Consistent Reduction in HAE Attack Rate With Lanadelumab Regardless of Baseline Attack Frequency: Interim Findings From the Phase 3 HELP Study Open-label Extension (OLE)

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Background

- Hereditary angioedema with C1 inhibitor deficiency (C1-INH-HAE, type 1/2) is a rare disease in which dysregulated plasma kallikrein activity leads to excessive production of bradykinin, resulting in unpredictable recurrent angioedema attacks.[1]
  - Symptoms range from mild to potentially life-threatening, leading to restrictions in daily life, reduced productivity at work or school, and emotional impairment, even in between attacks.[2,3]
- Long-term prophylaxis (LTP) of HAE attacks is an integral component of care for many patients; the goal is to lessen the heavy physical and emotional burden of disease and normalize daily life.[4,5]
- Lanadelumab, a long-acting highly specific fully human monoclonal antibody inhibitor of active plasma kallikrein,[6] is approved in several countries worldwide for the prevention of HAE attacks.*
  - The efficacy and safety of lanadelumab were characterized in the phase 3, randomized, double-blind, placebo-controlled HELP Study (NCT02586805)[7] and confirmed in the HELP open-label extension (OLE; NCT02741596).[8]
- The severity of HAE with respect to frequency of attacks varies greatly among individuals, and it is important that HAE treatments be effective regardless of disease severity.

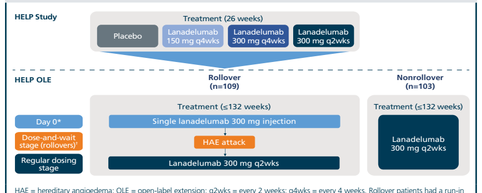
Objective

- To report interim findings from an exploratory analysis evaluating the efficacy and safety of lanadelumab in the HELP OLE by baseline HAE attack rate, both in patients who completed the HELP Study (rollovers), and in those who had not previously participated (nonrollovers).

Methods

- The study design of the HELP OLE is shown in **Figure 1**.

Figure 1: Design of the 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. †Regardless of when the first HAE attack occurred, there was a minimum of 10 days between the first and the second open-label dose.

- Eligible patients were ≥12 years of age with HAE type 1/2.
- The historical baseline HAE attack rate was ≥1 attack within a 4-week run-in period in the HELP Study for rollovers, and ≥1 investigator-confirmed attack in the previous 12 weeks for nonrollovers.
- The timing of lanadelumab administration was as follows:
  - Patients from the HELP Study received a single 300 mg lanadelumab dose at the time of the rollover and entered a dose-and-wait period. At the time of their first attack and thereafter (regular dosing stage), they received 300 mg every 2 weeks (q2wks).
  - Nonrollovers received lanadelumab 300 mg q2wks from day 0.
- Monthly HAE attack rate with lanadelumab (during the regular dosing stage for rollovers; from day 0 for nonrollovers) and safety were evaluated by baseline rates of <1, 1 to <2, 2 to <3, or ≥3 attacks/4 weeks.
- Analyses were performed using the safety population.
- Data collected up to August 31, 2018, were included in this analysis.

Results

Patient disposition and baseline characteristics

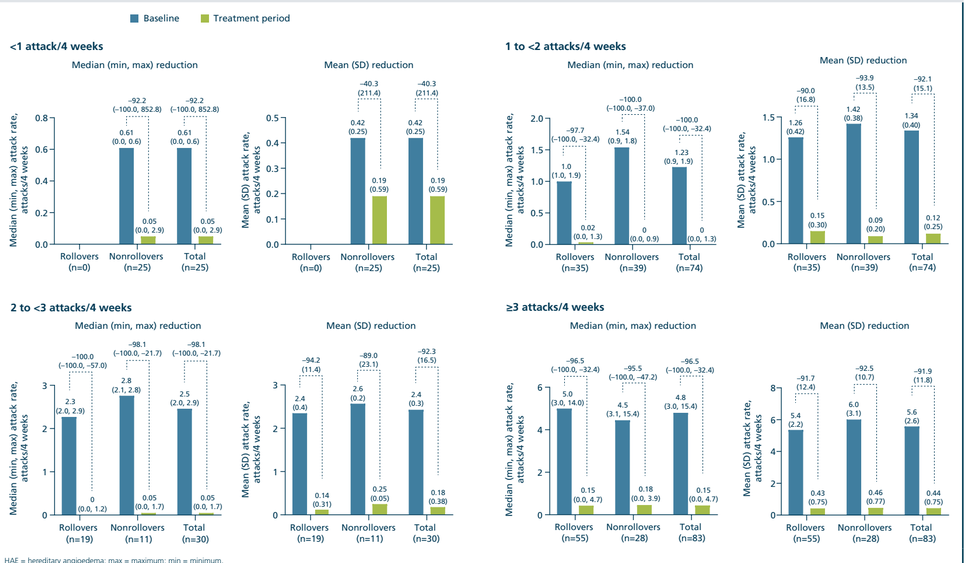
- A total of 212 patients were enrolled in the OLE; 109 rollovers and 103 nonrollovers (**Table 1**).

Table 1: Demographics and characteristics by baseline attack rate

Characteristic	Rollovers	Nonrollovers	Total N=212
<1 attack/4 weeks	**n=0**	**n=25**	**n=25**
Mean (SD) baseline attack rate*	–	0.4 (0.25)	0.4 (0.25)
Mean (SD) age, years	–	39.8 (15.09)	39.8 (15.09)
Mean (SD) age at symptom onset, years	–	10.5 (6.3)	10.5 (6.3)
Female, n (%)	–	19 (76.0)	19 (76.0)
Prior use of LTP, n (%)	–	16 (64.0)	16 (64.0)
C1-INH only	–	13 (52.0)	13 (52.0)
Androgens	–	3 (12.0)	3 (12.0)
No LTP use	–	9 (36.0)	9 (36.0)
History of laryngeal attacks, n (%)	–	12 (48.0)	12 (48.0)
1 to <2 attacks/4 weeks, n (%)	**n=35**	**n=39**	**n=74**
Mean (SD) baseline attack rate*	1.3 (0.42)	1.4 (0.38)	1.3 (0.40)
Mean (SD) age, years	36.8 (16.51)	36.6 (18.79)	36.7 (17.62)
Mean (SD) age at symptom onset, years	15.1 (9.20)	11.4 (5.36)	13.1 (7.60)
Female, n (%)	27 (77.1)	24 (61.5)	51 (68.9)
Prior use of LTP, n (%)	18 (51.4)	20 (51.3)	38 (51.4)
C1-INH only	15 (42.9)	15 (38.5)	30 (40.5)
Androgens	1 (2.9)	3 (7.7)	4 (5.4)
Androgens, C1-INH	1 (2.9)	1 (2.6)	2 (2.7)
Antifibrinolytics	1 (2.9)	0	1 (1.4)
Antifibrinolytics, C1-INH	0	1 (2.6)	1 (1.4)
No LTP use	17 (48.6)	19 (48.7)	36 (48.6)
History of laryngeal attacks, n (%)	16 (45.7)	24 (61.5)	40 (54.1)
2 to <3 attacks/4 weeks, n (%)	**n=19**	**n=11**	**n=30**
Mean (SD) baseline attack rate*	2.4 (0.38)	2.6 (0.25)	2.4 (0.35)
Mean (SD) age, years	40.7 (13.57)	38.8 (15.28)	40.0 (13.98)
Mean (SD) age at symptom onset, years	12.3 (7.08)	10.6 (7.27)	11.7 (7.07)
Female, n (%)	11 (57.9)	6 (54.5)	17 (56.7)
Prior use of LTP, n (%)	12 (63.2)	9 (81.8)	21 (70.0)
C1-INH only	10 (52.6)	8 (72.7)	18 (60.0)
Androgens	1 (5.3)	1 (9.1)	2 (6.7)
Androgens, antifibrinolytics, C1-INH	1 (5.3)	0	1 (3.3)
No LTP	7 (36.8)	2 (18.2)	9 (30.0)
History of laryngeal attacks, n (%)	12 (63.2)	6 (54.5)	18 (60.0)
≥3 attacks/4 weeks, n (%)	**n=55**	**n=28**	**n=83**
Mean (SD) baseline attack rate*	5.4 (2.2)	6.0 (3.14)	5.6 (2.57)
Mean (SD) age, years	45.5 (13.09)	43.6 (15.45)	44.8 (13.87)
Mean (SD) age at symptom onset, years	12.9 (10.45)	13.3 (10.08)	13.0 (10.27)
Female, n (%)	37 (67.3)	19 (67.9)	56 (67.5)
Prior use of LTP, n (%)	32 (58.2)	18 (64.3)	50 (60.2)
C1-INH only	28 (50.9)	17 (60.7)	45 (54.2)
Androgens	1 (1.8)	1 (3.6)	2 (2.4)
Androgens, C1-INH	3 (5.5)	0	3 (3.6)
No LTP	23 (41.8)	10 (35.7)	33 (39.8)
History of laryngeal attacks, n (%)	39 (70.9)	21 (75.0)	60 (72.3)

C1-INH = C1 inhibitor; HAE = hereditary angioedema; LTP = long-term prophylaxis.
*The baseline HAE attack rate was calculated for each patient as the number of investigator-confirmed HAE attacks occurring during the run-in period for rollovers or the number of HAE attacks occurring during the historical reporting period for nonrollovers divided by the number of days the patient contributed to the run-in period (rollovers) or historical reporting period (nonrollovers) multiplied by 28 days. For nonrollovers, the historical rate in the last 3 months prior to screening was used.

