Received: 22 June 2020 | Revised: 1 November 2020 | Accepted: 14 November 2020

DOI: 10.1111/all.14680

Allergy EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY EAACI WILEY

ORIGINAL ARTICLE

Atopic Dermatitis, Urticaria and Skin Disease

# Impact of lanadelumab on health-related quality of life in patients with hereditary angioedema in the HELP study

William R. Lumry[1] | Karsten Weller[2] | Markus Magerl[2] | Aleena Banerji[3] | Hilary J. Longhurst[4] | Marc A. Riedl[5] | Hannah B. Lewis[6] | Peng Lu[7] | Giovanna Devercelli[7] | Gagan Jain[7] | Marcus Maurer[2] | on behalf of the HELP Study Investigators

[1]Allergy Asthma Research Associates Research Center, Dallas, TX, USA

[2]Dermatological Allergology, Allergie-Centrum-Charité, Department of Dermatology and Allergy, Charité – Universitätsmedizin Berlin, Berlin, Germany

[3]Division of Rheumatology, Allergy and Immunology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

[4]Addenbrooke's Hospital, Cambridge University Hospitals NHS Foundation Trust, Cambridge, and University College London Hospitals, London, UK

[5]Division of Rheumatology, Allergy & Immunology, University of California San Diego, La Jolla, CA, USA

[6]ICON plc, London, UK

[7]Takeda Pharmaceutical Company Limited, Lexington, MA, USA

**Correspondence**
William R. Lumry, AARA Research Center, 10100 N. Central Expressway, Suite 100, Dallas, TX 75231, USA.
Email: LumryMD@AllergySpecialists.us

**Funding information**
Shire Human Genetic Therapies, Inc,, a Takeda company

## Abstract

**Background:** An objective of the phase 3 HELP Study was to investigate the effect of lanadelumab on health-related quality of life (HRQoL) in patients with hereditary angioedema (HAE).

**Methods:** Patients with HAE-1/2 received either lanadelumab 150 mg every 4 weeks (q4wks; *n* = 28), 300 mg q4wks (*n* = 29), 300 mg every 2 weeks (q2wks; *n* = 27), or placebo (*n* = 41) for 26 weeks (days 0–182). The Angioedema Quality of Life Questionnaire (AE-QoL) was administered monthly, consisting of four domain (functioning, fatigue/mood, fears/shame, nutrition) and total scores. The generic EQ-5D-5L questionnaire was administered on days 0, 98, and 182. Comparisons were made between placebo and (a) all lanadelumab-treated patients and (b) individual lanadelumab groups for changes in scores (day 0–182) and proportions achieving the minimal clinically important difference (MCID, −6) in AE-QoL total score.

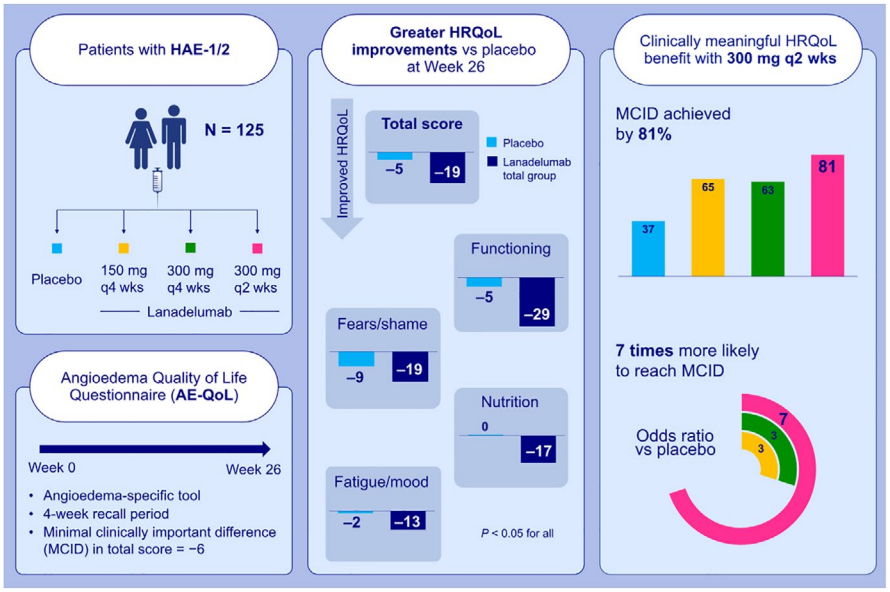
**Results:** Compared with the placebo group, the lanadelumab total group demonstrated significantly greater improvements in AE-QoL total and domain scores (mean change, −13.0 to −29.3; $p < 0.05$ for all); the largest improvement was in functioning. A significantly greater proportion of the lanadelumab total group achieved the MCID (70% vs 37%; $p = 0.001$). The lanadelumab 300 mg q2wks group had the highest proportion (81%; $p = 0.001$) and was 7.2 times more likely to achieve the MCID than the placebo group. Mean EQ-5D-5L scores at day 0 were high in all groups, indicating low impairment, with no significant changes at day 182.

**Conclusion:** Patients with HAE-1/2 experienced significant and clinically meaningful improvements in HRQoL measured by AE-QoL following lanadelumab treatment in the HELP Study.

See HELP Study Investigators in Acknowledgements

Peng Lu was a full-time employee of Takeda Pharmaceutical Company Limited at the time this analysis was conducted.

KEYWORDS
AE-QoL, hereditary angioedema, lanadelumab, long-term prophylaxis, quality of life




**GRAPHICAL ABSTRACT**

In the phase 3 HELP Study, HRQoL (health-related quality of life) of patients with HAE (hereditary angioedema)-1/2 was evaluated using the angioedema-specific AE-QoL (Angioedema Quality of Life Questionnaire). After 26 weeks, lanadelumab-treated patients experienced significantly greater HRQoL improvements than placebo-treated patients. Patients receiving lanadelumab 300 mg q2wks (every 2 weeks) were most likely to see clinically meaningful benefit, with 81% reaching the MCID (minimal clinically important difference) and seven times greater odds vs placebo for this achievement.

Abbreviations: AE-QoL, Angioedema Quality of Life Questionnaire; HAE, hereditary angioedema; HRQoL, health-related quality of life; MCID, minimal clinically important difference; q2wks, every 2 weeks; q4wks, every 4 weeks.

## 1 | INTRODUCTION

Hereditary angioedema (HAE) is a rare genetic disorder characterized by recurrent swellings of deep dermal/subcutaneous or mucosal/submucosal tissues resulting from a temporary increase in vascular permeability.[1] HAE is most commonly caused by deficient (type 1) or dysfunctional (type 2) C1 inhibitor (HAE-1/2, also referred to as C1-INH-HAE).[1] Although angioedema attacks are intermittent, the burden of disease for patients and caregivers can be substantial and enduring.[2] HAE attacks are unpredictable in frequency, severity, duration, and location.[1,3] They cause considerable pain and disfigurement, and laryngeal attacks carry the life-threatening risk of asphyxiation.[4,5] Despite full physical recovery between attacks, patients often continue to experience emotional distress and reduced health-related quality of life (HRQoL).[2] Patients have reported feeling anxious about their children inheriting the disease,[6] and feelings of anxiety and depression can trigger attacks.[7] In addition to the impact on patients, HAE has a considerable family and societal burden.[2,8] Absenteeism from work or education increases with attack severity and frequency, and reduced productivity between attacks and missed opportunities for career development have been reported.[4,9]

Significant advances have been made in expanding acute and prophylactic treatment options for patients with HAE; however, there is a continued need for effective, safe, and conveniently administered therapies.[10] One therapeutic approach is to target bradykinin, the mediator of tissue swelling in HAE-1/2. Dysregulation of plasma kallikrein resulting from insufficient functional C1 inhibitor causes excess bradykinin generation; elevated bradykinin levels have been detected at the swelling site during HAE attacks.[11,12] Lanadelumab is a fully human monoclonal antibody that specifically inhibits active plasma kallikrein to prevent bradykinin overproduction.[13]

Following phase 1 studies,[14,15] the randomized, double-blind, placebo-controlled, phase 3 HELP Study evaluated lanadelumab for HAE attack prevention in patients with HAE-1/2.[16] Patients aged ≥ 12 years ($N$ = 125) were randomized and treated with either placebo or lanadelumab 150 mg every 4 weeks (q4wks), 300 mg q4wks, or 300 mg every 2 weeks (q2wks). During the 26-week treatment period, all three lanadelumab regimens were superior to placebo for the primary and all secondary efficacy endpoints. In the lanadelumab 300 mg q2wks group, the least squares mean monthly HAE attack rate was 0.26 (95% CI 0.14–0.46; SE=0.08) compared with 1.97 (95% CI 1.64–2.36; SE=0.18) in the placebo group, representing a statistically significant reduction of 86.9% (95% CI 76.2–92.8; $p < 0.001$) vs placebo. Significantly greater proportions ($p < 0.001$) of patients remained attack-free with lanadelumab 300 mg q2wks than with placebo during both the full treatment period (44.4% vs 2.4%) and at steady state (days 70–182; 76.9%

vs 2.7%). Lanadelumab was generally well tolerated, with 98.5% of treatment-emergent adverse events (TEAEs) mild or moderate in severity and no treatment-related serious TEAEs.

Following completion of the HELP Study, lanadelumab was approved for the prevention of HAE attacks in patients aged ≥ 12 years in the United States,[17] European Union,[18] and several other countries and regions. The 2017 WAO/EAACI and 2019 International/Canadian guideline updates advocate that patients with HAE-1/2 are evaluated for long-term prophylactic treatment at every visit and that HRQoL is taken into consideration.[1,19] Evaluation of the effect of lanadelumab on patients' HRQoL was a tertiary objective of the HELP study. The Angioedema Quality of Life Questionnaire (AE-QoL), a validated angioedema-specific questionnaire,[20–22] was used to assess the effect of treatment on HRQoL. These results are reported herein.

## 2 | METHODS

### 2.1 | Study design

Details of the trial design and methodology have been reported elsewhere[16] and are briefly summarized in Figure S1. Eligible patients were aged ≥ 12 years with a documented diagnosis of HAE-1/2, had experienced ≥1 investigator-confirmed attack during a 4-week run-in period, and had received neither long-term prophylactic therapy for HAE within 2 weeks of the run-in period nor angiotensin-converting enzyme inhibitors or estrogen-containing medication within 4 weeks of screening. The study was conducted per International Conference on Harmonization Good Clinical Practice guidelines, the principles of the Declaration of Helsinki, and local ethical and legal requirements. At screening, written informed consent was obtained from all patients (or assent if aged < 18 years). Patients with attack rate reductions of ≥50% during the treatment period relative to the run-in period were defined as responders (responder categories: <50%, 50%–69%, 70%–89%, and 90%–100% reduction of attacks).

### 2.2 | Patient-reported outcome instruments

The AE-QoL is a self-administered validated measure that assesses angioedema-related QoL over a 4-week recall period.[20] The questionnaire consists of 17 items, each with a 5-point response scale ranging from 1 (never) to 5 (very often), used to produce a total score and four domain scores (functioning, fatigue/mood, fears/shame, and nutrition; Table S1). Scores are transformed linearly to a scale ranging from 0 to 100, with lower scores reflecting lower impairment and, therefore, better HRQoL. The minimal clinically important difference (MCID) is the minimum change in score that is meaningful to patients. For the AE-QoL total score, the predefined MCID is a reduction of 6 points.[21]

The 5-level EuroQoL 5-dimensional (EQ-5D-5L) instrument was also used to measure the general health status of a patient on the day of questionnaire administration, with higher scores indicating better health status.[23] EQ-5D-5L comprises a descriptive system of five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) that contribute to an index/utility score ranging from 0 to 1, and a separate visual analogue scale (VAS) to assess overall health ranging from 0 to 100.

### 2.3 | Data collection

The AE-QoL was administered before dosing during visits on days 0, 28 ± 3, 56 ± 3, 98 ± 3, 126 ± 3, 154 ± 3, and 182 ± 3. The EQ-5D-5L was administered before dosing on days 0, 98 ± 3, and 182 ± 3. For both instruments, additional assessments were conducted on day 238 ± 3 for patients who did not enter the HELP open-label extension. Adolescent patients received the same PRO instruments as were administered to adult patients.

### 2.4 | Statistical analyses

HRQoL was analyzed using the intent-to-treat population who received any study drug. At each data collection visit, comparisons with the placebo group were made by combining the three lanadelumab treatment groups (the lanadelumab total group) and by considering each of the three lanadelumab groups separately. No imputation was performed for missing values.

Descriptive statistics included mean (SD) and median by visit summarized for each treatment group and the lanadelumab total group. Summaries of changes in scores from day 0 to 182 were assessed for each treatment group and the lanadelumab total group, including analyses for prespecified demographic and clinical characteristic subgroups. Frequencies and proportions of patients achieving the responder definition (individual level meaningful change) in AE-QoL scores from day 0 to 182 were calculated with respect to (a) the MCID of 6 points in the AE-QoL total score and (b) a responder definition of 0.5 times baseline SD for sensitivity analyses.[24] Chi-squared tests were used to determine a statistical difference between groups, and logistic regression models fitted to estimate treatment effects, adjusting for covariates. Comparisons across the placebo and lanadelumab treatment groups used one-way analyses of variance and analyses of covariance adjusting for baseline scores. All analyses were conducted using SAS Version 9.4 (SAS Institute Inc). Statistical tests were two-sided with significance at the $\alpha = 0.05$ level; analyses were not adjusted for multiplicity.

Exploratory analyses were performed to investigate correlations between the change in AE-QoL scores (from day 0 to 182) and the primary and secondary endpoints of this study; correlation coefficients were calculated. In addition, exposure-response relationships between lanadelumab concentrations at steady state (minimum, maximum, and average) and change in Angioedema

Quality of Life Questionnaire (AE-QoL) scores were evaluated through best fit of linear models; a slope (non-flat line) with 95% CI that excluded the null hypothesis (non-zero) was interpreted as a statistically significant relationship. Exposure-response relationships were also assessed between change in AE-QoL scores and cleaved high-molecular-weight kininogen (cHWMK) concentration at steady state (measured by western blot assay using citrated plasma).[15]

## 3 | RESULTS

### 3.1 | Study population and patient characteristics

A total of 125 patients were randomized and treated: 28 with lanadelumab 150 mg q4wks, 29 with 300 mg q4wks, 27 with 300 mg q2wks, and 41 with placebo. Baseline demographics, clinical characteristics, and medical history were well balanced across all treatment groups (Table S2). The mean (SD) HAE attack rate during the 4-week run-in period was 3.7 (2.6) attacks/month. All placebo-treated patients and all except one lanadelumab-treated patient (in the 300 mg q4wks group) completed HRQoL assessments at day 0.

### 3.2 | AE-QoL at baseline and effect of treatment

At baseline, mean (SD) AE-QoL total scores for the lanadelumab 150 mg q4wks, 300 mg q4wks, 300 mg q2wks, and placebo groups, respectively, were 48.79 (20.34), 47.50 (21.94), 43.75 (16.77), and 42.79 (17.53). During the 26-week treatment period (day 0–182), patients treated with lanadelumab experienced statistically significant improvements in HRQoL compared with placebo as measured by the AE-QoL. For the lanadelumab total group, significant reductions vs placebo were observed in AE-QoL total score and across all domain scores (functioning, fatigue/mood, fears/shame, and nutrition; Figure 1A). The largest improvement was observed in the functioning domain.

When comparing the individual lanadelumab treatment groups with placebo, significant reductions were observed in AE-QoL total scores and functioning domain scores for each of the three

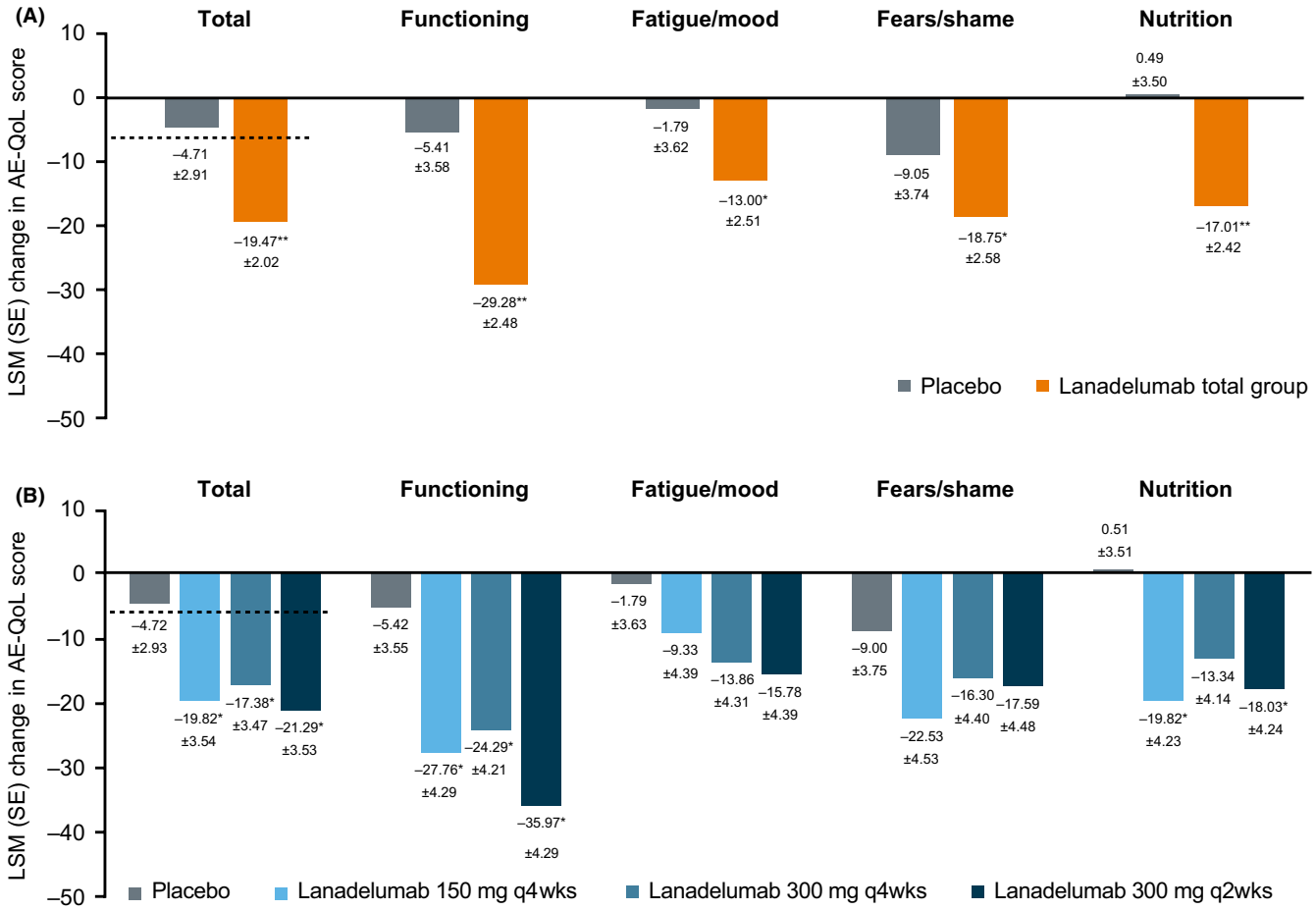



FIGURE 1 Mean change from baseline in AE-QoL total and domain scores from day 0 to 182 for the (A) lanadelumab total group and (B) individual lanadelumab treatment groups vs the placebo group. *$p < 0.05$; **$p < 0.01$. The lanadelumab total group and placebo group were compared using analysis of covariance, adjusting for baseline scores. The dotted line indicates the minimal clinically important difference (−6) in AE-QoL total score. AE-QoL, Angioedema Quality of Life Questionnaire; LSM, least squares mean; q2wks, every 2 weeks; q4wks, every 4 weeks

**TABLE 1** Proportions of patients in each treatment group achieving a clinically meaningful improvement in AE-QoL total score (MCID = 6) from day 0 to 182

| Treatment group | Percentage of patients achieving MCID (95% CI) | | | | |
|---|---|---|---|---|---|
| | AE-QoL total score | AE-QoL domain scores[a] | | | |
| | | Functioning | Fatigue/mood | Fears/shame | Nutrition |
| Placebo (*n* = 38) | 37 (22–54) | 53 (36–69) | 42 (26–59) | 45 (29–62) | 42 (26–59) |
| Lanadelumab 150 mg q4wks (*n* = 26) | 65* (44–83) | 73 (52–88) | 46 (27–67) | 81* (61–93) | 58 (37–77) |
| Lanadelumab 300 mg q4wks (*n* = 27) | 63 (42–81) | 78 (58–91) | 67 (46–83) | 67 (46–83) | 52 (32–71) |
| Lanadelumab 300 mg q2wks (*n* = 26) | 81* (61–93) | 81* (61–93) | 54 (33–73) | 73* (52–88) | 65 (44–83) |
| Lanadelumab total group (*n* = 79) | 70* (58–79) | 77* (66–86) | 56 (44–67) | 73* (62–83) | 58 (47–69) |

Abbreviations: AE-QoL, Angioedema Quality of Life Questionnaire; MCID, minimal clinically important difference; q2wks, every 2 weeks; q4wks, every 4 weeks.

[a]Although the MCID value of 6 has been determined only for the AE-QoL total score,[21] it was also used as the responder definition for the AE-QoL domain scores.

*$p < 0.05$ vs placebo.

**TABLE 2** Logistic regression model results for patients in each treatment group achieving a clinically meaningful improvement in AE-QoL total score (MCID = 6) from day 0 to 182

| Treatment group | OR | 95% CI | *p*-value |
|---|---|---|---|
| Lanadelumab 150 mg q4wks | 3.24 | 1.14–9.19 | 0.03 |
| Lanadelumab 300 mg q4wks | 2.91 | 1.05–8.10 | 0.04 |
| Lanadelumab 300 mg q2wks | 7.20 | 2.22–23.37 | <0.01 |
| Lanadelumab total group | 3.93 | 1.74–8.88 | <0.01 |

Abbreviations: AE-QoL, Angioedema Quality of Life Questionnaire; MCID, minimal clinically important difference; OR, odds ratio; q2wks, every 2 weeks; q4wks, every 4 weeks.

lanadelumab groups (Figure 1B). When assessing mean AE-QoL scores at each scheduled visit, improvements in HRQoL were observed at week 8 for all treatment groups, including placebo (Figure S2). Improvements in scores were generally maintained during subsequent visits from week 8 onwards in the lanadelumab treatment groups but not in the placebo group.

The change from baseline in AE-QoL total score was generally consistent across prespecified subgroups based on demographics and baseline clinical characteristics (Figure S3).

### 3.3 | Clinically meaningful improvements in HRQoL

Significantly more patients in the lanadelumab total group (70%) and the individual 150 mg q4wks and 300 mg q2wks treatment groups achieved the MCID of a 6-point reduction in AE-QoL total score compared with placebo (37%; Table 1). The highest proportion of patients reaching the MCID threshold, 81%, was in the lanadelumab 300 mg q2wks group. Similar results were obtained using a responder definition of 0.5 times baseline SD (Table S3).

Based on a logistic regression model, patients treated with lanadelumab had 2.9–7.2 times greater odds of achieving the MCID in AE-QoL total score than patients treated with placebo, with the highest odds associated with lanadelumab 300 mg q2wks (Table 2). Comparable results were obtained using a responder definition of 0.5 times baseline SD, with patients in the lanadelumab total group having significantly greater odds vs placebo of achieving the responder definition for the AE-QoL total score and all domain scores ($p < 0.01$ for all scores except fatigue/mood [$p = 0.04$]; data not shown).

### 3.4 | Descriptive analysis of responses in the functioning domain

A descriptive analysis of item-level responses in the functioning domain indicated greater improvements with lanadelumab than placebo at day 182 with respect to work, physical activity, leisure time, and social relations (Figure 2). All lanadelumab groups had reduced proportions of patients experiencing function-related restrictions at day 182, with the 300 mg q2wks group having the lowest proportion of patients in each of the four restriction categories at the end of the treatment period.

### 3.5 | Correlation between change from baseline AE-QoL scores and disease activity

Irrespective of the treatment received, a greater reduction in attack rate through day 182 compared with day 0 was linked to a greater improvement across all AE-QoL scores (Table 3). Weak but significant positive correlations were observed between the change in AE-QoL scores from day 0 to 182 and the reduction in HAE attack rate from day 0 to 182 with respect to the total score ($r = 0.25$, $p = 0.006$)

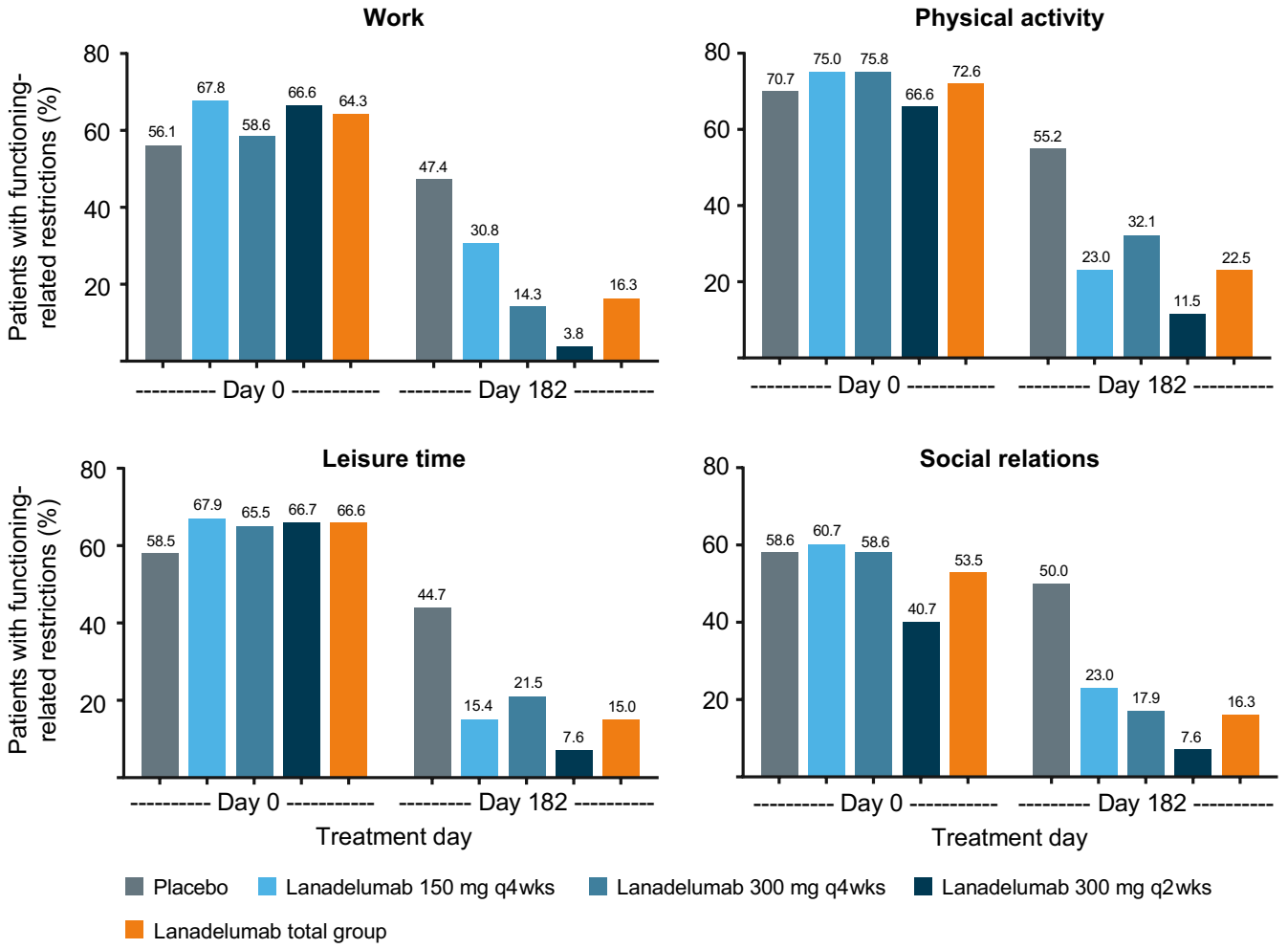



**FIGURE 2** Proportions of patients with functioning-related restrictions at day 0 and 182, measured using responses to items in the AE-QoL functioning domain (by treatment group). Items 1–4 of the AE-QoL comprise the functioning domain. Percentages reflect combined responses for patients who reported experiencing symptoms "occasionally," "often," and "very often." AE-QoL, Angioedema Quality of Life Questionnaire; q2wks, every 2 weeks; q4wks, every 4 weeks

and all domain scores except for fatigue/mood (Table S4). Weak positive correlations were also observed between some AE-QoL score reductions and the number of (a) HAE attacks, (b) moderate/severe attacks, and (c) attacks requiring acute treatment during the treatment period.

### 3.6 | Exposure-response relationship between change from baseline AE-QoL scores and lanadelumab treatment

Relationships between lanadelumab exposure and change in AE-QoL scores were interpreted as statistically significant if there was a slope (non-flat line) with 95% CI that was non-zero. Statistically significant inverse relationships were observed between the reduction in total score and lanadelumab $C_{ave,ss}$ and $C_{max,ss}$ ($p = 0.02$ for both), and between the change in functioning score and lanadelumab $C_{ave,ss}$, $C_{min,ss}$, and $C_{max,ss}$ ($p \leq 0.005$ for all). A statistically significant relationship was not detected between reduction in total score and cHWMK $C_{ave,ss}$, but was observed with reduction in functioning score and cHWMK $C_{ave,ss}$ ($p = 0.04$).

### 3.7 | EQ-5D-5L scores at baseline and effect of treatment

Baseline mean EQ-5D-5L index and VAS scores in all treatment groups were high, indicating very low impairment to HRQoL at day 0 (on the day of assessment). Mean index scores at day 0 were 0.89, 0.84, 0.87, and 0.89 in the placebo group and the lanadelumab 150 mg q4wks, 300 mg q4wks, and 300 mg q2wks groups, respectively; mean scores at day 182 (on the day of assessment) were 0.88, 0.89, 0.87, and 0.88, respectively. Mean VAS scores at day 0 were 81.9, 78.4, 82.8, and 81.2, respectively; mean scores at day 182 were 84.2, 83.3, 82.5, and 83.2, respectively. Mean change in index and VAS scores from day 0 to 182 was not statistically significant for any of the treatment groups.

**TABLE 3** Mean change from baseline in AE-QoL scores by responder analysis category for HAE attack rate reduction from day 0 to 182 (intent-to-treat population)

| | Responder analysis category[a] | | |
|---|---|---|---|
| | <50% reduction (*n* = 30) | 50%–69% reduction (*n* = 19) | 70%–89% reduction (*n* = 17) |
| Number (%)[b] of patients by treatment | | | |
| Placebo group (*n* = 38) | 27 (71.1) | 8 (21.1) | 1 (2.6) |
| Lanadelumab total group (*n* = 79) | 3 (3.8) | 11 (13.9) | 16 (20.3) |
| Mean (SD) change from baseline in AE-QoL score | | | |
| Total score | −2.99 (13.21) | −9.29 (15.81) | −14.81 (24.60) |
| Functioning | −6.6 (20.85) | −11.51 (32.63) | −24.39 (22.96) |
| Fatigue/mood | −1.17 (19.28) | −5.26 (17.91) | −8.82 (33.33) |
| Fears/shame | −3.06 (15.74) | −12.5 (13.89) | −14.71 (31.29) |
| Nutrition | −0.83 (17.04) | −5.26 (22.17) | −11.03 (30.58) |

Abbreviations: AE-QoL, Angioedema Quality of Life Questionnaire; HAE, hereditary angioedema; q2wks, every 2 weeks; q4wks, every 4 weeks.

[a]Any patient who achieved ≥50% reduction in attack rate during the treatment period compared with baseline was defined as a responder; prespecified thresholds included ≥50%, ≥70%, and ≥90%.

[b]Denominator for percentage calculation is the total number of patients in each treatment group with non-missing AE-QoL scores at day 0 and 182.

## 4 | DISCUSSION

The HELP Study was a randomized, double-blind pivotal trial in which lanadelumab was well tolerated and significantly reduced angioedema attacks in patients with HAE-1/2.[16] It assessed angioedema-specific patient-reported QoL using the AE-QoL, and the analyses reported here show that treatment with lanadelumab, as compared with placebo, significantly improves mean AE-QoL total scores and all four domain scores, particularly in the functioning domain. Mean AE-QoL scores per study visit indicated that although HRQoL improved by week 8 in all treatment groups, the improvements were maintained for the duration of the study only in the lanadelumab groups. The 4-week recall period for AE-QoL and schedule of data collection preclude conclusions on the precise timings for HRQoL improvement.

Clinically meaningful improvements in HRQoL with lanadelumab treatment were observed through the use of the well-established MCID of 6 points in AE-QoL total score.[21] Higher proportions of patients in all lanadelumab groups achieved the MCID by the end of the treatment period compared with the placebo group, with the highest proportion, 81%, in the 300 mg q2wks group. Patients in this group were seven times more likely to reach the MCID threshold than placebo-treated patients. Interestingly, there appeared to be a placebo effect during the first two assessments (at weeks 4 and 8) that disappeared over subsequent timepoints. It should be noted that mean monthly HAE attack rate (primary endpoint) in the placebo group during the HELP Study treatment period was 1.97, compared with 4.0 during the 4-week run-in period.[16] The placebo effect noted on HRQoL may therefore align with a similar effect observed on the HAE attack rate.

The marked QoL improvements shown with lanadelumab treatment were observed in a population with relatively severe disease at baseline, in which more than half of patients experienced ≥3 attacks per month during the run-in period, and approximately 65% had a history of laryngeal attacks. AE-QoL total score was shown to correlate well with anchor instruments that measure disease activity[21]; although the HELP Study was not powered for such analyses, correlation assessment was explored. Weak positive correlations were observed between AE-QoL scores and the primary and secondary efficacy endpoints, highlighting the importance of assessing both disease activity and overall HRQoL in routine clinical practice, as recommended by current guidelines.[1,19] Future studies should explore how disease control and changes in disease control with treatment, for example through utilization of the Angioedema Control Test,[25] are linked to HRQoL in patients with HAE.

These results are consistent with those in patients with chronic spontaneous urticaria, where only moderate correlations between HRQoL and disease activity were found,[26,27] suggesting that additional factors influence HRQoL in patients with chronic illnesses. Patients with HAE-1/2 express fears with respect to their children inheriting the disease[6] and missed opportunities for career development,[4,9] and the burden arising from such long-term impairment may not be substantially improved by reductions in disease activity that fall short of attack-free status.

When responders were categorized according to predefined thresholds, a consistent trend was observed for greater AE-QoL score improvements with greater attack rate reduction. Mean changes from baseline scores of −16 to −33 were observed for the group with a 90%–100% reduction in attack rate; 52 of these 54 patients (96.3%) had been treated with lanadelumab. Investigation of an exposure-response relationship indicated that higher lanadelumab exposure was associated with a greater improvement in overall HRQoL and, in particular, functioning-related HRQoL.

The significant burden of HAE beyond the physical impact of attacks was described by patients, caregivers, and family members at a public meeting held in September 2017 as part of the FDA's Patient-Focused Drug Development initiative.[28] Patient participants reported frequent disruptions to their presence at school or work, and to social, family, or physical activities, corroborating findings reported in the literature.[2,4,9] In the HELP Study, the large improvements in and correlations with AE-QoL functioning scores suggest that lanadelumab treatment can reduce the considerable impairment of work/education, social, and physical activities experienced by patients with HAE-1/2. Participants at the FDA's public meeting considered reduction in attack frequency to be the most clinically meaningful treatment effect, while route of administration was the most frequently selected factor affecting treatment choice. In addition to the favorable efficacy, safety, and HRQoL outcomes reported with lanadelumab treatment in the HELP Study, the subcutaneous administration and once- or twice-monthly dosing schedule present a convenient option for patients with HAE.

Initiatives such as the FDA's planned Patient-Focused Drug Development guidance reflect the increasing importance of including patient perspectives and patient experience in the drug development process.[29] Clinical and real-world studies of patients with HAE have utilized generic patient-reported outcome instruments[30–34] as well as combinations of generic tools with HAE-specific methodology.[6,35–37] Additionally, four separate disease- or symptom-specific instruments have now been proposed or developed.[20,21,38–41] A consensus has not been reached on the most appropriate assessment methods for patients with HAE-1/2. Along these lines, improvements across various QoL domains have previously been demonstrated with the use of C1-INH agents in the prophylactic treatment of HAE; however, due to differences in study designs and QoL instruments used, direct comparisons of findings cannot be made.[30,34,42]

Generic HRQoL tools may lack the specificity and sensitivity needed to accurately measure how this rare and chronic disease affects a patient's day-to-day life and to account for fluctuating symptoms.[20,43] Although the EQ-5D-5L is a tool used by payers and health technology agencies to estimate health utilities and is often requested as a key component in cost-effectiveness analyses, its suitability for capturing significant differences in health status over a period of time for a disease such as HAE, where health status is largely impacted by transient symptoms, may be limited by its single-day recall period. As such, the EQ-5D-5L results in this study may be less indicative of truly low impairment of HRQoL in patients with HAE, but rather demonstrate a lack of instrument sensitivity for measuring the impact of diseases characterized by fluctuating physical symptoms and asymptomatic periods. To overcome this limitation, some studies that successfully used the EQ-5D-5L to measure health status of patients with HAE administered the questionnaire during both attack-free days and separately during the last HAE attack.[33,37] Other studies have used generic instruments such as the Short Form (SF-) 36 or SF-12 Health Surveys, which have a 4-week recall period.[4,31,32,36]

The HELP Study was one of the first phase 3 trials in HAE to utilize a symptom-specific instrument designed for patients with any type of recurrent angioedema.[16,44] AE-QoL measures disease burden over a 4-week recall period, enabling monitoring of HRQoL both during and between angioedema attacks, an important consideration for a disease characterized by transient physical symptoms.[20] Patients with HAE-1/2 were among the population included during development of the AE-QoL,[20] and total scores were found to correlate well with generic questionnaires commonly used in HAE.[21] The AE-QoL is most sensitive to change in the functioning domain,[21] which may explain the magnitude and consistency of the improvements to functioning scores observed in this study across all lanadelumab treatment groups compared with other domain scores. The HAE-QoL instrument has been used to assess HRQoL in patients with HAE-1/2[38,39,45]; however, assessment of sensitivity to change and a validated MCID were not available at the time of HELP Study initiation.[43] In addition, the AE-QoL was better suited to this study than HAE-QoL because of its shorter recall period (4 weeks vs 6 months) and lower respondent burden (17 items vs 25 items).[39,46] Per the FDA's 2009 Guidance for Industry on patient-reported outcome measures,[47] shorter recall periods are preferable to avoid bias stemming from patients' reliance on memory and their state at the time of recall, while longer questionnaires can increase respondent burden and affect data quality and completeness.

A limitation of this analysis is that baseline mean EQ-5D-5L index and VAS scores across all treatment groups were close to the highest score achievable at day 0. These baseline scores indicated low impairment of health status on the day of assessment when measured by this generic instrument and left little to no room for improvement with study treatment. A further limitation of this analysis is the administration of AE-QoL to the 10 adolescent patients participating in the study, an age group for which the instrument has not been validated, and the use of the adult version of EQ-5D-5L in the same population. While a youth version (EQ-5D-Y) of this questionnaire is available for patients aged 12–15 years, the use of the adult version is permitted in adolescents and allowed for comparability across the entire patient population.

In conclusion, patient-reported outcome data collected during the HELP Study demonstrated that, compared with placebo, patients treated with lanadelumab experienced significant, consistent, and clinically meaningful improvements in HRQoL when measured using the angioedema-specific and validated AE-QoL. Patients treated with lanadelumab 300 mg q2wks had seven times greater odds of achieving the MCID in AE-QoL total score than placebo-treated patients. Marked improvements in the functioning domain suggest that lanadelumab treatment has the potential to reduce the impact of HAE on patients' ability to attend work/education and on their physical and social activities. In conjunction with the significant reductions in HAE attack rate and the high proportions of attack-free patients during the study, these HRQoL data indicate that long-term prophylactic therapy with lanadelumab is a promising treatment option that can improve the overall life quality of patients with HAE-1/2.

## ACKNOWLEDGEMENTS

The HELP Study was sponsored by Shire Human Genetic Therapies, Inc, a Takeda company. We thank Yi Wang, Senior Director, Clinical Pharmacology and Pharmacokinetics, Takeda Pharmaceutical Company Limited, for data collection on exposure-response relationships, and James Hao, Project Lead Biostatistician, Takeda Pharmaceutical Company Limited, for reviewing the manuscript. Under the direction of the authors, Alpa Parmar, PhD, CMPP, employee of Excel Medical Affairs, provided writing assistance for this manuscript. Editorial assistance in formatting, proofreading, copy editing, and fact checking also were provided by Excel Medical Affairs. Shire Human Genetic Therapies, Inc, a Takeda company, 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.

HELP Study Principal Investigators: Canada: J Hébert, B Ritchie, G Sussman, and WH Yang; Germany: M Magerl, I Martinez-Saguer, P Staubach; Italy: M Cicardi†, Jordan: M Shennak; Puerto Rico: RH Zaragoza-Urdaz; United Kingdom: HJ Longhurst; United States: J Anderson, A Banerji, AP Baptist, JA Bernstein, PB Boggs, PJ Busse, T Craig, M Davis-Lorton, S Gierer, RG Gower, D Harris, DI Hong, J Jacobs, DT Johnston, HH Li, RF Lockey, P Lugar, WR Lumry, ME Manning, DL McNeil, I Melamed, T Nickel, WR Otto, AA Petrov, C Radojicic, SM Rehman, MA Riedl, LB Schwartz, R Shapiro, E Sher, AM Smith, D Soteres, R Tachdjian, HJ Wedner, ME Weinstein, H Zafra.

†Deceased

## CONFLICTS OF INTEREST

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, consultant fees from BioCryst, CSL Behring, Fresenius Kabi, Pharming, and Takeda, and payments for lectures from CSL Behring, Pharming, and Takeda; and is a medical advisory board member of the US Hereditary Angioedema Association. K. Weller has received research grant support and/or honoraria for educational lectures and/or consultant fees from BioCryst, CSL Behring, Moxie, and Takeda. M. Magerl has received research grant support and/or speaker/consultancy fees from BioCryst, CSL Behring, KalVista, Octapharma, Pharming, and Takeda. A. Banerji has received institutional research/study support from BioCryst and Takeda; and/or honoraria for consulting from Alnylam, BioCryst, CSL Behring, KalVista, Pharming, Pharvaris, and Takeda, and is a medical advisory board member of the US Hereditary Angioedema Association. H. J. Longhurst has received research grant support and/or speaker/consultancy fees from Adverum, BioCryst, CSL Behring, GlaxoSmithKline, Octapharma, Pharming, Pharvaris, and Takeda. M. A. Riedl has received research grants from BioCryst, CSL Behring, Ionis, Pharming, and Takeda; consulting fees from Adverum, Attune, BioCryst, CSL Behring, Ionis, KalVista, Pharming, Pharvaris, and Takeda; and speaker honoraria from CSL Behring, Pharming, and Takeda; and is a medical advisory board member of the US Hereditary Angioedema Association. H. B. Lewis is a full-time employee of ICON plc. P. Lu was a full-time employee of Takeda at the time of the study and holds stock/stock options in Takeda; her current affiliation is Pharvaris B.V. G. Devercelli and G. Jain are full-time employees of and hold stock/stock options in Takeda. M. Maurer is or recently was a speaker and/or advisor for BioCryst, CSL Behring, KalVista, Moxie, Pharming, Pharvaris, and Takeda, and has received research funding from BioCryst, CSL Behring, Moxie, Pharming, and Takeda.

## AUTHOR CONTRIBUTIONS

G. Devercelli, G. Jain, and H. B. Lewis were involved in planning of the study and/or data analysis, and P. Lu was the clinical lead for the HELP Study from which the data were collected and contributed to clinical trial design; W. R. Lumry, K. Weller, M. Magerl, A. Banerji, H. J. Longhurst, M. A. Riedl, and M. Maurer were involved in data collection. All authors were involved in interpretation of results, writing of the manuscript or critically evaluating revisions, and approval of the final submission draft.

## ORCID

*Karsten Weller* https://orcid.org/0000-0003-4437-0313
*Marc A. Riedl* https://orcid.org/0000-0003-3460-1544
*Marcus Maurer* https://orcid.org/0000-0002-4121-481X

## REFERENCES

1. Maurer M, Magerl M, Ansotegui I, et al. The international WAO/EAACI guideline for the management of hereditary angioedema-The 2017 revision and update. *Allergy*. 2018;73(8):1575-1596.
2. Longhurst H, Bygum A. The humanistic, societal, and pharmaco-economic burden of angioedema. *Clin Rev Allergy Immunol*. 2016;51(2):230-239.
3. Banerji A. The burden of illness in patients with hereditary angioedema. *Ann Allergy Asthma Immunol*. 2013;111(5):329-336.
4. Lumry WR, Castaldo AJ, Vernon MK, Blaustein MB, Wilson DA, Horn PT. The humanistic burden of hereditary angioedema: impact on health-related quality of life, productivity, and depression. *Allergy Asthma Proc*. 2010;31(5):407-414.
5. Bork K, Hardt J, Witzke G. Fatal laryngeal attacks and mortality in hereditary angioedema due to C1-INH deficiency. *J Allergy Clin Immunol*. 2012;130(3):692-697.
6. Caballero T, Aygoren-Pursun E, Bygum A, et al. The humanistic burden of hereditary angioedema: results from the burden of illness study in Europe. *Allergy Asthma Proc*. 2014;35(1):47-53.
7. Fouche AS, Saunders EF, Craig T. Depression and anxiety in patients with hereditary angioedema. *Ann Allergy Asthma Immunol*. 2014;112(4):371-375.
8. Bygum A, Aygoren-Pursun E, Beusterien K, et al. Burden of illness in hereditary angioedema: a conceptual model. *Acta Derm Venereol*. 2015;95(6):706-710.
9. Aygören-Pürsün E, Bygum A, Beusterien K, et al. Socioeconomic burden of hereditary angioedema: results from the hereditary angioedema burden of illness study in Europe. *Orphanet J Rare Dis*. 2014;9:99.
10. Chen M, Riedl MA. Emerging therapies in hereditary angioedema. *Immunol Allergy Clin North Am*. 2017;37(3):585-595.
11. Kaplan AP, Joseph K. Pathogenesis of hereditary angioedema: the role of the bradykinin-forming cascade. *Immunol Allergy Clin North Am*. 2017;37(3):513-525.

12. Nussberger J, Cugno M, Cicardi M, Agostoni A. Local bradykinin generation in hereditary angioedema. *J Allergy Clin Immunol*. 1999;104(6):1321-1322.
13. Kenniston JA, Faucette RR, Martik D, et al. Inhibition of plasma kallikrein by a highly specific active site blocking antibody. *J Biol Chem*. 2014;289(34):23596-23608.
14. Chyung Y, Vince B, Iarrobino R, et al. A phase 1 study investigating DX-2930 in healthy subjects. *Ann Allergy Asthma Immunol*. 2014;113(4):460-466.
15. Banerji A, Busse P, Shennak M, et al. Inhibiting plasma kallikrein for hereditary angioedema prophylaxis. *N Engl J Med*. 2017;376(8):717-728.
16. 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*. 2018;320(20):2108-2121.
17. TAKHZYRO (lanadelumab-flyo) [Prescribing Information]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/761090s000lbl.pdf. Accessed April 15, 2020.
18. TAKHZYRO (lanadelumab) [Summary of Product Characteristics]. https://www.ema.europa.eu/documents/product-information/takhzyro-epar-product-information_en.pdf. Accessed April 15, 2020.
19. Betschel S, Badiou J, Binkley K, et al. The International/Canadian Hereditary Angioedema Guideline. *Allergy Asthma Clin Immunol*. 2019;15:72.
20. Weller K, Groffik A, Magerl M, et al. Development and construct validation of the angioedema quality of life questionnaire. *Allergy*. 2012;67(10):1289-1298.
21. Weller K, Magerl M, Peveling-Oberhag A, Martus P, Staubach P, Maurer M. The Angioedema Quality of Life Questionnaire (AE-QoL) - assessment of sensitivity to change and minimal clinically important difference. *Allergy*. 2016;71(8):1203-1209.
22. Kulthanan K, Chularojanamontri L, Rujitharanawong C, Weerasubpong P, Maurer M, Weller K. Angioedema Quality of Life Questionnaire (AE-QoL) - interpretability and sensitivity to change. *Health Qual Life Outcomes*. 2019;17(1):160.
23. EuroQol Research Foundation. EQ-5D-5L User Guide. 2019; https://euroqol.org/publications/user-guides/. Accessed April 15, 2020.
24. Norman GR, Sloan JA, Wyrwich KW. Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation. *Med Care*. 2003;41(5):582-592.
25. Weller K, Donoso T, Magerl M, et al. Validation of the Angioedema Control Test (AECT)-a patient-reported outcome instrument for assessing angioedema control. *J Allergy Clin Immunol Pract*. 2020;8(6):2050-2057
26. Weller K, Church MK, Kalogeromitros D, et al. Chronic spontaneous urticaria: how to assess quality of life in patients receiving treatment. *Arch Dermatol*. 2011;147(10):1221-1223.
27. Koti I, Weller K, Makris M, et al. Disease activity only moderately correlates with quality of life impairment in patients with chronic spontaneous urticaria. *Dermatology*. 2013;226(4):371-379.
28. US Food and Drug Administration. The Voice of the Patient: hereditary angioedema. Public Meeting: September 25, 2017. May 2018; https://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM609256.pdf. Accessed April 15, 2020.
29. US Food and Drug Administration. Plan for issuance of patient-focused drug development guidance. May 2017; https://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM563618.pdf. Accessed April 15, 2020.
30. Lumry WR, Miller DP, Newcomer S, Fitts D, Dayno J. Quality of life in patients with hereditary angioedema receiving therapy for routine prevention of attacks. *Allergy Asthma Proc*. 2014;35(5):371-376.
31. Bouillet L, Launay D, Fain O, et al. French National Reference Center for Hereditary Angioedema (CREAK). Hereditary angioedema with C1 inhibitor deficiency: clinical presentation and quality of life of 193 French patients. *Ann Allergy Asthma Immunol*. 2013;111(4):290-294.
32. Jindal NL, Harniman E, Prior N, Perez-Fernandez E, Caballero T, Betschel S. Hereditary angioedema: health-related quality of life in Canadian patients as measured by the SF-36. *Allergy Asthma Clin Immunol*. 2017;13:4.
33. Nordenfelt P, Dawson S, Wahlgren CF, Lindfors A, Mallbris L, Bjorkander J. Quantifying the burden of disease and perceived health state in patients with hereditary angioedema in Sweden. *Allergy Asthma Proc*. 2014;35(2):185-190.
34. Lumry WR, Craig T, Zuraw B, et al. Health-related quality-of-life with subcutaneous C1-inhibitor for prevention of attacks of hereditary angioedema. *J Allergy Clin Immunol Pract*. 2018;6(5):1733-1741.
35. Nordenfelt P, Nilsson M, Lindfors A, Wahlgren CF, Björkander J. Health-related quality of life in relation to disease activity in adults with hereditary angioedema in Sweden. *Allergy Asthma Proc*. 2017;38(6):447-455.
36. Aabom A, Andersen KE, Perez-Fernández E, Caballero T, Bygum A. Health-related quality of life in Danish patients with hereditary angioedema. *Acta Derm Venereol*. 2015;95(2):225-226.
37. Aygoren-Pursun E, Bygum A, Beusterien K, et al. Estimation of EuroQol 5-Dimensions health status utility values in hereditary angioedema. *Patient Prefer Adherence*. 2016;10:1699-1707.
38. Prior N, Remor E, Gomez-Traseira C, et al. Development of a disease-specific quality of life questionnaire for adult patients with hereditary angioedema due to C1 inhibitor deficiency (HAE-QoL): Spanish multi-centre research project. *Health Qual Life Outcomes*. 2012;10:82.
39. Prior N, Remor E, Perez-Fernandez E, et al. Psychometric field study of hereditary angioedema quality of life questionnaireforadults:HAE-QoL.*JAllergyClinImmunolPract*.2016;4(3):464-473.
40. Bonner N, Abetz-Webb L, Renault L, et al. Development and content validity testing of a patient-reported outcomes questionnaire for the assessment of hereditary angioedema in observational studies. *Health Qual Life Outcomes*. 2015;13:92.
41. Busse PJ, Christiansen SC, Birmingham JM, et al. Development of a health-related quality of life instrument for patients with hereditary angioedema living in the United States. *J Allergy Clin Immunol Pract*. 2019;7(5):1679-1683.
42. Greve J, Hahn J, Nordmann M, et al. Nanofiltrated C1-esterase-inhibitor in the prophylactic treatment of bradykinin-mediated angioedema. *Transfusion*. 2016;56(5):1022-1029.
43. Caballero T, Prior N. Burden of illness and quality-of-life measures in angioedema conditions. *Immunol Allergy Clin North Am*. 2017;37(3):597-616.
44. Riedl MA, Aygören-Pürsün E, Baker J, et al. Evaluation of avoralstat, an oral kallikrein inhibitor, in a Phase 3 hereditary angioedema prophylaxis trial: The OPuS-2 study. *Allergy*. 2018;73(9):1871-1880.
45. Zanichelli A, Azin GM, Cristina F, Vacchini R, Caballero T. Safety, effectiveness, and impact on quality of life of self-administration with plasma-derived nanofiltered C1 inhibitor (Berinert®) in patients with hereditary angioedema: the SABHA study. *Orphanet J Rare Dis*. 2018;13(1):51.
46. Bygum A, Busse P, Caballero T, Maurer M. Disease severity, activity, impact, and control and how to assess them in patients with hereditary angioedema. *Front Med (Lausanne)*. 2017;4:212.

47. US Food and Drug Administration. Guidance for industry. Patient-reported outcome measures: use in medical product development to support labeling claims. December 2009; https://www.fda.gov/media/77832/download. Accessed April 15, 2020.

## SUPPORTING INFORMATION

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

**How to cite this article:** Lumry WR, Weller K, Magerl M, et al; on behalf of the HELP Study Investigators. Impact of lanadelumab on health-related quality of life in patients with hereditary angioedema in the HELP study. *Allergy*. 2021;76:1188–1198. https://doi.org/10.1111/all.14680