days 4, 14, 28, 56, 84, 112, 140, 168, 182 196, 252, 308, 364 and 392

End point values	Lanadelumab 150 mg: Age 2 to <6 Years	Lanadelumab 150 mg: Age 6 to <12 Years		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	17		
Units: percentage of cHMWK				
arithmetic mean (standard deviation)				
Visit 1 Day 0 (n=4,16)	30.2500 (± 13.61017)	45.6438 (± 25.79470)		
Visit 2 Day 4(n=3,14)	16.4000 (± 8.94036)	32.2857 (± 17.89606)		
Visit 3 Day 14(n=4,17)	9.5750 (± 4.05740)	25.7176 (± 11.75565)		
Visit 4 Day 28(n=4.14)	18.8500 (± 14.15968)	26.1571 (± 11.76616)		
Visit 8 Day 56(n=3,15)	15.1333 (± 12.95582)	24.6267 (± 14.28963)		

Visit 12 Day 84(n=3,14)	18.2333 (± 17.91768)	24.7214 (± 12.84339)		
Visit 16 Day 112(n=3,12)	10.7333 (± 5.48118)	18.0000 (± 11.05992)		
Visit 20 Day 140(n=3,12)	15.2000 (± 16.96202)	16.3417 (± 12.53841)		
Visit 24 Day 168(n=3,12)	21.9000 (± 20.71545)	19.6167 (± 16.61762)		
Visit 26 Day 182(n=3,11)	17.9000 (± 14.29021)	18.6818 (± 10.54332)		
Visit 28 Day 196(n=3,14)	9.2000 (± 2.52389)	14.6571 (± 7.29939)		
Visit 36 Day 252(n=3,15)	15.2000 (± 13.16397)	16.3067 (± 10.26008)		
Visit 44 Day 308(n=3,16)	13.5333 (± 7.24316)	23.2750 (± 15.23577)		
Visit 52 Day 364(n=3,15)	10.7333 (± 2.87112)	14.4733 (± 8.51448)		
Visit 56 Day 392 EOS (n=3,14)	10.9000 (± 3.15753)	19.4286 (± 14.57677)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Immunogenicity Status as Positive or Negative

End point title	Number of Participants with Immunogenicity Status as Positive or Negative

End point description:

Immunogenicity was measured based on the presence or absence of neutralizing or non-neutralizing Anti-drug Antibody (ADA) in plasma. The Safety Analysis Set consisted of all participants who received study drug. Number analyzed are the number of participants with data available for given category.

End point type	Secondary

End point timeframe:

Day 0 (Pre-dose), Days 28, 84, 140, 182, 196, 252, 308, 364 and 392

End point values	Lanadelumab 150 mg: Age 2 to <6 Years	Lanadelumab 150 mg: Age 6 to <12 Years		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	17		
Units: participants				
Baseline (Day 0): ADA Negative(-),n=4,17	4	17		
Baseline (Day 0): ADA Positive(+),n=4,17	0	0		
Baseline (Day 0): ADA+ (Neutralizing),n=4,17	0	0		
Baseline(Day0):ADA+ (Non-neutralizing),n=4,17	0	0		
Visit 4 Day 28:ADA-,n=4,14	4	13		
Visit 4 Day 28:ADA+,n=4,14	0	1		

