Clinical trial results:
HELP Study®: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study to Evaluate DX-2930 For Long-Term Prophylaxis Against Acute Attacks of Hereditary Angioedema (HAE)

Summary

EudraCT number	2015-003943-20
Trial protocol	DE GB IT
Global end of trial date	13 April 2017

Results information

Result version number	v1 (current)
This version publication date	28 October 2017
First version publication date	28 October 2017

Trial information

Trial identification

Sponsor protocol code	DX-2930-03

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02586805
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Shire
Sponsor organisation address	300 Shire Way, Lexington, MA, United States, 02421
Public contact	Study Physician, Shire, 1 866-842-5335,
Scientific contact	Study Physician, Shire, 1 866-842-5335,

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	13 April 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	13 April 2017
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 efficacy of DX-2930 in preventing hereditary angioedema (HAE) attacks.

Protection of trial subjects:

This study was conducted in accordance with current applicable regulations, International Council for Harmonisation (ICH) 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	03 March 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	European Union: 29
Country: Number of subjects enrolled	Canada: 7
Country: Number of subjects enrolled	Jordan: 3
Country: Number of subjects enrolled	United States: 86
Worldwide total number of subjects	125
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)	10
Adults (18-64 years)	110
From 65 to 84 years	5

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 41 sites in the United States, United Kingdom, Italy, Germany, Canada and Jordan between 03 March 2016 (first subject first visit) and 13 April 2017 (last subject last visit).

Pre-assignment

Screening details:

A total of 159 subjects were screened and 126 subjects were randomized in the ratio of 3:2:2:2 to the placebo versus DX-2930-03 arms. Of them, 125 subjects were assigned to study treatment and one subject determined to be screen failure after randomization.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Subjects received placebo matched to DX-2930 subcutaneously (SC) once in every 2 weeks (q2wks)for 26 weeks.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects received placebo matched to DX-2930 SC for 26 weeks.

Arm title	Lanadelumab (DX-2930) 150 mg every 4 weeks

Arm description:

Subjects received 150 milligram (mg) dose of DX-2930 SC once in every 4 weeks (q4wks) and matched placebo SC q2wks between DX-2930 doses for 26 weeks.

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 DX-2930 SC for 26 weeks

Arm title	Lanadelumab (DX-2930) 300 mg every 4 weeks

Arm description:

Subjects received 300 mg dose of DX-2930 SC q4wks and matched placebo SC q2wks between DX-2930 doses for 26 weeks.

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 DX-2930 SC for 26 weeks

Arm title	Lanadelumab (DX-2930) 300 mg every 2 weeks

Arm description:

Subjects received 300 mg dose of DX-2930 SC q2wks for 26 weeks.

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 DX-2930 SC for 26 weeks

Number of subjects in period 1	Placebo	Lanadelumab (DX-2930) 150 mg every 4 weeks	Lanadelumab (DX-2930) 300 mg every 4 weeks
Started	41	28	29
Completed	35	27	26
Not completed	6	1	3
Consent withdrawn by subject	3	1	1
Physician decision	1	-	-
Adverse event, non-fatal	2	-	1
Lost to follow-up	-	-	1

Number of subjects in period 1	Lanadelumab (DX-2930) 300 mg every 2 weeks
Started	27
Completed	25
Not completed	2
Consent withdrawn by subject	2
Physician decision	-
Adverse event, non-fatal	-
Lost to follow-up	-

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Subjects received placebo matched to DX-2930 subcutaneously (SC) once in every 2 weeks (q2wks)for 26 weeks.	
Reporting group title	Lanadelumab (DX-2930) 150 mg every 4 weeks
Reporting group description:	
Subjects received 150 milligram (mg) dose of DX-2930 SC once in every 4 weeks (q4wks) and matched placebo SC q2wks between DX-2930 doses for 26 weeks.	
Reporting group title	Lanadelumab (DX-2930) 300 mg every 4 weeks
Reporting group description:	
Subjects received 300 mg dose of DX-2930 SC q4wks and matched placebo SC q2wks between DX-2930 doses for 26 weeks.	
Reporting group title	Lanadelumab (DX-2930) 300 mg every 2 weeks
Reporting group description:	
Subjects received 300 mg dose of DX-2930 SC q2wks for 26 weeks.	

Reporting group values	Placebo	Lanadelumab (DX-2930) 150 mg every 4 weeks	Lanadelumab (DX-2930) 300 mg every 4 weeks
Number of subjects	41	28	29
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	40.1	43.4	39.5
standard deviation	± 16.75	± 14.91	± 12.85
Gender categorical			
Units: Subjects			
Female	34	20	19
Male	7	8	10
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	3	1	2
Not Hispanic or Latino	38	27	27
Unknown or Not Reported	0	0	0

Reporting group values	Lanadelumab (DX-2930) 300 mg every 2 weeks	Total	
Number of subjects	27	125	
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	40.3		
standard deviation	± 13.35	-	

Gender categorical Units: Subjects			
Female	15	88	
Male	12	37	
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	3	9	
Not Hispanic or Latino	23	115	
Unknown or Not Reported	1	1	

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Subjects received placebo matched to DX-2930 subcutaneously (SC) once in every 2 weeks (q2wks)for 26 weeks.	
Reporting group title	Lanadelumab (DX-2930) 150 mg every 4 weeks
Reporting group description:	
Subjects received 150 milligram (mg) dose of DX-2930 SC once in every 4 weeks (q4wks) and matched placebo SC q2wks between DX-2930 doses for 26 weeks.	
Reporting group title	Lanadelumab (DX-2930) 300 mg every 4 weeks
Reporting group description:	
Subjects received 300 mg dose of DX-2930 SC q4wks and matched placebo SC q2wks between DX-2930 doses for 26 weeks.	
Reporting group title	Lanadelumab (DX-2930) 300 mg every 2 weeks
Reporting group description:	
Subjects received 300 mg dose of DX-2930 SC q2wks for 26 weeks.	

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

End point title	Rate of Investigator Confirmed Hereditary Angioedema (HAE) Attacks During 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 was analyzed using a generalized linear model (GLM) for count data assuming a poisson distribution with a log link function and Pearson chi-square scaling of standard errors to account for potential overdispersion. Intent-to-treat (ITT) population included all randomized subjects who received any exposure to the investigational product.	
End point type	Primary
End point timeframe:	
From Day 0 to Day 182	

End point values	Placebo	Lanadelumab (DX-2930) 150 mg every 4 weeks	Lanadelumab (DX-2930) 300 mg every 4 weeks	Lanadelumab (DX-2930) 300 mg every 2 weeks
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	41	28	29	27
Units: Attacks per 4 weeks				
least squares mean (confidence interval 95%)				
Attacks per 4 weeks	1.967 (1.640 to 2.358)	0.480 (0.313 to 0.735)	0.526 (0.358 to 0.771)	0.257 (0.145 to 0.458)

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Results from Poisson regression model with fixed effects for treatment group (categorical) and normalized baseline attack rate (continuous), and logarithm of time in days each subject was observed during treatment period as offset variable in model. Pearson chi-square scaling of standards errors was employed to account for potential overdispersion. Mean estimates are Least Squares (LS) means. Percent (%) change in mean rate corresponds to 100% * (estimated mean rate ratio - 1).

Comparison groups	Lanadelumab (DX-2930) 150 mg every 4 weeks v Placebo
Number of subjects included in analysis	69
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001 [1]
Method	Chi-squared
Parameter estimate	% change in mean rate (vs placebo)
Point estimate	-75.609
Confidence interval	
level	95 %
sides	2-sided
lower limit	-84.65
upper limit	-61.243

Notes:

[1] - p-values are adjusted for multiple testing.

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

Results from Poisson regression model with fixed effects for treatment group (categorical) and normalized baseline attack rate (continuous), and logarithm of time in days each subject was observed during treatment period as offset variable in model. Pearson chi-square scaling of standards errors was employed to account for potential overdispersion. Mean estimates are Least Squares (LS) means. Percent (%) change in mean rate corresponds to 100% * (estimated mean rate ratio - 1).

Comparison groups	Lanadelumab (DX-2930) 300 mg every 4 weeks v Placebo
Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001 [2]
Method	Chi-squared
Parameter estimate	% change in mean rate (vs placebo)
Point estimate	-73.271
Confidence interval	
level	95 %
sides	2-sided
lower limit	-82.379
upper limit	-59.456

Notes:

[2] - p-values are adjusted for multiple testing.

Statistical analysis title	Statistical analysis 3

Statistical analysis description:

Results from Poisson regression model with fixed effects for treatment group (categorical) and normalized baseline attack rate (continuous), and logarithm of time in days each subject was observed during treatment period as offset variable in model. Pearson chi-square scaling of standards errors was employed to account for potential overdispersion. Mean estimates are Least Squares (LS) means. Percent (%) change in mean rate corresponds to 100% * (estimated mean rate ratio - 1).

Comparison groups	Lanadelumab (DX-2930) 300 mg every 2 weeks v Placebo
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001 [3]
Method	Chi-squared
Parameter estimate	% change in mean rate (vs placebo)
Point estimate	-86.921
Confidence interval	
level	95 %
sides	2-sided
lower limit	-92.828
upper limit	-76.15

Notes:

[3] - p-values are adjusted for multiple testing.

Secondary: Rate of Investigator Confirmed Hereditary Angioedema (HAE) Attack Requiring Acute Treatment

End point title	Rate of Investigator Confirmed Hereditary Angioedema (HAE) Attack Requiring Acute Treatment

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 attack were performed using the GLM for count data assuming a poisson distribution with a log link function and Pearson chi-square scaling of standard errors to account for potential overdispersion. ITT population included all randomized subjects who received any exposure to the investigational product.

End point type	Secondary

End point timeframe:

From Day 0 to Day 182

End point values	Placebo	Lanadelumab (DX-2930) 150 mg every 4 weeks	Lanadelumab (DX-2930) 300 mg every 4 weeks	Lanadelumab (DX-2930) 300 mg every 2 weeks
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	41	28	29	27
Units: Attacks per 4 weeks				
least squares mean (confidence interval 95%)				
Attacks per 4 weeks	1.637 (1.337 to 2.005)	0.314 (0.184 to 0.535)	0.423 (0.276 to 0.648)	0.208 (0.109 to 0.396)

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Results from Poisson regression model with fixed effects for treatment group (categorical) and normalized baseline attack rate (continuous), and logarithm of time in days each subject was observed during treatment period as offset variable in model. Pearson chi-square scaling of standards errors was employed to account for potential overdispersion. Mean estimates are Least Squares (LS) means.

Percent (%) change in mean rate corresponds to 100% * (estimated mean rate ratio - 1).

Comparison groups	Placebo v Lanadelumab (DX-2930) 150 mg every 4 weeks
Number of subjects included in analysis	69
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001 [4]
Method	Chi-squared
Parameter estimate	% change in mean rate (vs placebo)
Point estimate	-80.842
Confidence interval	
level	95 %
sides	2-sided
lower limit	-89.169
upper limit	-66.114

Notes:

[4] - p-values are adjusted for multiple testing.

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

Results from Poisson regression model with fixed effects for treatment group (categorical) and normalized baseline attack rate (continuous), and logarithm of time in days each subject was observed during treatment period as offset variable in model. Pearson chi-square scaling of standards errors was employed to account for potential overdispersion. Mean estimates are Least Squares (LS) means. Percent (%) change in mean rate corresponds to 100% * (estimated mean rate ratio - 1).

Comparison groups	Placebo v Lanadelumab (DX-2930) 300 mg every 4 weeks
Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001 [5]
Method	Chi-squared
Parameter estimate	% change in mean rate (vs placebo)
Point estimate	-74.169
Confidence interval	
level	95 %
sides	2-sided
lower limit	-83.733
upper limit	-58.983

Notes:

[5] - p-values are adjusted for multiple testing.

Statistical analysis title	Statistical analysis 3

Statistical analysis description:

Results from Poisson regression model with fixed effects for treatment group (categorical) and normalized baseline attack rate (continuous), and logarithm of time in days each subject was observed during treatment period as offset variable in model. Pearson chi-square scaling of standards errors was employed to account for potential overdispersion. Mean estimates are Least Squares (LS) means. Percent (%) change in mean rate corresponds to 100% * (estimated mean rate ratio - 1).

Comparison groups	Placebo v Lanadelumab (DX-2930) 300 mg every 2 weeks

Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001 [6]
Method	Chi-squared
Parameter estimate	% change in mean rate (vs placebo)
Point estimate	-87.299
Confidence interval	
level	95 %
sides	2-sided
lower limit	-93.494
upper limit	-75.204

Notes:

[6] - p-values are adjusted for multiple testing.

Secondary: Rate of Moderate or Severe Investigator Confirmed Hereditary Angioedema (HAE) Attacks

End point title	Rate of Moderate or Severe Investigator Confirmed Hereditary Angioedema (HAE) Attacks

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). ITT population included all randomized subjects who received any exposure to the investigational product.

End point type	Secondary

End point timeframe:

From Day 0 to Day 182

End point values	Placebo	Lanadelumab (DX-2930) 150 mg every 4 weeks	Lanadelumab (DX-2930) 300 mg every 4 weeks	Lanadelumab (DX-2930) 300 mg every 2 weeks
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	41	28	29	27
Units: Attacks per 4 weeks				
least squares mean (confidence interval 95%)				
Attacks per 4 weeks	1.216 (0.971 to 1.522)	0.359 (0.221 to 0.581)	0.325 (0.199 to 0.529)	0.202 (0.106 to 0.386)

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Results from Poisson regression model with fixed effects for treatment group (categorical) and normalized baseline attack rate (continuous), and logarithm of time in days each subject was observed during treatment period as offset variable in model. Pearson chi-square scaling of standards errors was

employed to account for potential overdispersion. Mean estimates are Least Squares (LS) means. Percent (%) change in mean rate corresponds to 100% * (estimated mean rate ratio - 1).

Comparison groups	Placebo v Lanadelumab (DX-2930) 150 mg every 4 weeks
Number of subjects included in analysis	69
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001 [7]
Method	Chi-squared
Parameter estimate	% change in mean rate (vs placebo)
Point estimate	-70.497
Confidence interval	
level	95 %
sides	2-sided
lower limit	-82.696
upper limit	-49.699

Notes:

[7] - p-values are adjusted for multiple testing.

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

Results from Poisson regression model with fixed effects for treatment group (categorical) and normalized baseline attack rate (continuous), and logarithm of time in days each subject was observed during treatment period as offset variable in model. Pearson chi-square scaling of standards errors was employed to account for potential overdispersion. Mean estimates are Least Squares (LS) means. Percent (%) change in mean rate corresponds to 100% * (estimated mean rate ratio - 1).

Comparison groups	Placebo v Lanadelumab (DX-2930) 300 mg every 4 weeks
Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001 [8]
Method	Chi-squared
Parameter estimate	% change in mean rate (vs placebo)
Point estimate	-73.285
Confidence interval	
level	95 %
sides	2-sided
lower limit	-84.316
upper limit	-54.496

Notes:

[8] - p-values are adjusted for multiple testing.

Statistical analysis title	Statistical analysis 3

Statistical analysis description:

Results from Poisson regression model with fixed effects for treatment group (categorical) and normalized baseline attack rate (continuous), and logarithm of time in days each subject was observed during treatment period as offset variable in model. Pearson chi-square scaling of standards errors was employed to account for potential overdispersion. Mean estimates are Least Squares (LS) means. Percent (%) change in mean rate corresponds to 100% * (estimated mean rate ratio - 1).

Comparison groups	Placebo v Lanadelumab (DX-2930) 300 mg every 2 weeks

Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001 [9]
Method	Chi-squared
Parameter estimate	% change in mean rate (vs placebo)
Point estimate	-83.394
Confidence interval	
level	95 %
sides	2-sided
lower limit	-91.618
upper limit	-67.099

Notes:

[9] - p-values are adjusted for multiple testing.

Secondary: Rate of Investigator confirmed Hereditary Angioedema (HAE) Attacks During Day 14 Through Day 182

End point title	Rate of Investigator confirmed Hereditary Angioedema (HAE) Attacks During Day 14 Through Day 182

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 were analyzed by poisson regression during day 14 after study drug administration through day 182. ITT population included all randomized subjects who received any exposure to the investigational product.

End point type	Secondary

End point timeframe:

From Day 14 to Day 182

End point values	Placebo	Lanadelumab (DX-2930) 150 mg every 4 weeks	Lanadelumab (DX-2930) 300 mg every 4 weeks	Lanadelumab (DX-2930) 300 mg every 2 weeks
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	41	28	29	27
Units: Attacks per 4 weeks				
least squares mean (confidence interval 95%)				
Attacks per 4 weeks	1.988 (1.652 to 2.391)	0.445 (0.283 to 0.698)	0.489 (0.326 to 0.734)	0.218 (0.115 to 0.414)

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Results from Poisson regression model with fixed effects for treatment group (categorical) and normalized baseline attack rate (continuous), and logarithm of time in days each subject was observed during treatment period as offset variable in model. Pearson chi-square scaling of standards errors was employed to account for potential overdispersion. Mean estimates are Least Squares (LS) means. Percent (%) change in mean rate corresponds to 100% * (estimated mean rate ratio - 1).

Comparison groups	Placebo v Lanadelumab (DX-2930) 150 mg every 4 weeks

Number of subjects included in analysis	69
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001 [10]
Method	Chi-squared
Parameter estimate	% change in mean rate (vs placebo)
Point estimate	-77.622
Confidence interval	
level	95 %
sides	2-sided
lower limit	-86.253
upper limit	-63.572

Notes:

[10] - p-values are adjusted for multiple testing.

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

Results from Poisson regression model with fixed effects for treatment group (categorical) and normalized baseline attack rate (continuous), and logarithm of time in days each subject was observed during treatment period as offset variable in model. Pearson chi-square scaling of standards errors was employed to account for potential overdispersion. Mean estimates are Least Squares (LS) means. Percent (%) change in mean rate corresponds to 100% * (estimated mean rate ratio - 1).

Comparison groups	Placebo v Lanadelumab (DX-2930) 300 mg every 4 weeks
Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001 [11]
Method	Chi-squared
Parameter estimate	% change in mean rate (vs placebo)
Point estimate	-75.377
Confidence interval	
level	95 %
sides	2-sided
lower limit	-84.115
upper limit	-61.833

Notes:

[11] - p-values are adjusted for multiple testing.

Statistical analysis title	Statistical analysis 3

Statistical analysis description:

Results from Poisson regression model with fixed effects for treatment group (categorical) and normalized baseline attack rate (continuous), and logarithm of time in days each subject was observed during treatment period as offset variable in model. Pearson chi-square scaling of standards errors was employed to account for potential overdispersion. Mean estimates are Least Squares (LS) means. Percent (%) change in mean rate corresponds to 100% * (estimated mean rate ratio - 1).

Comparison groups	Placebo v Lanadelumab (DX-2930) 300 mg every 2 weeks
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001 [12]
Method	Chi-squared
Parameter estimate	% change in mean rate (vs placebo)
Point estimate	-89.008

Confidence interval	
level	95 %
sides	2-sided
lower limit	-94.325
upper limit	-78.707

Notes:

[12] - p-values are adjusted for multiple testing.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From start of study drug administration up to Day 238

Adverse event reporting additional description:

Adverse events were collected over the entire treatment period and were assigned to the treatment group without regard to the type of injection (that is placebo or active drug in the 150 mg q4wk and 300 mg q4wk groups).

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Placebo

Reporting group description:

Subjects received placebo matched to DX-2930 SC q2wks for 26 weeks.

Reporting group title	Lanadelumab (DX-2930) 150 mg every 4 weeks

Reporting group description:

Subjects received 150 mg dose of DX-2930 SC q4wks and matched placebo SC q2wks between DX-2930 doses for 26 weeks.

Reporting group title	Lanadelumab (DX-2930) 300 mg every 4 weeks

Reporting group description:

Subjects received 300 mg dose of DX-2930 SC q4wks and matched placebo SC q2wks between DX-2930 doses for 26 weeks.

Reporting group title	Lanadelumab (DX-2930) 300 mg every 2 weeks

Reporting group description:

Subjects received 300 mg dose of DX-2930 SC q2wks for 26 weeks.

Serious adverse events	Placebo	Lanadelumab (DX-2930) 150 mg every 4 weeks	Lanadelumab (DX-2930) 300 mg every 4 weeks
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 41 (2.44%)	0 / 28 (0.00%)	3 / 29 (10.34%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Meniscus injury			
subjects affected / exposed	0 / 41 (0.00%)	0 / 28 (0.00%)	1 / 29 (3.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			
Hereditary angioedema			

subjects affected / exposed	1 / 41 (2.44%)	0 / 28 (0.00%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Bipolar ii disorder			
subjects affected / exposed	0 / 41 (0.00%)	0 / 28 (0.00%)	1 / 29 (3.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Catheter site infection			
subjects affected / exposed	0 / 41 (0.00%)	0 / 28 (0.00%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	0 / 41 (0.00%)	0 / 28 (0.00%)	1 / 29 (3.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Lanadelumab (DX-2930) 300 mg every 2 weeks		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 27 (7.41%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Meniscus injury			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Congenital, familial and genetic disorders			
Hereditary angioedema			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			

Bipolar ii disorder			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Catheter site infection			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pyelonephritis			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Placebo	Lanadelumab (DX-2930) 150 mg every 4 weeks	Lanadelumab (DX-2930) 300 mg every 4 weeks
Total subjects affected by non-serious adverse events			
subjects affected / exposed	40 / 41 (97.56%)	25 / 28 (89.29%)	26 / 29 (89.66%)
Injury, poisoning and procedural complications			
Procedural pain			
subjects affected / exposed	4 / 41 (9.76%)	0 / 28 (0.00%)	1 / 29 (3.45%)
occurrences (all)	4	0	1
Congenital, familial and genetic disorders			
Hereditary angioedema			
subjects affected / exposed	40 / 41 (97.56%)	17 / 28 (60.71%)	20 / 29 (68.97%)
occurrences (all)	577	84	108
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 41 (0.00%)	1 / 28 (3.57%)	3 / 29 (10.34%)
occurrences (all)	0	2	5
Headache			
subjects affected / exposed	8 / 41 (19.51%)	3 / 28 (10.71%)	5 / 29 (17.24%)
occurrences (all)	10	10	8
Migraine			

subjects affected / exposed	4 / 41 (9.76%)	2 / 28 (7.14%)	0 / 29 (0.00%)
occurrences (all)	4	5	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 41 (2.44%)	0 / 28 (0.00%)	0 / 29 (0.00%)
occurrences (all)	1	0	0
Injection site bruising			
subjects affected / exposed	0 / 41 (0.00%)	3 / 28 (10.71%)	2 / 29 (6.90%)
occurrences (all)	0	5	2
Injection site discomfort			
subjects affected / exposed	0 / 41 (0.00%)	0 / 28 (0.00%)	2 / 29 (6.90%)
occurrences (all)	0	0	13
Injection site erythema			
subjects affected / exposed	1 / 41 (2.44%)	4 / 28 (14.29%)	2 / 29 (6.90%)
occurrences (all)	1	23	6
Injection site haematoma			
subjects affected / exposed	3 / 41 (7.32%)	1 / 28 (3.57%)	1 / 29 (3.45%)
occurrences (all)	3	1	2
Injection site haemorrhage			
subjects affected / exposed	1 / 41 (2.44%)	1 / 28 (3.57%)	0 / 29 (0.00%)
occurrences (all)	7	2	0
Injection site pain			
subjects affected / exposed	12 / 41 (29.27%)	13 / 28 (46.43%)	9 / 29 (31.03%)
occurrences (all)	71	123	68
Injection site paraesthesia			
subjects affected / exposed	0 / 41 (0.00%)	2 / 28 (7.14%)	0 / 29 (0.00%)
occurrences (all)	0	2	0
Injection site pruritus			
subjects affected / exposed	0 / 41 (0.00%)	1 / 28 (3.57%)	2 / 29 (6.90%)
occurrences (all)	0	1	2
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	1 / 41 (2.44%)	2 / 28 (7.14%)	0 / 29 (0.00%)
occurrences (all)	1	3	0
Abdominal pain			

subjects affected / exposed	2 / 41 (4.88%)	1 / 28 (3.57%)	2 / 29 (6.90%)
occurrences (all)	2	1	3
Abdominal pain upper			
subjects affected / exposed	4 / 41 (9.76%)	2 / 28 (7.14%)	0 / 29 (0.00%)
occurrences (all)	4	2	0
Diarrhoea			
subjects affected / exposed	2 / 41 (4.88%)	3 / 28 (10.71%)	0 / 29 (0.00%)
occurrences (all)	2	3	0
Nausea			
subjects affected / exposed	0 / 41 (0.00%)	1 / 28 (3.57%)	0 / 29 (0.00%)
occurrences (all)	0	1	0
Paraesthesia oral			
subjects affected / exposed	0 / 41 (0.00%)	0 / 28 (0.00%)	0 / 29 (0.00%)
occurrences (all)	0	0	0
Toothache			
subjects affected / exposed	0 / 41 (0.00%)	2 / 28 (7.14%)	1 / 29 (3.45%)
occurrences (all)	0	4	1
Vomiting			
subjects affected / exposed	1 / 41 (2.44%)	2 / 28 (7.14%)	0 / 29 (0.00%)
occurrences (all)	1	2	0
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	3 / 41 (7.32%)	0 / 28 (0.00%)	0 / 29 (0.00%)
occurrences (all)	3	0	0
Skin and subcutaneous tissue disorders			
Dermatitis contact			
subjects affected / exposed	0 / 41 (0.00%)	1 / 28 (3.57%)	2 / 29 (6.90%)
occurrences (all)	0	1	2
Pruritus			
subjects affected / exposed	0 / 41 (0.00%)	0 / 28 (0.00%)	0 / 29 (0.00%)
occurrences (all)	0	0	0
Rash			
subjects affected / exposed	2 / 41 (4.88%)	1 / 28 (3.57%)	3 / 29 (10.34%)
occurrences (all)	2	2	3
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	1 / 41 (2.44%)	0 / 28 (0.00%)	2 / 29 (6.90%)
occurrences (all)	2	0	2
Back pain			
subjects affected / exposed	4 / 41 (9.76%)	1 / 28 (3.57%)	0 / 29 (0.00%)
occurrences (all)	7	1	0
Musculoskeletal pain			
subjects affected / exposed	0 / 41 (0.00%)	2 / 28 (7.14%)	1 / 29 (3.45%)
occurrences (all)	0	2	1
Myalgia			
subjects affected / exposed	0 / 41 (0.00%)	1 / 28 (3.57%)	0 / 29 (0.00%)
occurrences (all)	0	1	0
Neck pain			
subjects affected / exposed	1 / 41 (2.44%)	1 / 28 (3.57%)	0 / 29 (0.00%)
occurrences (all)	1	1	0
Pain in extremity			
subjects affected / exposed	1 / 41 (2.44%)	2 / 28 (7.14%)	0 / 29 (0.00%)
occurrences (all)	1	2	0
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	3 / 41 (7.32%)	1 / 28 (3.57%)	0 / 29 (0.00%)
occurrences (all)	3	1	0
Hordeolum			
subjects affected / exposed	0 / 41 (0.00%)	0 / 28 (0.00%)	0 / 29 (0.00%)
occurrences (all)	0	0	0
Otitis externa			
subjects affected / exposed	0 / 41 (0.00%)	2 / 28 (7.14%)	0 / 29 (0.00%)
occurrences (all)	0	2	0
Rhinitis			
subjects affected / exposed	2 / 41 (4.88%)	0 / 28 (0.00%)	2 / 29 (6.90%)
occurrences (all)	2	0	3
Sinusitis			
subjects affected / exposed	1 / 41 (2.44%)	1 / 28 (3.57%)	0 / 29 (0.00%)
occurrences (all)	1	1	0
Upper respiratory tract infection			

subjects affected / exposed	2 / 41 (4.88%)	0 / 28 (0.00%)	2 / 29 (6.90%)
occurrences (all)	3	0	2
Urinary tract infection			
subjects affected / exposed	1 / 41 (2.44%)	2 / 28 (7.14%)	1 / 29 (3.45%)
occurrences (all)	1	2	1
Viral upper respiratory tract infection			
subjects affected / exposed	11 / 41 (26.83%)	3 / 28 (10.71%)	7 / 29 (24.14%)
occurrences (all)	16	5	10

Non-serious adverse events	Lanadelumab (DX-2930) 300 mg every 2 weeks		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	23 / 27 (85.19%)		
Injury, poisoning and procedural complications			
Procedural pain			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Congenital, familial and genetic disorders			
Hereditary angioedema			
subjects affected / exposed	15 / 27 (55.56%)		
occurrences (all)	45		
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Headache			
subjects affected / exposed	9 / 27 (33.33%)		
occurrences (all)	18		
Migraine			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 27 (7.41%)		
occurrences (all)	2		
Injection site bruising			

subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Injection site discomfort			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	10		
Injection site erythema			
subjects affected / exposed	2 / 27 (7.41%)		
occurrences (all)	7		
Injection site haematoma			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Injection site haemorrhage			
subjects affected / exposed	2 / 27 (7.41%)		
occurrences (all)	11		
Injection site pain			
subjects affected / exposed	14 / 27 (51.85%)		
occurrences (all)	67		
Injection site paraesthesia			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Injection site pruritus			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Abdominal pain			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Abdominal pain upper			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Diarrhoea			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	2		

Nausea subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 2		
Paraesthesia oral subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 2		
Toothache subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 1		
Vomiting subjects affected / exposed occurrences (all)	0 / 27 (0.00%) 0		
Respiratory, thoracic and mediastinal disorders Oropharyngeal pain subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 1		
Skin and subcutaneous tissue disorders Dermatitis contact subjects affected / exposed occurrences (all)	0 / 27 (0.00%) 0		
Pruritus subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 2		
Rash subjects affected / exposed occurrences (all)	0 / 27 (0.00%) 0		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	0 / 27 (0.00%) 0		
Back pain subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 1		
Musculoskeletal pain subjects affected / exposed occurrences (all)	0 / 27 (0.00%) 0		

Myalgia			
subjects affected / exposed	3 / 27 (11.11%)		
occurrences (all)	3		
Neck pain			
subjects affected / exposed	2 / 27 (7.41%)		
occurrences (all)	3		
Pain in extremity			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Hordeolum			
subjects affected / exposed	2 / 27 (7.41%)		
occurrences (all)	2		
Otitis externa			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Rhinitis			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Sinusitis			
subjects affected / exposed	2 / 27 (7.41%)		
occurrences (all)	2		
Upper respiratory tract infection			
subjects affected / exposed	2 / 27 (7.41%)		
occurrences (all)	2		
Urinary tract infection			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Viral upper respiratory tract infection			
subjects affected / exposed	10 / 27 (37.04%)		
occurrences (all)	12		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 December 2015	Updated list of inactive ingredients and description of treatments and updates were made on components of both lanadelumab and placebo; Updated description of run-in period; Updated individual study subject stopping rules; Expected number of subjects aged 12 to 17 to be enrolled in the study was added; Updated blinding and unblinding text; Updated order of the sample collections when multiple sample types were collected at the same time point; Updated study day through which treatment emergent adverse events (AEs) were defined; Updated subject withdrawal text.
21 April 2016	Modified exclusion criteria to exclude subjects who may have participated in a prior study to eliminate non-naive from the study analysis; Modified inclusion criteria for contraception requirements; Four additional pregnancy tests were scheduled for monitoring of pregnancy during treatment; Correction was made in study activities footnote #7 on pregnancy test at final follow-up visit; Clarified that no interim analysis was planned; An independent Data Safety Monitoring Board (DSMB) replaced the internal study safety committee (SSC), and its procedures were clarified; Period for reporting HAE attacks after the final follow-up visit was clarified; Collection of HAE attack data was clarified; Tertiary objective was rephrased for clarity; Four additional quality of life (QoL) assessments using the Angioedema-Quality of Life (AE-QoL) Questionnaire were added; A safety assessment parameter, 12-lead electrocardiogram (ECG), was added at Visit 16/Day 238 in the tables for "study activities schedules"; Efficacy evaluation period was updated to begin at Day 0 instead of Day 14; Description of primary endpoint was modified for assessment during the efficacy evaluation period rather than per week for consistency with the statistical model; Secondary endpoint was modified and removed from the rank order and was to be considered an exploratory endpoint; Description of the secondary endpoints was modified for assessment during efficacy evaluation period rather than per week to for consistency with the statistical model; Statistical methods were updated; Sample size determination was updated to be consistent with the updated statistical methods; A new section, Premature Closure of the Study, was added to include conditions that may warrant termination of the study or site; A new section, Data Handling Considerations, was added to include specifics regarding handling of data to prevent potential unblinding.
09 January 2017	An efficacy measure was added to rank ordered secondary efficacy endpoints for inclusion in the multiple testing procedure.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported