Long-term Efficacy and Safety of Lanadelumab for Prophylactic Treatment in Adolescent Patients With Hereditary Angioedema (HAE)

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Background

- Hereditary angioedema caused by C1 inhibitor deficiency or dysfunction (C1-INH-HAE; type 1/2) is as rare disorder characterized by unpredictable and recurrent swelling of the skin and mucous membranes.[1]
- Symptoms usually present during childhood or early adolescence; early age of symptom onset may be associated with more severe disease progression.[2]
  - HAE attacks recur throughout life, hampering school and work productivity and negatively impacting patients' emotional well-being.[3]
- Lanadelumab, a fully human monoclonocal antibody inhibitor of active plasma kallikrein,[4] 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)[5] and confirmed in the HELP open-label extension (OLE; NCT02741596).[6]
  - Given the early onset of symptoms, treatment of HAE in adolescent patients is of high interest.

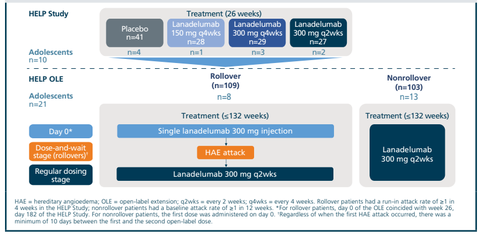
Objective

- To report efficacy and safety findings for lanadelumab treatment in adolescent patients with HAE type 1/2 (≥12 to <18 years of age) from the HELP Study and HELP OLE (cumulative through August 31, 2018).

Methods

- In the phase 3 study, patients ≥12 years of age with ≥1 investigator-confirmed attack over a 4-week period were randomized to receive placebo or subcutaneously administered lanadelumab (150 mg every 4 weeks [q4wks], 300 mg q4wks, or 300 mg every 2 weeks [q2wks]; **Figure 1**).
- Patients completing the HELP Study and continuing into the OLE (rollovers) received a single lanadelumab 300 mg dose until first attack (dose-and-wait period), and then 300 mg q2wks thereafter (regular dosing stage). Nonrollover patients (who had not participated in the HELP Study) received lanadelumab 300 mg q2wks from day 0 (**Figure 1**).
- HAE attack rate per month (28 days) and treatment-emergent adverse events (TEAEs; excluding HAE attacks) during the treatment period were recorded.
- A planned subgroup analysis of investigator-confirmed HAE attack rates in adolescent patients in the phase 3 study was performed using a Poisson regression model.
- In the OLE, for rollover patients, attack rate was reported for the regular dosing period. For nonrollover patients, attack rate was reported from day 0.

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.

Results

Patient disposition and baseline characteristics of adolescent patients

- 10 of 125 patients (8.0%) in the phase 3 study (placebo, n=4; 150 mg q4wks, n=1; 300 mg q4wks, n=3; 300mg q2wks, n=2), and 21 of 212 patients in the OLE (9.9%; 8 rollover, 13 nonrollover) were adolescents.
- Baseline characteristics were similar in adolescent patients in the phase 3 study and the OLE, including HAE attack rates (**Table 1**).
- The majority of patients received prior long-term prophylaxis (C1-INH only in the phase 3 study, and C1-INH only in the OLE for rollovers, or C1-INH and oral therapy for nonrollovers).

Table 1: Demographics and baseline characteristics for adolescent patients (≥12 to <18 years of age) in the phase 3 study and its extension

	Phase 3 study	Extension study
	Total	Total
N	**10**	**21**
Mean (SD) age, years	13.9 (1.94)	14.3 (1.61)
Female, n (%)	7 (70.0)	10 (47.6)
Race, n (%)		
White	8 (80.0)	20 (95.2)
Nonwhite	2 (20.0)	1 (4.8)
Mean (SD) BMI, kg/m²	23.6 (6.98)	25.2 (7.16)
Prior LTP use, n (%)		
No LTP use	4 (40.0)	8 (38.1)
C1-INH only	6 (60.0)	11 (52.4)
C1-INH and oral therapy*	0	2 (9.5)
Mean (SD) baseline HAE attack rate, attacks/month†	1.5 (1.06)	1.6 (1.02)

BMI = body mass index; C1-INH = C1 inhibitor; HAE = hereditary angioedema; LTP = long-term prophylaxis.
*Oral therapy includes androgens and antifibrinolytics. †Baseline for the rollover safety population was HAE attack rate during the run-in period in the phase 3 study. Baseline for the nonrollover population was the historical HAE attack rate in the 3 months before screening.

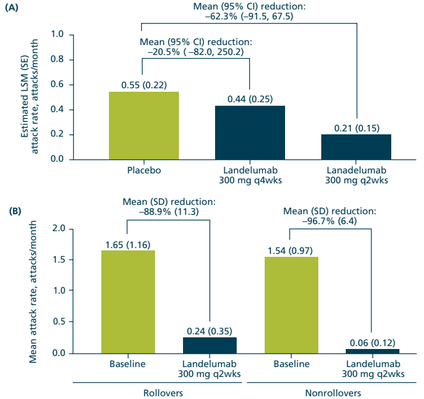
Attack rates

- Treatment with lanadelumab 300 mg q2wks reduced monthly HAE attack rates in adolescent patients by 62.3% versus placebo in the phase 3 study (**Figure 2A**) and by 88.9% and 96.7% versus baseline for rollovers and nonrollovers in the OLE, respectively (**Figure 2B**).
  - The percentage change in the phase 3 study was not statistically significant due to the small sample size.
- In the phase 3 study, a lower least squares mean (LSM) (SE) monthly attack rate was observed in patients treated with lanadelumab 300 mg q4wks (n=3; 0.44 [0.25]) or 300 mg q2wks (n=2; 0.21 [0.15]) compared with placebo (n=4; 0.55 [0.22]); this was not estimated in the 150 mg q4wks treatment arm because it included only 1 patient (**Figure 2A**). The estimated LSM (95% CI) monthly attack rate ratio (vs placebo) favored treatment with lanadelumab (**Figure 3**).

Safety

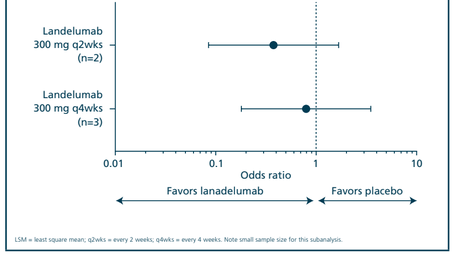
- In the phase 3 study, 3 patients had 13 nonserious, nonsevere lanadelumab-related TEAEs (**Table 2**). In the OLE, 11 patients had 117 nonserious, nonsevere lanadelumab-related TEAEs over a mean patient-time of 1.62 years.
  - Injection site pain was the most common TEAE considered related to lanadelumab treatment (**Table 3**).
    - In the OLE, 6 adolescent patients had ≥80% of doses self-administered, 9 patients had ≥80% of doses administered by study staff onsite, and 6 patients had mixed administration (<80% self-administration and <80% administration by study staff onsite).
- During the phase 3 study and the OLE, no serious or severe TEAEs were related to lanadelumab treatment, and there were no deaths or study discontinuations due to TEAEs.

Figure 2: (A) Estimated LSM monthly attack rate versus placebo for adolescent patients in the phase 3 study* and (B) mean (SD) monthly attack rates during the treatment period versus baseline for adolescent patients in the OLE



HAE = hereditary angioedema; LSM = least squares mean; OLE = open-label extension; q2wks = every 2 weeks; q4wks = every 4 weeks.
Percentage change from **(A)** placebo or **(B)** baseline shown above the bars. Baseline for the rollover safety population was HAE attack rate during the run-in period in the phase 3 study. Baseline for the nonrollover population was the historical HAE attack rate in the 3 months before screening.
*For the lanadelumab 150 mg q4wks group (n=1), the mean and median attack rate was 0, and the LSM attack rate was nonestimable.

Figure 3: Estimated LSM (95% CI) monthly attack rate ratio (vs placebo) for adolescent patients treated with lanadelumab 300 mg in the phase 3 study



LSM = least square mean; q2wks = every 2 weeks; q4wks = every 4 weeks. Note small sample size for this subanalysis.

