KONFIDENT-S Interim Analysis: Sebetralstat for HAE Attacks (Including Laryngeal)

Henriette Farkas,[1] Marc A. Riedl,[2] Emel Aygören-Pürsün,[3] William R. Lumry,[4] Andrea Zanichelli,[5,6] James Hao,[7] Matthew Iverson,[7] Michael D. Smith,[7] Christopher M. Yea,[8] Paul K. Audhya,[7] Jonathan A. Bernstein,[9,10] Marcus Maurer,[11,12] Danny M. Cohn[13]

[1]Hungarian Angioedema Center of Reference and Excellence, Semmelweis University, Budapest, Hungary; [2]University of California – San Diego, La Jolla, CA, USA; [3]University Hospital Frankfurt, Frankfurt, Germany; [4]AARA Research Center, Dallas, TX, USA; [5]IRCCS Policlinico San Donato, San Donato Milanese, Milan, Italy; [6]University of Milan, Milan, Italy; [7]KalVista Pharmaceuticals, Cambridge, MA, USA; [8]KalVista Pharmaceuticals, Salisbury, United Kingdom; [9]University of Cincinnati College of Medicine, Cincinnati, OH, USA; [10]Bernstein Clinical Research Center, Cincinnati, OH, USA; [11]Institute of Allergology, Charité–Universitätsmedizin Berlin, Berlin, Germany; [12]Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Immunology and Allergology, Berlin, Germany; [13]Amsterdam UMC, University of Amsterdam, Amsterdam, Netherlands

Presented at the Bradykinin Symposium; September 4-5, 2024; Berlin, Germany.

Disclosures

- Henriette Farkas has received research grant support from CSL Behring, Pharming, and Takeda, and has served as an advisor for these companies and for Astria Therapeutics, BioCryst Pharmaceuticals, Intellia Therapeutics, Ionis Pharmaceuticals, KalVista Pharmaceuticals, Ono Pharmaceutical, and Pharvaris.
- This study was funded by KalVista Pharmaceuticals

Background

Given that attacks are unpredictable and have the potential to rapidly progress, treatment guidelines recommend that patients

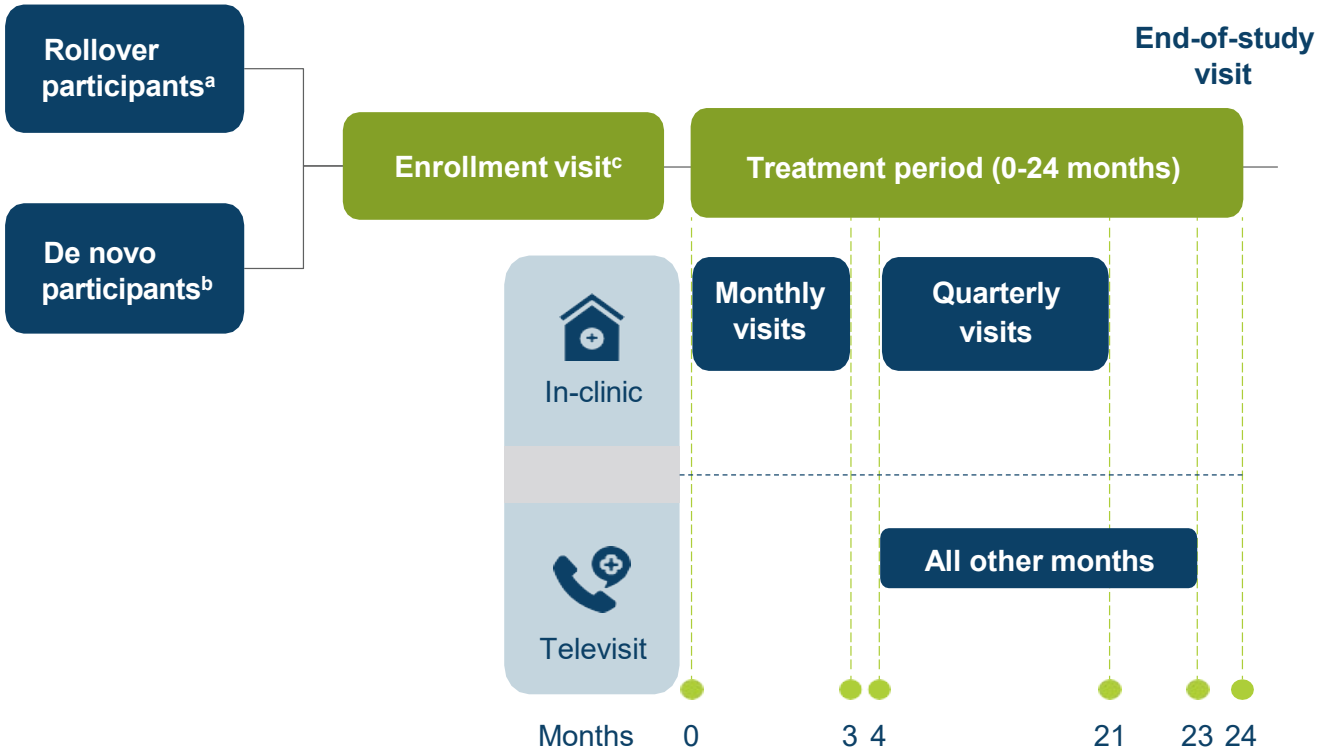
In the randomised, double-blind, placebo-controlled, phase 3 KONFIDENT crossover trial, oral on-demand sebetralstat provided faster symptom relief, reduction in attack severity, and complete attack resolution compared with placebo[3]

