Efficacy of Lanadelumab in Hereditary Angioedema Patients With and Without Prior Long-term Prophylaxis Use: Interim Results From the HELP Open-label Extension Study

Kim Paes,[1] Timothy Craig,[2] Jonathan A. Bernstein,[3] Hilary J. Longhurst,[4] Emel Aygören-Pürsün,[5] Christina Nurse,[1] Bruce L. Zuraw,[6] Joshua Jacobs,[7] on behalf of the HELP OLE Study Investigators

[1]Shire, a Takeda company, Lexington, MA, USA; [2]Department of Medicine, Pediatrics and Graduate Studies, Penn State University Hershey Medical Center, Hershey, PA, USA; [3]Bernstein Clinical Research Center, Cincinnati, OH, USA; [4]Addenbrooke's Hospital, Cambridge University Hospitals NHS Foundation Trust, Cambridge, and University College London Hospitals, London, UK; [5]Department for Children and Adolescents, Angioedema Centre, University Hospital Frankfurt, Goethe University, Frankfurt, Germany; [6]Division of Rheumatology, Allergy & Immunology, University of California San Diego, La Jolla, CA, USA; [7]Allergy and Asthma Clinical Research, Walnut Creek, CA, USA

Background

- Hereditary angioedema (HAE) is a rare chronic disease characterized by recurrent and debilitating attacks of tissue swelling.[1]
  - Long-term prophylaxis (LTP) of HAE type 1/2 aims to reduce disease burden by preventing/attenuating attacks. Guidelines recommend that LTP should be considered for all patients with severe symptoms.[1]
- Lanadelumab, a fully human monoclonal antibody targeting plasma kallikrein,[2] is approved in several countries for the prevention of HAE attacks.*
- In the phase 3 HELP Study (NCT02586805), lanadelumab-treated patients experienced statistically significant reductions in mean monthly HAE attack rate compared with placebo-treated patients, with consistent treatment effect regardless of prior LTP use.[3]
- The HELP open-label extension (OLE; NCT02741596) is evaluating long-term outcomes of treatment with lanadelumab 300 mg every 2 weeks (q2wks) in patients who completed the HELP Study (rollovers) and newly enrolled patients (nonrollovers).[4]

Objective

- To compare HAE attack reduction, as evident from pre-enrollment history, in patients with and without prior LTP use following long-term treatment with lanadelumab 300 mg q2wks using interim results from the HELP OLE.

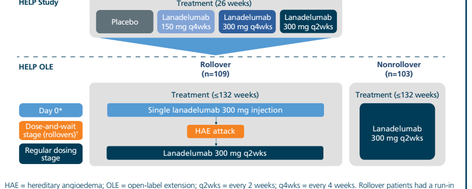
Methods

Patients
- Males and females ≥12 years of age with confirmed HAE type 1/2.
  - Rollover patients had a baseline attack rate of ≥1 attack/4 weeks during the run-in period of the HELP Study.
  - Nonrollover patients had a baseline attack rate of ≥1 attack/12 weeks as derived from patient-reported attack history.

Treatments
- Rollover patients continued immediately into the HELP OLE after completing HELP (**Figure 1**).
  - Patients received their first lanadelumab 300 mg dose on day 0 then underwent a dose-and-wait stage.
  - Patients received their second lanadelumab dose after the first attack, followed by 300 mg q2wks (regular dosing stage).
- Nonrollover patients received lanadelumab 300 mg q2wks starting on day 0.
  - Patients could receive both their existing LTP and lanadelumab for ≤3 weeks.

Analysis
- Analyses were performed using the safety population.
- The treatment period analyzed for rollover patients was the regular dosing stage.
- The treatment period for nonrollover patients was from day 0 to day 182.
- Attack rates during the treatment period were compared with baseline.
  - Monthly attack rates (attacks/4 weeks) were compared with historical rates for the 3 months preceding enrollment in the HELP Study (rollovers) or the HELP OLE (nonrollovers).
- Data collected up to August 31, 2018, were analyzed.

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

- A total of 212 patients received lanadelumab in the HELP OLE: 109 rollover (96.5% of HELP Study completers) and 103 nonrollover patients.
- Over half of patients had used prior LTP; the most common type was C1 inhibitor (C1-INH, intravenous; **Table 1**).
- Baseline patient characteristics were similar for the 2 largest subgroups (prior C1-INH only LTP and no prior LTP use; **Table 2**).

Table 1: Number of patients by prior LTP use

Prior LTP category, n (%)	Rollovers n=109	Nonrollovers n=103	Total N=212
Prior LTP			
C1-INH only	53 (48.6)	53 (51.5)	106 (50.0)
C1-INH and oral therapy*	5 (4.6)	2 (1.9)	7 (3.3)
Oral therapy*	4 (3.7)	8 (7.8)	12 (5.7)
No prior LTP	47 (43.1)	40 (38.8)	87 (41.0)

C1-INH = C1 inhibitor (intravenous); LTP = long-term prophylaxis.
*Oral therapy includes androgens (rollover, n=3; nonrollover, n=8) and antifibrinolytics (rollover, n=1; nonrollover, n=0).

Table 2: Baseline patient characteristics by prior LTP use

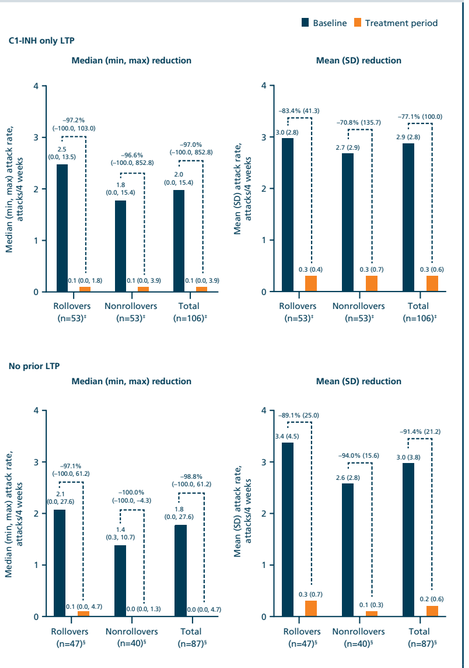
Characteristic	Rollovers n	Nonrollovers n	Total n
C1-INH only LTP	53	53	106
Mean (SD) age, years	41.1 (15.15)	38.8 (16.44)	39.9 (15.77)
Mean (SD) age at symptom onset, years	13.6 (10.93)	11.1 (8.43)	12.4 (9.80)
Female, n (%)	38 (71.7)	39 (73.6)	77 (72.6)
History of laryngeal attacks, n (%)	31 (58.5)	32 (60.4)	63 (59.4)
Baseline mean (SD) HAE attack rate (attacks/4 weeks)	3.9 (2.92)	2.7 (2.92)	3.3 (2.97)
No prior LTP	47	40	87
Mean (SD) age, years	41.6 (15.29)	39.9 (17.61)	40.8 (16.32)
Mean (SD) age at symptom onset, years	12.9 (7.98)	13.3 (5.30)	13.1 (6.84)
Female, n (%)	32 (68.1)	25 (62.5)	57 (65.5)
History of laryngeal attacks, n (%)	30 (63.8)	23 (57.5)	53 (60.9)
Baseline mean (SD) HAE attack rate (attacks/4 weeks)	3.1 (1.93)	2.6 (2.81)	2.9 (2.38)

C1-INH = C1 inhibitor (intravenous); HAE = hereditary angioedema; LTP = long-term prophylaxis.

HAE attack rates in the HELP OLE

- In 106 patients who had used prior C1-INH only LTP, treatment with lanadelumab 300 mg q2wks reduced HAE attack rates compared with baseline (**Figure 2**).
- Lanadelumab treatment also substantially reduced attack rates in 87 patients with no prior LTP use (**Figure 2**).
- Patients who used other previous LTP (n=19) also experienced reduced attack rates (data not shown).
- Results were comparable among rollover and nonrollover patients in all subgroups.

Figure 2: Monthly attack rate* and reduction from baseline† by prior LTP use

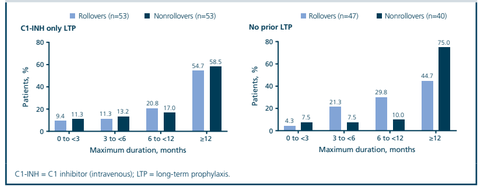


C1-INH = C1 inhibitor (intravenous); LTP = long-term prophylaxis; max = maximum; min = minimum. *During the HELP open-label extension (OLE) treatment period: from day 0 for nonrollover patients and during the regular dosing period for rollover patients. †Baseline was defined as the historical rate of HAE attacks in the 12 weeks before screening (for either the HELP Study [rollovers] or HELP OLE [nonrollovers]) divided by (30.4 multiplied by 3) and multiplied by 28 days; percentage reduction was calculated as the number of attacks per 28 days in the treatment period minus the number of attacks per 28 days in the previous 3 months, divided by the number of attacks per 28 days in the previous 3 months and multiplied by 100. ‡During the treatment period, n=51 (rollovers) and n=104 (total); percentage reduction was calculated for n=49 (rollovers), n=49 (nonrollovers), and n=98 (total). §Percentage reduction was calculated for n=46 (rollovers) and n=86 (total).

Extended attack-free period in the HELP OLE

- In the nonrollover population, 58.5% of patients with prior C1-INH only LTP and 75.0% of patients with no prior LTP use had a maximum duration of attack-free period of ≥12 months (**Figure 3**).
  - Although the mean number of attack-free days was similar for patients with and without prior LTP use, the average duration and maximum duration of an attack-free period was longer for nonrollover patients with no prior LTP use (**Table 3**).

Figure 3: Maximum duration of attack-free period by prior LTP use



C1-INH = C1 inhibitor (intravenous); LTP = long-term prophylaxis.

Table 3: Summary of attack-free period by prior LTP use

Characteristic	Rollovers n	Nonrollovers n
C1-INH only LTP	51	53
Number of attack-free days/month*		
Mean (SD)	27.4 (1.2)	27.2 (2.0)
Range	22.5–28.0	15.2–28.0
Average duration of attack-free period, days		
Mean (SD)	269.7 (205.4)	273.4 (208.4)
Range	10.6–621.0	3.9–656.0
Maximum duration of attack-free period, days		
Mean (SD)	356.8 (186.7)	372.5 (202.3)
Range	17.0–695.0	10.0–708.0
No prior LTP	47	40
Number of attack-free days/month*		
Mean (SD)	27.2 (2.1)	27.7 (0.7)
Range	14.4–28.0	24.6–28.0
Average duration of attack-free period, days		
Mean (SD)	262.7 (208.8)	381.4 (234.5)
Range	3.3–689.0	20.1–687.0
Maximum duration of attack-free period, days		
Mean (SD)	333.8 (173.0)	443.3 (197.2)
Range	14.0–689.0	30.0–687.0

C1-INH = C1 inhibitor (intravenous); LTP = long-term prophylaxis.
*A month was defined as 28 days.

Safety by type of prior LTP

- Safety profiles were generally comparable in patient subgroups by type of prior LTP, with the exception of a higher proportion of related treatment-emergent adverse events (TEAEs) in nonrollover patients who had prior C1-INH only LTP (**Table 4**).
- The most common related TEAEs were associated with the injection site (**Table 4**).
- There were no deaths, related serious TEAEs, or related severe TEAEs.
- 6 patients discontinued study treatment in the HELP OLE due to a TEAE.
  - 2 nonrollover patients with C1-INH only LTP (hypersensitivity [related] and elevated alanine aminotransferase, aspartate aminotransferase, and creatine phosphokinase [not related]).
  - 1 rollover patient with no prior LTP use (upper gastrointestinal hemorrhage and suspected pneumonia [not related]).
  - 3 nonrollover patients with no prior LTP use (hypersensitivity [related], elevated alanine aminotransferase and aspartate aminotransferase [not related], and pregnancy-related abdominal pain and vomiting [not related]).

Table 4: Most common related TEAEs (≥5% of patients in any subgroup)

TEAE, n (%)	Rollovers n	Nonrollovers n	Total n
C1-INH only LTP	53	53	106
Any related TEAE	21 (39.6)	38 (71.7)	59 (55.7)
Injection site pain	17 (32.1)	27 (50.9)	44 (41.5)
Injection site erythema	8 (15.1)	13 (24.5)	21 (19.8)
Injection site bruising	2 (3.8)	6 (11.3)	8 (7.5)
Injection site swelling	2 (3.8)	6 (11.3)	8 (7.5)
Injection site hemorrhage	2 (3.8)	3 (5.7)	5 (4.7)
Injection site pruritus	1 (1.9)	4 (7.5)	5 (4.7)
Injection site urticaria	0	3 (5.7)	3 (2.8)
Headache	0	3 (5.7)	3 (2.8)
No prior LTP	47	40	87
Any related TEAE	22 (46.8)	16 (40.0)	38 (43.7)
Injection site pain	17 (36.2)	13 (32.5)	30 (34.5)
Injection site erythema	4 (8.5)	3 (7.5)	7 (8.0)
Injection site bruising	3 (6.4)	4 (10.0)	7 (8.0)
Hypersensitivity	0	2 (5.0)	2 (2.3)

C1-INH = C1 inhibitor (intravenous); LTP = long-term prophylaxis; TEAE = treatment-emergent adverse event.

Conclusions

- **Long-term treatment with lanadelumab 300 mg q2wks led to consistent reductions in monthly HAE attack rates compared with 3-month historical experience.**
  - **Patients who used prior C1-INH only LTP experienced substantial reductions in attack rate after switching to lanadelumab.**
  - **Lanadelumab had a consistent treatment effect in patients who received C1-INH only LTP and those with no prior LTP use.**
  - **58.5% of patients with prior C1-INH only LTP and 75.0% of patients with no prior LTP use had a maximum duration of attack-free period of ≥12 months.**

*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.[1,2] 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.[1] and in Switzerland for the long-term prevention of attacks of HAE in patients ≥12 years of age.[1]

References: 1. Maurer M, *et al. Allergy.* 2018;73:1575-1596. **2.** Kanniston JA, *et al. J Biol Chem* 2014;289:23596-23608. **3.** Banerji A, *et al.*; HELP Investigators. *JAMA* 2018;320:2108-2121. **4.** Riedl MA, *et al. Clin Transl Allergy.*2017;7:36. **5.** Shire. Highlights of prescribing information. Takhzyro™ (lanadelumab-flyo) injection, for subcutaneous use. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/761090s000lbl.pdf. Accessed January 17, 2020. **6.** Shire Pharma Canada. Product monograph including patient medication information. Takhzyro™ (lanadelumab injection). https://www.shirecanada.com/-/media/shire/shirecglobal/shirecanada/pdf/files/product%20information/takhzyro-pm-en.pdf. Accessed January 17, 2020. **7.** European Medicines Agency. Takhzyro 300 mg solution for injection. Summary of product characteristics. http://ec.europa.eu/health/documents/community-register/2018/20181122143033/anx_143033_en.pdf. Accessed January 17, 2020. **8.** Takhzyro Australian product information. https://www.tga.gov.au/person/person-medicines-registration-new-chemical-entities-australia. Accessed January 17, 2020. **9.** Takhzyro Brazilian product information. http://portal.anvisa.gov.br/resultado-de-busca?p_p_id=101&p_p_lifecycle=0&p_p_state=maximized&p_p_mode=view&p_p_col_id=column-1&p_p_col_count=1&_101_struts_action=%2Fasset_publisher%2Fview_content&_101_assetEntryId=5676518&_101_type=content&_101_groupId=219201&_101_urlTitle=takhzyro-novo-registro&redirect=http%3A%2F%2Fportal.anvisa.gov.br%2Fresultado-de-busca%3Fp_p_id%3D3%26p_p_lifecycle%3D0%26p_p_state%3Dmaximized%26p_p_mode%3Dview%26_3_groupId%3D0%26_3_keywords%3Dtakhzyro%26_3_struts_action%3D%252Fsearch%252Fsearch%26_3_formDate%3D1441824476958. Accessed January 17, 2020. **10.** Swissmedic. Takhzyro, solution for injection. https://www.swissmedic.ch/swissmedic/en/home/humanarzneimittel/authorisations/authorised-medicinal-products-with-new-active-substances/takhzyro_injektionsloesung_lanadelumabum.html. Accessed January 17, 2020.