Table 2: TEAEs for adolescent patients*

	Phase 3 study										Extension study					
			Lanadelumab								Lanadelumab					
	Placebo		150 mg q4wks		300 mg q4wks		300 mg q2wks		Total		Rollovers		Nonrollovers		Total	
N	4		1		3		2		6		8		13		21	
	n (%)	m	n (%)	m	n (%)	m	n (%)	m	n (%)	m	n (%)	m	n (%)	m	n (%)	m
Any TEAE	2 (50.0)	6	1 (100.0)	3	2 (66.7)	4	2 (100.0)	23	5 (83.3)	30	8 (100)	63	12 (92.3)	132	20 (95.2)	195
Any related TEAE	1 (25.0)	1	1 (100.0)	1	0	0	2 (100.0)	12	3 (50.0)	13	3 (37.5)	29	8 (61.5)	88	11 (52.4)	117
Any serious TEAE†	0	0	0	0	0	0	1 (50.0)	1	1 (16.7)	1	1 (12.5)	1	0	0	1 (4.8)	1
Any related serious TEAE	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Any severe TEAE†	0	0	0	0	0	0	1 (50.0)	1	1 (16.7)	1	1 (12.5)	1	1 (7.7)	1	2 (9.5)	2
Any related severe TEAE	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Hospitalization due to TEAE	0	0	0	0	0	0	1 (50.0)	1	1 (16.7)	1	1 (12.5)	1	0	0	1 (4.8)	1

m = number of events; TEAE = treatment-emergent adverse event; q2wks = every 2 weeks; q4wks = every 4 weeks. *TEAEs exclude hereditary angioedema attacks. TEAEs are shown during the treatment period (day 0 to day 182) for the phase 3 study. †In the phase 3 study, 1 patient experienced a catheter site infection (rated as serious and severe). In the extension study, 1 rollover patient had suicidal ideation (rated as serious and severe), and 1 nonrollover patient experienced hypersensitivity to concomitant medications (cefdinir and nonsteroidal anti-inflammatory agent; rated as severe).

Table 3: Treatment-related TEAEs for adolescent patients*

	Phase 3 study										Extension study					
			Lanadelumab								Lanadelumab					
	Placebo		150 mg q4wks		300 mg q4wks		300 mg q2wks		Total		Rollovers		Nonrollovers		Total	
N	4		1		3		2		6		8		13		21	
	n (%)	m	n (%)	m	n (%)	m	n (%)	m	n (%)	m	n (%)	m	n (%)	m	n (%)	m
Injection site reaction																
Pain	0	0	1 (100.0)	1	0	0	2 (100.0)	2	3 (50.0)	3	3 (37.5)	24	7 (53.8)	68	10 (47.6)	92
Discomfort	0	0	0	0	0	0	1 (50.0)	10	1 (16.7)	10	0	0	0	0	0	0
Erythema	1 (25.0)	1	0	0	0	0	0	0	0	0	1 (12.5)	3	0	0	1 (4.8)	3
Bruising	0	0	0	0	0	0	0	0	0	0	0	0	1 (7.7)	7	1 (4.8)	7
Swelling	0	0	0	0	0	0	0	0	0	0	0	0	1 (7.7)	10	1 (4.8)	10
Pruritus	0	0	0	0	0	0	0	0	0	0	1 (12.5)	2	0	0	1 (4.8)	2
Urticaria	0	0	0	0	0	0	0	0	0	0	0	0	1 (7.7)	1	1 (4.8)	1
Headache	0	0	0	0	0	0	0	0	0	0	0	0	1 (7.7)	1	1 (4.8)	1
Insomnia	0	0	0	0	0	0	0	0	0	0	0	0	1 (7.7)	1	1 (4.8)	1

m = number of events; TEAE = treatment-emergent adverse event; q2wks = every 2 weeks; q4wks = every 4 weeks. TEAEs exclude hereditary angioedema attacks. *TEAEs are shown during the treatment period (day 0 to day 182) for the phase 3 study.

Conclusions

- **Treatment with lanadelumab reduced the monthly attack rate in adolescent patients in the phase 3 study and the OLE.**
  - **It should be noted that because of the low number of adolescent patients in the phase 3 study, any inferential conclusions regarding the HAE attack rate compared with placebo cannot be supported.**
- **Lanadelumab was well tolerated; no new safety signals were raised in this age group.**

*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.[7,8] 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,[9-11] and in Switzerland for the long-term prevention of attacks of HAE in patients ≥12 years of age.[12]

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