Visit 4 Day 28:ADA+(Neutralizing),n=4,14	0	0		
Visit 4 Day 28:ADA+(Non-neutralizing),n=4,14	0	1		
Overall TP-A:ADA-,n=4,16	4	13		
Overall TP-A:ADA+,n=4,16	0	3		
Overall TP-A:ADA+(Neutralizing),n=4,16	0	1		
Overall TP-A:ADA+(Non-neutralizing),n=4,16	0	3		
Overall TP-B:ADA-,n=3,16	3	15		
Overall TP-B:ADA+,n=3,16	0	1		
Overall TP-B:ADA+(Neutralizing),n=3,16	0	0		
Overall TP-B:ADA+(Non-neutralizing),n=3,16	0	1		
Overall Study Period:ADA-,n=4,16Overall Study Peri	4	13		
Overall Study Period:ADA+,n=4,16	0	3		
Overall Study Period:ADA+(Neutralizing),n=4,16	0	1		
Overall Study Period:ADA+(Non-neutralizing),n=4,16	0	3		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Up to approximately 115 weeks	
Adverse event reporting additional description:	
The Safety Analysis Set consists of all participants who received study drug. Due to dose modification, some participants were counted in both arms, and thus the overall number of participants analyzed in arms Lanadelumab 150 mg, q4wks and Lanadelumab 150 mg, q2wks were 11 and 18, respectively.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups	
Reporting group title	Lanadelumab 150 mg, q4wks
Reporting group description:	
Participants received lanadelumab SC injection at a dose of 150 mg for q4wks with over 52-week Treatment Period (26-week Treatment Period A and 26-week Treatment Period B).	
Reporting group title	Lanadelumab 150 mg, q2wks
Reporting group description:	
Participants received lanadelumab SC injection at a dose of 150 mg for q2wks over 52-week Treatment Period (26-week Treatment Period A and 26-week Treatment Period B).	

Serious adverse events	Lanadelumab 150 mg, q4wks	Lanadelumab 150 mg, q2wks	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 11 (0.00%)	0 / 18 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Lanadelumab 150 mg, q4wks	Lanadelumab 150 mg, q2wks	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 11 (54.55%)	15 / 18 (83.33%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin papilloma			
subjects affected / exposed	0 / 11 (0.00%)	3 / 18 (16.67%)	
occurrences (all)	0	4	
Vascular disorders			

Haematoma			
subjects affected / exposed	0 / 11 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	2	
General disorders and administration site conditions			
Injection site pain			
subjects affected / exposed	2 / 11 (18.18%)	6 / 18 (33.33%)	
occurrences (all)	12	76	
Injection site erythema			
subjects affected / exposed	2 / 11 (18.18%)	2 / 18 (11.11%)	
occurrences (all)	8	21	
Injection site swelling			
subjects affected / exposed	0 / 11 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	3	
Pyrexia			
subjects affected / exposed	0 / 11 (0.00%)	2 / 18 (11.11%)	
occurrences (all)	0	2	
Administration site pain			
subjects affected / exposed	1 / 11 (9.09%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Fatigue			
subjects affected / exposed	1 / 11 (9.09%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Feeling cold			
subjects affected / exposed	0 / 11 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Injection site injury			
subjects affected / exposed	1 / 11 (9.09%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Injection site reaction			
subjects affected / exposed	1 / 11 (9.09%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	0 / 11 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	0 / 11 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	2	
Nasal congestion			
subjects affected / exposed	2 / 11 (18.18%)	0 / 18 (0.00%)	
occurrences (all)	2	0	
Oropharyngeal discomfort			
subjects affected / exposed	1 / 11 (9.09%)	0 / 18 (0.00%)	
occurrences (all)	2	0	
Epistaxis			
subjects affected / exposed	0 / 11 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Oropharyngeal pain			
subjects affected / exposed	1 / 11 (9.09%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Rhinorrhoea			
subjects affected / exposed	0 / 11 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Psychiatric disorders			
Affect lability			
subjects affected / exposed	1 / 11 (9.09%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Investigations			
Eosinophil count increased			
subjects affected / exposed	0 / 11 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Skin abrasion			
subjects affected / exposed	1 / 11 (9.09%)	3 / 18 (16.67%)	
occurrences (all)	3	13	
Joint injury			
subjects affected / exposed	2 / 11 (18.18%)	0 / 18 (0.00%)	
occurrences (all)	2	0	
Arthropod bite			
subjects affected / exposed	0 / 11 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	