Figure 2: Monthly HAE attack rate and reduction from baseline by run-in attack rate*



HAE = hereditary angioedema; max = maximum; min = minimum.
*Percentage change from baseline corresponds to 100% multiplied by ([treatment period HAE attack rate minus baseline HAE attack rate] divided by baseline HAE attack rate).

- 39.2% (83/212) patients experienced ≥3 attacks/4 weeks at baseline.
- The majority (70.0%) of patients who experienced 2 to <3 attacks/4 weeks at baseline reported using prior LTP.
  - 60% of these patients reported using C1-INH as the sole LTP agent, whereas only 40.5% of patients experiencing 1 to <2 attacks/4 weeks at baseline reported using C1-INH as the sole agent for prior LTP.
- Among patients experiencing ≥3 attacks/4 weeks at baseline, 72.3% had a history of laryngeal attacks.

Attack rates

- Treatment with lanadelumab 300 mg q2wks reduced HAE attacks versus baseline regardless of the run-in attack rate, with similar findings in rollover and nonrollover patients (**Figure 2**).
  - Median percentage reduction in HAE attacks was >90% across all run-in attack frequencies.
  - Mean percentage reduction in HAE attacks was lower for patients with <1 attack/4 weeks at baseline (40.3%) compared with reductions in patients with higher run-in attack frequencies (91.9–92.3%).

Safety

- The safety profile of lanadelumab was comparable across all baseline HAE attack rates.
- The most frequent treatment-emergent adverse events that were considered to be related to treatment were injection site–related events (eg, pain, erythema, bruising, and swelling), elevated liver enzymes, and dizziness (**Table 2**).

Table 2: Most common related TEAEs* (≥5% of patients total)

TEAE, n (%)	Rollovers	Nonrollovers	Total N=212 Total
<1 attack/4 weeks	**n=0**	**n=25**	**n=25**
Any related TEAE	–	18 (72.0)	18 (72.0)
Injection site pain	–	14 (56.0)	14 (56.0)
Injection site erythema	–	5 (20.0)	5 (20.0)
Injection site bruising	–	4 (16.0)	4 (16.0)
Injection site pruritus	–	3 (12.0)	3 (12.0)
Injection site swelling	–	3 (12.0)	3 (12.0)
ALT increased	–	2 (8.0)	2 (8.0)
AST increased	–	2 (8.0)	2 (8.0)
Dizziness	–	2 (8.0)	2 (8.0)
1 to <2 attacks/4 weeks	**n=35**	**n=39**	**n=74**
Any related TEAE	16 (45.7)	21 (53.8)	37 (50.0)
Injection site pain	14 (40.0)	17 (43.6)	31 (41.9)
Injection site erythema	4 (11.4)	6 (15.4)	10 (13.5)
Injection site bruising	2 (5.7)	3 (7.7)	5 (6.8)
Injection site swelling	2 (5.7)	2 (5.1)	4 (5.4)
2 to <3 attacks/4 weeks	**n=19**	**n=11**	**n=30**
Any related TEAE	7 (36.8)	7 (63.6)	14 (46.7)
Injection site pain	5 (26.3)	3 (27.3)	8 (26.7)
Injection site erythema	2 (10.5)	1 (9.1)	3 (10.0)
Injection site discoloration	1 (5.3)	1 (9.1)	2 (6.7)
≥3 attacks/4 weeks	**n=55**	**n=28**	**n=83**
Any related TEAE	23 (41.8)	14 (50.0)	37 (44.6)
Injection site pain	18 (32.7)	10 (35.7)	28 (33.7)
Injection site erythema	7 (12.7)	4 (14.3)	11 (13.3)
Injection site bruising	2 (3.6)	3 (10.7)	5 (6.0)

ALT = alanine aminotransferase; AST = aspartate aminotransferase; TEAE = treatment-emergent adverse event.
*Excluding hereditary angioedema attack–related events.

Conclusions

- **In the HELP OLE, treatment with lanadelumab resulted in marked reductions in monthly HAE attack rates regardless of baseline attack frequency, consistent with the results of the pivotal study.**
- **Differences in baseline attack rate did not impact the safety profile of lanadelumab.**

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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.[9,10] Lanadelumab is 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,[11,12] and in Switzerland for the long-term prevention of attacks of HAE in patients ≥12 years of age.[14]

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