The objectives of the KONFIDENT-S trial are to assess the safety and effectiveness of long-term use of sebetralstat as an on-demand treatment of HAE attacks in adolescents and adults with HAE-C1INH

HAE, hereditary angioedema; HAE-C1INH, HAE with C1-inhibitor deficiency.

1. Maurer M et al. *Allergy*. 2022;77:1961-1990. 2. Busse PJ et al. *J Allergy Clin Immunol Pract*. 2021;9:132-150. 3. Riedl M et al. *New Engl J Med*. 2024;391:32-43.

KONFIDENT-S Open-Label Extension Trial Design



Multiple real-world elements were incorporated into the trial design, including televisits, portable multidose packs, and the elimination of a need to contact a call center or investigator before, during, or after attacks.

Inclusion criteria (up to 150 participants):

- ≥12 years of age
- ≥2 documented HAE attacks within 3 months

Treatment:

- Participants were instructed to self-administer sebetralstat 600 mg (2 x 300-mg tablets) as early as possible after attack onset
- A second administration was allowed if warranted

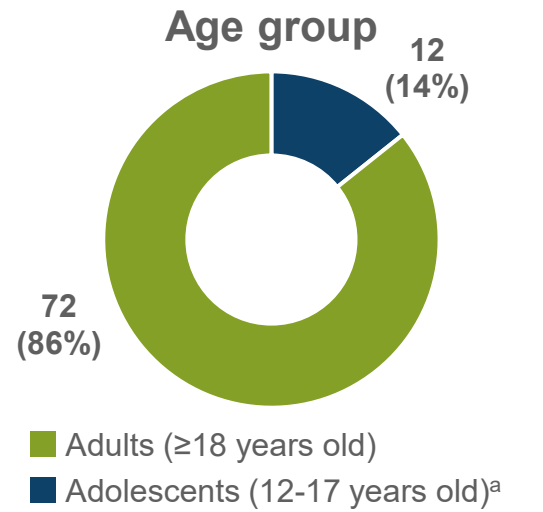
Endpoints:

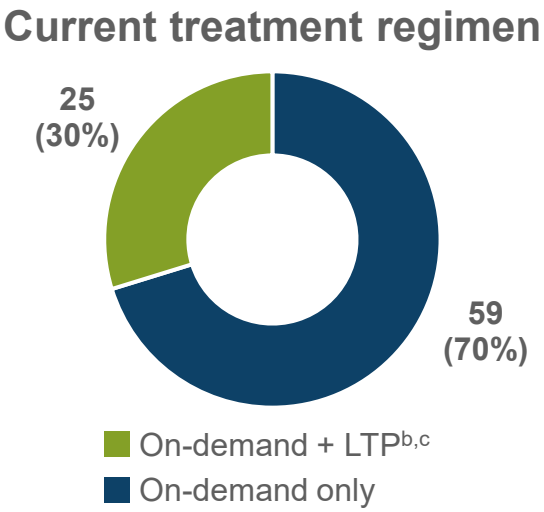
- Safety (adverse events)
- Time to beginning of symptom relief (by PGI-C)[d]
- Time to first reduction in severity (by PGI-S)[d]
- Time to complete attack resolution (by PGI-S)[e]

NCT05505916, EudraCT: 2021-001176-42. PGI-C, Patient Global Impression of Change; PGI-S, Patient Global Impression of Severity.
[a]Completed the phase 3 KONFIDENT trial. [b]All other participants, including those who participated in the phase 2 trial. [c]For de novo participants, the enrollment visit is a screening visit. [d]Within 12 hours. [e]Within 24 hours.
Note: Data cutoff date of 31 January 2024.

