Supplementary Online Content

Banerji A, Riedl MA, Bernstein JA, et al. Effect of lanadelumab compared with placebo on prevention of hereditary angioedema attacks: a randomized clinical trial. *JAMA*. doi:10.1001/jama.2018.16501

This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods 1. Inclusion and Exclusion Criteria

Inclusion Criteria

Each patient must have met the following criteria to be enrolled in this study:

1. Males and females ≥12 years of age at the time of screening.
2. Documented diagnosis of hereditary angioedema (type I or II) based upon all of the following:
    - Documented clinical history consistent with hereditary angioedema (subcutaneous or mucosal, nonpruritic swelling episodes without accompanying urticaria).
    - Diagnostic testing results obtained during screening that confirmed hereditary angioedema type I or II:
        - C1 inhibitor functional level <40% of the normal level. Patients with functional C1 inhibitor level 40%-50% of the normal level may have been enrolled if they also had a C4 level below the normal range. Patients may have begun participating in the run-in period before these diagnostic results were available. Patients may have been retested if results were incongruent with clinical history or were believed by the investigator to have been confounded by recent long-term prophylaxis use.
        - At least 1 of the following: ≤30 years of age at reported onset of first angioedema symptoms, a family history consistent with hereditary angioedema type I or II, or C1q within the normal range.
3. Experienced a baseline rate of ≥1 investigator-confirmed hereditary angioedema attack per 4 weeks as confirmed during the run-in period.
4. Adult patients and caregivers of patients <18 years of age willing and able to read, understand, and sign an informed consent form. Patients 12-17 years of age, whose caregiver provided informed consent, willing and able to read, understand, and sign an assent form.
5. Males and females who were fertile and sexually active must have adhered to contraception requirements for the duration of the study as follows:
    - Females of childbearing potential must have agreed to be abstinent or it was recommended to use highly effective forms of contraception from screening through 30 days after the final study visit. This included progestin-only oral contraceptive associated with inhibition of ovulation (oral, injectable, or implantable), intrauterine device (all types), or intrauterine hormone releasing systems. Notes: (1) A female whose male partner had a vasectomy must have agreed to use 1 additional form of medically acceptable contraception; and (2) Use of a male condom with or without spermicide or cervical cap, diaphragm or sponge with spermicide, or a combination (double-barrier methods) was not considered highly effective.
    - Females of nonchildbearing potential, defined as surgically sterile (status post hysterectomy, bilateral oophorectomy, or bilateral tubal ligation) or postmenopausal for ≥12 months did not require contraception during the study.
    - Males, including males who were surgically sterile (post vasectomy), with female partners of childbearing potential must have agreed to be abstinent or use a medically acceptable form of contraception from screening through 60 days after the final study visit.

Exclusion Criteria

Patients who met any of the following criteria were excluded from the study:

1. Concomitant diagnosis of another form of chronic recurrent angioedema, such as acquired angioedema, hereditary angioedema with normal C1 inhibitor (also known as hereditary angioedema type III), idiopathic angioedema, or recurrent angioedema associated with urticaria.

2. Participated in a prior lanadelumab study.
3. Dosed with an investigational drug or exposure to an investigational device within 4 weeks of screening.
4. Exposed to angiotensin-converting enzyme inhibitors or any estrogen-containing medications with systemic absorption (such as oral contraceptives or hormonal replacement therapy) within 4 weeks of screening.
5. Exposed to androgens (eg, stanozolol, danazol, oxandrolone, methyltestosterone, or testosterone) within 2 weeks of entering the run-in period.
6. Used long-term prophylactic therapy for hereditary angioedema (C1 inhibitor, attenuated androgens, or antifibrinolytics) within 2 weeks of entering the run-in period.
7. Used short-term prophylactic therapy for hereditary angioedema within 7 days of entering the run-in period. Short-term prophylaxis was defined as C1 inhibitor, attenuated androgens, or antifibrinolytics used to avoid angioedema complications from medically indicated procedures.
8. Any of the following liver function test abnormalities: alanine aminotransferase >3 × upper limit of normal, or aspartate aminotransferase >3 × upper limit of normal, or total bilirubin >2 × upper limit of normal (unless the bilirubin elevation was a result of Gilbert's syndrome).
9. Pregnancy or breastfeeding.
10. Patient had any condition that, in the opinion of the investigator or sponsor, could have compromised their safety or compliance, precluded successful conduct of the study, or interfered with interpretation of the results (eg, history of substance abuse or dependence, significant pre-existing illness or other major comorbidity that the investigator considered could have confounded the interpretation of study results).

eMethods 2. Criteria for Investigator-Confirmed Hereditary Angioedema Attacks

To be confirmed as a hereditary angioedema attack, the event must have had symptoms or signs consistent with an attack in ≥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.

Despite the presence of these symptoms, the investigator may still have clinically determined that the event did not represent a hereditary angioedema attack if there were features that strongly refuted such a diagnosis. For example, the reported event was accompanied by symptoms that were not consistent with a hereditary angioedema attack (eg, urticaria), the reported event persisted well beyond the typical time course of a hereditary angioedema attack, or there was a likely alternate etiology for the event (eg, the patient's abdominal symptoms were attributable to a viral gastroenteritis outbreak in the household). To be counted as a unique attack distinct from the previous attack, the new symptoms must have occurred ≥24 hours after resolution of the symptoms from the prior attack.

eMethods 3. Treatment Period Dosing Schedule

Dose No.	Dose Day/Week	Lanadelumab 150 mg Every 4 Weeks	Lanadelumab 300 mg Every 4 Weeks	Lanadelumab 300 mg Every 2 Weeks	Placebo
1	Day 0/week 0	Lanadelumab	Lanadelumab	Lanadelumab	Placebo
2	Day 14/week 2	Placebo	Placebo	Lanadelumab	Placebo
3	Day 28/week 4	Lanadelumab	Lanadelumab	Lanadelumab	Placebo
4	Day 42/week 6	Placebo	Placebo	Lanadelumab	Placebo
5	Day 56/week 8	Lanadelumab	Lanadelumab	Lanadelumab	Placebo
6	Day 70/week 10	Placebo	Placebo	Lanadelumab	Placebo
7	Day 84/week 12	Lanadelumab	Lanadelumab	Lanadelumab	Placebo
8	Day 98/week 14	Placebo	Placebo	Lanadelumab	Placebo
9	Day 112/week 16	Lanadelumab	Lanadelumab	Lanadelumab	Placebo
10	Day 126/week 18	Placebo	Placebo	Lanadelumab	Placebo
11	Day 140/week 20	Lanadelumab	Lanadelumab	Lanadelumab	Placebo
12	Day 154/week 22	Placebo	Placebo	Lanadelumab	Placebo
13	Day 168/week 24	Lanadelumab	Lanadelumab	Lanadelumab	Placebo
–	Day 182/week 26	No dose	No dose	No dose	No dose

Note: lanadelumab drug product was provided at a nominal concentration of 150-mg/mL solution. For each 300 mg dose of lanadelumab, each patient received a total of 2 mL, divided into 2 separate 1.0-mL subcutaneous injections of lanadelumab. For each 150 mg dose of lanadelumab, each patient received 2 separate 1.0-mL subcutaneous injections where 1 injection was lanadelumab and the other was placebo. For each placebo dose, each patient received 2 separate 1.0-mL subcutaneous injections of placebo.

eMethods 4. Assessment of Attacks and Adverse Events

During the study, patients were instructed to contact the study site within 72 hours of the onset of an attack. Attack details were assessed by trained site personnel following HAE Attack Assessment and Reporting Procedures (see protocol in Supplement 1) and confirmed by the site investigator. Patients were asked to provide the following information when reporting an attack:

- Date and time symptoms of an attack were first experienced
- Description of symptoms experienced, including location(s)
- Impact on activity and whether any assistance or medical intervention was required, including hospitalizations or emergency department visits
- Any medications used to treat the attacks
- If the attack resolved, date and time the patient was no longer experiencing symptoms

Attack severity was rated (per the Division of Microbiology and Infectiousn Diseases Adult Toxicity Table[1]) as mild (transient or mild discomfort [<48 hours]; no medical intervention/therapy required), moderate (mild to moderate limitation in activity; some assistance required; no or minimal medical intervention/therapy required), or severe (marked limitation in activity, assistance required; medical intervention/therapy required, hospitalizations possible), or life threatening (extreme limitation in activity, significant assistance required, significant medical intervention/therapy required, hospitalization or hospice care probable).[1]

Weekly communication between the patient and the study site was required to ensure capture of adverse events (AEs). AEs were collected over the entire treatment period. Although placebo injections were administered to the lanadelumab every 4 weeks groups to maintain blinding, AEs were captured and analyzed by treatment group regardless of injection type. AEs of special interest based on potential class effect of a monoclonal antibody or kallikrein inhibitor were captured. These included hypersensitivity reactions or disorders of coagulation (bleeding or hypercoagulation).

In this study, the primary endpoint (efficacy), HAE attacks, were also recorded as AEs. Thus, to avoid complicating the interpretation of safety, 2 mutually exclusive subgroups of AEs based on whether the AE was identified in electronic data capture (EDC) as a patient-reported HAE attack or not, were defined as follows:

1. Non-HAE attack reported AEs included the subset of AEs identified in EDC as not a reported HAE attack. Essentially, this was all AEs excluding HAE attack reported events. The severity of AEs were assessed according to tables from the Division of Microbiology and Infectious Diseases toxicity.[1,2]
2. HAE attack reported AEs included the subset of AEs identified in EDC as a reported HAE attack. This included investigator-confirmed HAE attacks. Severity of the angioedema attack was assessed in accordance with the criteria described in eMethods.[2]

Reference

1. National Institute of Allergy and Infectious Diseases. Division of Microbiology and Infectious Diseases (DMID) adult toxicity table. November 2007. Draft https://www.niaid.nih.gov/sites/default/files/dmidadulttox.pdf. Accessed October 4, 2017.
2. National Institute of Allergy and Infectious Diseases. Division of Microbiology and Infectious Diseases (DMID) pediatric Toxicity Table. November 2007. Draft https://www.niaid.nih.gov/sites/default/files/dmidpedtox.pdf. Accessed October 4, 2017.

eMethods 5. Statistical Analysis

The primary and secondary endpoints were tested in the following order:

1. Number of investigator-confirmed HAE attacks during treatment period (days 0-182)
2. Number investigator-confirmed HAE attacks requiring acute treatment during the treatment period (days 0-182)
3. Number of moderate or severe investigator-confirmed HAE attacks during the treatment period (days 0-182)
4. Number of investigator-confirmed HAE attacks occurring on day 14 after administration of study drug through day 182 (days 14-182).

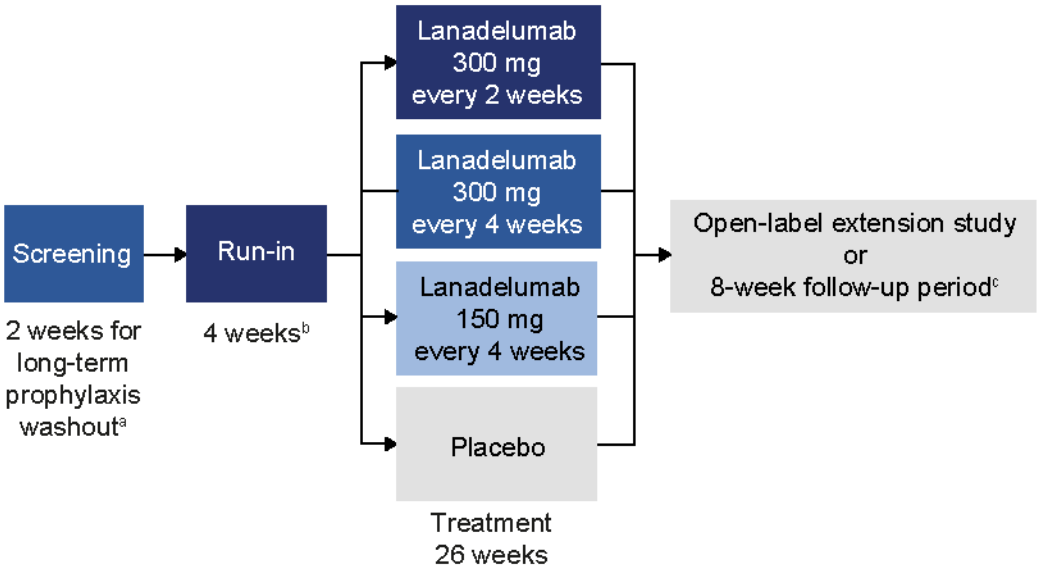
The primary and secondary efficacy endpoints for each lanadelumab treatment group were compared with the placebo group using a generalized linear model for Poisson-distributed count data accounting for overdispersion; treatment group and normalized baseline attack rate were fixed effects and the logarithm of time (days) each patient was observed during the treatment period was an offset variable. The comparisons between dose groups and placebo were performed separately with equal weights for each test set at 1.67% significance level (α/3 2-sided, Bonferroni adjustment). Additional details can be found in the statistical analysis plan (Supplement 1).

A tipping point analysis was conducted to measure the potential effect of missing data on the reliability of the primary efficacy analysis. To assess the consistency of the treatment effect across subgroups, the primary efficacy analysis was performed by type of prior long-term prophylaxis used, run-in attack rate category, sex, and BMI. Additionally, the impact of region on the primary efficacy endpoint was assessed by including a binary covariate (US vs non-US) in the primary analysis model.

Exploratory binary and continuous endpoints for each lanadelumab treatment group were compared with the placebo group without adjustment for multiplicity, using Fisher's exact test and t-test, respectively. The observed portion of the treatment period was used for the analysis of binary outcomes.

Change in Angioedema Quality of Life Questionnaire total and domaine scores from days 0-182 were compared across the lanadelumab dose regimens and placebo using analysis of covariance adjusting for baseline scores with pairwise *t* test using the Tukey-Kramer approximation. Chi-squared tests were used to assess the difference in the proportion of patients achieving a responder definition (minimal clinically important difference of –6) in change in the total Angioedema Quality of Life Questionnaire score from days 0-182, across treatments vs placebo. Logistic regression models were fit to estimate treatment effects on achievement of responder definition, adjusting for other relevant covariates.

eFigure1. Study Design

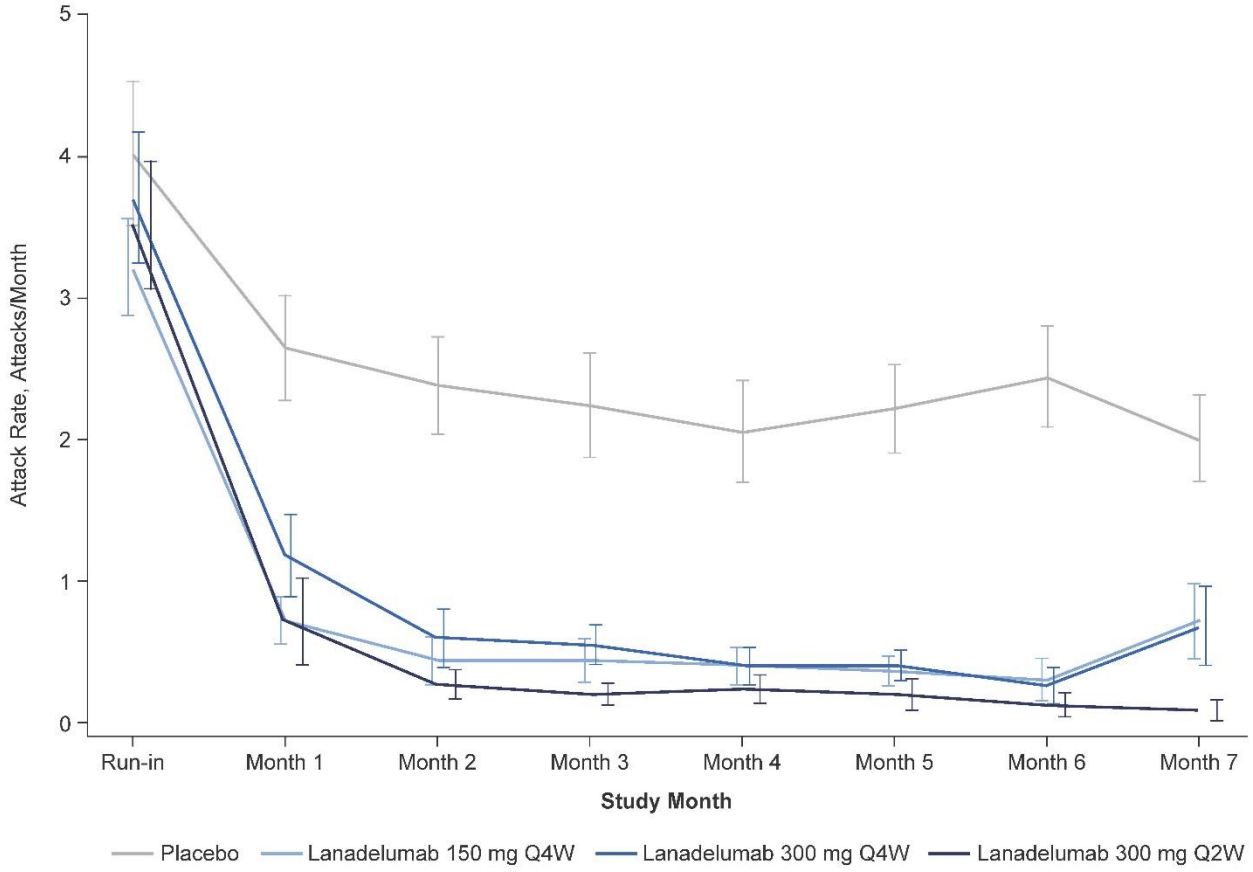


[a] Long-term prophylaxis washout only applicable to patients ≥18 years of age.

[b] Patients who experienced ≥3 investigator-confirmed attacks before the end of the 4 weeks may have exited the run-in period early and proceeded to enrollment and randomization. Patients without ≥1 investigator-confirmed attack after 4 weeks of run-in may have extended their run-in for another 4 weeks, during which time they needed to have ≥2 investigator-confirmed attacks to proceed to enrollment and randomization. To be eligible for enrollment, patients who had their run-in extended were required to complete the full 8-week run-in period before entering the treatment period. Patients who did not meet the minimum attack rate during the run-in period or were otherwise determined to be ineligible due to screening assessments were considered screen failures. Patients who were screen failures were not allowed to rescreen into the study.

[c] Eight-week follow-up period included assessments of safety, hereditary angioedema attacks, quality of life, and antidrug antibodies.

eFigure 2. Mean HAE Attack Rates by Study Month and Treatment Group



The mean (SE) investigator-confirmed HAE attack rate (attacks/month) by each study month (including the run-in period and 2 weeks after the last dose on Day 168 [6 months]) is shown.

eTable 1. HELP Study Administrative Structure

Publication Steering Committee	Aleena Banerji, MD (cochair) Marcus Maurer, MD (cochair) Jonathan A. Bernstein, MD Marco Cicardi, MD Hilary J. Longhurst, MD Marc A. Riedl, MD Bruce L. Zuraw, MD Benjamin Miller, PharmD Michael Craig, MSc Jovanna Baptista, MS Jennifer Schranz, MD
Sponsor	Dyax Corp. (an indirect wholly owned subsidiary of Shire plc.) 300 Shire Way Lexington, MA 02421
Clinical and Medical Monitoring	Jennifer Schranz, MD (Canada, Europe, Jordan, United States) Vice President, Clinical Development, Shire 300 Shire Way Lexington, MA 02421
Clinical Program Support	Ayman Ibrahim, MD Clinical Development, Shire 300 Shire Way Lexington, MA 02421
Study Monitoring	Rho, Inc. (United STates) 6330 Quadrangle Drive Chapel Hill, NC 27517 Triumpharma (Jordan) 07 Bldg., Al-Yarooty St. PO Box 2233 Amman 11941, Jordan Red Maple Trials Incorporated (Canada) 2935 Conroy Road, Unit 110 Ottawa, ON K1G 6C6, Canada Dyax Corp. (an indirect, wholly owned subsidiary of Shire plc.) (Europe) 300 Shire Way Lexington, MA 02421
Pharmacovigilance	Shire 300 Shire Way Lexington, MA 02421
Central Clinical Laboratory	Q Squared Solutions 1600 Terrell Mill Road SE, Suite 100 Marietta, GA 30067
Antidrug Antibody Analysis	Charles River Laboratory 8025 Lamon Avenue Skokie, IL 60077
C1 Inhibitor Functional Assay and C4 Testing	National Jewish Health 1400 Jackson Street Denver, CO 80206
Data Management	Shire

	300 Shire Way Lexington, MA 02421 Rho, Inc. (United States) 6330 Quadrangle Drive Chapel Hill, NC 27517
Interactive Web-Based Randomization System	Rho, Inc. (United States) 6330 Quadrangle Drive Chapel Hill, NC 27517
Biostatistics Analysis	Shire 300 Shire Way Lexington, MA 02421 Rho, Inc. (United States) 6330 Quadrangle Drive Chapel Hill, NC 27517
Health-Related Quality of Life Analysis	ICON Clinical Research Limited South County Business Park Leopardstown Dublin 18, Ireland

eTable 2. Duration of Treatment for Patients Who Discontinued

Planned Treatment Group	Patient	Completed the Study	Days in Treatment Period	Reason for Discontinuation
Placebo	1	No	28	Adverse event
	2	No	43	Withdrawal by patient
	3	No	155	Withdrawal by patient
	4	No	13	Adverse event
	5	No	189	Physician decision
	6	No	55	Withdrawal by patient
Lanadelumab 150 mg Q4W	7	No	113	Withdrawal by patient
Lanadelumab 300 mg Q4W	8	No	142	Adverse event
	9	No	183	Lost to follow-up
	10	No	73	Withdrawal by patient
Lanadelumab 300 mg Q2W	11	No	35	Withdrawal by patient
	12	No	186	Withdrawal by patient

Abbreviations: Q2W, every 2 weeks; Q4W, every 4 weeks.

eTable 3. Number of Patients by Duration of Run-in Period

Duration of Run-in Period, Weeks, No. (%)	Lanadelumab 150 mg Every 4 Weeks (n = 28)	Lanadelumab 300 mg Every 4 Weeks (n = 29)	Lanadelumab 300 mg Every 2 Weeks (n = 27)	Placebo (n = 41)
<4	12 (42.9)	12 (41.4)	11 (40.7)	18 (43.9)
4	9 (32.1)	8 (27.6)	7 (25.9)	14 (34.1)
>4 to <8	7 (25.0)	8 (27.6)	9 (33.3)	9 (22.0)
≥8	0	1 (3.4)	0	0

eTable 4. Number of Patients by Run-in Attack Rate Category

Run-in Attack Rate Category, Attacks/mo, No. (%)	Lanadelumab 150 mg Every 4 Weeks (n = 28)	Lanadelumab 300 mg Every 4 Weeks (n = 29)	Lanadelumab 300 mg Every 2 Weeks (n = 27)	Placebo (n = 41)
1 to <2	10 (35.7)	9 (31.0)	7 (25.9)	12 (29.3)
2 to <3	3 (10.7)	5 (17.2)	6 (22.2)	8 (19.5)
3 to <4	7 (25.0)	3 (10.3)	7 (25.9)	3 (7.3)
4 to <5	3 (10.7)	1 (3.4)	1 (3.7)	4 (9.8)
5 to <10	5 (17.9)	10 (34.5)	6 (22.2)	12 (29.3)
10 to <15	0	1 (3.4)	0	2 (4.9)

Run-in hereditary angioedema attack rate is calculated as the number of HAE attacks occurring in the run-in period divided by the number of days the patient contributed to the run-in period multiplied by 28 days.

eTable 5. Primary Attack Location During Run-in and Treatment Period

Location, No. (%), Attacks, No.	Lanadelumab 150 mg Every 4 Weeks (n = 28)	Lanadelumab 300 mg Every 4 Weeks (n = 29)	Lanadelumab 300 mg Every 2 Weeks (n = 27)	Placebo (n = 41)
Run-in period				
HAE attacks	28 (100), 81	29 (100), 77	27 (100), 78	41 (100), 127
Abdominal	20 (71.4), 29	19 (65.5), 30	14 (51.9), 21	27 (65.9), 61
Laryngeal	4 (14.3), 4	1 (3.4), 1	1 (3.7), 1	0
Peripheral	22 (78.6), 48	22 (75.9), 46	24 (88.9), 56	33 (80.5), 66
Treatment period				
HAE attacks	17 (60.7), 84	20 (69.0), 105	15 (55.6), 46	40 (97.6), 572
Abdominal	14 (50.0), 38	17 (58.6), 78	9 (33.3), 23	35 (85.4), 245
Laryngeal	1 (3.6), 3	1 (3.4), 1	3 (11.1), 3	8 (19.5), 11
Peripheral	10 (35.7), 43	12 (41.4), 26	9 (33.3), 20	37 (90.2), 316

Abbreviation: HAE, hereditary angioedema.

eTable 6. Duration of Attacks

Location, No. (%), Attacks, No.	Lanadelumab 150 mg Every 4 Weeks (n = 28)	Lanadelumab 300 mg Every 4 Weeks (n = 29)	Lanadelumab 300 mg Every 2 Weeks (n = 27)	Placebo (n = 41)
Run-in period				
No.	28	29	27	41
HAE attack duration, mean (SD), h	38.9 (32.57)	28.0 (21.62)	35.6 (23.34)	31.2 (24.64)
Mean HAE attack duration categories, No. (%)				
<12 h	7 (25.0)	8 (27.6)	2 (7.4)	9 (22.0)
12 to 24 h	5 (17.9)	7 (24.1)	9 (33.3)	11 (26.8)
>24 to 48 h	6 (21.4)	10 (34.5)	10 (37.0)	13 (31.7)
>48 h	10 (35.7)	4 (13.8)	6 (22.2)	8 (19.5)
Treatment period[a]				
No.	17	20	15	40
HAE attack duration, mean (SD), h	35.6 (24.89)	26.0 (21.10)	26.6 (22.73)	33.5 (23.41)
Difference vs placebo (95% CI), h	2.1 (-12.4 to 16.6)	-7.4 (-19.5 to 4.7)	-6.9 (-21.2 to 7.4)	-
P value[b]	.770	.222	.330	
Mean HAE attack duration categories, No. (%)				
No attacks	11 (39.3)	9 (31.0)	12 (44.4)	1 (2.4)
<12 h	4 (14.3)	6 (20.7)	5 (18.5)	8 (19.5)
12 to 24 h	2 (7.1)	6 (20.7)	3 (11.1)	10 (24.4)
>24 to 48 h	7 (25.0)	6 (20.7)	4 (14.8)	12 (29.3)
>48 h	4 (14.3)	2 (6.9)	3 (11.1)	10 (24.4)

Mean attack duration is the average for each patient's attacks.

[a] Includes only patients with attacks.

[b] P value from t-test.

eTable 7. Summary of On-Demand Treatment for Attacks and the Use of Supportive Therapies for Symptoms

Patients, No. (%), Attacks, No.	Lanadelumab 150 mg Every 4 Weeks (n = 28)	Lanadelumab 300 mg Every 4 Weeks (n = 29)	Lanadelumab 300 mg Every 2 Weeks (n = 27)	Lanadelumab Total (n = 84)	Placebo (n = 41)
Run-in period					
Total no. of attacks	28 (100), 81	29 (100), 77	27 (100), 78	84 (100), 236	41 (100), 127
On-demand medication use					
Any on-demand medication	25 (89.3), 61	27 (93.1), 69	23 (85.2), 67	75 (89.3), 197	37 (90.2), 111
Ecallantide	3 (10.7), 5	6 (20.7), 8	1 (3.7), 3	10 (11.9), 16	2 (4.9), 2
Icatibant	13 (46.4), 28	13 (44.8), 41	13 (48.1), 32	39 (46.4), 101	22 (53.7), 38
Nanofiltered/plasma-derived C1 inhibitor	12 (42.9), 32	14 (48.3), 28	12 (44.4), 34	38 (45.2), 94	22 (53.7), 77
Nanofiltered C1 inhibitor	5 (17.9), 10	5 (17.2), 9	6 (22.2), 12	16 (19.0), 31	6 (14.6), 24
Plasma-derived C1 inhibitor	8 (28.6), 22	9 (31.0), 19	6 (22.2), 22	23 (27.4), 63	16 (39.0), 53
Recombinant C1 inhibitor	0	1 (3.4), 1	1 (3.7), 2	2 (2.4), 3	0
Fresh frozen plasma	0	0	0	0	1 (2.4), 1
Supportive treatment					
Any supportive treatment	7 (25.0), 12	2 (6.9), 2	4 (14.8), 7	13 (15.5), 21	5 (12.2), 6
Intravenous fluids	1 (3.6), 1	1 (3.4), 1	0	2 (2.4), 2	0
Pain medication	5 (17.9), 9	2 (6.9), 2	2 (7.4), 5	9 (10.7), 16	3 (7.3), 4
Oxygen	0	0	0	0	0
Antiemetic	1 (3.6), 1	1 (3.4), 1	0	2 (2.4), 2	1 (2.4), 2
Other	3 (10.7), 4	0	2 (7.4), 2	5 (6.0), 6	3 (7.3), 3
Treatment period (days 0-182)					
Total no. of attacks	17 (60.7), 84	20 (69.0), 105	15 (55.6), 46	52 (61.9), 235	40 (97.6), 572
On-demand medication use					
Any on-demand medication	14 (50.0), 55	16 (55.2), 87	12 (44.4), 38	42 (50.0), 180	40 (97.6), 506
Ecallantide	1 (3.6), 1	6 (20.7), 18	0	7 (8.3), 19	5 (12.2), 12
Icatibant	9 (32.1), 25	11 (37.9), 69	10 (37.0), 20	30 (35.7), 114	27 (65.9), 172
Nanofiltered/plasma-derived C1 inhibitor	7 (25.0), 31	4 (13.8), 7	6 (22.2), 26	17 (20.2), 64	27 (65.9), 362
Nanofiltered C1 inhibitor	3 (10.7), 10	2 (6.9), 2	4 (14.8), 12	9 (10.7), 24	8 (19.5), 141

Plasma-derived C1 inhibitor	5 (17.9), 21	2 (6.9), 5	3 (11.1), 14	10 (11.9), 40	21 (51.2), 223
Recombinant C1 inhibitor	0	1 (3.4), 1	0	1 (1.2), 1	0
Fresh frozen plasma	0	0	0	0	0
Supportive treatment					
Any supportive treatment	6 (21.4), 16	2 (6.9), 8	1 (3.7), 2	9 (10.7), 26	13 (31.7), 30
Intravenous fluids	0	1 (3.4), 1	1 (3.7), 1	2 (2.4), 2	2 (4.9), 2
Pain medication	5 (17.9), 15	2 (6.9), 8	0	7 (8.3), 23	10 (24.4), 20
Oxygen	0	0	0	0	0
Antiemetic	4 (14.3), 4	1 (3.4), 1	1 (3.7), 1	6 (7.1), 6	3 (7.3), 8
Other	2 (7.1), 2	1 (3.4), 1	1 (3.7), 1	4 (4.8), 4	4 (9.8), 7

Patients may have used >1 on-demand treatment and/or supportive treatment for a single attack.

eTable 8. Efficacy Outcomes by Subgroups

Endpoint	Lanadelumab 150 mg Every 4 Weeks (n = 28)	Lanadelumab 300 mg Every 4 Weeks (n = 29)	Lanadelumab 300 mg Every 2 Weeks (n = 27)	Placebo (n = 41)
By long-term prophylaxis use before study entry				
Long-term prophylaxis				
n	12	20	14	24
Attacks/mo, mean (95% CI)[a,b]	0.48 (0.25 to 0.92)	0.59 (0.38 to 0.92)	0.31 (0.16 to 0.62)	2.15 (1.70 to 2.71)
Difference from placebo, mean (95% CI)[c]	-1.67 (-2.26 to -1.07)	-1.56 (-2.12 to -1.00)	-1.84 (-2.37 to -1.30)	-
P value	< .001	< .001	< .001	
Rate ratio relative to placebo, mean (95% CI)[b]	0.22 (0.11 to 0.45)	0.27 (0.17 to 0.45)	0.14 (0.07 to 0.30)	-
P value	< .001	< .001	< .001	
No long-term prophylaxis				
n	16	9	13	17
Attacks/mo, mean (95% CI)[a,b]	0.44 (0.24 to 0.81)	0.39 (0.18 to 0.87)	0.20 (0.07 to 0.60)	1.76 (1.30 to 2.38)
Difference from placebo, mean (95% CI)[c]	-1.32 (-1.90 to -0.73)	-1.37 (-1.96 to -0.78)	-1.56 (-2.14 to -0.98)	-
P value	< .001	< .001	< .001	
Rate ratio relative to placebo, mean (95% CI)[b]	0.25 (0.13 to 0.49)	0.22 (0.10 to 0.51)	0.11 (0.04 to 0.36)	-
P value	< .001	< .001	< .001	
By run-in period attack rate group				
1 to <2 attacks/mo				
n	10	9	7	12
Attacks/mo, mean (95% CI)[a,b]	0.46 (0.25 to 0.85)	0.18 (0.07 to 0.51)	0.07 (0.01 to 0.47)	0.94 (0.63 to 1.41)
Difference from placebo, mean (95% CI) [c]	-0.48 (-0.95 to -0.01)	-0.76 (-1.18 to -0.33)	-0.87 (-1.28 to -0.47)	-
P value	.046	< .001	< .001	
Rate ratio relative to placebo, mean (95% CI) [b]	0.49 (0.24 to 1.02)	0.20 (0.07 to 0.58)	0.07 (0.01 to 0.52)	-
P value	.055	.003	.009	
2 to <3 attacks/mo				
n	3	5	6	8

Attacks/mo, mean (95% CI)[a,b]	0.20 (0.05 to 0.81)	0.49 (0.25 to 0.99)	0.25 (0.10 to 0.61)	2.14 (1.64 to 2.80)
Difference from placebo, mean (95% CI) [c]	-1.94 (-2.58 to -1.30)	-1.65 (-2.31 to -0.99)	-1.89 (-2.50 to -1.28)	-
P value	< .001	< .001	< .001	
Rate ratio relative to placebo, mean (95% CI) [b]	0.09 (0.02 to 0.39)	0.23 (0.11 to 0.48)	0.12 (0.05 to 0.30)	-
P value	.001	< .001	< .001	
≥3 attacks/mo				
n	15	15	14	21
Attacks/mo, mean (95% CI)[a,b]	0.57 (0.31 to 1.06)	0.79 (0.49 to 1.29)	0.38 (0.18 to 0.81)	2.71 (2.12 to 3.46)
Difference from placebo, mean (95% CI) [c]	-2.14 (-2.90 to -1.38)	-1.92 (-2.67 to -1.17)	-2.33 (-3.05 to -1.61)	-
P value	< .001	< .001	< .001	
Rate ratio relative to placebo, mean (95% CI) [b]	0.21 (0.11 to 0.41)	0.29 (0.17 to 0.50)	0.14 (0.06 to 0.31)	-
P value	< .001	< .001	< .001	
By Sex				
Female				
n	20	19	15	34
Attacks/mo, mean (95% CI)[a,b]	0.42 (0.25 to 0.71)	0.59 (0.38 to 0.90)	0.28 (0.13 to 0.58)	1.94 (1.59 to 2.36)
Difference from placebo, mean (95% CI) [c]	-1.52 (-1.96 to -1.08)	-1.35 (-1.79 to -0.91)	-1.66 (-2.09 to -1.23)	-
P value	< .001	< .001	< .001	
Rate ratio relative to placebo, mean (95% CI) [b]	0.22 (0.12 to 0.38)	0.30 (0.19 to 0.48)	0.14 (0.07 to 0.30)	-
P value	< .001	< .001	< .001	
Male				
n	8	10	12	7
Attacks/mo, mean (95% CI)[a,b]	0.57 (0.25 to 1.26)	0.39 (0.16 to 0.93)	0.21 (0.08 to 0.59)	2.20 (1.40 to 3.45)
Difference from placebo, mean (95% CI) [c]	-1.64 (-2.71 to -0.57)	-1.81 (-2.86 to -0.77)	-1.99 (-2.99 to -0.98)	-
P value	.003	< .001	< .001	
Rate ratio relative to placebo, mean (95% CI) [b]	0.26 (0.10 to 0.63)	0.18 (0.07 to 0.47)	0.10 (0.03 to 0.29)	-
P value	.003	< .001	< .001	

By BMI group[d]				
18.5 to <25 kg/m^2				
n	11	6	6	12
Attacks/mo, mean (95% CI)[a,b]	0.33 (0.14 to 0.79)	0.24 (0.06 to 0.92)	0.11 (0.01 to 0.88)	1.76 (1.20 to 2.60)
Difference from placebo, mean (95% CI) [c]	-1.43 (-2.16 to -0.70)	-1.52 (-2.27 to -0.77)	-1.66 (-2.37 to -0.94)	-
P value	*P* < .001	*P* < .001	*P* < .001	
Rate ratio relative to placebo, mean (95% CI) [b]	0.19 (0.07 to 0.48)	0.14 (0.04 to 0.55)	0.06 (0.01 to 0.52)	-
P value	< .001	.005	.010	
25 to <30 kg/m^2				
n	8	12	10	13
Attacks/mo, mean (95% CI)[a,b]	0.55 (0.25 to 1.23)	0.68 (0.38 to 1.21)	0.36 (0.15 to 0.83)	2.29 (1.67 to 3.13)
Difference from placebo, mean (95% CI) [c]	-1.74 (-2.58 to -0.90)	-1.61 (-2.41 to -0.81)	-1.93 (-2.69 to -1.17)	-
P value	< .001	< .001	< .001	
Rate ratio relative to placebo, mean (95% CI) [b]	0.24 (0.10 to 0.57)	0.30 (0.16 to 0.56)	0.16 (0.07 to 0.38)	-
P value	.001	*P* < .001	*P* < .001	
18.5 to ≥30 kg/m^2				
n	8	8	9	11
Attacks/mo, mean (95% CI)[a,b]	0.69 (0.36 to 1.35)	0.62 (0.33 to 1.18)	0.23 (0.08 to 0.67)	2.35 (1.68 to 3.29)
Difference from placebo, mean (95% CI) [c]	-1.66 (-2.57 to -0.74)	-1.73 (-2.59 to -0.86)	-2.12 (-2.94 to -1.29)	-
P value	*P* < .001	*P* < .001	*P* < .001	
Rate ratio relative to placebo, mean (95% CI) [b]	0.30 (0.14 to 0.62)	0.26 (0.13 to 0.54)	0.10 (0.03 to 0.30)	-
P value	.001	*P* < .001	*P* < .001	

Abbreviation: BMI, body mass index.

[a] Attack rates are presented as a model-based mean attacks/4 weeks.

[b] Results are from a Poisson regression model accounting for overdispersion; treatment group and normalized baseline attack rate were fixed effects and the logarithm of time (days) each patient was observed during the treatment period was an offset variable. All *P* values (Wald test) reported vs placebo and are unadjusted.
[c] Estimated from a nonlinear function of the model parameters. All *P* values (Wald test) reported vs placebo.
[d] Only 1 patient was in the <18.5 kg/m^2 BMI group, and is not presented here.

eTable 9. Tipping Point Analysis

	Lanadelumab 150 mg Every 4 Weeks (n = 28)	**Lanadelumab 300 mg Every 4 Weeks (n = 29)**	**Lanadelumab 300 mg Every 2 Weeks (n = 27)**	**Placebo (n = 41)**
Patients missing data, No. (%)[a]	1 (3.6)	2 (6.9)	2 (7.4)	5 (12.2)
Value of the tipping point δ[b]	27	22	35	
Rate ratio vs placebo (95% CI)[c]	0.400 (0.186-0.862)	0.495 (0.277-0.886)	0.317 (0.121-0.831)	
P value	.019	.018	.020	

See the statistical analysis plan (Supplement 1) for details on the methodology used for the analysis. Using the multiple imputation approach, patients who did not complete the treatment period, with the early discontinuation day before day 182, had their hereditary angioedema attack data for the missing part of the study randomly imputed using the primary analysis model and an assumption that events occur with the same underlying rate within an individual. Next, a multiplication factor with progressively more conservative assumptions on higher post-dropout attack rates was applied to patients treated with lanadelumab. The analysis indicated that the post-discontinuation HAE attack rate would need to be 27, 22, and 35 times as high as during the study (ie, the tipping points), respectively, for the 3 lanadelumab treatment groups, to reverse the significance finding over placebo (type I error rate equals 0.05/3=0.0167 for each comparison). The high level of implausibility of the tipping points strongly supports the robustness of the primary efficacy results.

[a]Patients missing data are patients who did not complete the treatment period (days 0-182).

[b]The value of δ represents a multiplicative effect on the imputed rate of attacks for patients who are missing data during the treatment period. The tipping point is the value of δ at which the results of the study comparison are reversed and the *P* value is ≥0.0167 (α/3) for the treatment group vs placeo.

[c]The rate ratios are the estimates from the Poisson model after combining the estimates from the 1000 simulations using Rubin's rules.

eTable 10. Number of Patients by Geographical Region

Region, No. patients (%)	Lanadelumab 150 mg Every 4 Weeks (n = 28)	Lanadelumab 300 mg Every 4 Weeks (n = 29)	Lanadelumab 300 mg Every 2 Weeks (n = 27)	Lanadelumab total (n = 84)	Placebo (n = 41)
United States	20 (71.4)	23 (79.3)	18 (66.7)	61 (72.6)	25 (61.0)
Canada	1 (3.6)	1 (3.4)	2 (7.4)	4 (4.8)	3 (7.3)
Europe	6 (21.4)	4 (13.8)	7 (25.9)	17 (20.2)	12 (29.3)
Jordan	1 (3.6)	1 (3.4)	0	2 (2.4)	1 (2.4)

eTable 11. Mean Number of Attacks Days 0-182, Adjusted by Geographical Region

	Lanadelumab 150 mg Every 4 Weeks (n = 28)	**Lanadelumab 300 mg Every 4 Weeks (n = 29)**	**Lanadelumab 300 mg Every 2 Weeks (n = 27)**	**Placebo (n = 41)**
Mean number of attacks days 0-182				
Attacks/mo (95% CI)	0.49 (0.32-0.75)	0.55 (0.37-0.81)	0.26 (0.15-0.47)	1.99 (1.65-2.39)
Difference from placebo (95% CI), attacks/mo	-1.50 (-1.92 to -1.08)	-1.44 (-1.85 to -1.03)	-1.72 (-2.11 to -1.33)	-
P value	< .001	< .001	< .001	
Rate ratio relative to placebo (95% CI)	0.25 (0.15-0.39)	0.27 (0.18-0.42)	0.13 (0.07-0.24)	-
P value	< .001	< .001	< .001	

Attack rates are model-based mean attacks/month, with a month defined as 4 weeks. Results are from a Poisson regression model accounting for overdispersion; treatment group and normalized baseline attack rate were fixed effects and the logarithm of time (days) each patient was observed during the treatment period was an offset variable. Region (US versus non-US) was included as a categorical covariate. All *P* values reported vs placebo.

eTable 12. Listing of Patients Who Discontinued During Treatment Due to Adverse Events

Patient Number	Treatment Group	Reason for Discontinuation
1	Lanadelumab 300 mg every 4 weeks	Severe related treatment-emergent adverse events (elevated aspartate transaminase/alanine transaminase) on day 139
2	Placebo	Related treatment-emergent adverse event (tension headache) of moderate severity on day 1 (9 hours)
3	Placebo	Not related moderate hereditary angioedema attack on day 12

Patient 1 was a 43-year-old male with hereditary angioedema type I (diagnosed at 12 years of age) with a baseline history of obesity, hyperlipidemia, diabetes mellitus, fatty liver, and hypertension. The patient withdrew due to isolated, asymptomatic, and transient elevation of aspartate transaminase (143 U/L) and alanine transaminase (140 U/L) classified as related and severe on day 139. Concomitant suspect medications included metoprolol, sitagliptin/metformin, metformin, icatibant, and a 5-day history of acetaminophen use for headache immediately before the observed aspartate transaminase/alanine transaminase elevation. Aspartate transaminase (45 U/L) and alanine transaminase (73 U/L) returned or trended to normal range on last available contact.

eTable 13. Summary of Serious Treatment-Emergent Adverse Events

Event, No. (%)	Lanadelumab 150 mg Every 4 Weeks (n = 28)	Lanadelumab 300 mg Every 4 Weeks (n = 29)	Lanadelumab 300 mg Every 2 Weeks (n = 27)	Lanadelumab Total (n = 84)	Placebo (n = 41)
Any serious treatment-emergent adverse event	0	3 (10.3)	1 (3.7)	4 (4.8)	0
Catheter site infection	0	0	1 (3.7)	1 (1.2)	0
Pyelonephritis	0	1 (3.4)	0	1 (1.2)	0
Meniscus injury	0	1 (3.4)	0	1 (1.2)	0
Bipolar II disorder	0	1 (3.4)	0	1 (1.2)	0

eTable 14. Summary of Activated Partial Thromboplastin Time

Time Point, No. Category, No. (%)	Lanadelumab 150 mg Every 4 Weeks (n = 28)	Lanadelumab 300 mg Every 4 Weeks (n = 29)	Lanadelumab 300 mg Every 2 Weeks (n = 27)	Lanadelumab Total (n = 84)	Placebo (n = 41)
Day 0/week 0	28	29	27	84	41
Low, clinically significant	0	0	0	0	0
Low, not clinically significant	0	1 (3.4)	1 (3.7)	2 (2.4)	0
Normal	28 (100)	28 (96.6)	25 (92.6)	81 (96.4)	40 (97.6)
High, not clinically significant	0	0	1 (3.7)	1 (1.2)	1 (2.4)
High, clinically significant	0	0	0	0	0
Day 28/week 4	27	29	26	82	39
Low, clinically significant	0	0	0	0	0
Low, not clinically significant	0	0	0	0	0
Normal	27 (100)	27 (93.1)	17 (65.4)	71 (86.6)	38 (97.4)
High, not clinically significant	0	2 (6.9)	7 (26.9)	9 (11.0)	1 (2.6)
High, clinically significant	0	0	2 (7.7)	2 (2.4)	0
Day 56/week 8	26	29	25	80	37
Low, clinically significant	0	0	0	0	0
Low, not clinically significant	0	0	0	0	0
Normal	26 (100)	25 (86.2)	21 (84.0)	72 (90.0)	35 (94.6)
High, not clinically significant	0	4 (13.8)	4 (16.0)	8 (10.0)	1 (2.7)
High, clinically significant	0	0	0	0	1 (2.7)
Day 98/week 14	27	27	22	76	35
Low, clinically significant	0	0	0	0	0
Low, not clinically significant	0	0	0	0	0
Normal	27 (100)	24 (88.9)	17 (77.3)	68 (89.5)	32 (91.4)
High, not clinically significant	0	3 (11.1)	4 (18.2)	7 (9.2)	3 (8.6)
High, clinically significant	0	0	1 (4.5)	1 (1.3)	0
Day 140/week 20	27	26	23	76	35
Low, clinically significant	0	0	0	0	0
Low, not clinically significant	0	0	0	0	1 (2.9)

Normal	24 (88.9)	22 (84.6)	19 (82.6)	65 (85.5)	34 (97.1)
High, not clinically significant	3 (11.1)	4 (15.4)	3 (13.0)	10 (13.2)	0
High, clinically significant	0	0	1 (4.3)	1 (1.3)	0
Day 182/early termination	26	28	25	79	38
Low, clinically significant	0	0	0	0	0
Low, not clinically significant	0	0	0	0	0
Normal	26 (100)	24 (85.7)	21 (84.0)	71 (89.9)	38 (100)
High, not clinically significant	0	4 (14.3)	4 (16.0)	8 (10.1)	0
High, clinically significant	0	0	0	0	0
Day 238/follow-up	1	1	0	2	2
Low, clinically significant	0	0	0	0	0
Low, not clinically significant	0	0	0	0	0
Normal	1 (100)	1 (100)	0	2 (100)	2 (100)
High, not clinically significant	0	0	0	0	0
High, clinically significant	0	0	0	0	0

eTable 15. Shift Table of Highest Activated Partial Thromboplastin Time

Abbreviation: ULN, upper limit of normal.

Activated Partial Thromboplastin Time (Post-treatment)	Placebo (n = 41)		Lanadelumab Total (n = 84)	
	Pretreatment		Pretreatment	
	≤1.5 × ULN, No. (%)	>1.5 × ULN, No. (%)	≤1.5 × ULN, No. (%)	>1.5 × ULN, No. (%)
≤1.5 × ULN	41 (100)	0	83 (98.8)	0
>1.5 × ULN	0	0	1 (1.2)	0

eTable 16. Clinically Significant Activated Partial Thromboplastin Time Results

Patient	Visit	Result, sec	Range Flag	Clinically Significant Flag
Placebo				
1	Screening	29.2	N	
	Day 0/week 0	34.1	N	
	Day 28/week 4	49.5	H	No
	Day 56/week 8	47.8	H	Yes
	Day 98/week 14	40.1	H	No
	Day 140/week 20	26.6	N	
	Day 182/end of treatment	24.8	N	
Lanadelumab 300 mg every 2 weeks				
2	Screening	32.7	N	
	Day 0/week 0	28.5	N	
	Day 28/week 4	40	H	Yes
	Day 56/week 8	39.1	N	
	Day 140/week 20	59.7	H	No
	Day 182/end of treatment	35.6	N	
3	Screening	24.2	N	
	Day 0/week 0	23.3	N	
	Day 28/week 4	33.3	N	
	Day 56/week 8	30.8	N	
	Day 98/week 14	42.5	H	Yes
	Day 140/week 20	39.5	N	
	Day 182/end of treatment	37.3	N	
4	Screening	40.2	H	No
	Day 0/week 0	30.6	N	
	Day 28/week 4	54.9	H	Yes
	Day 56/week 8	30	N	
	Day 98/week 14	42.5	H	No
	Day 140/week 20	36.8	N	
	Day 182/end of treatment	38.8	N	
5	Screening	32.2	N	
	Day 0/week 0	42.3	H	No
	Day 28/week 4	49.4	H	No
	Day 56/week 8	48.1	H	No
	Day 98/week 14	50	H	No
	Day 140/week 20	49.3	H	Yes
	Day 182/end of treatment	35	N	

Abbreviations: H, high; N, normal.
Reference range is 20.6-39.9 seconds.

eTable 17. Summary of Immunogenicity Response

Parameter, No. (%)	Lanadelumab 150 mg Every 4 Weeks (n = 28)	Lanadelumab 300 mg Every 4 Weeks (n = 29)	Lanadelumab 300 mg Every 2 Weeks (n = 27)	Lanadelumab Total (n = 84)	Placebo (n = 41)
Antidrug antibody prevalence[a]	5 (17.9)	3 (10.3)	4 (14.8)	12 (14.3)	3 (7.3)
Antidrug antibody incidence[b]	5 (17.9)	3 (10.3)	2 (7.4)	10 (11.9)	2 (4.9)
Pre-existing antidrug antibody[c]	0	1 (3.4)	2 (7.4)	3 (3.6)	1 (2.4)
Treatment induced[d]	5 (17.9)	2 (6.9)	2 (7.4)	9 (10.7)	2 (4.9)
Treatment boosted[e]	0	1 (3.4)[f]	0	1 (1.2)	0
Non-neutralizing antidrug antibody	3 (10.7)	3 (10.3)	4 (14.8)	10 (11.9)	3 (7.3)
Neutralizing antidrug antibody	2 (7.1)	0	0	2 (2.4)	0

No. denotes the number of patients experiencing the event.
[a] Prevalence was defined as the proportion of the study population having drug-reactive antibodies (including pre-existing antibodies) at any time point.
[b] Incidence was defined as the proportion of the study population found to have seroconverted or boosted their pre-existing antidrug antibodies during the study period.
[c] Pre-existing antidrug antibody refers to a signal detected before treatment.
[d] Treatment-induced responses were characterized by a negative pretreatment sample with ≥1 positive sample at a subsequent time point.
[e] Treatment-boosted responses were characterized by a positive pretreatment sample that was boosted to a higher level following drug administration.
[f] One additional patient with pre-existing antidrug antibodies had a positive sample post dose; however, because the titer was the same as the pretreatment sample it was not considered to be treatment boosted.

eTable 18. Summary of Positive Immunogenicity Results

Patient	Visit	Result	Titer	Neutralizing Antibody	Result Category
Placebo					
1	Day 0/week 0 Day 56/week 8 Day 98/week 14 Day 140/week 20 Day 182/end of treatment Day 238/follow-up	Positive Negative Negative Negative Negative Negative	20 NA NA NA NA NA	Negative NA NA NA NA NA	Pre-existing antidrug antibody Non-neutralizing antidrug antibody
2	Day 0/week 0 Day 56/week 8 Day 98/week 14 Day 140/week 20 Day 182/end of treatment	Negative Negative Negative Negative Positive	NA NA NA NA 20	NA NA NA NA Negative	Treatment induced Non-neutralizing antidrug antibody
3	Day 0/week 0 Day 56/week 8 Day 98/week 14 Day 140/week 20 Day 182/end of treatment	Negative Negative Positive Negative Negative	NA NA 640 NA NA	NA NA Negative NA NA	Treatment induced Transient Non-neutralizing antidrug antibody
Lanadelumab 150 mg every 4 weeks					
4	Day 0/week 0 Day 56/week 8 Day 98/week 14 Day 140/week 20 Day 182/end of treatment	Negative Negative Negative Positive Positive	NA NA NA 40 640	NA NA NA **Positive** **Positive**	Treatment induced **Neutralizing antidrug antibody**
5	Day 0/week 0 Day 56/week 8 Day 98/week 14 Day 140/week 20 Day 182/end of treatment	Negative Negative Negative Positive Positive	NA NA NA 20 40	NA NA NA Negative Negative	Treatment induced Non-neutralizing antidrug antibody
6	Day 0/week 0 Day 98/week 14 Day 140/week 20 Day 182/end of treatment	Negative Positive Positive Positive	NA CNBD 40 160	NA **Positive** **Positive** Negative	Treatment induced **Neutralizing antidrug antibody**

7	Day 0/week 0 Day 56/week 8 Day 98/week 14 Day 140/week 20 Day 182/end of treatment	Negative Negative Negative Negative Positive	NA NA NA NA 20	NA NA NA NA Negative	Treatment induced Non-neutralizing antidrug antibody
8	Day 0/week 0 Day 56/week 8 Day 98/week 14 Day 140/week 20 Day 182/end of treatment	Negative Negative Negative Positive Positive	NA NA 20 20 20	NA NA NA Negative Negative	Treatment induced Non-neutralizing antidrug antibody
Lanadelumab 300 mg every 4 weeks					
9	Day 0/week 0 Day 56/week 8 Day 98/week 14 Day 140/week 20 Day 182/end of treatment	Negative Negative Negative Positive Negative	NA NA NA 40 NA	NA NA NA Negative NA	Treatment induced Transient Non-neutralizing antidrug antibody
10	Day 0/Week 0 Day 56/week 8 Day 98/week 14 Day 140/week 20 Day 182/end of treatment	Positive Negative Negative Positive Positive	40 NA NA 20 128	Negative NA NA Negative Negative	Pre-existing antidrug antibody Treatment boosted Non-neutralizing antidrug antibody
11	Day 0/week 0 Day 56/week 8 Day 98/week 14 Unscheduled Day 182/end of treatment	Negative Negative Negative Positive Negative	NA NA NA 40 NA	NA NA NA Negative NA	Treatment induced Transient Non-neutralizing antidrug antibody
Lanadelumab 300 mg every 2 weeks					
12	Day 0/week 0 Day 56/week 8 Day 98/week 14 Day 140/week 20 Day 182/end of treatment	Negative Negative Negative Negative Positive	NA NA NA NA 20	NA NA NA NA Negative	Treatment induced Non-neutralizing antidrug antibody
13	Day 0/week 0 Day 56/week 8 Unscheduled Day 140/week 20 Day 182/end of treatment	Positive Negative Negative Negative Negative	160 NA NA NA NA	Negative NA NA NA NA	Pre-existing antidrug antibody Non-neutralizing antidrug antibody

14	Day 0/week 0 Day 56/week 8 Day 98/week 14 Day 140/week 20 Day 182/end of treatment	Positive Negative Negative Positive Negative	20 NA NA 20 NA	Negative NA NA Negative NA	Pre-existing antidrug antibody Non-neutralizing antidrug antibody
15	Day 0/week 0 Day 56/week 8 Day 98/week 14 Day 140/week 20 Day 182/end of treatment	Negative Negative Positive Positive Negative	NA NA CNBD 320 NA	NA NA Negative Negative NA	Treatment induced Non-neutralizing antidrug antibody

Abbreviations: CNBD, could not be determined; NA, not applicable.