Lanadelumab, a Fully Human Monoclonal Antibody Inhibitor of Plasma Kallikrein, Provides Sustained Pharmacokinetics and Pharmacodynamics Following Long-term Treatment in Patients With Hereditary Angioedema (HAE)

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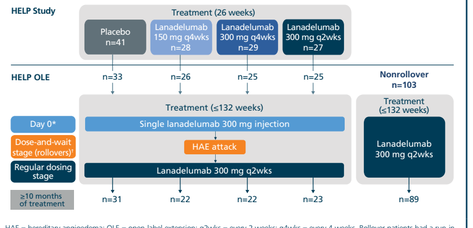
Introduction

- Hereditary angioedema (HAE) is a rare disease caused by mutations in the C1 inhibitor (C1-INH) gene, resulting in deficiency of C1-INH protein or function.[1]
- Patients with HAE suffer from unpredictable intermittent attacks of subcutaneous or submucosal edema of the face, larynx, gastrointestinal tract, limbs, and/or genitalia, which may last for several days.
- Patients are often prescribed long-term prophylaxis to prevent attacks.[1]
- Lanadelumab is a fully human monoclonal antibody inhibitor of plasma kallikrein[2] that is approved in several countries for the prevention of HAE attacks in patients ≥12 years of age.*
  - Inhibition of plasma kallikrein prevents the production of bradykinin (a peptide that causes vasodilation, which leads to edema) and 2-chain high molecular weight kininogen (cHMWK; a marker of plasma kallikrein activity).[3]
- 2 phase 3 studies of lanadelumab have been conducted in patients with HAE (**Figure 1**).

HELP (DX-2930-03; NCT02586805)[4]	• Evaluated pharmacokinetics (PK), pharmacodynamics (PD), safety, and efficacy. • 125 patients randomized to placebo or lanadelumab 300 mg every 2 weeks (q2wks), 300 mg every 4 weeks (q4wks), or 150 mg q4wks for 6 months.
HELP open-label extension (OLE; DX-2930-04; NCT02741596)[5]	• Ongoing study to evaluate long-term PK, PD, safety, and efficacy. • 212 patients received lanadelumab 300 mg q2wks for up to 33 months. • Data collected up to August 31, 2018, were included in this interim analysis. • Rollover patients from HELP received a single dose on day 1 of the OLE, then underwent a dose-and-wait period. Following their first attack, they received 300 mg q2wks. • Nonrollover patients received 300 mg q2wks starting on day 1.

Figure 1: Design of the HELP Study and HELP OLE



HAE = hereditary angioedema; OLE = open-label extension; q2wks = every 2 weeks; q4wks = every 4 weeks. Rollover patients had a run-in attack rate of ≥1 in 4 weeks in the HELP Study; nonrollover patients had a baseline attack rate of ≥1 in 12 weeks. *For rollover patients, day 0 of the OLE coincided with week 26, day 182 of the HELP Study. For nonrollover patients, the first dose was administered on day 0. [3]Regardless of when the first HAE attack occurred, there was a minimum of 10 days between the first and the second open-label dose.

Objective

- To assess the sustainability of PK and PD during long-term treatment with lanadelumab.

Methods

- The PK and PD of lanadelumab were compared in the following populations using sparse sampling:
  - 25 patients in HELP who received 300 mg q2wks for 6 months and then rolled into the OLE (HELP 300 mg q2wks).
  - 23 rollovers in the OLE who received 300 mg q2wks in HELP and also received lanadelumab for ≥10 months in the OLE (OLE 300 mg q2wks rollovers).
  - 187 patients in the OLE (98 rollovers and 89 nonrollovers combined) who received lanadelumab for ≥10 months in the OLE (OLE rollovers and nonrollovers).
- Analyses did not include the dose-and-wait period for rollovers.
- Analyses were performed using previously established population PK (PopPK) and PK/PD models.
  - The PopPK model consisted of 1 compartment with linear elimination and a first-order rate of absorption following subcutaneous administration of lanadelumab.[6]
  - An indirect response model was used for the PK/PD modeling of cHMWK. Lanadelumab is expected to suppress cHMWK levels through a 53.5% inhibition of its rate of formation (K_{in}).[7]

Results

Sustainability of concentrations during long-term lanadelumab treatment

- Observed individual trough concentration-time profiles showed that lanadelumab levels were comparable among patients in the HELP 300 mg q2wks, OLE 300 mg q2wks rollover, and OLE rollover and nonrollover groups (**Figure 2**).
- A PopPK model was used to assess the concentration-time profiles and PK parameters of lanadelumab in the OLE.
  - The PK parameters for OLE 300 mg q2wks rollovers were comparable to those for OLE rollovers and nonrollovers (**Table**).

Sustainability of cHMWK activity during long-term lanadelumab treatment

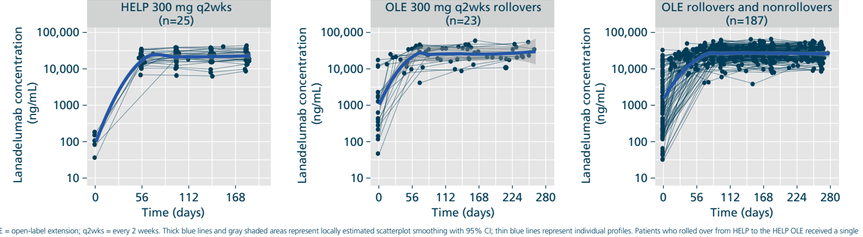
- Observed individual trough concentration-time profiles showed that cHMWK levels were comparable among the HELP 300 mg q2wks, OLE 300 mg q2wks rollover, and OLE rollover and nonrollover groups (**Figure 3**).

Table: Descriptive statistics of lanadelumab exposure parameters in the HELP OLE from the population PK model

	Geometric mean (geometric %CV) Median [range]							
Population	**CL/F, L/hour**	**Vc/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}, hours**	**$t_{1/2}$, hours**
OLE 300 mg q2wks (n=23)	0.0293 (41.2) 0.0287 [0.0180–0.0768]	15.2 (28.1) 14.2 [8.77–29.7]	423 (40.7) 447 [167–712]	30.1 (40.7) 31.9 [11.9–50.8]	34.4 (39.2) 36.6 [13.9–58.0]	23.9 (44.4) 24.8 [8.89–41.4]	244 (3.2) 245 [225–252]	359 (16.8) 354 [249–506]
OLE rollovers and nonrollovers (n=187)	0.0268 (35.9) 0.0250 [0.0127–0.0768]	13.6 (27.3) 13.0 [7.62–29.7]	467 (36.8) 493 [167–1020]	33.3 (36.8) 35.2 [11.9–72.8]	38.2 (36.3) 40.0 [13.9–82.2]	26.2 (38.6) 27.2 [8.89–5.89]	245 (3.4) 245 [215–276]	352 (13.7) 353 [249–506]

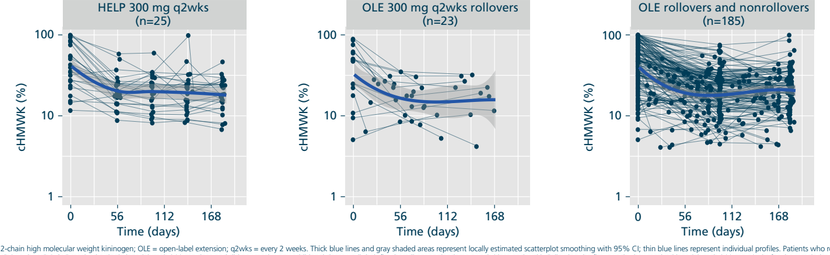
$AUC_{tau,ss}$ = area under the curve over the dosing interval at steady state; $C_{ave,ss}$ = average concentration at steady state; $C_{max,ss}$ = maximum concentration at steady state; $C_{min,ss}$ = minimum concentration at steady state; CL/F = apparent clearance; CV = coefficient of variation; OLE = open-label extension; PK = pharmacokinetic; $t_{1/2}$ = terminal elimination half-life; t_{max} = time to maximum concentration; q2wks = every 2 weeks; V/F = apparent volume of distribution.