Participant Demographics and Disease-specific History

	All participants N=84	Participants experiencing laryngeal attacks n=7
Age, median (IQR), years	35.0 (22.0 to 47.0)	31.0 (25.0 to 56.0)
Sex, female, n (%)	54 (64.3)	5 (71.4)
Race, n (%)		
White	63 (75.0)	7 (100.0)
Asian	12 (14.3)	0
Other	2 (2.4)	0
Not reported	7 (8.3)	0
BMI, median (IQR), kg/m^2	25.6 (22.3 to 31.1)	29.3 (19.9 to 31.0)
HAE-C1INH type, n (%)		
Type 1	77 (91.7)	7 (100.0)
Type 2	7 (8.3)	0





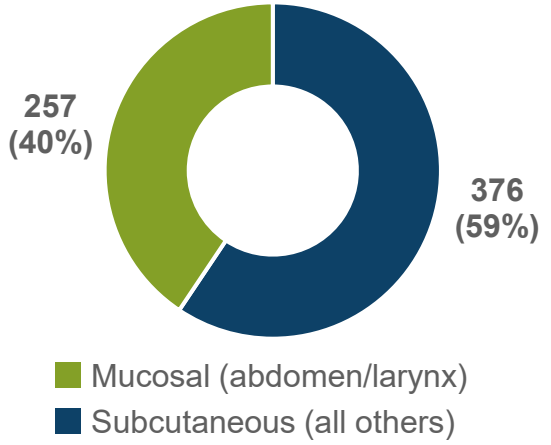
BMI, body mass index; IQR, interquartile range; HAE-C1INH, hereditary angioedema with C1-inhibitor deficiency; LTP, long-term prophylaxis; n/N, number of participants.
[a]Of the 7 participants who experienced a laryngeal attack, 1 (14%) was an adolescent (12-17 years old).
[b]Of the 25 participants using LTP, 13 (52%) used berotralstat, 5 (20%) used lanadelumab, and 7 (28%) used C1-inhibitor agents.
[c]Of the 7 participants who experienced laryngeal attacks, 3 (43%) were using LTP.
Note: Data cutoff date of 31 January 2024.

Attack Characteristics

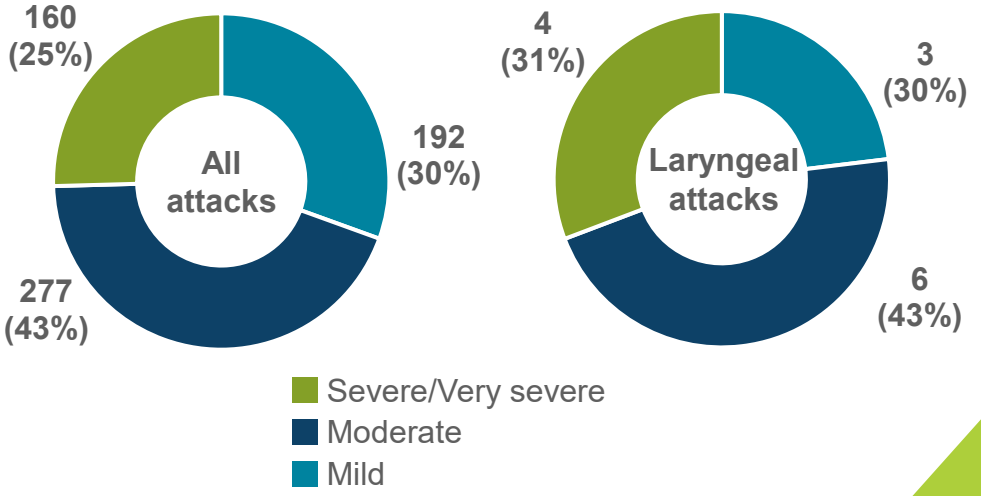
	Sebetralstat-treated attacks N=640
Primary attack locations,[a,b] n (%)	
Abdomen	244 (38.1)
Arms/hands	190 (29.7)
Legs/feet	154 (24.1)
Head/face/neck	56 (8.8)
Torso	43 (6.7)
Genitals	37 (5.8)
Larynx/throat	14 (2.2)