Funding and acknowledgments: We thank all patients, investigators, and their study staff. The HELP Study and HELP OLE were sponsored by Shire Human Genetic Therapies, Inc., a Takeda company, Lexington, MA, USA. Under the direction of the authors, Alpa Parmar, PhD, CMPP, employee of Excel Medical Affairs, provided writing assistance in formatting, proofreading, copyediting, and fact-checking also was 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 poster. The interpretation of the data was made by the authors independently.

Disclosures: K. Paes and C. Nurse are full-time employees of Shire and hold stock/options in Takeda. T. Craig reports grants and personal fees for consultations, research, and speaking from CSL Behring, Pharming, and Shire*; grants and personal fees for speaking from Grifols; grants and personal fees for research and consultations from BioCryst; and advisory board membership for the US Hereditary Angioedema Association. J.A. Bernstein has been a clinical investigator for BioCryst, CSL Behring, Pharming, and Shire*; speaker for CSL Behring, Pharming, and Shire*; consultant for BioCryst, CSL Behring, Pharming, Ionis/Akcea, KalVista, Pharming, and Shire*; and is an advisory board member of the US Hereditary Angioedema Association. H.J. Longhurst has received research grant support and/or speaker honoraria from BioCryst, CSL Behring, Pharming, and Shire*. E. Aygören-Pürsün has received honoraria, research funding, and/or travel grants from Actelion, Attenurx, BioCryst, CSL Behring, KalVista, Pharming, and/or Shire* and/or served as a consultant for these companies. B.L. Zuraw has received consulting fees from Adverum, BioCryst, CSL Behring, and Shire.* I. Jacobs has received grants and personal fees from BioCryst, CSL Behring, and Shire*; and personal fees from Pharming.
*A Takeda company.

HELP OLE Study Investigators: Canada: J. Hébert, R. Ritchie, D. Soloman, W.H. Yang; **Germany:** S. Ambarkhanova, E. Aygören-Pürsün, C. Escuredo Ettinghausen, M. Magerl, I. Martinez-Saguer, M. Maurer, P. Staubach, S. Zimmermann; **Italy:** M. Cicardi, S. Perego, M.A. Wu, A. Zanichelli; **Jordan:** A. Al-Ghazawi, M. Sheniak; **Puerto Rico:** R.H. Zaragoza-Urdaz; **United Kingdom:** S. Bahal, G. Boyajian, R. Ghurye, J. Gully, S. Kann-Alkhan, H.J. Longhurst, T. Rahman, S. Tadros, N. Verma, E. Zinser; **United States:** J. Anderson, A. Banerji, A.P. Baptist, J.A. Bernstein, P.B. Boggs, P.J. Busse, S. Christiansen, T. Craig, M. Davis-Lorton, S. Gierer, R.G. Gower, D. Harris, D.I. Hong, I. Jacobs, D.T. Johnston, E.S. Levitch, W.H. Li, R.F. Lockey, P. Lugar, W.R. Lumry, M.E. Manning, D.L. Mickel, I. Melamed, T. Mostofi, T. Nickel, W.R. Otto, A.A. Petrov, K. Poarch, C. Radojcic, S.M. Rehman, M.A. Riedl, L.B. Schwartz, R. Shapiro, E. Sher, A.M. Smith, T.D. Smith, D. Soteres, R. Tachdjian, H.J. Wedner, M.E. Weinstein, H. Zafra, B.L. Zuraw.

Presented at the American Academy of Asthma, Allergy & Immunology Annual Meeting, March 13–16, 2020, Philadelphia, PA

Mobile and environmentally friendly e-posters

3 ways to access the poster

Send an SMS:
Text 197589
To 43704 (USA only)
+44 7860 033 046 (rest of world)

Scan QR code

Access online
www.shirecongressposters.com/197589

No personal information is stored - standard charges may apply.