

## Inhibiting Plasma Kallikrein for Hereditary Angioedema Prophylaxis

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### ABSTRACT

#### BACKGROUND

Hereditary angioedema with C1 inhibitor deficiency is characterized by recurrent, unpredictable swelling episodes caused by uncontrolled plasma kallikrein generation and excessive bradykinin release resulting from cleavage of high-molecular-weight kininogen. Lanadelumab (DX-2930) is a new kallikrein inhibitor with the potential for prophylactic treatment of hereditary angioedema with C1 inhibitor deficiency.

#### METHODS

We conducted a phase 1b, multicenter, double-blind, placebo-controlled, multiple-ascending-dose trial. Patients with hereditary angioedema with C1 inhibitor deficiency were randomly assigned in a 2:1 ratio to receive either lanadelumab (24 patients) or placebo (13 patients), in two administrations 14 days apart. Patients assigned to lanadelumab were enrolled in sequential dose groups: total dose of 30 mg (4 patients), 100 mg (4 patients), 300 mg (5 patients), or 400 mg (11 patients). The pharmacodynamic profile of lanadelumab was assessed by measurement of plasma levels of cleaved high-molecular-weight kininogen, and efficacy was assessed by the rate of attacks of angioedema during a prespecified period (day 8 to day 50) in the 300-mg and 400-mg groups as compared with the placebo group.

#### RESULTS

No discontinuations occurred because of adverse events, serious adverse events, or deaths in patients who received lanadelumab. The most common adverse events that emerged during treatment were attacks of angioedema, injection-site pain, and headache. Dose-proportional increases in serum concentrations of lanadelumab were observed; the mean elimination half-life was approximately 2 weeks. Lanadelumab at a dose of 300 mg or 400 mg reduced cleavage of high-molecular-weight kininogen in plasma from patients with hereditary angioedema with C1 inhibitor deficiency to levels approaching that from patients without the disorder. From day 8 to day 50, the 300-mg and 400-mg groups had 100% and 88% fewer attacks, respectively, than the placebo group. All patients in the 300-mg group and 82% (9 of 11) in the 400-mg group were attack-free, as compared with 27% (3 of 11) in the placebo group.

#### CONCLUSIONS

In this small trial, administration of lanadelumab to patients with hereditary angioedema with C1 inhibitor deficiency reduced cleavage of high-molecular-weight kininogen and attacks of angioedema. (Funded by Dyax; ClinicalTrials.gov number, NCT02093923.)

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**H**EREDITARY ANGIOEDEMA WITH C1 INHIBITOR deficiency is a rare genetic disease that is characterized by recurrent swelling episodes, typically affecting the subcutaneous or submucosal tissues of the hands and feet, abdomen, face, larynx, or genitourinary tract.<sup>1</sup> Swelling of the larynx can be life-threatening because of the risk of asphyxiation.<sup>2</sup> The disease is caused by a deficiency or dysfunction of C1 inhibitor, a key regulator of the complement, coagulation, and kallikrein–kinin cascades. In hereditary angioedema with C1 inhibitor deficiency, activation of the kallikrein–kinin cascade leads to uncontrolled generation of plasma kallikrein and consequent proteolysis of high-molecular-weight kininogen. This results in excessive bradykinin production, which causes vasodilatation, vascular leakage, and subsequent angioedema and pain.<sup>3</sup>

All patients with hereditary angioedema with C1 inhibitor deficiency must have ready access to an on-demand medication for treatment of acute attacks.<sup>4–6</sup> In addition, some patients benefit from prophylactic treatment, on the basis of a variety of criteria, including the frequency and severity of attacks, a history of airway swelling, and patient preference.<sup>4–6</sup> Currently approved prophylactic therapies include attenuated androgens (e.g., danazol) and a plasma-derived C1 inhibitor (Cinryze, Shire). Although both treatments significantly reduce the frequency and severity of attacks,<sup>7,8</sup> they have potential shortcomings. Androgens are daily medications and may have side effects; studies indicate that approximately 25% of patients with hereditary angioedema with C1 inhibitor deficiency who receive androgens discontinue them owing to unacceptable side effects.<sup>9–12</sup> The C1 inhibitor is administered intravenously every 3 to 4 days, which is difficult for some patients, and carries a theoretical risk of infection and loss of venous access owing to repetitive administration. Neither attenuated androgens nor the C1 inhibitor prevents all attacks of angioedema. Although on-demand treatments, if administered at the beginning of an attack, usually halt the attack and shorten the time to symptom resolution, patients may still have disruptions to their daily activities and anxiety associated with the unpredictable and life-threatening nature of the attacks. Thus, despite several new therapies, the burden of disease in

hereditary angioedema with C1 inhibitor deficiency remains high, with a substantial negative effect on quality of life.<sup>13–15</sup>

Lanadelumab (DX-2930) is a recombinant, fully human immunoglobulin monoclonal antibody inhibitor of kallikrein that has potential for prophylactic treatment of hereditary angioedema with C1 inhibitor deficiency.<sup>16,17</sup> We report findings from a phase 1b trial evaluating this new drug for the long-term prevention of attacks of angioedema.

## METHODS

### TRIAL DESIGN

This was a phase 1b, multicenter, randomized, double-blind, placebo-controlled, multiple-ascending-dose trial of subcutaneous administrations of lanadelumab in patients with hereditary angioedema with C1 inhibitor deficiency. The objectives were to assess safety and side-effect profile, characterize the pharmacokinetic and pharmacodynamic characteristics, and evaluate the immunogenicity of multiple subcutaneous lanadelumab administrations. In addition, the frequency of attacks of angioedema and the use of on-demand therapy were determined in higher-dose groups.

There were four dose groups (30 mg, 100 mg, 300 mg, and 400 mg), with lanadelumab administered in a staggered, dose-escalating fashion. Eligible patients were randomly assigned in a 2:1 ratio to receive either the active drug or placebo within a group. (Additional details on the trial agents are provided in the Supplementary Appendix, available with the full text of this article at NEJM.org.) If patients had attacks of angioedema, they followed standard-of-care on-demand treatment as prescribed by their physician.

The sponsor (Dyax) designed the trial with input from all the authors. The protocol (available at NEJM.org) was approved by the institutional review board or ethics committee at each participating institution. All the patients provided written informed consent before enrollment. Data were gathered by trial investigators and staff in collaboration with the sponsor. The first and subsequent drafts of the manuscript were written by the first two authors. All the authors reviewed and edited the manuscript and made the decision to submit it for publication. Editorial and technical support in the prepara-



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tion of the manuscript was provided by a professional medical writer at Dyax and by Excel Scientific Solutions. All the authors contributed to data interpretation and had access to the full data (nondisclosure agreements were in place). The authors vouch for the integrity and completeness of the data and all analyses and for adherence of the trial to the protocol. Statistical analyses were performed by ICON.

#### PATIENT RECRUITMENT

Patients were at least 18 years of age and had a documented diagnosis of type I or II hereditary angioedema with C1 inhibitor deficiency, with the diagnosis based on their meeting all the following criteria: a clinical history consistent with hereditary angioedema with C1 inhibitor deficiency, a C1 inhibitor antigen or functional level less than 40% of the normal level (patients with a C1 inhibitor antigen or functional level 40 to 50% of the normal level could be enrolled if they also had a C4 level below the normal range and a family history consistent with type I or II hereditary angioedema with C1 inhibitor deficiency), and an age at reported onset of first angioedema symptoms of 30 years or younger or a family history consistent with type I or II hereditary angioedema with C1 inhibitor deficiency. Patients must have had two or more attacks of angioedema per year, with at least one attack in the previous 6 months. Patients were excluded if they had received long-term prophylactic medications for hereditary angioedema with C1 inhibitor deficiency in the previous 90 days, used a C1 inhibitor within 7 days before trial enrollment, had participated in another investigational study in the previous 90 days, or had exposure within the previous 5 years to a monoclonal antibody or recombinant protein bearing an Fc domain.

#### BLOOD SAMPLING AND PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSES

Blood was obtained from patients with hereditary angioedema with C1 inhibitor deficiency and from healthy controls to assess the C4 level, C1 inhibitor antigen and functional level, and level of antidrug antibody and for pharmacokinetic and pharmacodynamic analyses. Samples were obtained before administration of each dose of lanadelumab or placebo (days 1 and 15) and on days 2, 4, 8, 16, 18, 22, 29, 36, 50, 64, 92, and

120 in all four dose groups. (Details are provided in the Supplementary Appendix.)

#### EFFICACY

Prespecified efficacy analyses were performed on data from patients in the higher-dose lanadelumab groups (300 mg or 400 mg) or in the placebo group who had had two or more attacks of angioedema during the 3 months before enrollment. Thus, the analyses included patients who had a reasonable probability of having one or more attacks during the 6-week interval from day 8 to day 50 (primary efficacy analysis population). The primary efficacy end point was the number of attacks of angioedema per week from day 8 to day 50. A post hoc modified intention-to-treat efficacy analysis was performed that excluded two patients. One patient prematurely discontinued the trial after one dose, and the other patient was found after trial enrollment not to have met the criteria for hereditary angioedema with C1 inhibitor deficiency (C1 inhibitor testing was not consistent with type I or II hereditary angioedema despite historical laboratory tests indicating otherwise). (For a discussion of the patients' removal, see the Supplementary Appendix.)

#### SAFETY

Safety variables were adverse events, including serious adverse events; vital signs (blood pressure while the patient was sitting or in the supine position, heart rate, oral body temperature, and respiratory rate); physical examination; clinical laboratory testing (hematologic measurements, clinical chemical analyses, coagulation tests, and urinalysis); 12-lead electrocardiography; and plasma levels of antidrug antibodies (details of safety variables are provided in the Supplementary Appendix).

#### STATISTICAL ANALYSIS

Statistical analysis and programming of tables were performed with the use of SAS software (SAS Institute). We analyzed rates of attacks of angioedema using a mixed model of repeated measurements with the assumption of a Poisson distribution and using the baseline attack rate as a covariate. Missing data were not imputed. For additional details on the statistical analyses, see the Supplementary Appendix.

## RESULTS

## BASELINE CHARACTERISTICS OF THE PATIENTS

A total of 37 patients with hereditary angioedema with C1 inhibitor deficiency were randomly assigned to one of five groups (four lanadelumab dose groups and a placebo group). The majority of the patients were women (62%), although the 300-mg group had a higher percentage of men than women (80% vs. 20%). The mean age was 39.9 years (range, 18 to 71). All the patients were white, and 1 identified as Hispanic or Latino. Patient characteristics are shown in Table 1. The mean number of attacks of angioedema in the previous 3 months was similar in patients who received lanadelumab and those who received placebo, as was the number of attacks in the previous 12 months. A total of 84% of the patients had a diagnosis of type I hereditary angioedema, 11% had a diagnosis of type II, and 5% had an unspecified type (either type I or type II). Among the 29 patients who had received on-

demand treatment for attacks of angioedema during the previous 3 months, icatibant (17 patients) was the most common therapy.

## SAFETY

The safety population included all randomly assigned patients who received at least one dose of lanadelumab or placebo (24 patients received lanadelumab, and 13 received placebo); this population was evaluated for safety in all four dose groups (Table S1 in the Supplementary Appendix). No notable differences in adverse events were apparent across dose groups. A total of 58% of the patients who received lanadelumab and 77% of those who received placebo had at least one adverse event that emerged during treatment (Table 2). Adverse events that occurred in at least 5 patients overall were attacks of angioedema, injection-site pain, and headache. Rates of these adverse events were not appreciably higher among patients who received lanadelumab than among those who received placebo.

**Table 1. Baseline Characteristics of Patients with Hereditary Angioedema with C1 Inhibitor Deficiency.\***

Characteristic	Lanadelumab Dose Group				Total Lanadelumab (N=24)	Placebo (N=13)	All Patients (N=37)
	30 mg (N=4)	100 mg (N=4)	300 mg (N=5)	400 mg (N=11)			
Sex — no. (%)							
Male	1 (25)	1 (25)	4 (80)	2 (18)	8 (33)	6 (46)	14 (38)
Female	3 (75)	3 (75)	1 (20)	9 (82)	16 (67)	7 (54)	23 (62)
Age — yr							
Mean	46.3±15.5	36.3±18.0	33.2±10.0	40.5±14.3	39.3±14.1	41.2±13.7	39.9±13.8
Range	23–55	25–63	22–46	20–68	20–68	18–71	18–71
Attacks of angioedema in the previous 12 mo							
Mean	7.0±4.2	10.5±6.7	14.8±12.4	35.2±38.8	22.1±29.1	22.7±35.9	22.3±31.2
Range	3–12	5–20	6–36	11–144	3–144	3–140	3–144
Attacks of angioedema in the previous 3 mo							
Mean	2.0±0.8	3.5±1.7	3.6±3.1	9.5±9.0	6.0±7.0	6.3±8.9	6.1±7.6
Range	1–3	2–5	1–9	3–36	1–36	0–35	0–36
History of laryngeal attack — no. (%)							
Yes	0	1 (25)	2 (40)	8 (73)	11 (46)	6 (46)	17 (46)
No	4 (100)	3 (75)	3 (60)	3 (27)	13 (54)	7 (54)	20 (54)

\* Plus-minus values are means ±SD.

**Table 2. Summary of Adverse Events.**

Event	Lanadelumab Dose Group				Total Lanadelumab (N=24)	Placebo (N=13)	All Patients (N=37)
	30 mg (N=4)	100 mg (N=4)	300 mg (N=5)	400 mg (N=11)			
	<i>number of patients (percent)</i>						
Adverse events that emerged during treatment*	1 (25)	3 (75)	2 (40)	8 (73)	14 (58)	10 (77)	24 (65)
Attack of angioedema	0	3 (75)	1 (20)	5 (45)	9 (38)	9 (69)	18 (49)
Injection-site pain	1 (25)	2 (50)	0	3 (27)	6 (25)	3 (23)	9 (24)
Headache	0	2 (50)	1 (20)	1 (9)	4 (17)	3 (23)	7 (19)
Treatment-related adverse events†	1 (25)	2 (50)	0	4 (36)	7 (29)	5 (38)	12 (32)
Injection-site pain	1 (25)	2 (50)	0	3 (27)	6 (25)	3 (23)	9 (24)
Headache	0	1 (25)	0	1 (9)	2 (8)	2 (15)	4 (11)
Injection-site erythema	0	0	0	1 (9)	1 (4)	2 (15)	3 (8)

\* An adverse event was considered to have emerged during treatment if the time of onset was after administration of a trial agent through the day 120 postdose final follow-up visit or, in the event that the time of onset preceded administration of the trial agent, the adverse event increased in severity during the 120-day postdose follow-up period. Shown are events that occurred in at least five patients during the trial. A total of 25% of the patients who received lanadelumab and 38% of those who received placebo had a severe adverse event that emerged during treatment.

† These events were considered to be related to a trial agent by a trial investigator who was unaware of the trial-group assignments.

A total of 25% of the patients who received lanadelumab and 38% of those who received placebo had a severe adverse event that emerged during treatment.

A total of 29% of the patients who received lanadelumab and 38% of those who received placebo had an adverse event that was considered by trial investigators, who were unaware of the trial-group assignments, to be treatment-related (Table 2). The most common treatment-related adverse events were injection-site pain (occurring in 25% of the patients who received lanadelumab and in 23% of those who received placebo) and headache (occurring in 8% of the patients who received lanadelumab and in 15% of those who received placebo). Two patients who received lanadelumab had severe adverse events that were considered to be treatment-related: one patient (in the 30-mg group) had injection-site pain that lasted for 1 minute, and another (in the 400-mg group) had worsening headache and ongoing night sweats. There were no deaths or discontinuations due to an adverse event that emerged during treatment and no important safety signals in patients who received lanadelumab or placebo. There were no serious adverse events in patients who received lanadel-

umab. One serious adverse event, pneumonia, occurred on day 87 in one patient who received placebo.

#### ANTIDRUG ANTIBODIES

Two of the patients included in the safety analysis were confirmed to be positive for antidrug antibodies. One patient (30-mg dose group) tested positive at day 120, and the other patient (400-mg dose group) tested positive at day 92. All antidrug antibodies were nonneutralizing. There was no evidence of loss of pharmacokinetic or pharmacodynamic effect of lanadelumab in either patient who was positive for antidrug antibodies.

#### PHARMACOKINETIC AND PHARMACODYNAMIC CHARACTERISTICS

The pharmacokinetic analysis population included all randomly assigned patients with hereditary angioedema with C1 inhibitor deficiency who received at least one dose of lanadelumab and had sufficient blood samples (22 patients); the pharmacodynamic analysis population included these patients plus the 13 patients who received at least one dose of placebo (total, 35 patients) (Table S1 in the Supplementary Appendix).



Drug levels of lanadelumab were dose-dependent and had a prolonged half-life, typical of a human monoclonal antibody. The maximum plasma concentration of lanadelumab increased with increasing dose, and the half-life ranged from 13.8 to 15.0 days (Fig. 1A). In addition, sustained quantifiable drug concentrations were observed through day 120 in all lanadelumab dose groups. These characteristics were consistent with values obtained in a phase 1a study involving healthy volunteers.<sup>16</sup>

Two different methods were used to determine kallikrein activity. A Western blot assay measured cleaved high-molecular-weight kininogen, the endogenous substrate of kallikrein, as a biomarker of its activity. Predose plasma across all patients with hereditary angioedema with C1 inhibitor deficiency when they were asymptomatic (Fig. 1B) contained a mean ( $\pm$ SE) level of cleaved high-molecular-weight kininogen of  $51.0 \pm 4.2\%$  (95% confidence interval [CI], 43.6 to 59.9). In contrast, predose samples obtained from healthy controls without hereditary angioedema with C1 inhibitor deficiency contained a mean level of cleaved high-molecular-weight kininogen of  $8.3 \pm 0.5\%$  (95% CI, 7.2 to 9.4). Therefore, plasma from patients with hereditary angioedema with C1 inhibitor deficiency had higher levels of circulating cleaved high-molecular-weight kininogen than plasma from healthy controls. No significant differences in mean levels of cleaved high-molecular-weight kininogen were observed between the 30-mg dose group or the 100-mg dose group and the placebo group.

An evaluation of mean plasma levels of cleaved high-molecular-weight kininogen showed significant reductions ( $P < 0.05$ ) from predose levels in the 300-mg and 400-mg dose groups in samples obtained on day 8 and on day 22. Maximum reductions in levels of cleaved high-molecular-weight kininogen in the 300-mg and 400-mg dose groups occurred on day 22, which approximates the time to maximum plasma concentration of the drug after the second lanadelumab administration. Furthermore, in these dose groups, the level of cleaved high-molecular-weight kininogen approached that observed in healthy volunteers ( $8.3 \pm 0.5\%$ ), which shows the pharmacodynamic activity of lanadelumab and suggests its potential to normalize the instability of plasma with respect to excess contact-system activation in patients with hereditary angioedema with C1 inhibitor deficiency. In addition,

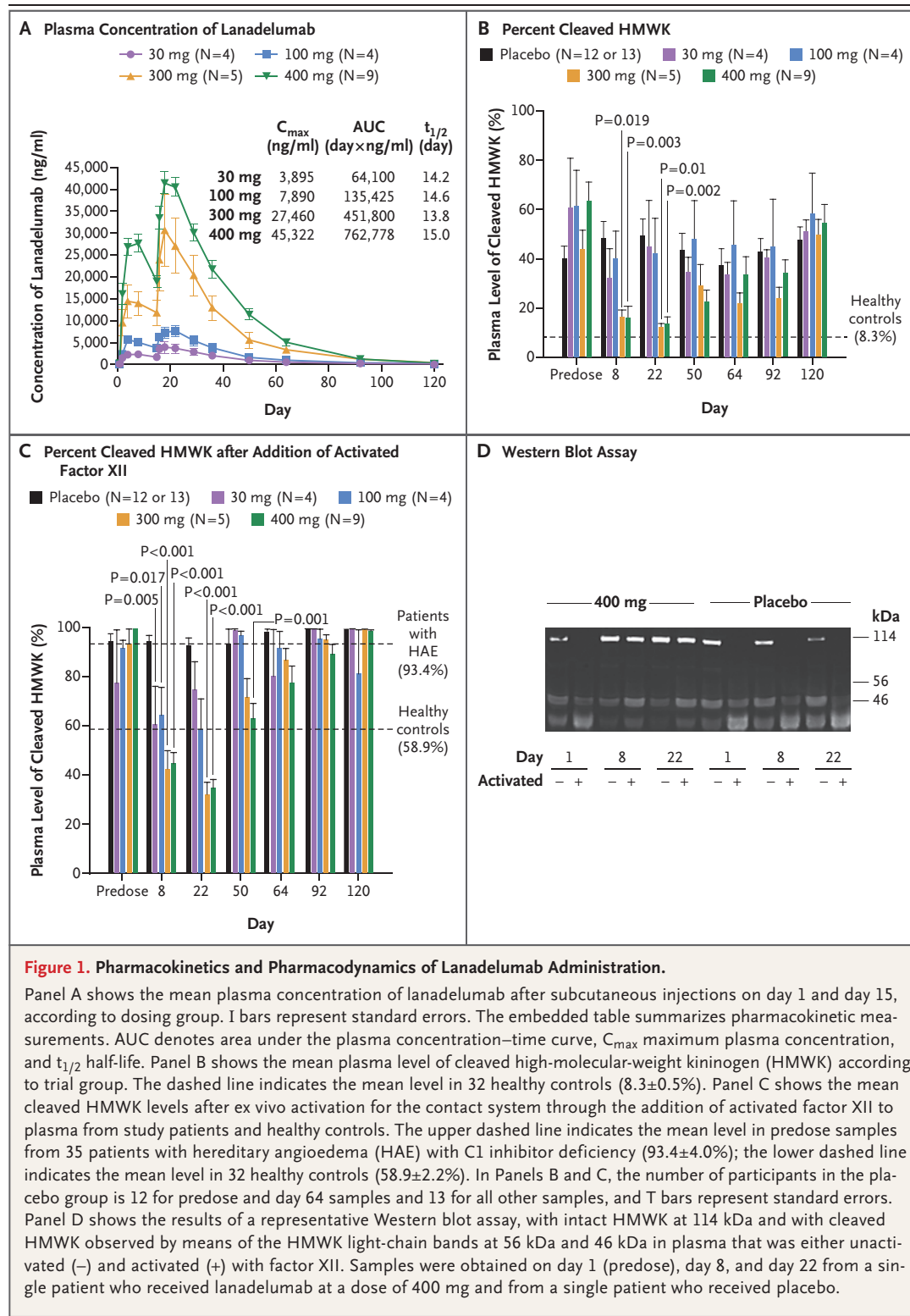
lanadelumab suppressed activated factor XII-mediated increases in the percent of cleaved high-molecular-weight kininogen in a dose-dependent manner (Fig. 1C and 1D).

The pharmacodynamic activity of lanadelumab was also evaluated with the use of a fluorogenic assay, which showed dose-dependent kallikrein inhibition in samples obtained from patients in the 100-mg, 300-mg, and 400-mg dose groups (Fig. S1 in the Supplementary Appendix). Minimal levels of inhibition were observed in the 30-mg dose group and in the placebo group. After the second administration of lanadelumab in the 100-mg, 300-mg, and 400-mg dose groups, peak inhibition values of approximately 30%, 60%, and 70%, respectively, were observed. The inhibition was time-dependent and aligned closely with the plasma concentrations of lanadelumab, findings that suggest that the effect of lanadelumab treatment correlates with its biologic activity.

#### EFFICACY

We evaluated the efficacy of lanadelumab by assessing the incidence of attacks of angioedema among patients with hereditary angioedema with C1 inhibitor deficiency who were assigned to the 300-mg, 400-mg, and placebo groups and who received two doses of the trial agent (Table S1 in the Supplementary Appendix). All the patients (receiving lanadelumab or placebo) included in this analysis had a historical baseline attack rate of 2 or more attacks in the 3 months before enrollment. The baseline rate of attacks of angioedema per week was 0.33 in the 300-mg group, 0.55 in the 400-mg group, and 0.39 in the placebo group (Table 3). With the removal of the 2 patients in the 400-mg group for the modified intention-to-treat analysis, the rate of attacks did not change significantly (0.52 attacks per week).

Between day 8 and day 50, all the patients in the 300-mg group were attack-free, as compared with 3 of 11 patients (27%) in the placebo group, representing a rate of attacks per week of 0 versus 0.37 ( $P < 0.001$ ). Nine of 11 patients (82%) in the 400-mg group were attack-free, representing a rate of attacks per week (0.05) that was significantly lower than the rate with placebo ( $P = 0.005$ ). Patients in the 300-mg group, 400-mg group, and combined 300-mg and 400-mg groups had 100%, 88%, and 91% fewer attacks, respectively, than patients in the placebo group. In the post hoc modified intention-to-treat analysis (exclud-



**Figure 1. Pharmacokinetics and Pharmacodynamics of Lanadelumab Administration.**

Panel A shows the mean plasma concentration of lanadelumab after subcutaneous injections on day 1 and day 15, according to dosing group. I bars represent standard errors. The embedded table summarizes pharmacokinetic measurements. AUC denotes area under the plasma concentration–time curve,  $C_{max}$  maximum plasma concentration, and  $t_{1/2}$  half-life. Panel B shows the mean plasma level of cleaved high-molecular-weight kinogen (HMWK) according to trial group. The dashed line indicates the mean level in 32 healthy controls ( $8.3\pm 0.5\%$ ). Panel C shows the mean cleaved HMWK levels after ex vivo activation for the contact system through the addition of activated factor XII to plasma from study patients and healthy controls. The upper dashed line indicates the mean level in predose samples from 35 patients with hereditary angioedema (HAE) with C1 inhibitor deficiency ( $93.4\pm 4.0\%$ ); the lower dashed line indicates the mean level in 32 healthy controls ( $58.9\pm 2.2\%$ ). In Panels B and C, the number of participants in the placebo group is 12 for predose and day 64 samples and 13 for all other samples, and T bars represent standard errors. Panel D shows the results of a representative Western blot assay, with intact HMWK at 114 kDa and with cleaved HMWK observed by means of the HMWK light-chain bands at 56 kDa and 46 kDa in plasma that was either unactivated (–) and activated (+) with factor XII. Samples were obtained on day 1 (predose), day 8, and day 22 from a single patient who received lanadelumab at a dose of 400 mg and from a single patient who received placebo.

ing 2 patients in the 400-mg group), the 400-mg group had 95% fewer attacks than the placebo group ( $P=0.002$ ), and the combined 300-mg and

400-mg groups had 97% fewer attacks than the placebo group ( $P<0.001$ ).

Table S2 in the Supplementary Appendix

**Table 3. Attacks of Angioedema in the Lanadelumab 300-mg and 400-mg Groups and the Placebo Group.\***

Trial Group	At Baseline†	Day 8 to Day 50	P Value‡
<b>Lanadelumab 300 mg</b>			
Patient no. — attacks/wk			
1	0.23	0	
2	0.15	0	
3	0.69	0	
4	0.23	0	
Patients 1–4			
Mean attacks/wk	0.33	0	
Relative decrease vs. placebo in rate of attacks — %			
Primary analysis§	NA	100	<0.001
Modified analysis¶	NA	100	<0.001
<b>Lanadelumab 400 mg</b>			
Patient no. — attacks/wk			
5	0.31	0	
6	0.23	0	
7	0.69	0	
8	0.62	0	
9	0.62	0.33	
10	2.77	0	
11	0.46	0.17	
12	0.69	0	
13	0.46	0	
14	0.69	0	
15	0.46	0	
Patients 5–15			
Mean attacks/wk	0.55	0.05	
Relative decrease vs. placebo in rate of attacks — %			
Primary analysis§	NA	88	0.005
Modified analysis¶	NA	95	0.002
<b>Placebo</b>			
Patient no. — attacks/wk			
16	0.23	0	
17	0.31	0.67	
18	0.46	0.67	
19	2.69	0.67	
20	0.23	1.50	
21	0.31	0.33	
22	0.46	0.17	
23	0.54	0.33	
24	0.23	0.17	
25	0.23	0	
26	0.54	0	



**Table 3. (Continued.)**

Trial Group	At Baseline <sup>†</sup>	Day 8 to Day 50	P Value <sup>‡</sup>
Mean attacks/wk in patients 16–26	0.39	0.37	

\* Only patients who had had at least two attacks of angioedema in the 3 months before enrollment were included. NA denotes not applicable.

<sup>†</sup> Baseline was defined as the 3 months before day 1 of dosing.

<sup>‡</sup> The P value is for the comparison with placebo from day 8 to day 50.

§ The result is based on general estimating equation (GEE) analysis of repeated counts per week during the observation period (days 8 to 50). The baseline rate of attacks of angioedema per week is a covariate, trial group is a fixed effect, and trial participant is a random effect in the GEE model with an independent working correlation structure. The observed rate of attacks per week was 0% in the 300-mg group, and thus an arbitrarily small value (0.000001) was imputed for the variable of the rate of attacks for a random patient in the 300-mg group at week 2 to enable the GEE analysis to converge.

¶ Two patients in the 400-mg group were excluded from the modified efficacy analysis: one patient who received only one dose of lanadelumab and was subsequently lost to follow-up and one patient who did not have type I or II hereditary angioedema.

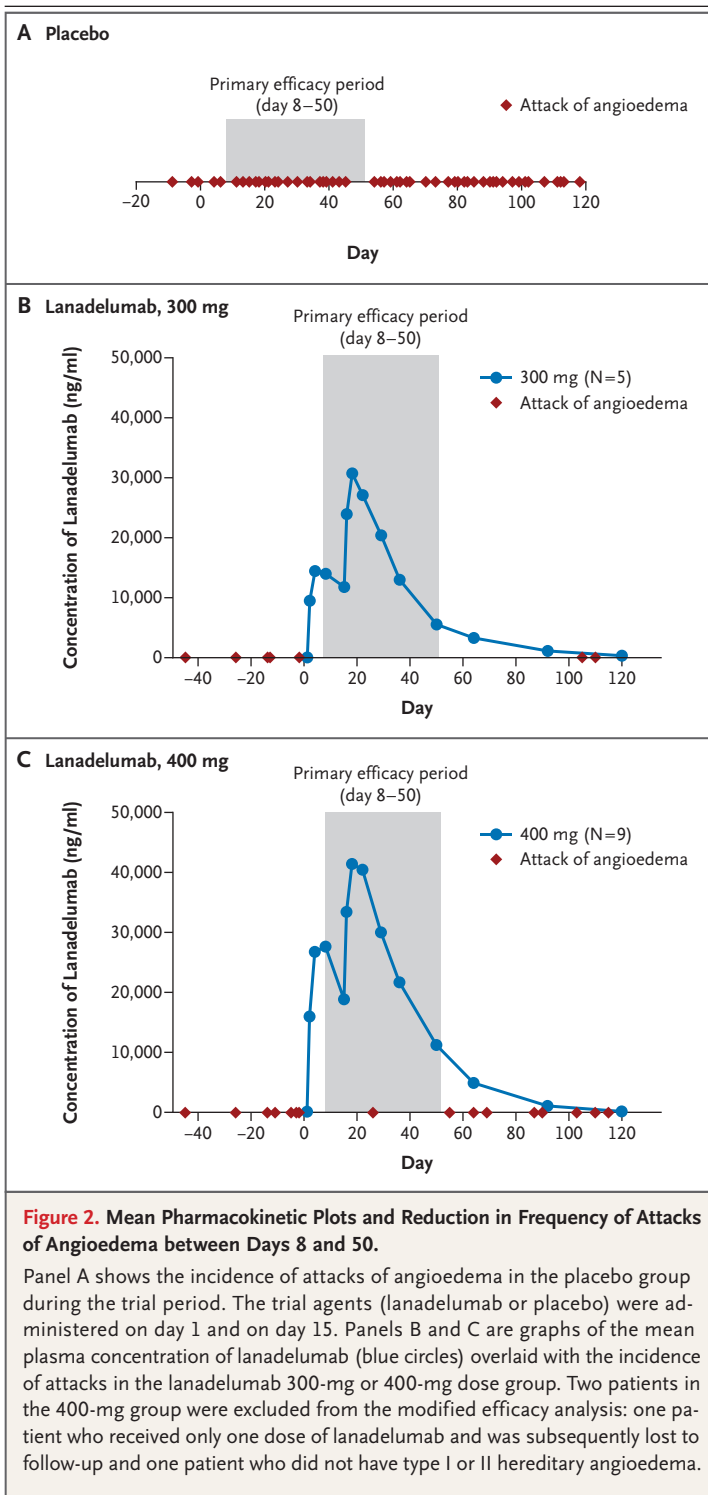
shows the characteristics of attacks of angioedema (location, severity, and on-demand treatment) that occurred during the period from day 8 to day 50 in patients with hereditary angioedema with C1 inhibitor deficiency who were included in the prespecified primary efficacy analysis. These data suggest a consistent response to treatment, regardless of baseline severity. The moderate and severe attacks that occurred in the patient who received only one dose of lanadelumab (and was therefore not included in the modified intention-to-treat efficacy analysis) are included in that table.

Figure 2A shows the incidence of attacks of angioedema during the trial period among patients who received placebo. We next examined the relationship between lanadelumab drug exposure and the incidence of attacks. In order to correlate drug exposure and the incidence of attacks, the mean plasma concentrations of lanadelumab were plotted against the days when attacks occurred in the 300-mg and 400-mg groups (Fig. 2B and 2C). During the primary efficacy window (day 8 to day 50), the incidence of attacks decreased among patients who received lanadelumab at a dose of 300 mg or 400 mg, with attacks reemerging when the drug concentration decreased. The one attack that occurred during the efficacy period was a mild peripheral attack that resolved within 8 hours without treatment. Although the 30-mg and 100-mg groups were not included in the primary analysis population, the incidence of attacks also decreased in these groups (Fig. S2 in the Supplementary Appendix).

## DISCUSSION

This 6-week phase 1b trial involving patients with hereditary angioedema with C1 inhibitor deficiency suggests that two administrations of lanadelumab 14 days apart are safe at a total dose of up to 400 mg. In the primary efficacy and modified intention-to-treat analyses, two administrations of lanadelumab at a total dose of 300 mg or 400 mg appeared to be effective in preventing attacks of angioedema, resulting in 100% and 88% fewer attacks, respectively, than the number of attacks with placebo. The pharmacokinetic profile of lanadelumab was linear and dose-dependent and had a prolonged half-life of approximately 14 days, typical of a human monoclonal antibody. The decrease in attacks of angioedema strongly correlated with drug exposure, which corroborated the results of the efficacy analysis. In addition, pharmacodynamic results confirmed kallikrein inhibition in a dose-dependent and time-dependent manner. Results from the Western blot assay suggested the potential to normalize levels of cleaved high-molecular-weight kininogen to those of healthy controls after doses of 300 mg or greater. We believe that the observed effects of lanadelumab, both the pharmacodynamic characteristics and the decrease in the rate of attacks, provide proof of concept that lanadelumab has the potential to correct the pathophysiological abnormality underlying attacks of angioedema and may be a new therapeutic option for hereditary angioedema with C1 inhibitor deficiency.

Unregulated kallikrein is a key pathophysio-



logical defect that is responsible for the development of attacks of angioedema, and the importance of kallikrein as a drug target has been

validated through the effectiveness of ecallantide (Kalbitor, Dyax), which specifically targets kallikrein.<sup>18</sup> The Western blot biomarker assay measuring cleaved high-molecular-weight kininogen provides evidence that lanadelumab causes a dose-dependent decrease of kallikrein activity in patients with hereditary angioedema with C1 inhibitor deficiency. At baseline, patients with hereditary angioedema with C1 inhibitor deficiency had elevated plasma levels of cleaved high-molecular-weight kininogen; this finding is similar to those of previous reports.<sup>19</sup> To minimize intersite variability, all sites obtained and processed plasma in a standardized fashion and added protease inhibitors to minimize cleavage (Fig. S3 in the Supplementary Appendix).<sup>19,20</sup>

The 300-mg and 400-mg doses reduced cleaved high-molecular-weight kininogen in both unactivated and activated factor XII samples to levels approaching those observed in healthy controls. In addition, the activity of lanadelumab, evaluated with the use of the fluorogenic assay, showed dose-dependent kallikrein inhibition in samples collected from the 100-mg, 300-mg, and 400-mg dose groups (Fig. S1 in the Supplementary Appendix). Collectively, these results show the activity of lanadelumab and suggest its ability to potentially normalize the instability of plasma with respect to excess contact-system activation in patients with hereditary angioedema with C1 inhibitor deficiency. Furthermore, the reduction in attacks of angioedema observed during periods of high drug exposure suggests that prolonged inhibition of kallikrein is an effective prophylactic approach to hereditary angioedema with C1 inhibitor deficiency.

This phase Ib trial supports the continued investigation of lanadelumab. No patients discontinued the trial because of adverse events, and the low incidence and severity of adverse events and the type of events did not indicate a safety signal. Fletcher factor deficiency, a condition characterized by a severe congenital deficiency of prekallikrein, suggests limited risk from long-term kallikrein inhibition, since there are no obvious clinical complications directly attributable to the defect.<sup>21-24</sup> Although the efficacy results of this trial are encouraging, the duration of the trial was relatively short. A phase 3 trial evaluating the safety and efficacy of 6 months of lanadelumab treatment is under way (ClinicalTrials.gov number, NCT02586805).

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#### APPENDIX

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