- Participants treated a median of 5 attacks with sebetralstat (IQR, 2 to 8; range, 1 to 37)
  - 20 participants treated ≥9 attacks

Primary pooled attack locations[c]

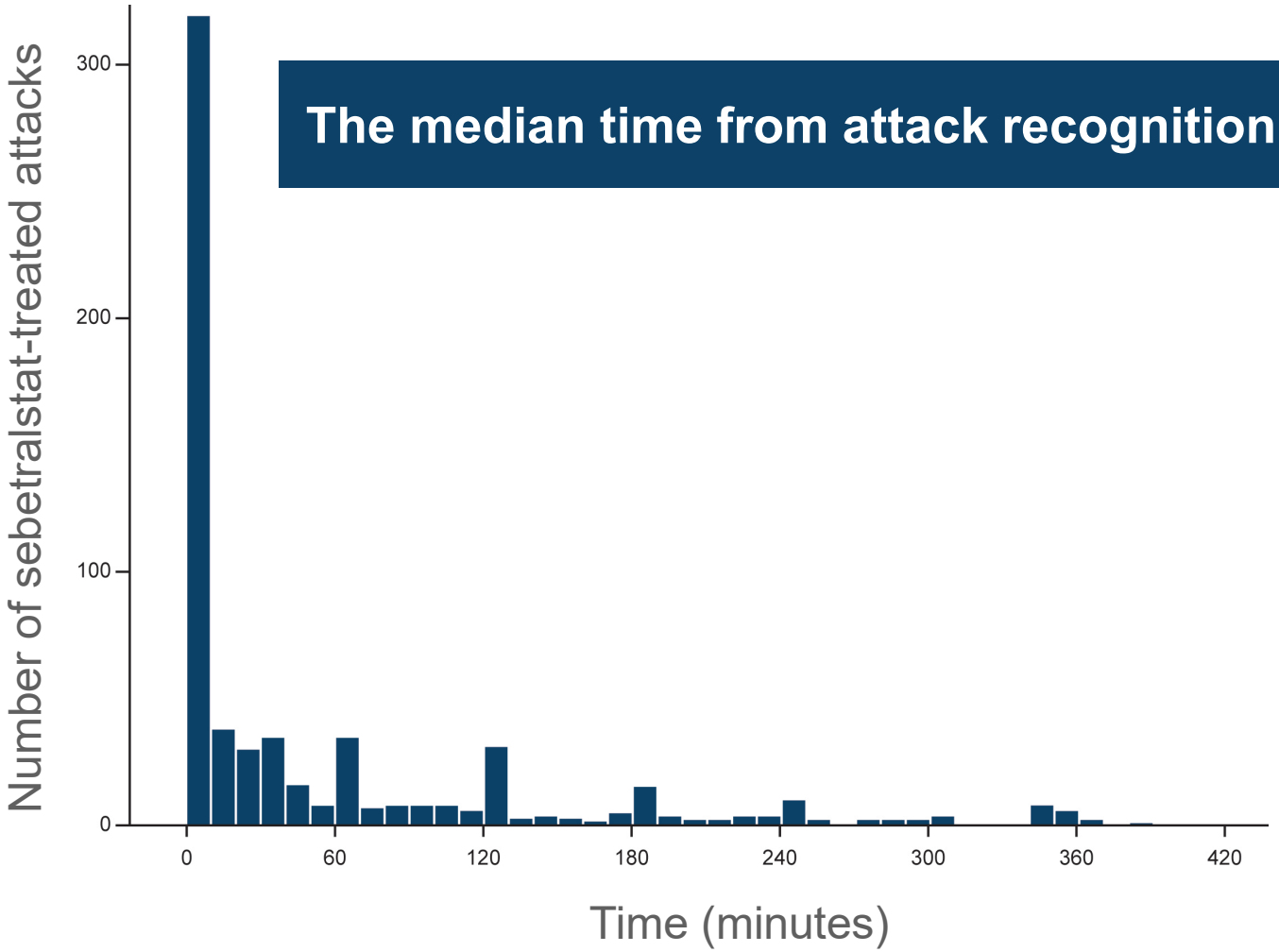


Baseline PGI-S category[d]



IQR, interquartile range; n/N, number of participants; PGI-S, Patient Global Impression of Severity.
[a]Participants who had multiple attack locations were counted once in each reported location. [b]Missing, n (%) = 7 (1.1).
[c]Mucosal locations include the abdomen and the larynx, throat, or both. Subcutaneous locations include all other locations.
[d]None, n (%) = 4 (0.6); Missing, n (%) = 7 (1.1). In laryngeal: None, n (%) = 1 (7.1).
Note: Data cutoff date of 31 January 2024.

Time from Attack Recognition to Sebetralstat Administration



The median time from attack recognition to treatment was 9 minutes (IQR, 1 to 69)

- 14 laryngeal attacks (2.2%) were treated with sebetralstat
  - Median time from onset of attack to first administration of 8 minutes (IQR, 1 to 27)
- In KONFIDENT, the median time from attack recognition to treatment was 41 minutes (IQR, 6 to 140)[1]

IQR, interquartile range. Note: Data cutoff date of 31 January 2024.

[1]Riedl M et al. *N Engl J Med* 2024;391:32-43.

Interim Safety Results (640 Attacks Treated with Sebetralstat)

	All participants N=84
Any TEAE	47 (56.0)
Treatment-related	**8 (9.5)**
Serious TEAE	3 (3.6)
Treatment-related	**0**
Severe TEAE	5 (6.0)
Treatment-related	**1 (1.2)**
Any TEAE leading to permanent discontinuation	4 (4.8)
Treatment-related	**2 (2.4)**
Any TEAE leading to death	0

- **Severe treatment-related TEAE:** one incident of grade 3 diarrhea that started 1 day prior to sebetralstat administration was assessed as unrelated by the investigator after the data cutoff (attack location: arms/ hands/legs/feet)
- **Treatment-related TEAE leading to permanent discontinuation:** one incident of grade 2 skin burning sensation (arms/hands) and 1 incident of grade 2 nausea (abdominal)

The safety profile of sebetralstat was consistent with that observed in the KONFIDENT trial

N, number of participants; TEAE, treatment-emergent adverse event.
Note: Data cutoff date of 31 January 2024.

Interim Efficacy Results

	KONFIDENT-S All treated attacks N=640	KONFIDENT-S Laryngeal attacks n=14	KONFIDENT[1] Attacks treated with 600 mg n=93
Time to beginning of symptom relief within 12 hours, hours			
Median (IQR)	1.80 (0.95 to 5.45)	1.3 (0.5 to 5.3)	1.79 (1.02 to 3.79)
Time to reduction in attack severity within 12 hours, hours			
Median (IQR)	6.57 (1.61 to >12)	1.5 (0.8 to 6.1)	7.75 (2.19 to >12)
Time to complete resolution within 24 hours, hours			
Median (IQR)	21.02 (7.22 to >24)	6.8 (1.8 to >24)	24.00 (7.54 to >24)

- Through 24 hours, 486 attacks (75.9%) were treated with one dose of sebetralstat
  - 149 attacks (23.3%) were treated with two doses of sebetralstat
- Conventional on-demand treatments were used for 36 attacks (5.6%) within 12 hours of the first dose of sebetralstat
  - Conventional on-demand treatment were used within 12 hours after first taking sebetralstat 600 mg for 8 attacks (8.6%) in KONFIDENT[1]

IQR, interquartile range; n/N, number of participants. Note: Data cutoff date of 31 January 2024.

[1]Riedl M et al. *N Engl J Med* 2024;391:32-43.

Key Takeaways

- Data from this OLE trial show that **oral sebetralstat enabled participants to treat attacks early**, consistent with global HAE treatment guidelines
  - Median time to treatment was shorter in the KONFIDENT-S OLE trial (9 minutes [IQR, 1 to 69]) than in the phase 3 KONFIDENT trial (41 minutes [IQR, 6 to 140]),[1] potentially reflecting the real-world nature of KONFIDENT-S
- In this OLE trial, **safety and efficacy results with sebetralstat were consistent** with those observed in the randomised phase 3 KONFIDENT trial[1]
- **Results in attacks involving the larynx were consistent** with those observed across all attacks in both KONFIDENT[1] and KONFIDENT-S

KONFIDENT-S OLE trial is ongoing; additional interim analyses are planned.
As of 21 August 2024, 129 participants have treated 1516 attacks (32 laryngeal) with sebetralstat.

HAE, hereditary angioedema; IQR, interquartile range; OLE, open-label extension

1. Riedl M et al. *New Engl J Med.* 2024;391:32-43.