




ORIGINAL ARTICLE

Atopic Dermatitis, Urticaria and Skin Disease

Long-term prevention of hereditary angioedema attacks with lanadelumab: The HELP OLE Study

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Funding information

This study was sponsored by Shire Human Genetic Therapies, Inc., a Takeda company. Under the direction of the authors, Sophia Shumyatsky, PharmD, CMPP, employee of Excel Medical Affairs, provided writing assistance for this manuscript. Editorial assistance in formatting, proofreading, copyediting, and fact-checking also was provided by Excel Medical Affairs. Takeda Development Center Americas, Inc. provided funding to Excel Medical Affairs for support in writing and editing this manuscript. The interpretation of the data was made by the authors independently.

Abstract

Background: The aim was to evaluate long-term effectiveness and safety of lanadelumab in patients ≥ 12 y old with hereditary angioedema (HAE) 1/2 (NCT02741596).

Methods: Rollover patients completing the HELP Study and continuing into HELP OLE received one lanadelumab 300 mg dose until first attack (dose-and-wait period), then 300 mg q2wks (regular dosing stage). Nonrollovers (newly enrolled) received lanadelumab 300 mg q2wks from day 0. Baseline attack rate for rollovers: ≥ 1 attack/4 weeks (based on run-in period attack rate during HELP Study); for nonrollovers: historical attack rate ≥ 1 attack/12 weeks. The planned treatment period was 33 months.

Results: 212 patients participated (109 rollovers, 103 nonrollovers); 81.6% completed ≥ 30 months on study (mean [SD], 29.6 [8.2] months). Lanadelumab markedly reduced mean HAE attack rate (reduction vs baseline: 87.4% overall). Patients were attack free for a mean of 97.7% of days during treatment; 81.8% and 68.9% of patients were attack free for ≥ 6 and ≥ 12 months, respectively. Angioedema Quality-of-Life total and domain scores improved from day 0 to end of study. Treatment-emergent adverse events (TEAEs) (excluding HAE attacks) were reported by 97.2% of patients;

Abbreviations: HAE, hereditary angioedema; q2wks, every 2 weeks, OLE, open-label extension.

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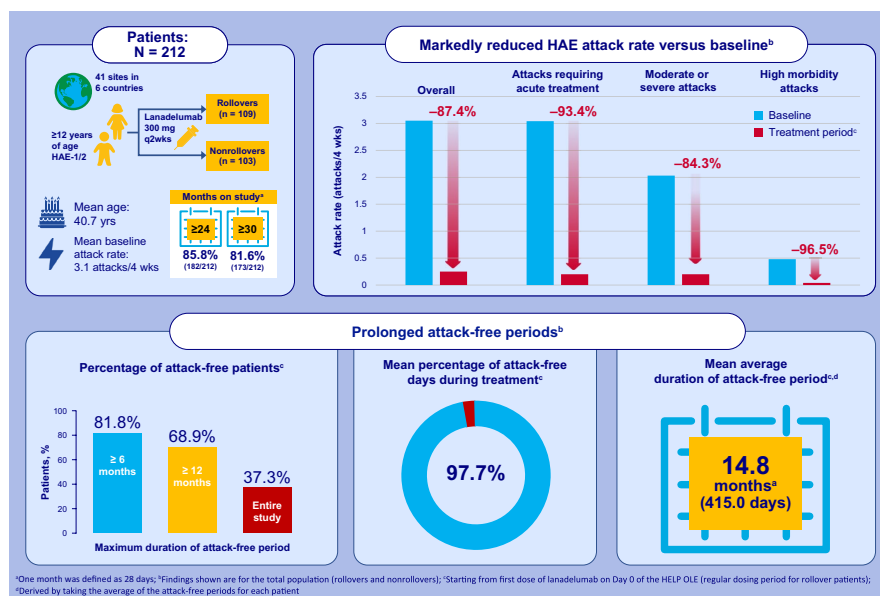
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most commonly injection site pain (47.2%) and viral upper respiratory tract infection (42.0%). Treatment-related TEAEs were reported by 54.7% of patients. Most injection site reactions resolved within 1 hour (70.2%) or 1 day (92.6%). Six (2.8%) patients discontinued due to TEAEs. No treatment-related serious TEAEs or deaths were reported. Eleven treatment-related TEAEs of special interest were reported by seven (3.3%) patients.

Conclusion: Lanadelumab demonstrated sustained efficacy and acceptable tolerability with long-term use in HAE patients.

KEYWORDS

HAE, HAE attacks, HELP OLE, hereditary angioedema, lanadelumab, long-term prophylaxis



GRAPHICAL ABSTRACT

Lanadelumab markedly reduced mean HAE attack rates versus baseline. Most patients were exposed to lanadelumab for an extended time and experienced prolonged attack-free intervals. The final results from the HELP OLE further support the long-term tolerability of lanadelumab 300 mg q2wks previously shown in the HELP Study and confirm the sustained benefit of treatment for long-term prevention of HAE attacks. Abbreviations: HAE, hereditary angioedema; q2wks, every 2 weeks, OLE, open label extension

1 | INTRODUCTION

Hereditary angioedema (HAE) is a rare disease primarily caused by mutations in the *SERPING1* gene, leading to C1-inhibitor (C1-INH) deficiency and/or dysfunction (HAE type 1 or 2 [HAE-1/2]).¹ Symptoms manifest as recurrent, often painful attacks characterized by swelling of subcutaneous or submucosal tissues. Abdominal attacks can be severely debilitating, and laryngeal attacks can be fatal owing to risk of asphyxiation.²⁻⁵

The chronic and unpredictable nature of HAE, coupled with the risk of severe attacks and temporary disfigurement, contributes to restrictions on daily activities, reduced productivity at work or school, emotional impairment, and a fear of future attacks that continues to affect patients even during attack-free periods.^{6,7} Importantly, the frequency of attacks does not correlate

with their severity⁵ (even the first laryngeal edema attack can be fatal),⁸ and the historical anatomical location of attacks does not predict future attack sites. Long-term prophylaxis (LTP) aims to reduce the heavy physical and psychological burden of this disease; the quest to achieve prolonged attack-free periods or attain complete control and normalize patients' daily lives is a continuing goal.^{1,5,9,10}

Enhanced understanding of the underlying pathophysiology of HAE, including the critical role plasma kallikrein plays in its pathogenesis,¹¹ has substantially broadened the treatment armamentarium of targeted agents for this disease. Lanadelumab is a subcutaneously administered fully human monoclonal antibody that acts as a potent and specific inhibitor of active plasma kallikrein.¹² This agent is approved in the United States,¹³ the European Union,¹⁴ and several other countries and regions for the prevention of HAE

attacks in patients 12 years of age or over and is recommended as a first-line option for LTP by the International/Canadian Hereditary Angioedema Guideline and the US HAE Association Medical Advisory Board 2020 guidelines for the management of hereditary angioedema.^{15,16}

In the phase 3, randomized, double-blind HELP (Hereditary angioEdema Long-term Prophylaxis) Study (NCT02586805), lanadelumab (300 mg every 2 weeks [q2wks]) decreased HAE attack rates by ~87% compared with placebo ($p < 0.001$), and ~44% of patients were attack free during the 26 week treatment period (days 0-182).¹⁷ Additionally, findings from *ad hoc* analyses have demonstrated that efficacy of lanadelumab is evident from the first 2 weeks of treatment and is sustained.¹⁸

HAE is a lifelong disease; evaluating the patient experience with LTP over extended time periods provides valuable insight and helps fill current gaps in knowledge. The phase 3 open-label extension of the HELP Study (HELP OLE; NCT02741596) evaluated lanadelumab use over a mean of approximately 30 months of treatment; key findings are presented herein.

2 | METHODS

This study was conducted in accordance with the International Council for Harmonisation Good Clinical Practice Guideline, the principles of the Declaration of Helsinki, and other applicable local ethical and legal requirements. Patients' informed consent and assent were obtained.

2.1 | Study design

The design of the HELP OLE has been previously described in detail by Riedl et al.¹⁹ In brief, all patients with HAE-1/2 who completed the HELP Study were able to immediately enter the HELP OLE (rollovers), and eligible patients who had not previously participated were also able to enter (nonrollovers) (Figure S1). All patients, caregivers, investigators, and study site staff were blinded to the treatment assignment patients had received in the HELP Study until the conclusion of the HELP OLE.

The timing at which lanadelumab was administered differed for rollovers and nonrollovers. Rollover patients received a single 300 mg dose on day 0 (which coincided with the last visit [day 182] of the HELP Study), and treatment was then paused until patients experienced their first investigator-confirmed HAE attack—this period was the dose-and-wait stage. Upon occurrence of their first attack, patients received their second dose and then continued to receive lanadelumab 300 mg q2wks for the remainder of the study—this period was the regular dosing stage. In contrast, non-rollover patients received lanadelumab 300 mg from day 0 and continued receiving this dose q2wks for the remainder of the study. Importantly, efficacy analyses for rollover patients were based on occurrence of attacks during the regular dosing stage (ie, the first HAE attack during the dose-and-wait period was not counted), whereas efficacy analyses for nonrollover patients were based on attacks occurring from day 0.

An amendment to the study protocol was implemented from the time the study design for the HELP OLE was initially described,¹⁹

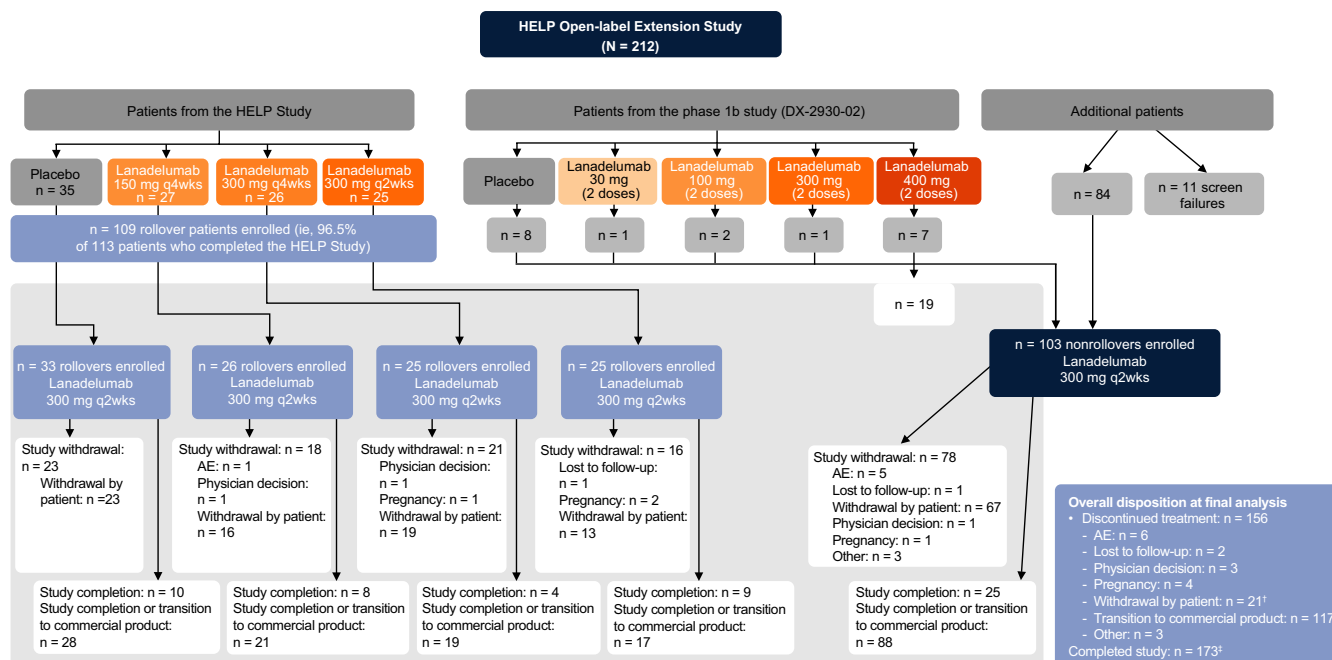


FIGURE 1 Patient disposition. [†]The category “withdrawal by patient” also included patients who transitioned to the commercial product (n = 117); see Table S1. [‡]The number of patients who completed the study (n = 173) includes patients who transitioned to the commercial product (n = 117), as well those who remained in the study for its entire duration (n = 56). AE, adverse event; q2wks, every 2 weeks; q4wks, every 4 weeks

extending the planned treatment duration from 364 days to 924 days (132 calendar weeks or 33 months [4 weeks/month]).

2.2 | Patient eligibility

For both rollover and nonrollover patients, key eligibility criteria included an age of 12 years or over and a documented diagnosis of HAE-1/2; the full list of inclusion and exclusion criteria have been described previously.¹⁹ Notably, the baseline attack rate for rollover patients (≥ 1 attack/4 weeks) was based on their attack rate during the run-in period of the HELP Study, whereas eligible nonrollover patients were required to have a self-reported historical attack rate of ≥ 1 attack within 12 weeks.

2.3 | Study objectives and assessments

The primary objective of the HELP OLE was to evaluate long-term safety of repeated lanadelumab dosing. Secondary objectives included evaluation of long-term efficacy in preventing attacks, and characterization of the dosing frequency (based on the duration of time between the first open-label dose for rollover patients and their first HAE attack). The planned safety and efficacy outcome measures have been described previously.¹⁹ As with the HELP Study,¹⁷ efficacy in the HELPOLE was assessed by analyzing the number of investigator-confirmed HAE attacks during the treatment period, expressed as a monthly HAE attack rate (a month was defined as 28 days). Attack rates were analyzed for rollover and nonrollover patients.

Exploratory analyses evaluated outcomes related to the attack-free period, including number of attack-free days, percentage of patients who were attack free during the treatment period, and duration of the attack-free period. The validated Angioedema Quality of Life Questionnaire (AE-QoL) was among the patient-reported outcome tools used to evaluate patients' quality of life (QoL). This symptom-specific QoL questionnaire measures four dimensions with a total of 17 items. Scores range from 0 to 100—the higher the score, the greater the QoL impairment. The minimal clinically important difference for the AE-QoL total score is defined as a change of 6 points.^{20,21}

2.4 | Statistical and analytical plan

All statistical analyses were performed using SAS[®] Version 9.3 or higher (SAS Institute, Cary, NC, USA). Time to first investigator-confirmed HAE attack for rollover patients was summarized using Kaplan-Meier methods. All analyses in this study were performed using the safety population (all patients with any exposure to open-label lanadelumab). For categorical variables, the number and percentage of patients in each category are presented. For continuous variables, the number of patients, mean, median, SD, minimum, and maximum values are presented. No formal hypothesis testing was performed.

3 | RESULTS

3.1 | Lanadelumab exposure, patient demographics, and baseline characteristics

A total of 212 patients were treated with lanadelumab, including 109 rollovers and 103 nonrollovers. Of patients enrolled, 173 (81.6%) either completed the HELP OLE ($n = 56$) or voluntarily withdrew and transitioned to the commercial product when lanadelumab became available ($n = 117$). Patient disposition is shown in Figure 1; reasons for study withdrawal are shown in Table S1. Patients were exposed to lanadelumab over a mean (SD) of 29.6 (8.2) months (median [range], 33.0 [1.4-34.2] months). The majority of patients (92.5%) completed ≥ 12 months in the study; 81.6% completed ≥ 30 months (Table 1).

Baseline demographics and clinical characteristics of enrolled patients are shown in Table 1. Patients were predominantly female (67.5%) and had HAE-1 (89.2%). The mean baseline attack rate was 3.1 attacks/4 weeks. Most patients (59.4%) had received prior LTP (50.0% with C1-INH only; 6.1% with oral therapy only; 3.3% with C1-INH and oral therapy).

3.2 | Efficacy evaluations

3.2.1 | Attack rate reduction versus baseline

Excluding the dose-and-wait period in rollover patients, a total of 1181 HAE attacks occurred during the treatment period. As shown in Table 2, the maximum HAE attack severity was moderate for 34.0% of patients and severe for 20.1%. Attacks most often affected the abdomen.

Treatment with lanadelumab reduced the mean HAE attack rate by 87.4% overall compared with baseline (92.4% for rollovers, 82.0% for nonrollovers). Marked reductions were also shown in the rate of attacks requiring acute treatment (93.4%), moderate or severe attacks (84.3%), and high-morbidity attacks (96.5%; Figure 2A). Most patients (96.6%) achieved a reduction in HAE attacks of $\geq 50\%$ during the treatment period; 75.5% of patients achieved a reduction of $\geq 90\%$ (Figure 2B). Of note, the mean (SD) attack rate per month of 3.1 (2.7) at baseline was reduced to 0.4 (0.9) within 1 month following the start of treatment; a line graph depicting mean percentage change in monthly attack rate from baseline over time is shown in Figure S2. Overall, 196 of 209 patients with available data (93.8%) had < 1 investigator-confirmed HAE attack per month during the treatment period.

3.2.2 | Achievement of attack-free intervals during the treatment period (regular dosing stage for rollovers)

Following the first dose of lanadelumab (regular dosing stage for rollovers), the majority of patients were attack free for a period of

TABLE 1 Lanadelumab exposure and baseline demographics/clinical characteristics

	Rollovers (n = 109)	Nonrollers (n = 103)	Total (N = 212)
Time on study, months ^a			
Mean (SD)	29.7 (8.2)	29.5 (8.2)	29.6 (8.2)
Range	1.4-34.2	1.5-34.2	1.4-34.2
Time intervals, months, n (%)			
≥6	103 (94.5)	99 (96.1)	202 (95.3)
≥12	101 (92.7)	95 (92.2)	196 (92.5)
≥18	96 (88.1)	93 (90.3)	189 (89.2)
≥24	95 (87.2)	87 (84.5)	182 (85.8)
≥30	90 (82.6)	83 (80.6)	173 (81.6)
Age, mean (range), years			
<18, n (%)	8 (7.3)	13 (12.6)	21 (9.9)
18 to <65, n (%)	95 (87.2)	85 (82.5)	180 (84.9)
≥65, n (%)	6 (5.5)	5 (4.9)	11 (5.2)
Female sex, n (%)			
	75 (68.8)	68 (66.0)	143 (67.5)
White race, n (%)			
	99 (90.8)	99 (96.1)	198 (93.4)
BMI, mean (SD), kg/m ²			
	28.3 (6.8)	28.4 (7.5)	28.4 (7.2)
Geographic region, n (%)			
United States	73 (67.0)	74 (71.8)	147 (69.3)
Canada	6 (5.5)	7 (6.8)	13 (6.1)
Europe	27 (24.8)	12 (11.7)	39 (18.4)
Jordan	3 (2.8)	10 (9.7)	13 (6.1)
Age at symptom onset, mean (SD), years			
	13.5 (9.5)	11.6 (7.3)	12.6 (8.6)
HAE type, n (%)			
Type 1	100 (91.7)	89 (86.4)	189 (89.2)
Type 2	9 (8.3)	12 (11.7)	21 (9.9)
History of laryngeal attacks, n (%)			
	67 (61.5)	63 (61.2)	130 (61.3)
Baseline attack rate (attacks/4 weeks ^b)			
Mean (SD)	3.52 (2.48)	2.55 (2.75)	3.05 (2.66)
Median (range)	3.00 (1.0-14.0)	1.84 (0.0-15.4)	2.00 (0.0-15.4)
Baseline attack rate group (attacks/4 weeks), n (%)			
<1	0	25 (24.3)	25 (11.8)
1 to <2	35 (32.1)	39 (37.9)	74 (34.9)
2 to <3	19 (17.4)	11 (10.7)	30 (14.2)
≥3	55 (50.5)	28 (27.2)	83 (39.2)
Primary attack location, n (%) ^c			
Abdominal	89 (81.7)	92 (89.3)	181 (85.4)
Peripheral	85 (78.0)	87 (84.5)	172 (81.1)
Laryngeal	21 (19.3)	23 (22.3)	44 (20.8)
Prior use of LTP (category), n (%)			
C1-INH only	53 (48.6)	53 (51.5)	106 (50.0)
Oral therapy ^d	4 (3.7)	9 (8.7)	13 (6.1)
C1-INH and oral therapy ^d	5 (4.6)	2 (1.9)	7 (3.3)
No LTP	47 (43.1)	39 (37.9)	86 (40.6)

(Continues)

TABLE 1 (Continued)

Abbreviations: BMI, body mass index; C1-INH, C1-inhibitor; HAE, hereditary angioedema; LTP, long-term prophylaxis.

^aThe start of exposure was defined as the first dose date; the end of exposure was defined as the end of the open-label treatment period or early discontinuation date, whichever was earlier.

^bBaseline attack rate was calculated as the number of investigator-confirmed HAE attacks occurring during the run-in period of the HELP Study for rollover patients or the number of HAE attacks during the historical reporting period of last 3 months for nonrollover patients, divided by the number of days patients contributed to these periods, multiplied by 28 days.

^cPatients may have been counted in >1 category.

^dOral therapy includes androgens and antifibrinolytics.

≥6 months (81.8%) and ≥12 months (68.9% [Figure 2C]). Overall, 37.3% of patients were attack free throughout the entire study period. Patients were attack free for a mean (SD) of 97.7% (6.0%) of days during treatment, and the mean average duration of the attack-free period was 14.8 months (415.0 days). The average maximum duration of the attack-free period was 19.4 months (543.1 days [Table 2]).

3.2.3 | Dosing frequency analysis for rollover patients

The estimated percentage of rollover patients experiencing a first HAE attack by week 10 (day 70) of the dose-and-wait period (after five elimination half-lives) is shown in Figure 3. By week 4, 39.4%, 50.0%, 49.3%, and 20.0% of patients previously assigned to the placebo, lanadelumab 150 mg every 4 weeks (q4wks), lanadelumab 300 mg q4wks, and lanadelumab 300 mg q2wks groups in the HELP Study, respectively, experienced their first attack. By week 10, the respective percentages were 78.8%, 65.4%, 67.8%, and 44.0%. The median (95% CI) time to first attack for patients previously assigned to each of these treatment groups was 35 (26-45) days, 31 (13-81) days, 53 (19-85) days, and 76 (41-111) days, respectively.

3.2.4 | AE-QoL Questionnaire

QoL, as assessed by the AE-QoL total and domain scores, improved markedly from day 0 to the end of study (Table 2). Both rollovers and nonrollovers achieved the minimal clinically important difference for the AE-QoL total score: the mean (SD) change in total score from baseline was -10.2 (17.9) and -19.5 (21.3) for rollovers and nonrollovers, respectively. For all domains, greater changes in AE-QoL scores from baseline (Day 0 of the HELP OLE) were observed in nonrollover than rollover patients. Of note, however, the average baseline AE-QoL scores for nonrollover patients were relatively high in comparison to the rollover patients (the baseline scores for rollovers reflect scores at the end of treatment during the HELP Study; AE-QoL scores in lanadelumab-treated patients in the HELP Study significantly declined versus placebo across all domains early during the treatment period).²² Additional findings showed that most of the improvements in AE-QoL scores during the HELP OLE were observed during the early follow-up period (from day 0 to day 56),

before reaching a plateau, and scores were generally maintained during subsequent visits.

3.3 | Safety

3.3.1 | Treatment-emergent adverse events

The majority of patients (97.2%) reported ≥1 treatment-emergent adverse event (TEAE) (96.3% rollovers; 98.1% nonrollovers). Most TEAEs were of mild or moderate severity. No deaths occurred during the study. As shown in Table 3, the most frequently reported TEAEs were injection site pain (47.2%), viral upper respiratory tract infection (42.0%), upper respiratory tract infection (25.9%), and headache (24.5%). Treatment-related TEAEs were reported by 54.7% of patients, most commonly injection site reactions (ISRs). There were no reports of serious treatment-related TEAEs. Adverse events resulting in treatment discontinuation are shown in Table S1.

A total of 38 patients experienced 69 severe TEAEs (excluding HAE attacks). Events occurring in ≥2 patients overall included gastroenteritis, pneumonia, urinary tract infection, foot fracture, tendonitis, ALT increased, AST increased, and vomiting. Three patients experienced five severe TEAEs that were considered related to treatment, including four events of liver enzyme elevations (all of which were transient and self-limiting) and one event of hypersensitivity reaction (which ultimately resolved but led to treatment discontinuation) (Table S2). A total of 21 (9.9%) patients experienced 31 serious TEAEs (excluding HAE attacks); none were deemed related to lanadelumab treatment. One serious TEAE resulted in study discontinuation (upper gastrointestinal hemorrhage [upper gastrointestinal bleeding] following ingestion of a caustic substance).

ISR-related events were reported for 2287 of 11,899 (19.2%) lanadelumab injections administered during the study. Most were mild (98.8%); none were severe or serious. Most ISRs resolved within 30 minutes (62.2%), 1 hour (70.2%), or 1 day (92.6%).

3.3.2 | Adverse events of special interest

Fourteen patients experienced a total of 27 prespecified adverse events of special interest (AESI), defined as hypercoagulability events and bleeding events (Table S3). Most were single events reported by one patient each, with the exception of injection site

TABLE 2 Secondary and tertiary outcomes

	Rollovers	Nonrollovers	Total
Maximum attack severity, n (%)			
n	106	103	209
Attack free	37 (34.9)	41 (39.8)	78 (37.3)
Mild	9 (8.5)	9 (8.7)	18 (8.6)
Moderate	39 (36.8)	32 (31.1)	71 (34.0)
Severe	21 (19.8)	21 (20.4)	42 (20.1)
Primary attack location			
Number of attacks	649	532	1181
Abdominal	415 (63.9)	303 (57.0)	718 (60.8)
Laryngeal	17 (2.6)	27 (5.1)	44 (3.7)
Peripheral	217 (33.4)	202 (38.0)	419 (35.5)
Attack-free periods			
n	106	103	209
Number of attack-free days/4 weeks ^a			
Mean (SD)	27.3 (1.6)	27.4 (1.8)	27.3 (1.7)
Range	14.4-28.0	15.1-28.0	14.4-28.0
Average duration of attack-free periods, months ^b			
Mean (SD)	13.6 (11.4)	16.1 (13.2)	14.8 (12.4)
Range	0.12-32.5	0.15-34.2	0.12-34.2
Average maximum duration of attack-free period, months ^c			
Mean (SD)	18.0 (10.3)	20.9 (11.9)	19.4 (11.2)
Range	0.5-32.5	0.46-34.2	0.46-34.2
AE-QoL ^d			
n (missing)	90 (7)	81 (16)	-
Change in AE-QoL domain scores and total score from day 0 through end of study, mean (SD)			
-			
Fatigue/Mood	-7.4 (23.8)	-11.6 (25.8)	-
Fear/Shame	-12.9 (19.2)	-22.22 (24.3)	-
Functioning	-11.1 (24.3)	-26.2 (27.7)	-
Nutrition	-7.22 (26.1)	-18.28 (24.4)	-
Total score	-10.2 (17.9)	-19.5 (21.3)	-

Abbreviation: AE-QoL, Angioedema Quality of Life Questionnaire.

^aAn attack-free day was defined as a calendar day with no investigator-confirmed hereditary angioedema attack. One month is considered to be 4 weeks (28 days). n values represent the number of patients with attack rate data during the treatment period. Three rollovers who were still in the dose-and-wait period at the end of the study, or who discontinued during the dose-and-wait period, were not included in the analyses.

^bDerived by taking the average of the attack-free periods for each patient.

^cDerived by taking the maximum of the individual attack-free periods experienced for each patient.

(Continues)

TABLE 2 (Continued)

^dThe AE-QoL is a validated, angioedema-specific quality-of-life instrument consisting of 17 items covering four domains (Functioning, Fatigue/Mood, Fears/Shame, Nutrition), based on a 4 week recall period. Scores range from 0 to 100; lower scores indicate lower impairment, and higher scores indicate greater impairment. The minimal clinically important difference has been shown to be 6 points.^{20,21}

erythema (n = 2), hypersensitivity (n = 4), and vaginal hemorrhage (n = 2); no anaphylaxis or anaphylactoid reactions were reported.

Seven (3.3%) patients reported 11 AESIs that were considered related to lanadelumab—six events of ISRs (four patients; 1.9%), four events of hypersensitivity reactions (four patients; 1.9%), and one event of maculopapular rash (one patient; 0.5%). No events of disordered coagulation were considered related to lanadelumab. Four patients discontinued treatment due to AESIs—three events of hypersensitivity and one event of upper gastrointestinal bleeding.

3.3.3 | Clinical laboratory values and vital signs

There were no notable trends over time in mean laboratory values or vital signs; no new safety signals were raised. A total of 10 patients (five rollovers, five nonrollovers) had peak alanine aminotransferase levels >3 times the upper level of normal. The increases were transient and levels recovered during the treatment period.

3.3.4 | Immunogenicity

At baseline, 3 of 210 patients with available data (1.4%, all rollovers) had positive anti-drug antibodies (ADAs), but none were neutralizing. At the time of final analysis, anti-lanadelumab antibodies were detected in 21 (9.9%) patients (13 rollovers, 8 nonrollovers). Of these, 6 patients (2.8%) developed neutralizing ADAs (3 rollovers, 3 nonrollovers). However, the occurrence of ADAs and neutralizing antibodies had no impact on efficacy or safety of lanadelumab.

4 | DISCUSSION

The HELP OLE is the largest study conducted to date in patients with HAE-1/2, with 212 patients receiving treatment. Of note, although a total of 156 of 212 patients discontinued the study before its completion, 117 of these patients transitioned to the commercial product when lanadelumab became available. Importantly, the majority of patients were exposed to lanadelumab treatment for an extended period of time (81.6% of patients completed ≥30 months in the study). Inclusion of both rollover and nonrollover patients allowed for the evaluation of safety and effectiveness of lanadelumab in a more varied HAE population, with nonrollover patients more closely mimicking the real-world setting with regard to a broader baseline attack rate and prior use of LTP agents. Findings provide support for

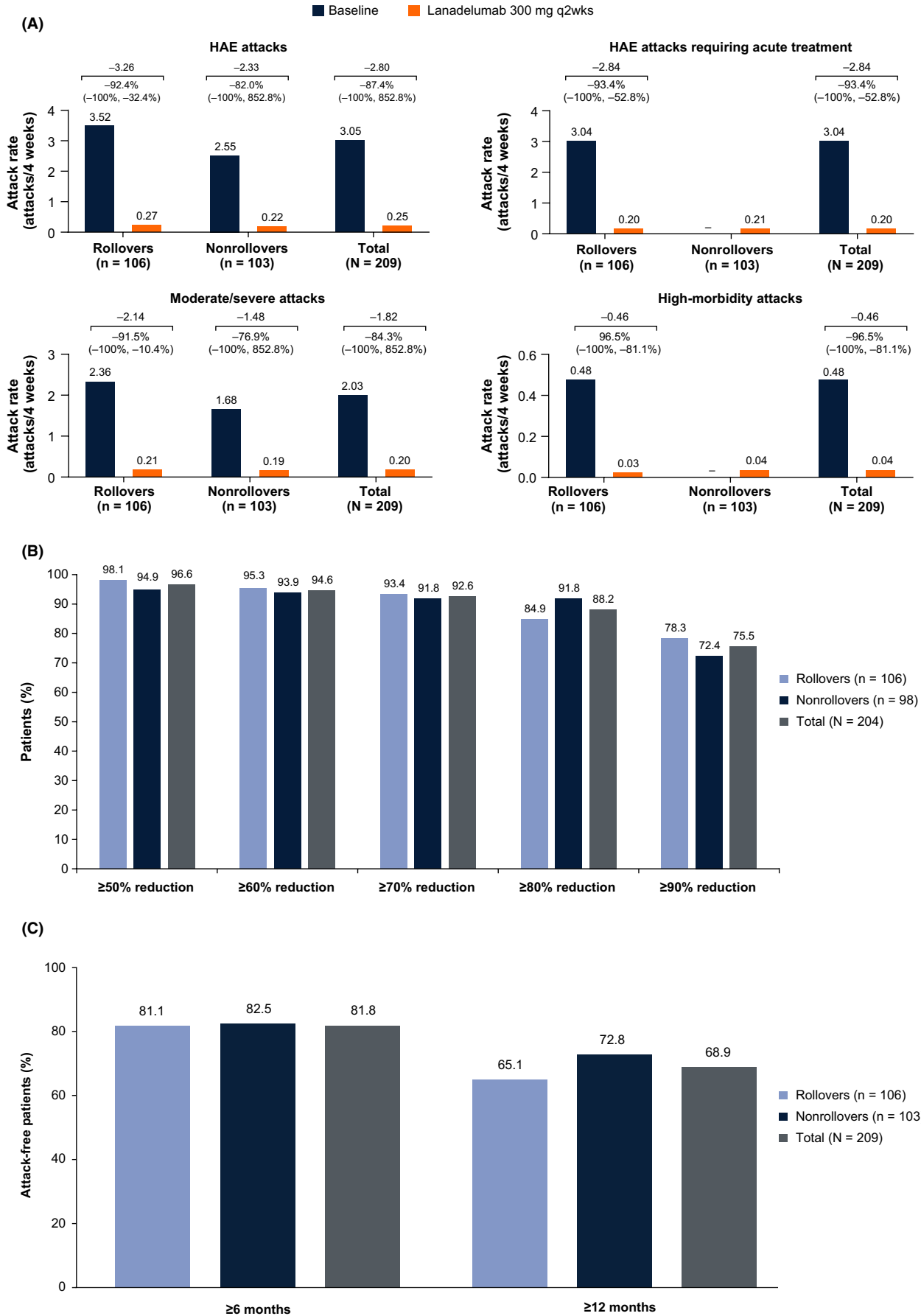


FIGURE 2 HAE attack reduction (A), responder analysis (B), and percentage of patients with maximum attack-free period ≥ 6 months or ≥ 12 months (C). (A) Values above bars are mean attack rates. Mean change from baseline and mean (minimum, maximum) percentage change from baseline are shown. Baseline data were not available for nonrollover patients' HAE attacks requiring acute treatment or for their high-morbidity attacks. n values represent the number of patients with attack rate data during the treatment period. Three rollover patients who discontinued the study during the dose-and-wait period were not included in the analyses. Analyses were performed based on reported HAE Attack Assessment and Reporting Procedures severity, as follows: Mild—Transient or mild discomfort; Moderate—Mild to moderate limitation in activity, some assistance needed; Severe—Marked limitation in activity, assistance required. High-morbidity attacks were defined as any attack that had ≥ 1 of the following characteristics: severe, resulted in hospitalization (except hospitalization for observation <24 hours), hemodynamically significant (systolic blood pressure <90 mmHg, required intravenous hydration, or associated with syncope/near-syncope), or laryngeal involvement. (B) For each patient, the percentage reduction was calculated as the baseline attack rate minus the treatment period attack rate (regular dosing stage for rollover patients) divided by the baseline attack rate, multiplied by 100. Patients may appear in >1 group as applicable, based on their percentage reduction. Patients who had an attack rate of zero at baseline were excluded from the analysis. HAE, hereditary angioedema; q2wks, every 2 weeks

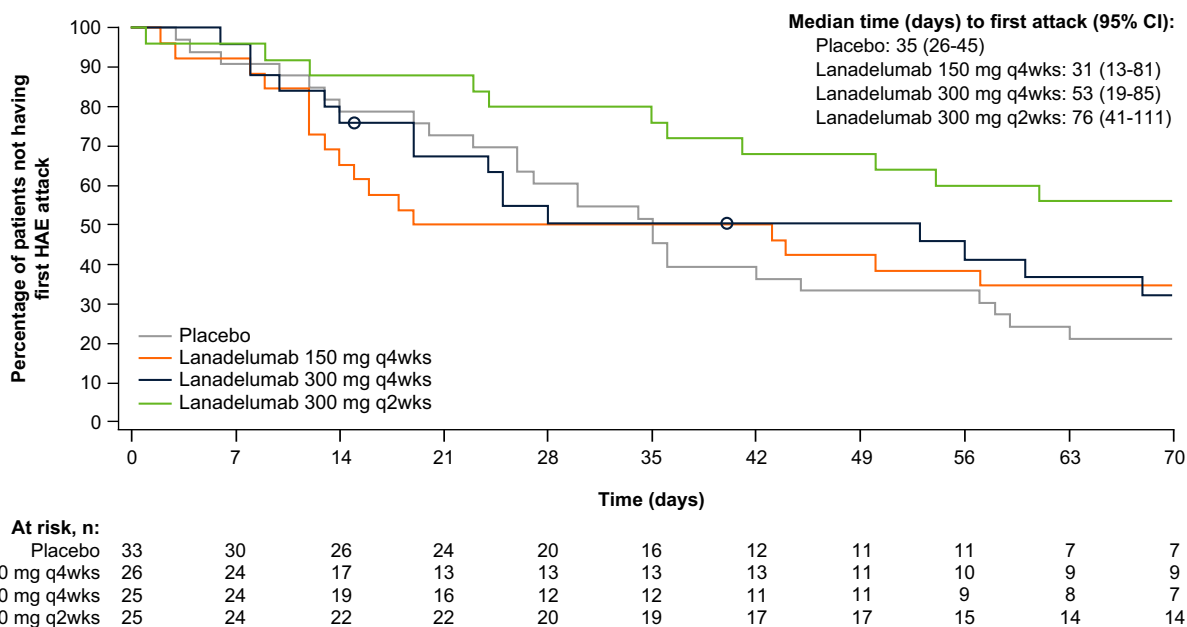


FIGURE 3 Time to first HAE attack during the dose-and-wait period (rollover safety population). Open circles on the lines refer to censored patients—those who discontinued the study prior to having an attack. HAE, hereditary angioedema; q2wks, every 2 weeks; q4wks, every 4 weeks

the long-term and sustained efficacy of lanadelumab 300 mg q2wks in preventing HAE attacks. Reductions in attack rates in nonrollover patients were similar to those observed over a 6-month treatment period in the HELP Study¹⁷ and were similar to reductions shown during the regular dosing stage in rollover patients. Overall, the mean attack rate was reduced by 87.4% compared with baseline.

Of note, overall percentage reductions from baseline were slightly lower for nonrollovers compared with rollover patients (82.0% vs 92.4%, respectively). This may have occurred, in part, because of differences in how the baseline attack rate was defined for the two patient populations (ie, for nonrollovers, the rate was based on the patient-reported number of attacks during the previous 3 months [introducing the potential for recall bias], rather than on the observed attack rate during the run-in period of the HELP Study for rollovers). Also, for nonrollover patients, baseline attack rates reflected possible LTP with C1-INH, attenuated androgens, or antifibrinolytics prior to study enrollment. Given the lower baseline

attack rate in nonrollover patients (2.6 attacks/4 weeks, compared with 3.5 attacks/4 weeks for rollovers), the percentage change from baseline may have been more variable. Regardless, at the end of the treatment period, the attack rate was comparable for both patient groups (0.27 attacks/4 weeks and 0.22 attacks/4 weeks for rollovers and nonrollovers, respectively).

On average, patients were attack free for approximately 98% of days during treatment, and the average duration of the attack-free period was >14 months. Nearly 70% of patients experienced an attack-free period of ≥ 12 months, supporting the sustained efficacy of lanadelumab over an extended treatment period.

Both rollover and nonrollover patients achieved the minimal clinically important difference for the AE-QoL total score. For all domains, greater changes in AE-QoL scores from baseline were observed in nonrollovers than in rollovers, primarily due to the relatively lower average baseline AE-QoL scores in rollover patients, resulting from lanadelumab treatment during the HELP study.²²

TABLE 3 TEAEs (excluding HAE attack-related events)

	Rollovers (n = 109)	Nonrollovers (n = 103)	Total (N = 212)
Any TEAEs	105 (96.3)	101 (98.1)	206 (97.2)
TEAEs occurring in ≥10% of total patients			
Injection site pain	45 (41.3)	55 (53.4)	100 (47.2)
Viral upper respiratory tract infection	51 (46.8)	38 (36.9)	89 (42.0)
Upper respiratory tract infection	30 (27.5)	25 (24.3)	55 (25.9)
Headache	29 (26.6)	23 (22.3)	52 (24.5)
Injection site erythema	16 (14.7)	20 (19.4)	36 (17.0)
Arthralgia	11 (10.1)	16 (15.5)	27 (12.7)
Back pain	16 (14.7)	10 (9.7)	26 (12.3)
Injection site bruising	13 (11.9)	13 (12.6)	26 (12.3)
Diarrhea	13 (11.9)	10 (9.7)	23 (10.8)
Sinusitis	13 (11.9)	10 (9.7)	23 (10.8)
Influenza	13 (11.9)	9 (8.7)	22 (10.4)
Nausea	13 (11.9)	9 (8.7)	22 (10.4)
Urinary tract infection	10 (9.2)	12 (11.7)	22 (10.4)
Any treatment-related TEAEs	50 (45.9)	66 (64.1)	116 (54.7)
Treatment-related TEAEs reported in ≥3% of total patients			
Injection site pain	40 (36.7)	50 (48.5)	90 (42.5)
Injection site erythema	14 (12.8)	20 (19.4)	34 (16.0)
Injection site bruising	8 (7.3)	11 (10.7)	19 (9.0)
Injection site swelling	3 (2.8)	9 (8.7)	12 (5.7)
Injection site pruritus	4 (3.7)	6 (5.8)	10 (4.7)
Serious TEAEs ^a	12 (11.0)	9 (8.7)	21 (9.9)
Severe TEAEs	16 (14.7)	22 (21.4)	38 (17.9)
Treatment-related severe TEAEs	0	3 (2.9)	3 (1.4)
Investigator-reported AESIs ^b	8 (7.3)	5 (4.9)	13 (6.1)
Deaths due to TEAEs	0	0	0
Hospitalizations due to TEAEs	12 (11.0)	9 (8.7)	21 (9.9)
Discontinuations due to TEAEs	1 (0.9)	5 (4.9)	6 (2.8)

Note: Values are n (%). Percentages are based on all patients in the safety population. Patients were counted once per category per analysis population. TEAEs were defined as AEs with onset at the time of or following the start of treatment with study medication, or medical conditions present prior to the start of treatment but increasing in severity or relationship at the time of or following the start of treatment.

Abbreviations: AE, adverse event; AESI, adverse event of special interest; HAE, hereditary angioedema; TEAE, treatment-emergent adverse event.

^aNone of the serious TEAEs were related to treatment.

^bAESIs were defined as hypersensitivity reactions and disordered coagulation (hypercoagulability events and bleeding events); AESIs are listed in Table S3.

These findings likely reflect a treatment benefit of lanadelumab (ie, patients who had not been previously treated reported greater improvement after initiating treatment, compared with patients who had received treatment previously). Additionally, improvements were primarily observed during days 0 to 56 before a plateau was reached, suggesting that QoL improvements are achieved early during treatment with lanadelumab. However, improvements were generally maintained over extended treatment periods.

During the dose-and-wait period, lanadelumab plasma concentrations decreased. An increasing number of rollover patients experiencing their first attack was observed over time after a single dose administration, regardless of their previously assigned treatment group in the HELP Study. Overall, patients who received lanadelumab 300 mg q2wks in the HELP Study had a relatively long median duration of time to the first attack. However, the analysis of time to first attack should be interpreted with caution because

these patients are not directly comparable with one another. Plasma lanadelumab concentrations at the end of the HELP Study differed widely among patients (based on the treatment group to which they were assigned), complicating the interpretation of findings. Furthermore, time to first attack during the dose-and-wait stage in the HELP OLE is not reflective of patients' HELP Study dose and administration schedule. For instance, patients in the 300 mg q4wks dosing arm in the HELP Study received a dose 2 weeks "early" upon entering the HELP OLE; their time to first attack was likely lengthened. Importantly, for rollover patients previously in the placebo group (who received their first lanadelumab dose on day 0 of the HELP OLE), it is evident that a larger proportion of patients began to experience attacks during the first 2-4 weeks, suggesting that lanadelumab dosing with an interval longer than q4wks places patients at increased risk of HAE attacks. Hence, the currently approved lanadelumab labeling recommends a starting dose of 300 mg q2wks, with the option to extend dosing to q4wks in patients who are well controlled (ie, attack free [for >6 months, per the US label]).¹³

The long-term safety profile of lanadelumab in the HELP OLE is consistent with safety findings reported in the HELP Study¹⁷; no new lanadelumab treatment-related TEAEs or safety signals were identified. ISRs were the most frequently reported TEAEs. The majority of ISRs were mild in severity, resolved within a day, and did not lead to study discontinuation. Additionally, the overall incidence of AESIs was low, and the occurrence of ADAs and neutralizing antibodies had no impact on efficacy or safety of lanadelumab.

Several limitations of the HELP OLE study are worthy of mention. Firstly, as inherent in an open-label study design, patients were aware that they were receiving active treatment and rollover patients were aware that they were not receiving treatment during the dose-and-wait period; this knowledge may have influenced the reporting of outcomes. Next, rollover patients with a shorter time to first attack completed the dose-and-wait period more quickly and were able to progress to the regular dosing stage earlier than those with a longer time to first attack. As such, the follow-up period differs for rollover patients, resulting in a potential selection bias for patients with an extended study experience. Also, as mentioned earlier, baseline attack rate measurements for nonrollover patients may be underestimated, given that some patients received concomitant LTP prior to enrolling in the study. Additionally, baseline data were not available for nonrollover patients for select efficacy outcomes, such as HAE attack rate for attacks requiring acute treatment and for high-morbidity attacks, limiting the conclusions that can be drawn for those measures in the nonrollover group.

In conclusion, minimizing the occurrence of HAE attacks and restoring normality in patients' daily lives are key goals of LTP treatment and are increasingly being emphasized in HAE management guidelines. Achievement of prolonged attack-free intervals with newer targeted agents is helping to transform the life experience and expectations of patients with HAE. The final results from the HELP OLE are consistent with findings from the pivotal HELP Study and the known safety and efficacy profile of lanadelumab. These findings

in an expanded study population further support the long-term tolerability of lanadelumab 300 mg q2wks and confirm the sustained benefit of treatment for the long-term prevention of HAE attacks.

ACKNOWLEDGMENTS

We thank Kim Paes and Peng Lu (former employees of Takeda Pharmaceutical Company Limited) for providing clinical development support for this study.

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*Deceased.

CONFLICT OF INTEREST

A. Banerji has received institutional research/study support from BioCryst and Takeda and/or honoraria for consulting from BioCryst, CSL Behring, KalVista, Pharming, Pharvaris, and Takeda. J.A. Bernstein has been or is currently a clinical investigator for BioCryst, CSL Behring, Ionis, KalVista, Pharming, and Takeda; a speaker for CSL Behring, Pharming, and Takeda; a consultant for BioCryst, CSL Behring, Fresenius Kabi, Ionis, KalVista, Pharming, and Takeda; and a member of the hereditary angioedema medical advisory board. D.T. Johnston has received consulting/speaker fees from CSL Behring, Pharming, and Takeda, and consulting fees from BioCryst and REGENXBIO. W.R. Lumry is a member of advisory boards for BioCryst, CSL Behring, and Takeda; has received research grants from BioCryst, CSL Behring, Ionis, and Takeda; has received consulting fees from BioCryst, CSL Behring, Fresenius Kabi, Pharming, and Takeda; payments for lectures from CSL Behring, Pharming, and Takeda; and is an advisory board member of the US Hereditary Angioedema Association. M. Magerl has received research grant support and/or speaker/consultancy fees from BioCryst, CSL Behring, KalVista, Pharming, and Takeda. M. Maurer has received research grant support and/or speaker/consultancy fees from Adverum, BioCryst, CSL Behring, KalVista, Pharming, Pharvaris, and Takeda. I. Martinez-Saguer has received research grant support and/or speaker/consultancy fees from BioCryst, CSL Behring, KalVista, Pharming, and Takeda. A. Zanichelli has received speaker/consultancy fees from BioCryst, CSL Behring, Pharming, and Takeda. J. Hao, N. Inhaber, and M. Yu are full-time employees of and hold stock/stock options in Takeda. M.A. Riedl has received research grants from BioCryst, CSL Behring, Pharming, and Takeda; has received consulting fees from Adverum, Attune, BioCryst, CSL Behring, Ionis, KalVista, Pharming, and Takeda; payments for lectures from CSL Behring, Pharming, and Takeda; and is an advisory board member of the US Hereditary Angioedema Association.

AUTHOR CONTRIBUTIONS

J. Hao, N. Inhaber, and M. Yu contributed to study design. J. Hao participated in data acquisition. All authors participated in data analysis and/or interpretation, participated in drafting the manuscript or revising it for critically important intellectual content, and approved the final draft.

DATA AVAILABILITY STATEMENT

The datasets, including the redacted study protocol, redacted statistical analysis plan, and individual participants' data supporting the results reported in this article, will be made available within three months from initial request, to researchers who provide a methodologically sound proposal. The data will be provided after its de-identification, in compliance with applicable privacy laws, data protection, and requirements for consent and anonymization.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Banerji A, Bernstein JA, Johnston DT, et al. Long-term prevention of hereditary angioedema attacks with lanadelumab: The HELP OLE Study. *Allergy*. 2022;77:979–990. <https://doi.org/10.1111/all.15011>