Contusion			
subjects affected / exposed	0 / 11 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Fall			
subjects affected / exposed	0 / 11 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Ligament sprain			
subjects affected / exposed	0 / 11 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Limb injury			
subjects affected / exposed	0 / 11 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Skin laceration			
subjects affected / exposed	1 / 11 (9.09%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 11 (9.09%)	2 / 18 (11.11%)	
occurrences (all)	1	3	
Eye disorders			
Diplopia			
subjects affected / exposed	0 / 11 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Eye inflammation			
subjects affected / exposed	0 / 11 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 11 (9.09%)	2 / 18 (11.11%)	
occurrences (all)	1	3	
Tooth loss			
subjects affected / exposed	0 / 11 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	2	
Abdominal pain upper			
subjects affected / exposed	0 / 11 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Toothache			

subjects affected / exposed	0 / 11 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	1 / 11 (9.09%)	1 / 18 (5.56%)	
occurrences (all)	1	1	
Dermatitis allergic			
subjects affected / exposed	0 / 11 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Pruritus			
subjects affected / exposed	0 / 11 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Urticaria			
subjects affected / exposed	0 / 11 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Skin abrasion			
subjects affected / exposed	1 / 11 (9.09%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 11 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Growing pains			
subjects affected / exposed	0 / 11 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Limb discomfort			
subjects affected / exposed	0 / 11 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	1 / 11 (9.09%)	2 / 18 (11.11%)	
occurrences (all)	1	2	
Rhinitis			
subjects affected / exposed	1 / 11 (9.09%)	1 / 18 (5.56%)	
occurrences (all)	1	2	
Upper respiratory tract infection			

subjects affected / exposed	0 / 11 (0.00%)	2 / 18 (11.11%)	
occurrences (all)	0	2	
Adenoiditis			
subjects affected / exposed	1 / 11 (9.09%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Asymptomatic COVID-19			
subjects affected / exposed	1 / 11 (9.09%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
COVID-19			
subjects affected / exposed	0 / 11 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Gastroenteritis viral			
subjects affected / exposed	0 / 11 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Influenza			
subjects affected / exposed	0 / 11 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Otitis media			
subjects affected / exposed	0 / 11 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Paronychia			
subjects affected / exposed	0 / 11 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Pharyngitis streptococcal			
subjects affected / exposed	0 / 11 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Sinusitis			
subjects affected / exposed	0 / 11 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 11 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 August 2019	The primary purpose of this amendment was to make following changes: The protocol requirements for reporting Serious Adverse Events (SAEs) have been updated. Revised self-administration instructions to allow participants aged 6 years or older to self-administer lanadelumab only after they have received appropriate training and assessed by the investigator as being capable of self-treatment. Participants less than 6 years of age must have a parent/caregiver self-administer lanadelumab. Removed the requirement for eligibility to include "a family history consistent with HAE I or II, or C1q within the normal range" since these elements are not necessary. Added the requirement to exclude participants with a known hypersensitivity to the investigational product or its components as a new exclusion criterion. The assay used for HIV testing at screening has been revised to a more robust testing procedure. The volume of blood to be collected from each participant has been decreased in consideration of the pediatric population. Removed non-applicable Adverse Event (AE) guidance on "Symptoms of the Disease under Study", as all angioedema attacks are reported as AEs in this study.
22 June 2021	The primary purpose of this amendment was to make following changes: Sponsor approval and emergency contact information has been updated to reflect the current medical monitor. Individual participant participation duration was revised to clarify that maximum duration for study participation is 72 weeks. Participants receiving treatment q2wks may complete the study in 70 weeks. Revised follow-up period to 2-4 weeks as follow-up period depends on the treatment schedule. Participants receiving treatment q2wks will have a 2-week follow-up period (EOS Visit at Day 378); participants receiving treatment q4wks will have a 4-week follow-up period (EOS Visit at Day 392). The interim analysis summarizing data up to Treatment Period A has been removed as it is no longer planned. EOS/ET visit in footnote "a" was incorrectly written as Day 292. This has been corrected to Day 392. Text regarding Study DX-2930-04 as "ongoing" has been removed as this study has been completed. Severity categorization for AEs was revised to clarify a portion of the protocol template language that is incongruous with program data collection and analysis procedures in the previous HAE clinical studies.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported