Clinical trial results:
HELP Study ExtensionTM: An Open-Label Study to Evaluate the Long-Term Safety and Efficacy of DX-2930 for Prevention Against Acute Attacks of Hereditary Angioedema (HAE)

Summary

EudraCT number	2015-005255-27
Trial protocol	GB DE IT
Global end of trial date	31 October 2019

Results information

Result version number	v1 (current)
This version publication date	09 May 2020
First version publication date	09 May 2020

Trial information

Trial identification

Sponsor protocol code	DX-2930-04

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02741596
WHO universal trial number (UTN)	-
Other trial identifiers	IND: 116647

Notes:

Sponsors

Sponsor organisation name	Shire
Sponsor organisation address	300 Shire Way, Lexington, United States, MA 02421
Public contact	Study Director, Shire, 1 866-842-5335, ClinicalTransparency@shire.com
Scientific contact	Study Director, Shire, 1 866-842-5335, ClinicalTransparency@shire.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	31 October 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	31 October 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the trial was to evaluate the long-term safety of repeated subcutaneous (SC) administrations of lanadelumab (DX-2930).

Protection of trial subjects:

This study was conducted in accordance with International Council for Harmonisation of Good Clinical Practice, the principles of the Declaration of Helsinki, as well as other applicable local ethical and legal requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 May 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 147
Country: Number of subjects enrolled	Canada: 13
Country: Number of subjects enrolled	European Union: 39
Country: Number of subjects enrolled	Jordan: 13
Worldwide total number of subjects	212
EEA total number of subjects	0

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)	21
Adults (18-64 years)	180
From 65 to 84 years	11

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 43 sites across United States, Canada, Europe and Jorden between 26 May 2016 (first subject first visit) and 31 October 2019 (last subject last visit).

Pre-assignment

Screening details:

A total of 212 subjects were enrolled and received treatment in two groups (Rollover subjects [109] and Non-rollover subjects [103]). Subjects who rolled from the DX-2930-03 (2015-005255-27) study were in Rollover group and subjects who were directly enrolled into this DX-2930-04 study were in Non-rollover group.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Rollover Subjects

Arm description:

Subjects who rolled from the DX-2930-03 (2015-005255-27) study received 300 milligrams (mg) of DX-2930 subcutaneous (SC) injection on Day 0 followed by a second dose after subjects reported their first HAE attack and continued to receive repeated SC administrations of 300 mg DX-2930 every 2 weeks (q2wks) throughout the treatment period (up to 924 days). A wash-out period of a minimum of 10 days and a maximum of 18 days were required between subsequent administrations.

Arm type	Experimental
Investigational medicinal product name	Lanadelumab
Investigational medicinal product code	DX-2930
Other name	SHP643
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects received SC injection DX-2930 for q2wks up to 924 days.

Arm title	Non-rollover Subjects

Arm description:

Subjects who directly entered in to this DX-2930-04 study received 300 mg of DX-2930 SC injection on Day 0 and continued to receive SC administrations of 300 mg DX-2930 every 2 weeks throughout the treatment period (up to 924 days).

Arm type	Experimental
Investigational medicinal product name	Lanadelumab
Investigational medicinal product code	DX-2930
Other name	SHP643
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects received SC injection DX-2930 for q2wks up to 924 days.

Number of subjects in period 1	Rollover Subjects	Non-rollover Subjects
Started	109	103
Completed	31	25
Not completed	78	78
Physician decision	2	1
Subject withdrawn - to commercial product	54	63
Pregnancy	3	1
Adverse event	1	5
Subject withdrawn - Other	17	4
Unspecified	-	3
Lost to follow-up	1	1

Baseline characteristics

Reporting groups	
Reporting group title	Rollover Subjects
Reporting group description:	
Subjects who rolled from the DX-2930-03 (2015-005255-27) study received 300 milligrams (mg) of DX-2930 subcutaneous (SC) injection on Day 0 followed by a second dose after subjects reported their first HAE attack and continued to receive repeated SC administrations of 300 mg DX-2930 every 2 weeks (q2wks) throughout the treatment period (up to 924 days). A wash-out period of a minimum of 10 days and a maximum of 18 days were required between subsequent administrations.	
Reporting group title	Non-rollover Subjects
Reporting group description:	
Subjects who directly entered in to this DX-2930-04 study received 300 mg of DX-2930 SC injection on Day 0 and continued to receive SC administrations of 300 mg DX-2930 every 2 weeks throughout the treatment period (up to 924 days).	

Reporting group values	Rollover Subjects	Non-rollover Subjects	Total
Number of subjects	109	103	212
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	41.9	39.5	
standard deviation	± 14.74	± 16.71	-
Gender categorical Units: Subjects			
Female	75	68	143
Male	34	35	69
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	2	0	2
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	8	2	10
White	99	99	198
More than one race	0	1	1
Unknown or Not Reported	0	1	1
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	8	5	13
Not Hispanic or Latino	101	97	198
Unknown or Not Reported	0	1	1

End points

End points reporting groups

Reporting group title	Rollover Subjects

Reporting group description:

Subjects who rolled from the DX-2930-03 (2015-005255-27) study received 300 milligrams (mg) of DX-2930 subcutaneous (SC) injection on Day 0 followed by a second dose after subjects reported their first HAE attack and continued to receive repeated SC administrations of 300 mg DX-2930 every 2 weeks (q2wks) throughout the treatment period (up to 924 days). A wash-out period of a minimum of 10 days and a maximum of 18 days were required between subsequent administrations.

Reporting group title	Non-rollover Subjects

Reporting group description:

Subjects who directly entered in to this DX-2930-04 study received 300 mg of DX-2930 SC injection on Day 0 and continued to receive SC administrations of 300 mg DX-2930 every 2 weeks throughout the treatment period (up to 924 days).

Primary: Number of Subjects With Treatment-emergent Adverse Events (TEAEs)

End point title	Number of Subjects With Treatment-emergent Adverse Events (TEAEs)[1]

End point description:

An adverse event (AE) was any untoward medical occurrence in a clinical trial subject whether or not it appeared to had a causal relationship with the treatment administered. Treatment-emergent AEs are defined as AEs with onset at the time of or following the first exposure to open-label DX-2930 in this study, or medical conditions present prior to the start of treatment but increasing in severity or relationship at the time of or following the start of treatment.

End point type	Primary

End point timeframe:

From start of the study up to follow-up (Day 952)

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: No statistical testing was performed for the primary end point.

End point values	Rollover Subjects	Non-rollover Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	109	103		
Units: Subjects				
Subjects with any TEAE	105	101		

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of Investigator Confirmed Hereditary Angioedema (HAE) Attacks During the Treatment Period

End point title	Rate of Investigator Confirmed Hereditary Angioedema (HAE) Attacks During the Treatment Period

End point description:

HAE attack was defined as a discrete episode during which the subject progressed from no angioedema

to symptoms of angioedema. The treatment period investigator-confirmed HAE attack rate was calculated for each subject as the number of investigator-confirmed HAE attacks occurring during the treatment period (regular dosing stage of the treatment period for rollover subjects) divided by the number of days the subject contributed to the treatment period multiplied by 28 days. Rate of investigator-confirmed HAE attacks during the treatment period was reported. Safety population was analysed, which included all subjects who received any study drug after entering the DX-2930-04 study. Here, the number of subjects analyzed signifies subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Up to Day 924

End point values	Rollover Subjects	Non-rollover Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	106	103		
Units: Attacks per month				
arithmetic mean (standard deviation)	0.27 (± 0.581)	0.22 (± 0.521)		

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of Investigator-Confirmed Hereditary Angioedema (HAE) Attacks Requiring Acute Treatment During the Treatment Period

End point title	Rate of Investigator-Confirmed Hereditary Angioedema (HAE) Attacks Requiring Acute Treatment During the Treatment Period

End point description:

HAE attack was defined as a discrete episode during which the subject progressed from no angioedema to symptoms of angioedema. Rate of investigator-confirmed HAE attacks requiring acute treatment for each subject as the number of investigator-confirmed HAE attacks occurring during the treatment period (regular dosing stage of the treatment period for rollover subjects) divided by the number of days the subject contributed to the treatment period multiplied by 28 days. Safety population was analysed, which included all subjects who received any study drug after entering the DX-2930-04 study. Here, the number of subjects analyzed signifies subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Up to Day 924

End point values	Rollover Subjects	Non-rollover Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	106	103		
Units: Attacks per month				
arithmetic mean (standard deviation)	0.20 (± 0.430)	0.21 (± 0.517)		

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of Moderate or Severe Hereditary Angioedema (HAE) Attacks During the Treatment Period

End point title	Rate of Moderate or Severe Hereditary Angioedema (HAE) Attacks During the Treatment Period

End point description:

HAE attack was defined as a discrete episode during which the subject progressed from no angioedema to symptoms of angioedema. Moderate and severe investigator-confirmed HAE attacks were the attacks that were moderate or severe as per the HAE attack assessment and reporting procedures (HAARP) defined severity. The overall severity of attack was determined by the investigator using following definitions: mild (transient or mild discomfort), moderate (mild to moderate limitation in activity), severe (marked limitation in activity). Safety population was analysed, which included all subjects who received any study drug after entering the DX-2930-04 study. Here, the number of subjects analysed signifies subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Up to Day 924

End point values	Rollover Subjects	Non-rollover Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	106	103		
Units: Attacks per month				
arithmetic mean (standard deviation)	0.21 (± 0.479)	0.19 (± 0.512)		

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of High-Morbidity Hereditary Angioedema (HAE) Attacks During the Treatment Period

End point title	Rate of High-Morbidity Hereditary Angioedema (HAE) Attacks During the Treatment Period

End point description:

HAE attack was defined as a discrete episode during which the subject progressed from no angioedema to symptoms of angioedema. High-morbidity Hereditary Angioedema (HAE) attack was defined as any attack that had at least one of the following characteristics: severe, resulted in hospitalization (except hospitalization for observation lesser than [<] 24 hours), hemodynamically significant (systolic blood pressure <90 millimetre of mercury [mmHg], required intravenous hydration, or associated with syncope or near-syncope) or laryngeal edema. Number of high-morbidity HAE attacks during the treatment period was analysed and reported using the methods for the overall number of investigator-confirmed HAE attacks with the exception of the monthly line graphs. Safety population was analysed, which included all subjects who received any study drug after entering the DX-2930-04 study. Here the number of subjects analysed signifies subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Up to Day 924

End point values	Rollover Subjects	Non-rollover Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	106	103		
Units: Attacks per month				
arithmetic mean (standard deviation)	0.03 (± 0.085)	0.04 (± 0.103)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to First Investigator-Confirmed Hereditary Angioedema (HAE) Attacks During in Rollover Subjects

End point title	Time to First Investigator-Confirmed Hereditary Angioedema (HAE) Attacks During in Rollover Subjects

End point description:

HAE attack was defined as a discrete episode during which the subject progressed from no angioedema to symptoms of angioedema. Time to first investigator-confirmed HAE attack was calculated from the time of first open-label dose to the start time of the first investigator-confirmed HAE attack. Time to the first investigator-confirmed HAE attack was analysed and reported only in rollover safety population. Rollover Safety Population was analysed, which included subset of subjects who participated in the DX-2930-03 (2015-005255-27) study and received any study drug after entering the DX-2930-04 study (that is any exposure to open-label DX-2930).

End point type	Secondary

End point timeframe:

Up to Day 924

End point values	Rollover Subjects	Non-rollover Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	109	0[2]		
Units: Days				
median (inter-quartile range (Q1-Q3))	43 (18 to 97)	(to)		

Notes:

[2] - End point was planned only for rollover subjects. hence, non-rollover subjects were not evaluated.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From start of study drug administration up to follow-up (Day 952)	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups	
Reporting group title	Rollover Subjects
Reporting group description:	
Subjects who rolled from the DX-2930-03 (2015-005255-27) study received 300 milligrams (mg) of DX-2930 subcutaneous (SC) injection on Day 0 followed by a second dose after subjects reported their first HAE attack and continued to receive repeated SC administrations of 300 mg DX-2930 every 2 weeks (q2wks) throughout the treatment period (up to 924 days). A wash-out period of a minimum of 10 days and a maximum of 18 days were required between subsequent administrations.	
Reporting group title	Non-Rollover Subjects
Reporting group description:	
Subjects who directly entered in to this DX-2930-04 study received 300 mg of DX-2930 SC injection on Day 0 and continued to receive SC administrations of 300 mg DX-2930 every 2 weeks throughout the treatment period (up to 924 days).	

Serious adverse events	Rollover Subjects	Non-Rollover Subjects	
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 109 (11.01%)	9 / 103 (8.74%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Fibrosarcoma			
subjects affected / exposed	0 / 109 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Lymphoedema			
subjects affected / exposed	1 / 109 (0.92%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Ovarian cyst			

subjects affected / exposed	1 / 109 (0.92%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 109 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	1 / 109 (0.92%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Major depression			
subjects affected / exposed	1 / 109 (0.92%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal ideation			
subjects affected / exposed	1 / 109 (0.92%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Accidental exposure to product			
subjects affected / exposed	1 / 109 (0.92%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incision site inflammation			
subjects affected / exposed	0 / 109 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound dehiscence			
subjects affected / exposed	0 / 109 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cardiac disorders			
Coronary artery stenosis			
subjects affected / exposed	0 / 109 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 109 (0.92%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	0 / 109 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Hypochromic anaemia			
subjects affected / exposed	1 / 109 (0.92%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Anal fissure			
subjects affected / exposed	0 / 109 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			
subjects affected / exposed	1 / 109 (0.92%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 109 (0.92%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			

subjects affected / exposed	1 / 109 (0.92%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	1 / 109 (0.92%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Cervical spinal stenosis			
subjects affected / exposed	1 / 109 (0.92%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar spinal stenosis			
subjects affected / exposed	1 / 109 (0.92%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rheumatoid arthritis			
subjects affected / exposed	1 / 109 (0.92%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic lupus erythematosus			
subjects affected / exposed	0 / 109 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Breast abscess			
subjects affected / exposed	1 / 109 (0.92%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 109 (0.92%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Localised infection			
subjects affected / exposed	0 / 109 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis viral			
subjects affected / exposed	0 / 109 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 109 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 109 (0.00%)	1 / 103 (0.97%)	
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	Rollover Subjects	Non-Rollover Subjects	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	100 / 109 (91.74%)	96 / 103 (93.20%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	4 / 109 (3.67%)	6 / 103 (5.83%)	
occurrences (all)	9	7	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 109 (0.92%)	6 / 103 (5.83%)	
occurrences (all)	3	8	
Blood creatine phosphokinase increased			
subjects affected / exposed	7 / 109 (6.42%)	5 / 103 (4.85%)	
occurrences (all)	8	8	
Injury, poisoning and procedural complications			

Contusion			
subjects affected / exposed	8 / 109 (7.34%)	4 / 103 (3.88%)	
occurrences (all)	9	4	
Fall			
subjects affected / exposed	6 / 109 (5.50%)	3 / 103 (2.91%)	
occurrences (all)	6	3	
Ligament sprain			
subjects affected / exposed	6 / 109 (5.50%)	12 / 103 (11.65%)	
occurrences (all)	7	14	
Procedural pain			
subjects affected / exposed	7 / 109 (6.42%)	4 / 103 (3.88%)	
occurrences (all)	9	5	
Nervous system disorders			
Headache			
subjects affected / exposed	29 / 109 (26.61%)	23 / 103 (22.33%)	
occurrences (all)	70	37	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	10 / 109 (9.17%)	10 / 103 (9.71%)	
occurrences (all)	15	12	
Injection site bruising			
subjects affected / exposed	13 / 109 (11.93%)	13 / 103 (12.62%)	
occurrences (all)	21	72	
Injection site erythema			
subjects affected / exposed	16 / 109 (14.68%)	20 / 103 (19.42%)	
occurrences (all)	40	103	
Injection site pain			
subjects affected / exposed	45 / 109 (41.28%)	55 / 103 (53.40%)	
occurrences (all)	737	994	
Injection site pruritus			
subjects affected / exposed	4 / 109 (3.67%)	6 / 103 (5.83%)	
occurrences (all)	5	14	
Injection site swelling			
subjects affected / exposed	6 / 109 (5.50%)	11 / 103 (10.68%)	
occurrences (all)	49	26	
Peripheral swelling			

subjects affected / exposed	7 / 109 (6.42%)	1 / 103 (0.97%)	
occurrences (all)	11	1	
Pyrexia			
subjects affected / exposed	3 / 109 (2.75%)	8 / 103 (7.77%)	
occurrences (all)	4	8	
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	2 / 109 (1.83%)	6 / 103 (5.83%)	
occurrences (all)	2	6	
Abdominal pain			
subjects affected / exposed	11 / 109 (10.09%)	11 / 103 (10.68%)	
occurrences (all)	13	12	
Abdominal pain upper			
subjects affected / exposed	4 / 109 (3.67%)	7 / 103 (6.80%)	
occurrences (all)	4	7	
Constipation			
subjects affected / exposed	6 / 109 (5.50%)	4 / 103 (3.88%)	
occurrences (all)	6	4	
Diarrhoea			
subjects affected / exposed	13 / 109 (11.93%)	10 / 103 (9.71%)	
occurrences (all)	16	11	
Dyspepsia			
subjects affected / exposed	8 / 109 (7.34%)	3 / 103 (2.91%)	
occurrences (all)	8	3	
Nausea			
subjects affected / exposed	13 / 109 (11.93%)	9 / 103 (8.74%)	
occurrences (all)	16	14	
Toothache			
subjects affected / exposed	6 / 109 (5.50%)	5 / 103 (4.85%)	
occurrences (all)	9	6	
Vomiting			
subjects affected / exposed	7 / 109 (6.42%)	4 / 103 (3.88%)	
occurrences (all)	8	4	
Respiratory, thoracic and mediastinal disorders			

Asthma			
subjects affected / exposed	6 / 109 (5.50%)	2 / 103 (1.94%)	
occurrences (all)	6	3	
Cough			
subjects affected / exposed	7 / 109 (6.42%)	7 / 103 (6.80%)	
occurrences (all)	7	8	
Nasal congestion			
subjects affected / exposed	7 / 109 (6.42%)	2 / 103 (1.94%)	
occurrences (all)	7	2	
Oropharyngeal pain			
subjects affected / exposed	8 / 109 (7.34%)	8 / 103 (7.77%)	
occurrences (all)	9	9	
Skin and subcutaneous tissue disorders			
Dermatitis contact			
subjects affected / exposed	7 / 109 (6.42%)	3 / 103 (2.91%)	
occurrences (all)	7	3	
Pruritus			
subjects affected / exposed	6 / 109 (5.50%)	1 / 103 (0.97%)	
occurrences (all)	7	1	
Rash			
subjects affected / exposed	8 / 109 (7.34%)	5 / 103 (4.85%)	
occurrences (all)	8	5	
Urticaria			
subjects affected / exposed	7 / 109 (6.42%)	3 / 103 (2.91%)	
occurrences (all)	8	3	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	8 / 109 (7.34%)	5 / 103 (4.85%)	
occurrences (all)	9	5	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	11 / 109 (10.09%)	16 / 103 (15.53%)	
occurrences (all)	20	17	
Back pain			
subjects affected / exposed	16 / 109 (14.68%)	10 / 103 (9.71%)	
occurrences (all)	29	12	

Musculoskeletal pain			
subjects affected / exposed	8 / 109 (7.34%)	9 / 103 (8.74%)	
occurrences (all)	8	10	
Myalgia			
subjects affected / exposed	7 / 109 (6.42%)	3 / 103 (2.91%)	
occurrences (all)	10	5	
Pain in extremity			
subjects affected / exposed	12 / 109 (11.01%)	9 / 103 (8.74%)	
occurrences (all)	13	12	
Infections and infestations			
Acute sinusitis			
subjects affected / exposed	7 / 109 (6.42%)	7 / 103 (6.80%)	
occurrences (all)	10	11	
Bronchitis			
subjects affected / exposed	5 / 109 (4.59%)	8 / 103 (7.77%)	
occurrences (all)	7	10	
Gastroenteritis			
subjects affected / exposed	4 / 109 (3.67%)	11 / 103 (10.68%)	
occurrences (all)	5	14	
Gastroenteritis viral			
subjects affected / exposed	5 / 109 (4.59%)	10 / 103 (9.71%)	
occurrences (all)	5	11	
Gastrointestinal infection			
subjects affected / exposed	6 / 109 (5.50%)	4 / 103 (3.88%)	
occurrences (all)	7	4	
Influenza			
subjects affected / exposed	13 / 109 (11.93%)	9 / 103 (8.74%)	
occurrences (all)	17	10	
Otitis media			
subjects affected / exposed	6 / 109 (5.50%)	4 / 103 (3.88%)	
occurrences (all)	7	4	
Pharyngitis streptococcal			
subjects affected / exposed	3 / 109 (2.75%)	6 / 103 (5.83%)	
occurrences (all)	3	8	
Sinusitis			

subjects affected / exposed	13 / 109 (11.93%)	10 / 103 (9.71%)	
occurrences (all)	13	11	
Upper respiratory tract infection			
subjects affected / exposed	30 / 109 (27.52%)	25 / 103 (24.27%)	
occurrences (all)	51	54	
Urinary tract infection			
subjects affected / exposed	10 / 109 (9.17%)	13 / 103 (12.62%)	
occurrences (all)	12	21	
Viral upper respiratory tract infection			
subjects affected / exposed	51 / 109 (46.79%)	38 / 103 (36.89%)	
occurrences (all)	119	87	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 June 2016	The tertiary objective to characterize the pharmacokinetics (PK) and pharmacodynamics (PD) profile of lanadelumab was clarified to indicate administration would be SC. Three additional tertiary objectives were added to obtain more comprehensive information: * To evaluate safety and efficacy in the non-rollover population of switching from from long-term prophylactic (LTP) treatment to lanadelumab * To evaluate breakthrough attack characteristics while receiving lanadelumab compared to historical baseline * To evaluate subject experience with self-administration of lanadelumab including ease of SC administration of lanadelum The number of non-rollover subjects was increased from at least 50 subjects up to a maximum of 100 subjects. Enrollment of subjects 12 to 17 years age was revised to be at least 15 including the estimated 10 rollover subjects from Study DX-2930-03 (2015-005255-27). Therefore, the total enrollment for the study was updated to be at least 150, but not more than 250. The study was extended in duration from 6 months to approximately 1 year and subsequently the number of doses of study drug a subject could receive was increased. Study Activities Schedule was revised to accommodate study assessments at dosing Visits 14 through 26. Follow-up visits (following end of treatment) are now occurring at Days 264, 378, and 392 (Visits 27, 28, and 29). Efficacy endpoints were revised from mean rates to number of attacks. The study was extended in duration from 6 months to approximately 1 year and subsequently the number of doses of study drug a subject could receive was increased. Efficacy endpoints were revised from mean rates to number of attacks. The efficacy evaluation period was updated to begin at Day 0 instead of Day 14 to be consistent with the intent-to-treat analysis principle.
20 January 2017	Clarified that subjects in Study DX-2930-03 (2015-005255-27) can be consented for enrollment in Study DX-2930-04 on or after Day 168 of Study DX-2930-03 (2015-005255-27). Removed remnant text regarding the requirement to complete a 2-week washout period before entering the treatment period for non-rollover subjects on LTP for HAE. Washout period does not exist for non-rollover subjects. Removed safety analysis category called “pretreatment group” since a pretreatment period does not exist in this study.

29 June 2017	A new tertiary objective and related measurement have been added to evaluate exploratory biomarker(s) of angioedema disease-state bioactivity in blood. Additional biomarker assessments have been added to the study to evaluate the effect of lanadelumab on disease activity. A new tertiary efficacy objective and related measurement have been added to better understand the clinical response to rescue medications while on lanadelumab therapy. * Objective: To assess the clinical response of rescue medications for the treatment of acute angioedema attacks while on lanadelumab therapy (applicable for subjects >= 18 years of age) * Measurement: Subject response to rescue medications. A new tertiary objective was added to assess subjects' satisfaction with lanadelumab. * Objective: To assess treatment satisfaction * Measurement: Treatment satisfaction was to be measured using the Treatment Satisfaction Questionnaire for Medication (TSQM-9). The TSQM-9 was to be a 9-item validated instrument. The treatment period was extended from 12 to up to 30 months to accommodate the additional changes to the study described above. The requirement that each attack be confirmed by the investigator within 72 hours for non-serious AE attacks was expanded to 7 calendar days. Note: This refers only to confirmation of attacks, not reporting of serious adverse events (SAEs) or AEs. Electrocardiogram (ECG) were to be assessed through Day 364, at the end of the study, and when clinically required. The following subgroup analysis was added to the statistical section for consistency with statistical analysis used in Study DX-2930-03 (2015-005255-27): "History of laryngeal HAE attacks (history of laryngeal attack, no history of laryngeal attack)."

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported