

ARTICLE

Pharmacokinetics, Pharmacodynamics, and Exposure-Response of Lanadelumab for Hereditary Angioedema

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Hereditary angioedema (HAE) with C1 inhibitor deficiency is a rare disorder characterized by unpredictable, potentially life-threatening recurrent angioedema attacks. Lanadelumab is a fully human monoclonal antibody with selective binding to active plasma kallikrein, and prevents the formation of cleaved high molecular weight kininogen (cHMWK) and bradykinin, thereby preventing HAE attacks. The clinical pharmacology of lanadelumab was characterized following subcutaneous administration in 257 subjects (24 healthy subjects and 233 patients with HAE). The pharmacokinetics of lanadelumab were described using a one-compartment model with first-order rate of absorption and linear clearance, showing slow absorption and a long half-life (14.8 days). A covariate analysis retained body weight and health status on apparent clearance (CL/F) and body weight on volume of distribution (V/F). Population estimates of CL/F and V/F were 0.0249 L/hour (0.586 L/day) and 12.8 L, respectively. An indirect-response I_{max} model showed 53.7% maximum suppression in cHMWK formation with a low potential for interactions with concomitant medications (analgesic, anti-inflammatory, and antirheumatic medications). A 300 mg dose administered Q2W was associated with a mean steady-state minimum concentration (C_{min,ss}; 25.4 µg/mL) that was ~ 4.5-fold higher than the half-maximal inhibitory concentration for cHMWK reduction (5.71 µg/mL). Exposure-response analyses suggest that 300 mg Q2W dosing was associated with a significantly reduced HAE attack rate, prolonged time to first attack after treatment initiation, and lower need for concomitant medications. The response was comparable across patient body weight groups. Findings from this analysis support the dosing rationale for lanadelumab to prevent attacks in patients with HAE.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

✓ Hereditary angioedema (HAE) is a long-term, debilitating, and potentially life-threatening disease caused by C1-inhibitor deficiency. Lanadelumab is a fully human monoclonal antibody inhibitor of plasma kallikrein that is effective in preventing attacks in patients with HAE.

WHAT QUESTION DID THIS STUDY ADDRESS?

✓ What are the pharmacokinetic and pharmacodynamic characteristics of lanadelumab, and how are they related to the observed efficacy of lanadelumab in preventing HAE attacks?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

✓ Lanadelumab clearance and volume of distribution are dependent on body weight; however, significant attack rate reduction is still observed in patients with high body weight, and dose adjustment is not necessary. The findings of this study provide a greater understanding of the factors driving the efficacy and safety of lanadelumab to ensure optimal use.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

✓ Selective binding of lanadelumab to plasma kallikrein provides a novel approach for long-term prophylaxis against HAE attacks.

Hereditary angioedema (HAE) is a rare, debilitating, and potentially life-threatening disease with an estimated prevalence of 1 in 50,000.¹ It manifests clinically as unpredictable, intermittent attacks of subcutaneous or submucosal edema of the face, larynx, gastrointestinal tract, limbs, and/or genitalia. Swelling may last several days, and most patients have

multiple attacks per year.² Symptoms usually begin during childhood, sometimes as young as age 2 years, and persist throughout life.² HAE is caused by mutations in *SERPING1*, the gene encoding C1 inhibitor (C1-INH), resulting in deficiency of C1-INH protein or function.³ C1-INH is involved in regulating the contact, complement, and coagulation

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systems.³ In the contact system, C1-INH is the natural inhibitor of plasma kallikrein. Dysregulated contact system activation and subsequent uncontrolled plasma kallikrein activity lead to production of cleaved high molecular weight kininogen (cHMWK) and the edema-inducing peptide bradykinin, which initiates signaling pathways leading to HAE attacks. Management of patients with HAE involves on-demand medications to treat attacks when they occur, and long-term or short-term prophylaxis to prevent attacks.^{1,2}

Lanadelumab is a fully human immunoglobulin G1 monoclonal antibody that binds specifically to active plasma kallikrein.⁴ It is approved in several countries for the prevention of HAE attacks in patients ≥ 12 years of age. In clinical trials, treatment with lanadelumab significantly reduced attack rates in patients with HAE, and this was associated with a reduction in cHMWK levels.^{5,6} The pharmacokinetics (PK), pharmacodynamics (PD), exposure-response relationships, and potential interactions of lanadelumab with rescue medications (for treatment of attacks that occur during long-term prophylaxis), and with medications commonly used concomitantly in patients with HAE, were characterized using data from clinical studies to support the dosing rationale for long-term prophylaxis with lanadelumab in patients with HAE.

METHODS

Study subjects

All studies were conducted in accordance with International Conference on Harmonisation Good Clinical Practice guidelines and the principles of the Declaration of Helsinki, as well as applicable local ethical and legal requirements. All study subjects (healthy volunteers, patients with HAE, and/or caregivers) provided written informed consent (or assent from patients < 18 years of age) prior to the conduct of any study-related activities. Protocols and informed consent forms were approved by local ethics review committees.

Clinical studies and populations

Data were obtained from lanadelumab-treated subjects in four clinical studies (study details in **Tables S1 and S2**): a phase I double-blind study of PK and safety following single ascending doses in 24 healthy male and female subjects 18–55 years old (DX-2930-01; NCT01923207)⁷; a phase Ib double-blind, multiple ascending dose study of PK, PD, and safety over 120 days and efficacy from days 8–50 in 24 male and female patients ≥ 18 years old with HAE (DX-2930-02; NCT02093923)⁵; a phase III, multicenter, randomized, double-blind, placebo-controlled study evaluating PK, PD, safety, and efficacy in 84 patients ≥ 12 years old with HAE over 26 weeks (HELP, DX-2930-03; NCT02586805)⁶; an ongoing open-label, long-term safety and efficacy extension study in 212 patients ≥ 12 years old with HAE (HELP OLE, DX-2930-04; NCT02741596).⁸ Patients in HELP OLE included “rollovers” who continued from HELP, and “non-rollovers” who did not participate in HELP.

Measurement of plasma lanadelumab and cHMWK levels

Plasma samples were collected from study subjects at pre-specified time points for measurement of lanadelumab and cHMWK levels using enzyme-linked immunosorbent assay

and Western blot, respectively. Analytical methods have been described previously.⁵ Samples below the limit of quantitation were set to missing. Missing observations due to samples that were not collected or that were lost/compromised were excluded from the analysis. Data collected for HELP OLE between May 26, 2016, and September 1, 2017, were used in these analyses.

Population PK analysis

Population PK (PopPK) analyses were performed to assess sources of variability in lanadelumab PK using data from healthy volunteers and from patients with HAE across four clinical studies. Various compartmental models were constructed to optimally describe the PK of lanadelumab following subcutaneous administration (Method S1). The base model included a description of the relationship between plasma concentration and time; allometric functions accounting for the effect of body weight on clearance and volume parameters (estimated exponent); a variance component characterizing interindividual variability in model parameters; and a residual unexplained variability component (modeled using additive, proportional, or mixed models). Structural and residual error model discrimination were based on standard model diagnostics (minimum objective function value decrease, precision and accuracy of parameter estimation, and successful model convergence) and determined by looking at pertinent graphical representations of goodness of fit. Shrinkage of interindividual random effects was also evaluated.

Relationships between covariates and interindividual random effects of PK parameters were first explored graphically to assess covariates likely to affect PK parameters of interest. Following initial visual inspection of the covariates, specific covariates were considered in a stepwise approach based on scientific/clinical interest, mechanistic plausibility, and *a priori* knowledge about covariate effects (Method S2). Intrinsic covariates included age, sex, race, body weight, estimated glomerular filtration rate, liver function markers, baseline C1-INH and C4 levels, occurrence of an HAE attack within 7 days of lanadelumab concentration measurement, baseline disease severity in patients with HAE, presence of antidrug antibodies or neutralizing antibodies, and health status. Extrinsic covariates included injection site, self-administration, and use of rescue and concomitant medications. The covariate analysis was performed using a forward inclusion ($-2 \log$ -likelihood > 6.63 ; $P < 0.01$ for one degree of freedom) and backward exclusion ($-2 \log$ -likelihood > 10.83 ; $P < 0.001$ for one degree of freedom) procedure.⁹

The final PopPK models were evaluated using diagnostic plots and visual predictive check stratified by study. Concentration-time profiles were simulated ($n = 1,000$) using the final model. The 95% confidence interval of the 2.5th, 50th, and 97.5th percentiles of predicted-corrected concentrations were compared with the corresponding percentiles of observed-corrected concentrations.¹⁰

The PopPK model was used to simulate rich concentration-time profiles at steady-state for patients in HELP and HELP OLE. The following PK parameters at steady-state were derived using noncompartmental methods: AUC over a dosing interval ($AUC_{\tau,ss}$); maximum, minimum, and average concentrations ($C_{\max,ss}$, $C_{\min,ss}$, and $C_{\text{ave},ss}$, respectively);

and time to maximum concentration over a dosing interval ($T_{\max,ss}$).

PopPK/PD analysis of cHMWK

As there was a delay between the time of lanadelumab measurement and the PD response, an indirect-response Imax model was used to assess the relationship between PopPK-predicted individual lanadelumab concentrations and observed cHMWK levels in patients with HAE.¹¹ Goodness of fit and qualification of the PK/PD model for cHMWK as well as covariate analyses were performed using approaches similar to the PopPK model.

Exposure-response analysis of efficacy: Number of HAE attacks per month

A longitudinal exposure-response model was used to simultaneously assess the impact of treatment duration and drug exposure on efficacy (i.e., reduction in attack rate). The exposure-response analysis was performed with data from HELP, using the $C_{\text{ave},ss}$ of lanadelumab over each month and the attack rate for each month. The population time-response and exposure-response models of lanadelumab and the monthly attack rate were modeled using a logarithm of the Poisson distribution. The models considered included both linear and saturating maximum effect (E_{max})-type models, and time-fixed, as well as time-varying effects.¹²

Exposure-response analysis: Time to first HAE attack

A Cox proportional hazard regression model was developed to assess the probability of being attack-free over time following the first lanadelumab dose as a function of lanadelumab $C_{\text{ave},ss}$, which was included in the model as a continuous parameter and applied to the hazard model as follows:

$$\log h_i(t) = \alpha(t) + \beta_1(x_i) \quad (1)$$

where $\log h_i(t)$ is the natural logarithm of the hazard ratio at time t for the i th individual; x_i is the exposure covariate; $\alpha(t)$ is baseline hazard; and β_1 is the regression coefficient related to the exposure metric. This model was used to derive the estimated hazard ratio for specific increments of $C_{\text{ave},ss}$ across quartiles.

An exposure-response analysis was performed for the number of attack-free days following administration of the first open-label dose in rollover patients in HELP OLE. Exposure parameters that were derived included AUC_{0-HAE} (AUC from the first open-label dose to the time of the first attack), $C_{\text{max},0-HAE}$, and $C_{\text{min},0-HAE}$. The number of attack-free days was modeled as continuous data. A sigmoidal E_{max} model driven by AUC_{0-HAE} was used to quantify the exposure-response relationship as presented below:

$$\text{HAE Attack Free Days} = E_0 + E_{\text{max}} * \left(\frac{AUC_{0-HAE}^Y}{EAUC_{50}^Y + AUC_{0-HAE}^Y} \right) \quad (2)$$

Software

The PopPK and PK/PD analyses were performed using Phoenix NLME (version 7.2; Certara USA, Inc. Princeton,

NJ, USA). Dataset construction and exploration and figure generation were performed using R (version 3.3.1 or higher; R Foundation for Statistical Computing, Vienna, Austria). Exposure-response analyses were performed using R (version 3.4.2) or NONMEM (version 7.3; ICON plc, Dublin, Ireland).

RESULTS

Demographics and baseline characteristics of healthy subjects and patients with HAE in each study are presented in **Tables S3 and S4**. A total of 257 unique study subjects (mean age, 39.3 years (range 12.0–75.0 years); mean body weight, 81.2 kg (range 36.7–178 kg)) were included in the PopPK analysis, including 24 healthy subjects and 233 patients with HAE; 166 (64.6%) females; and 128 (49.81%) and 11 (4.28%) patients with mild and moderate renal impairment, respectively.

PK and PD of lanadelumab

Mean observed plasma lanadelumab concentrations in healthy subjects⁷ and in patients with HAE increased with higher doses and dosing frequencies (**Figure 1**). Absorption was slow, with peak concentrations observed at ~ 7 days after dosing. The concentration-time profiles showed a mono-exponential terminal phase, and steady-state was estimated to be reached at approximately week 10.

Mean observed cHMWK levels decreased over time following treatment with lanadelumab. Lanadelumab doses of 300 and 400 mg administered 14 days apart in study DX-2930-02 resulted in similar levels of cHMWK suppression, suggesting a plateauing of the response, and then slowly returned to baseline ~ 110 days after the first dose.⁵ In HELP, a gradual reduction of cHMWK levels was observed for the 150 mg Q4W regimen, whereas levels were reduced more rapidly with the 300 mg Q4W and 300 mg Q2W regimens; the effect appeared to plateau after 56 days of dosing, although this was affected by the sparse sampling schedule.

A one-compartment model with a first-order rate of absorption and linear clearance (CL/F) provided an adequate characterization of the concentration-time profile of lanadelumab (**Table S5**). A PopPK model with both linear and nonlinear clearance did not improve the goodness of fit. Covariate testing showed that lanadelumab PK parameters were not affected by the occurrence of on-treatment HAE attacks; rescue medication use; concomitant use of analgesics, antibiotics, or antihistamines; the site of injection; or self-administration (**Figures S1–S20**).

In HELP, 5.64% of postdose samples from lanadelumab-treated patients were positive for antidrug antibodies (titer 20–1280), and 1.25% were positive for neutralizing antibodies. In rollover and non-rollover subjects in HELP OLE, 5.24% and 4.78% of samples, respectively, were positive for antidrug antibodies (titer 20–10,240); 1.9% and 1.44% of samples, respectively, were positive for neutralizing antidrug antibodies (**Figures S21–S26**). The presence of antidrug antibodies (as a time-varying covariate) did not have a statistically significant impact on the CL/F of lanadelumab. Overall, covariates retained in the final PopPK model included body weight and health status on CL/F, and body weight on volume of distribution (V/F; **Tables S5–S10**).

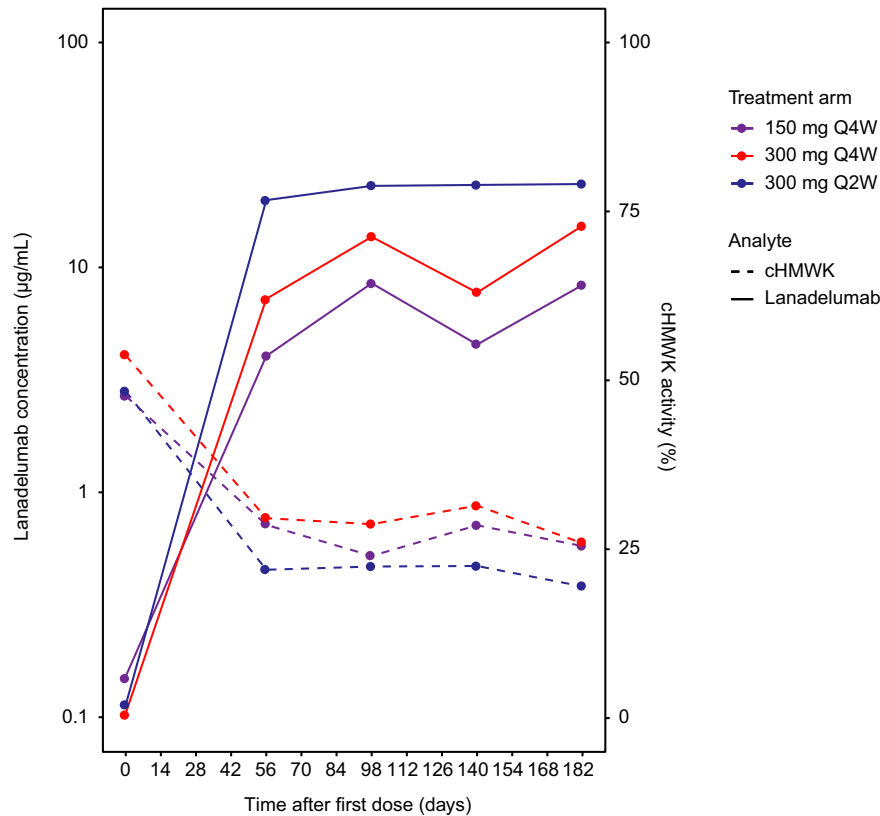


Figure 1 Pharmacokinetic and pharmacodynamic profiles of lanadelumab and cHMWK in patients with HAE in HELP. Lanadelumab concentration-time profiles in healthy subjects (DX-2930-01) and in study DX-2930-02 were published previously.^{5,7} cHMWK, cleaved high molecular weight kininogen; HAE, hereditary angioedema.

Population estimates of CL/F and V/F derived with the final PopPK model were 0.0249 L/hour (0.586 L/day) and 12.8 L, respectively. Interindividual variability of CL/F and V/F were low, with estimated values of 31.7% and 29.6%, respectively (Table S11). Absorption following subcutaneous administration was slow, with an absorption half-life of 37 hours, and complete drug absorption expected within ~ 7 days. The typical half-life of lanadelumab associated with the terminal phase was ~ 14 days. Standard goodness-of-fit and visual predictive checks derived with the final PopPK model are presented in Figures S27–S29. Observed concentrations vs. both individual-predicted and population-predicted values fell along the line of identity in all four studies, and the prediction-corrected visual predictive check showed that the observed data were largely within the simulated range. Lanadelumab PK parameters in HELP are summarized by dosing regimen in Table 1. PK parameters for rollover and non-rollover patients in HELP OLE were similar to those in patients who received the 300 mg Q2W regimen in HELP (Tables S12 and S13). PK parameters were also comparable across age groups among adolescent, adult, and elderly patients in HELP OLE (Tables S14–S16).

An indirect-response I_{max} model of cHMWK was used to assess cHMWK levels over time in patients with HAE (Table S17). Standard goodness-of-fit and visual predictive checks derived with the final PopPK/PD model were adequate and are presented in Figures S30 and S31. Sources

of variability in PD parameters were explored (Figures S32–S40), and only the effect of health status on K_{in} (the rate of cHMWK formation) was included in the final model. Typical K_{in} and K_{out} (the rate of cHMWK degradation) were 11.8%/hour and 0.367 hour⁻¹, respectively. Typical I_{max} was 53.7%, suggesting that lanadelumab suppresses cHMWK levels through a 53.7% inhibition of K_{in} . The estimated half maximal inhibitory concentration (IC_{50}) for lanadelumab (concentration associated with 50% reduction in cHMWK level) was 5.71 µg/mL. Mean $C_{min,ss}$ values for the 150 Q4W and 300 mg Q4W regimens (4.81 and 8.77 µg/mL, respectively) were close to the IC_{50} , whereas mean $C_{min,ss}$ for the 300 mg Q2W regimen (25.4 µg/mL) was ~ 4.5-fold higher than the IC_{50} . Concentrations of lanadelumab are expected to exceed the IC_{50} ~ 15 hours after the first dose of the 300 mg Q2W and 300 mg Q4W regimens and remain so over almost the entire duration of the 168-day treatment period. On the other hand, concentrations exceeded the IC_{50} 38 hours after the first dose in the 150 mg Q4W regimen, and remained higher for ~ 80% of the duration of the treatment period. Simulations showed that the time required for cHMWK values to return to within 5% of baseline following the last dose for the 150 Q4W, 300 mg Q4W, and 300 mg Q2W regimens in the HELP study was 139, 154, and 163 days, respectively (Figure S41). Thus, inhibition of cHMWK formation (and, therefore, inhibition of plasma kallikrein activity) by lanadelumab is sustained but reversible.

Table 1 Summary of lanadelumab PK parameters in patients with HAE in HELP

Population	CL/F (L/hour)	V/F (L)	AUC _{tau,ss} (µg × day/mL)	C _{ave,ss} (µg/mL)	C _{max,ss} (µg/mL)	C _{min,ss} (µg/mL)	T _{max} (hour)	t _{1/2} (hour)
150 mg Q4W								
n	28	28	28	28	28	28	28	28
Mean (%CV)	0.0278 (24.3)	14.1 (20.8)	233 (24.3)	8.31 (24.3)	12.0 (25.1)	4.81 (29.1)	124 (21.1)	357 (13.5)
Median (range)	0.0278 (0.0173–0.0458)	14.8 (9.03–19.3)	218 (132–346)	7.77 (4.73–12.3)	11.4 (7.22–17.6)	4.47 (2.42–7.75)	120 (96.0–217)	351 (291–443)
300 mg Q4W								
n	29	29	29	29	29	29	29	29
Mean (%CV)	0.0309 (32.2)	14.9 (29.8)	441 (31.0)	15.8 (31.0)	23.3 (34.1)	8.77 (32.0)	124 (21.6)	340 (13.3)
Median (range)	0.0292 (0.0168–0.0583)	14.9 (8.39–27.7)	425 (217–740)	15.2 (7.74–26.4)	22.3 (11.1–40.4)	8.66 (2.97–14.7)	121 (73.0–191)	340 (234–416)
300 mg Q2W								
n	27	27	27	27	27	27	27	27
Mean (%CV)	0.0337 (45.7)	16.6 (28.9)	408 (33.9)	29.2 (33.9)	34.4 (32.5)	25.4 (36.2)	98.6 (9.2)	361 (16.5)
Median (range)	0.0295 (0.0188–0.0822)	15.2 (10.2–31.3)	422 (140–625)	30.1 (10.0–44.6)	35.5 (12.1–53.7)	24.0 (8.56–42.4)	97.4 (74.3–121)	352 (258–507)

AUC_{tau,ss}, area under the curve over the dosing interval at steady-state; C_{ave,ss}, average concentration at steady-state; C_{max,ss}, maximum concentration at steady-state; C_{min,ss}, minimum concentration at steady state; CL/F, apparent clearance; CV, coefficient of variability; HAE, hereditary angioedema; PK, pharmacokinetic; t_{1/2}, terminal half-life; T_{max}, time to maximum concentration; V/F, apparent volume of distribution.

PK parameters were derived from simulated rich concentration–time profiles using the population PK model.

Exposure-response analysis: Average monthly HAE attack rate

Simulated concentration–time profiles of lanadelumab in patients with HAE and the corresponding observed monthly attack rate for each treatment group in HELP are presented in **Figure 2**. Lanadelumab treatment resulted in a rapid attack rate reduction after the first dose in all groups, and this was sustained after repeated administrations. The 300 mg Q2W regimen was associated with the largest attack rate reduction over the treatment period.

The final longitudinal exposure–response model included the effect of time (placebo) and a drug effect captured with a saturable function (E_{max} model with average concentrations achieving half maximal effect (EC₅₀)) driven by time-varying exposure of lanadelumab (C_{ave,ss}), as well as a “delay” parameter to account for the temporal build-up in effect. This longitudinal exposure–response model was associated with an adequate prediction of efficacy, with a close alignment of observed and predicted attack rate at each month (**Figure 3**). A marked reduction in the attack rate was observed at month 1. Mean C_{ave,ss} over 4 weeks following dosing of lanadelumab 150 mg Q4W, 300 mg Q4W, and 300 mg Q2W were associated with average attack rates of 0.583, 0.473, and 0.411 attacks/month, respectively. The steepness of the exposure–response function of lanadelumab increased over time, with an apparent plateauing of effect at months 5–6. At month 6, the average attack rate was markedly lower (0.105, 0.0673, and 0.0499 attacks/month, respectively), suggesting that further significant improvement is unlikely after dosing for 6 months. The model estimated an E_{max} of –3.74 attacks/month and an EC₅₀ of 4.03 µg/mL. Mean C_{ave,ss} for the 150 mg Q4W, 300 mg Q4W, and 300 mg Q2W dosing regimens were 2.1-fold, 3.9-fold, and 7.2-fold higher than the EC₅₀, respectively (**Table S18**).

Exposure-response analysis: Time to first attack

The time to first attack after initiation of study treatment in relation to C_{ave,ss} quartiles for lanadelumab and cHMWK in HELP are shown in **Figure 4**. The median time to a 50% probability of the first attack after starting treatment with placebo was ~ 1 week. A significant prolongation in the median time to first attack was observed over higher quartiles of C_{ave,ss}: first, second, third, and fourth quartiles of C_{ave,ss} values were associated with a median time to first HAE attack of 1.56, 5.69, 8.30, and 14.3 weeks, respectively. The majority of patients treated with lanadelumab 300 mg Q2W had C_{ave,ss} values in the fourth quartile (**Table S19**). Correspondingly, a greater suppression of cHMWK (Q1 and Q2) was associated with longer time to the first HAE attack.

Using data from HELP, a Cox proportional hazard regression model was developed to analyze the probability of occurrence of the first attack after initiation of lanadelumab treatment as a function of lanadelumab exposure (**Table S20**). A typical lanadelumab C_{ave,ss} increase of 1 µg/mL was associated with a statistically significant lower risk of the first HAE attack (P < 0.0001). For example, when C_{ave,ss} increased from Q1 to Q2 (a typical increment of 3.8 µg/mL), the estimated hazard ratio was 0.82, suggesting that this increase in C_{ave,ss} is associated with an 18% lower risk of the first HAE attack (**Table S21**).

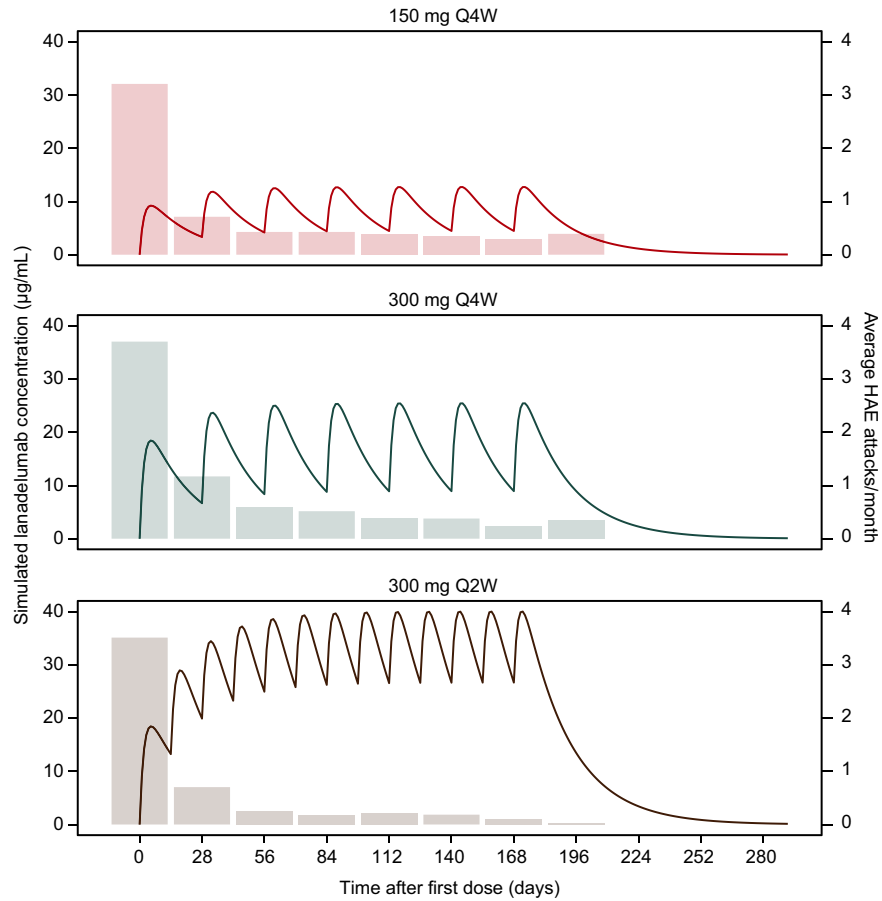


Figure 2 Simulated lanadelumab plasma concentrations and observed attack rate over time by treatment group in HELP. Lines represent simulated mean lanadelumab concentrations; bars represent attack rates. HAE, hereditary angioedema.

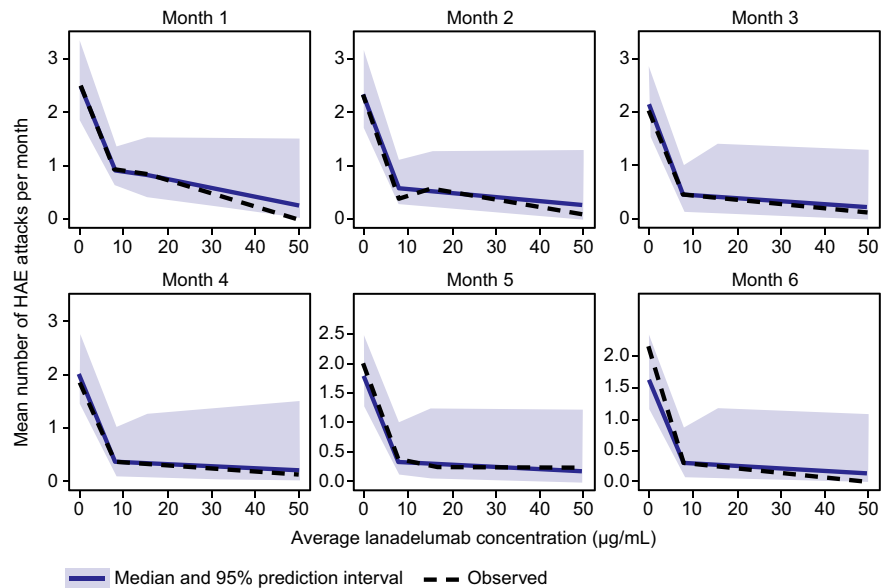


Figure 3 Mean number of attacks per month as a function of lanadelumab exposure in HELP. HAE, hereditary angioedema.

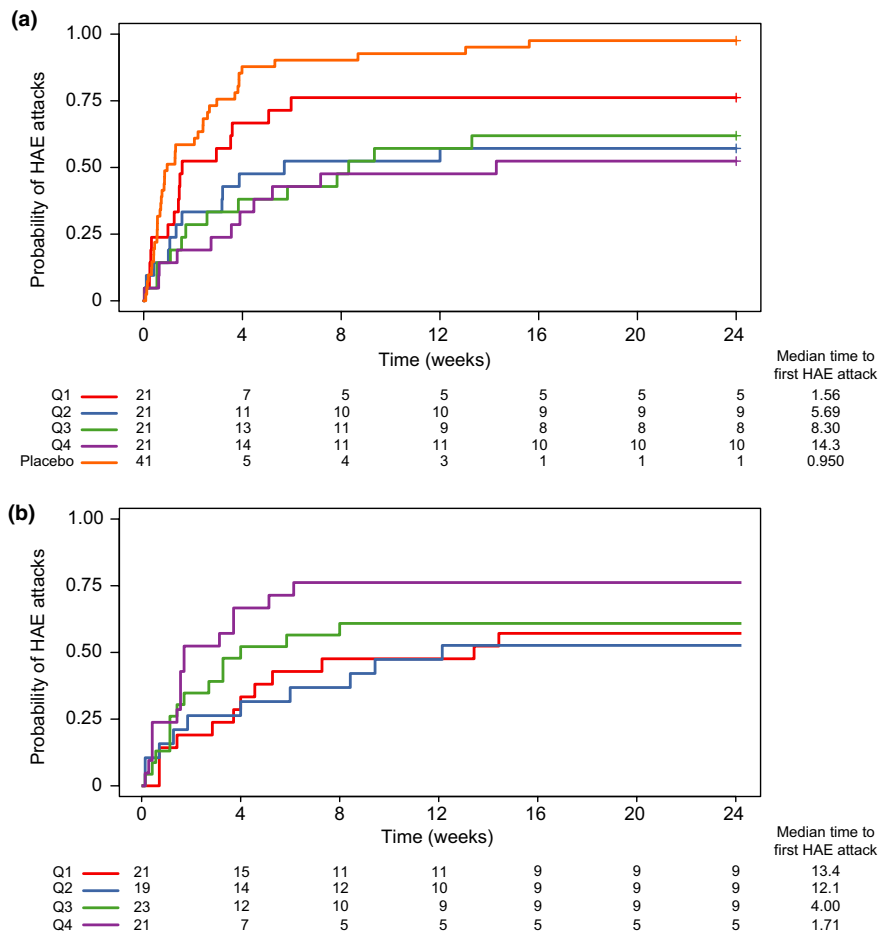


Figure 4 Time to first attack as a function of lanadelumab and cHMWK exposure in HELP. Q1, Q2, Q3, and Q4 are the first, second, third, and fourth quartiles of $C_{ave,ss}$, respectively, for lanadelumab (a) and cHMWK (b). Lanadelumab: Q1 = 5.24–9.00 $\mu\text{g/mL}$; Q2 = 9.01–14.2 $\mu\text{g/mL}$; Q3 = 14.3–22.4 $\mu\text{g/mL}$; Q4 = 22.5–47.6 $\mu\text{g/mL}$. cHMWK: Q1 = 20.1–21.3%; Q2 = 21.4–21.9%; Q3 = 21.9–22.7%; Q4 = 22.7–23.9%. $C_{ave,ss}$: average concentration at steady-state; cHMWK, cleaved high molecular weight kininogen; HAE, hereditary angioedema.

The exposure-response relationship for the time to the first attack following the first open-label dose in rollover patients in HELP OLE is presented in **Figure 5**. A steep sigmoidal exposure-response relationship was observed (estimated Hill effect of 2.95) whereby lanadelumab AUC_{0-HAE} values (AUC from the first open-label dose until the time of the first attack) were associated with a marked increase in time to the first attack (**Table S22**), with a maximum effect of 104.2 days. Patients who received the 300 mg Q2W regimen in HELP had the longest time to the first attack (83.7 days) after rolling over into HELP OLE compared with patients who received the 150 mg Q4W (55.7 days) or 300 mg Q4W regimens (54.2 days).

Exposure-response analysis: Effect on concomitant medication use

There was a statistically significant relationship between lanadelumab exposure and the probability of concomitant use of analgesic (acetaminophen), anti-inflammatory, and antirheumatic medications, but not antihistamines, for $\geq 20\%$ of the treatment duration. Patients with higher exposure had a lower need for concomitant medication use (**Figures S42–S44**).

Effect of body weight on PK, PD, and response

The effect of body weight on lanadelumab exposure parameters in HELP was explored (**Figure S45**). Although lanadelumab $C_{ave,ss}$ values decreased with higher body weight, all values remained markedly above the IC_{50} , particularly for patients who received the 300 mg Q2W regimen. The majority of $C_{ave,ss}$ values for patients in the 300 mg Q2W dosing regimen remained above the IC_{90} (18.8 $\mu\text{g/mL}$), except for 4 patients who had a body weight of 74.0, 118.0, 128.8, and 150.0 kg, respectively. Although lanadelumab exposure was 30% lower in patients with higher body weight, a marked suppression of cHMWK and reduction in attack rate was observed (**Tables S23–S24**). The PD response was comparable between the body weight groups; patients with low and high body weight presented a similar percentage of attack-free days from days 1–182 (96.7% and 96.3%, respectively) and 70–182 (97.7% and 96.9%), monthly HAE attack rates (0.477 and 0.460 attacks/month), total number of attacks (2.73 and 2.88 attacks), and average duration of attack (6.35 and 6.46 hours).

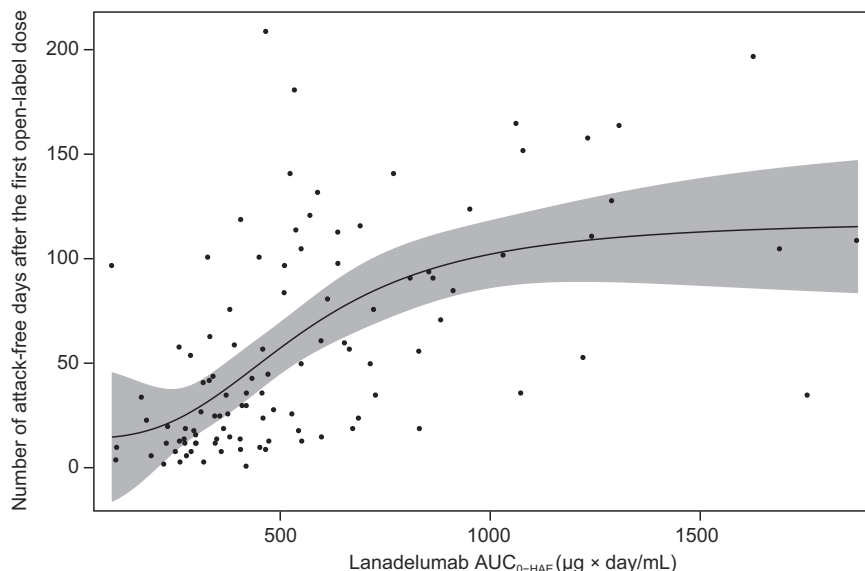


Figure 5 Number of days to the first attack after the first open-label lanadelumab dose as a function of lanadelumab exposure for rollover patients in HELP OLE. Black dots represent observed data. The black solid line and shaded area represent the model-predicted mean and associated 95% confidence interval. The parameter E_0 was 14.0 days, suggesting that an AUC_{0-HAE} value of zero (i.e., placebo) would be associated with 14 attack-free days after the first dose. The maximum effect (E_{max}) was 104.2 days, suggesting that the highest AUC_{0-HAE} value (1,874 $\mu\text{g} \times \text{day/mL}$) was associated with 104.2 days to the first attack. AUC_{0-HAE} , area under the curve from the first open-label dose until the time of the first attack; HAE, hereditary angioedema.

DISCUSSION

Currently, long-term prophylaxis for HAE includes C1-INH replacement therapies requiring dosing every 3–4 days either via i.v.^{13,14} or by s.c. injections¹⁵; androgens, which are associated with poor tolerability¹⁶; and antifibrinolytics, which have limited efficacy.¹⁷ Lanadelumab, the first approved fully human monoclonal antibody therapeutic for HAE, is well-tolerated and highly effective in preventing attacks.⁶ In addition, it has the advantage of a long half-life, as is typical for monoclonal antibodies,^{18–20} allowing an extended dosing interval. The PopPK/PD and exposure-response analyses described herein used clinical data collected following s.c. administration. Although the absolute bioavailability of lanadelumab in humans is unknown, the approximate bioavailability for s.c. administration in cynomolgus monkeys was 66% (internal data on file), suggesting that high absolute bioavailability in humans would be expected.

Although prekallikrein is present in plasma at a concentration of ~ 500 nM, it was estimated that only 30–110 nM is converted to active plasma kallikrein during an HAE attack.⁴ Based on the current analysis, the mean (range) $C_{ave,ss}$ of lanadelumab for the 300 mg Q2W dosing regimen was 29.2 (10.0–44.6) $\mu\text{g/mL}$, which corresponds to 200 (68.5–305) nM after correcting for molecular weight (145,716.2 Da). The range of $C_{ave,ss}$ values of lanadelumab are expected to be sufficient for binding active plasma kallikrein, resulting in reduction in cHMWK formation, and ultimately a suppression in the formation of bradykinin, which prevents the triggering events of HAE.

Inhibition of plasma kallikrein activity, as indicated by decreased levels of cHMWK, occurred rapidly following the first lanadelumab dose and was sustained throughout the treatment period. This, in turn, corresponded with clinical benefit (i.e., attack prevention) within the first month of treatment;

lanadelumab concentrations following 300 mg dosing reached the IC_{50} within 15 hours of administration, and delayed the first attack by at least 54 days. Although a significant attack rate reduction was observed with the lanadelumab 150 mg Q4W and 300 mg Q4W regimens in HELP, administration of a 300 mg Q2W regimen is optimal for achievement of therapeutic efficacy. Lanadelumab exposure with 300 mg Q2W was associated with the fastest and highest extent of cHMWK suppression over time, correlating with the longest time to the first HAE attack following initiation of treatment, the lowest average monthly attack rate, and the highest number of attack-free days after the first lanadelumab dose of HELP OLE in rollover patients. Exposure-response analyses of efficacy suggest that further improvement in HAE control is achieved by longer chronic treatment with this regimen, with maximum effect achieved by 6 months. Findings from these analyses are expected to be corroborated by the long-term results of HELP OLE⁸ once the study is completed.

The prophylactic effect of lanadelumab is potentially attributable to the attainment of a “biological steady state” of the contact system that is dysregulated in HAE. Inhibition of plasma kallikrein, and, thus, reduction in the formation of cHMWK, ultimately suppresses production of bradykinin, which prevents the triggering events of HAE. Importantly, cHMWK levels in patients with HAE are not abolished entirely, but are reduced to levels observed in subjects without HAE, indicating that treatment with lanadelumab returns patients to homeostasis. In addition, the inhibition of plasma kallikrein by lanadelumab was reversible, as shown by the slow return of cHMWK levels to baseline.

The PopPK, PK/PD, and exposure-response analyses support dosing of lanadelumab for long-term prophylaxis against HAE attacks in patients across a wide range of demographic

and baseline disease characteristics. Variability of clearance and volume of distribution were dependent mainly on body weight, which is not unexpected, based on reports for other monoclonal antibodies.¹⁹ However, our analyses suggest that this difference is not clinically relevant, and weight-based dosing of lanadelumab is not expected to provide additional clinical benefit relative to the current fixed dosing regimens. Optimal suppression of cHMWK and significant reduction of attack rates was observed in patients with high body weight who received the 300 mg Q2W dosing regimen in HELP. Drug exposure in these patients was markedly higher than both the IC₅₀ for cHMWK suppression and the EC₅₀ for the reduction in attack rate, and exposure for most patients was also greater than IC₉₀.

The PopPK analysis suggests that dose adjustment is not required in this and other subpopulations, as there was no impact of age, sex, baseline disease severity, or other patient characteristics on lanadelumab PK/PD. The apparent impact of health status can be considered negligible, as drug exposure in both healthy subjects and in patients with HAE was high enough to not warrant further dose adjustment. Furthermore, the presence of confirmed antidrug antibodies and neutralizing antibodies did not have any effect on the PK and exposure parameters of lanadelumab, nor did the concomitant use of rescue medications or other medications that are commonly used for treatment of attack-related symptoms. Fixed dosing has the potential advantage of fewer dosing errors, and this may be clinically important for patients who self-administer lanadelumab. Furthermore, variability in lanadelumab exposure from fixed dosing would not be expected to impact lanadelumab safety, given the favorable safety profile that has been demonstrated across several different dosing regimens in patients with a wide range in body weights.⁶

The PK/PD characteristics of lanadelumab support its use as a safe, effective, and convenient therapeutic option for prevention of angioedema attacks. Data from ongoing studies, including a long-term clinical study,⁸ a prevention study in pediatric patients with HAE,²¹ and real-world studies of lanadelumab in patients with HAE,^{22,23} will provide further understanding of how lanadelumab can be used effectively in patients across the HAE disease spectrum.

Supporting Information. Supplementary information accompanies this paper on the *Clinical and Translational Science* website (www.cts-journal.com).

Acknowledgments. Nathalie Gosselin, PhD, of Certara Strategic Consulting, assisted with data analysis. Shirley Teng, PhD, CMPP, of Excel Medical Affairs, provided editorial and writing assistance, which was funded by Shire Human Genetic Therapies, a Takeda company.

Funding. The clinical studies described in this manuscript were funded by Dyax Corp. (now Shire Human Genetic Therapies, a Takeda company, Lexington, MA).

Conflicts of Interest. P.M. and Y.W. are employees of and own stocks in Takeda. J.F.M., N.K., and C.C. are employees of Certara, which was contracted by Shire, a Takeda company, to conduct the analysis for this study.

Author Contributions. Y.W., J.F.M., N.K., and C.C. wrote the manuscript. Y.W. and P.M. designed the research. Y.W. and P.M. performed the research. Y.W., J.F.M., N.K., C.C., and P.M. analyzed the data.

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