Figure 2: Observed lanadelumab concentrations during treatment with lanadelumab 300 mg q2wks in HELP and the HELP OLE



OLE = open-label extension; q2wks = every 2 weeks. Thick blue lines and gray shaded areas represent locally estimated scatterplot smoothing with 95% CI; thin blue lines represent individual profiles. Patients who rolled over from HELP to the HELP OLE received a single lanadelumab 300 mg dose and did not receive any additional doses until their first hereditary angioedema attack (dose and wait). Following the first attack, patients received lanadelumab 300 mg q2wks for the remainder of the treatment period. Nonrollovers received lanadelumab 300 mg q2wks throughout the treatment period.

Figure 3: Observed cHMWK activity during treatment with lanadelumab 300 mg q2wks in HELP and the HELP OLE



cHMWK = 2-chain high molecular weight kininogen; OLE = open-label extension; q2wks = every 2 weeks. Thick blue lines and gray shaded areas represent locally estimated scatterplot smoothing with 95% CI; thin blue lines represent individual profiles. Patients who rolled over from HELP to the HELP OLE received a single lanadelumab 300 mg dose and did not receive any additional doses until their first hereditary angioedema attack (dose and wait). Following the first attack, they received lanadelumab 300 mg q2wks for the remainder of the treatment period. Nonrollovers received lanadelumab 300 mg q2wks throughout the treatment period. cHMWK values were not available for 2 patients in the combined rollover/nonrollover group.

- A population PK/PD model was used to assess longitudinal cHMWK activity in the OLE.
  - The mean K_{in}, rate of degradation (K_{out}), and maximum inhibitory effect (I_{max}) of cHMWK for patients in the HELP 300 mg q2wks group were similar to those for OLE 300 mg q2wks rollovers.
  - Values of average concentration at steady state (C_{ave}) were also similar in the 2 groups.

Population	Mean K_{in}	Mean K_{out}	Mean I_{max}	Geometric mean C_{ave}
HELP 300 mg q2wks (n=25)	12.0%/h	0.361 h^{-1}	0.570%	19.3%
OLE 300 mg q2wks rollovers (n=23)	12.4%/h	0.385 h^{-1}	0.536%	21.0%

Sustainability of efficacy during long-term lanadelumab treatment

- The sustainability of lanadelumab PK/PD following long-term treatment corresponded with low HAE attack rates.
  - Attack rates were comparable between patients in the HELP 300 mg q2wks group (n=25; 0.257 attacks/4 weeks) and OLE rollovers and nonrollovers (n=187; 0.220 attacks/4 weeks).

Conclusions

- **Lanadelumab demonstrated sustained PK, PD, and exposure response over long-term treatment.**
  - **PK/PD in patients who received lanadelumab 300 mg q2wks for 6 months in HELP was similar before and after the patients rolled into the HELP OLE and received lanadelumab 300 mg q2wks for ≥10 months.**
  - **PK/PD characteristics were also similar in the combined group of rollover and nonrollover patients who received ≥10 months of treatment in the OLE.**

*Lanadelumab is approved as prophylaxis to prevent attacks of HAE in patients ≥12 years of age in the United States and for the routine prevention of attacks in patients ≥12 years of age in Canada.[8,9] Lanadelumab also was approved in the European Union, Australia, and Brazil for the routine prevention of recurrent attacks of HAE in patients ≥12 years of age,[10–12] and in Switzerland for the long-term prevention of attacks of HAE in patients ≥12 years of age.[13]

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