R098

On-demand Treatment of Laryngeal Hereditary Angioedema Attacks with Sebetralstat: Pooled Analysis from KONFIDENT and KONFIDENT-S

Emel Aygören-Pürsün,[1] Jonathan A. Bernstein,[2] William R. Lumry,[3] Paul K. Audhya,[4] James Hao,[4] Michael D. Smith,[4] Christopher M. Yea,[4] Marc A. Riedl[5]

[1]University Hospital Frankfurt, Goethe University Frankfurt, Frankfurt, Germany; [2]University of Cincinnati College of Medicine and Bernstein Clinical Research Center, Cincinnati, OH, USA; [3]AARA Research Center, Dallas, TX, USA; [4]KalVista Pharmaceuticals, Salisbury, United Kingdom, and Cambridge, MA, USA; [5]University of California, San Diego, La Jolla, CA, USA

Background

- People living with hereditary angioedema with C1-inhibitor deficiency (HAE-C1INH) experience unpredictable, painful, and debilitating attacks of tissue swelling that can be life-threatening when involving the larynx[1-3]
- Laryngeal attacks occur in >50% of people living with HAE at least once in their lifetime and, given the potential for rapid progression, may be fatal without prompt administration of on-demand treatment, including in patients receiving long-term prophylaxis (LTP)[3-5]
- Sebetralstat, a plasma kallikrein inhibitor, is the first orally administered therapy to be evaluated in a phase 3 trial for the on-demand treatment of HAE-C1INH attacks.[6] In KONFIDENT, sebetralstat resulted in significantly faster beginning of symptom relief versus placebo, regardless of attack severity or location[7]
  - Subgroup analysis of attacks involving the larynx in KONFIDENT was not feasible due to the small sample size

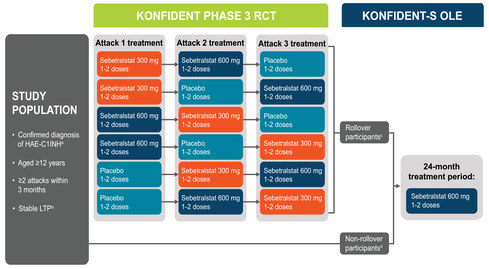
Objective

- This analysis evaluated the effectiveness of sebetralstat as an on-demand treatment for attacks involving the larynx using pooled data from the phase 3 KONFIDENT trial (NCT05259917) and the ongoing KONFIDENT-S OLE study (NCT05505916)

Methods

- In the double-blind, randomized, placebo-controlled, 3-way crossover phase 3 KONFIDENT trial[6] mild-to-moderate attacks involving the larynx were eligible for study treatment (**Figure 1**)
- In the ongoing KONFIDENT-S OLE study[8] attacks involving the larynx of any severity were eligible to be treated with sebetralstat 600 mg
- The primary efficacy endpoint was the time to beginning of symptom relief, defined as a Patient Global Impression of Change (PGI-C) rating of at least "A Little Better" for 2 consecutive time points within 12 hours
- The key secondary endpoints were the time to reduction in severity, defined as an improved rating on the Patient Global Impression of Severity (PGI-S) scale at ≥2 consecutive time points within 12 hours, and time to complete attack resolution, defined as a PGI-S rating of "None" within 24 hours
- Safety was assessed by adverse event reporting, physical examinations, vital signs, electrocardiograms, and laboratory assessments
- Subgroup analyses are not powered for efficacy and must be interpreted with caution

Figure 1. KONFIDENT and KONFIDENT-S Trial Designs



Pooled population:
All participants who treated at least 1 attack with sebetralstat 600 mg

HAE-C1INH, hereditary angioedema due to deficiency C1 inhibitor; LTP, long-term prophylaxis; OLE, open-label extension; RCT, randomized controlled trial.

[a]Participants must have had access to conventional on-demand treatment.
[b]Participants receiving LTP were required to be on a stable dose for ≥3 months prior to screening.
[c]Completed the phase 3 KONFIDENT trial.
[d]All other participants, including those who participated in the phase 2 trial (NCT04208412).

Results

Participants and Attacks

- As of January 31, 2024, 16 attacks involving the larynx in 8 participants were treated with sebetralstat 600 mg in KONFIDENT and KONFIDENT-S (**Table 1**), representing 2.2% of the total attacks treated with sebetralstat 600 mg in the phase 3 program at the time of data cutoff

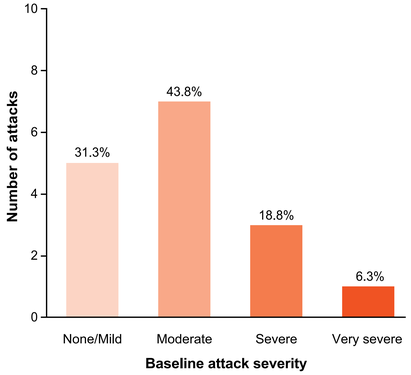
Table 1. Participant Demographics and Disease Characteristics

	Participants with ≥1 attacks involving the larynx[a] n=8
Age, median (IQR), years	35.5 (26.5-57.0)
Sex, female, n (%)	6 (75.0)
BMI, median (IQR), kg/m^2	29.7 (23.6-31.1)
Race, n (%)	
White	8 (100)
HAE-C1INH type, n (%)	
Type 1	8 (100)
Time since HAE-C1INH diagnosis, median (IQR), years	18.1 (6.0-26.0)
Current treatment regimen, n (%)	
On-demand only	4 (50.0)
On-demand + LTP[b]	4 (50.0)

BMI, body mass index; HAE-C1INH, hereditary angioedema due to deficiency of C1 inhibitor; IQR, interquartile range; LTP, long-term prophylaxis.

[a]Includes participants who experienced an attack involving the larynx treated with sebetralstat 600 mg in KONFIDENT or KONFIDENT-S.
[b]The LTP agents were lanadelumab (n=2) and berotralstat (n=2).

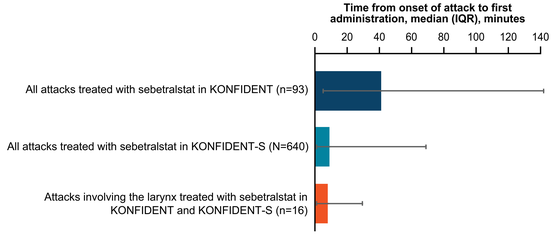
Figure 2. Baseline Attack Severity in Attacks Involving the Larynx



PGI-S, Patient Global Impression of Severity.

- At baseline, 12 (75%) attacks were affecting the larynx only and 4 (25%) attacks were affecting the larynx and other locations
- Most (68.9%) attacks involving the larynx had a PGI-S rating of moderate (43.8%), severe (18.8%), or very severe (6.3%) at baseline

Figure 3. Time to Sebetralstat Administration



Time to treatment reported for attacks treated with sebetralstat 600 mg.

- The median time to oral sebetralstat administration to treat an attack involving the larynx was 8 minutes (IQR: 1-30) (**Figure 3**)

Table 2. Primary and Secondary Endpoints

	All attacks treated with sebetralstat in KONFIDENT n=93	All attacks treated with sebetralstat in KONFIDENT-S n=640	Attacks involving the larynx treated with sebetralstat in KONFIDENT and KONFIDENT-S n=16
Time to beginning of symptom relief,[a] median (IQR), hours	1.79 (1.02-3.79)	1.80 (0.95-5.45)	1.52 (0.69-6.07)
Time to reduction in severity,[b] median (IQR), hours	7.75 (2.19->12)	6.57 (1.61->12)	1.69 (0.81-6.82)
Time to complete attack resolution,[c] median (IQR), hours	24.00 (7.54->24)	21.02 (7.22->24)	9.74 (1.78->24)

IQR, interquartile range; PGI-C, Patient Global Impression of Change; PGI-S, Patient Global Impression of Severity.

[a]Defined as a PGI-C of at least "A Little Better" for 2 consecutive time points within 12 hours.
[b]Defined as a decrease in the PGI-S rating for 2 consecutive time points within 12 hours.
[c]Defined as a PGI-S of "None" within 24 hours.

- The efficacy of sebetralstat in treating attacks involving the larynx was consistent with that observed for all attacks in both KONFIDENT and KONFIDENT-S (**Table 2**)
  - In attacks involving the larynx, the median time to beginning of symptom relief was 1.52 hours (IQR: 0.69-6.07), the median time to reduction in severity was 1.69 hours (IQR: 0.81-6.82), and median time to complete attack resolution was 9.74 hours (IQR: 1.78->24)

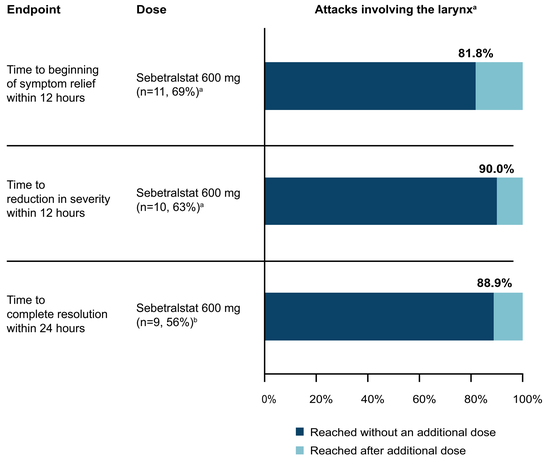
Table 3. Administration of Conventional On-demand Treatment or an Additional Dose of Sebetralstat

	All attacks treated with sebetralstat in KONFIDENT n=93	All attacks treated with sebetralstat in KONFIDENT-S n=640	Attacks involving the larynx treated with sebetralstat in KONFIDENT and KONFIDENT-S n=16
Additional administration of sebetralstat through 24 hours[a]	37 (39.8)	154 (24.1)	7 (43.8)
Conventional on-demand treatment[b,c]	8 (8.6)	36 (5.6)	2 (12.5)[d]

Values are in n (%).

[a]Participants were instructed to administer the optional additional dose of sebetralstat 600 mg ≥3 hours after the first dose. In KONFIDENT, a second administration of study treatment was not permitted for attacks involving the larynx. However, a second administration of sebetralstat 600 mg was permitted for attacks involving the larynx in KONFIDENT-S.
[b]Attacks involving the larynx could be treated with conventional on-demand treatment at any time and all participants were instructed to treat immediately with conventional on-demand treatment if laryngeal attack symptoms worsened following initial study treatment.
[c]Includes conventional on-demand treatment administered within 12 hours of first administration sebetralstat 600 mg in KONFIDENT or KONFIDENT-S.
[d]One participant reported administering conventional on-demand treatment one minute after sebetralstat administration (the endpoint was censored at 12 hours). One participant met the primary endpoint 1.26 hours after administering sebetralstat, but reported administering conventional on-demand treatment 11.7 hours after administering sebetralstat.

Figure 4. The Proportion of Attacks Involving the Larynx that Reached the Primary and Key Secondary Endpoints without an Additional Dose



[a]In KONFIDENT, a second administration of study treatment was not permitted for attacks involving the larynx. However, a second administration of sebetralstat 600 mg was permitted in KONFIDENT-S.
[b]Proportion of attacks involving the larynx which reached the endpoint within 12 hours.
[c]Proportion of attacks involving the larynx which reached the endpoint within 24 hours.

- Over 81.8% of attacks involving the larynx that reached the primary and key secondary endpoints did so without administration of an additional dose of sebetralstat (**Figure 4**)

Table 4. Safety

	Participants with ≥1 attacks involving the larynx[a] n=8
Any TEAE	2 (25.0)
Treatment-related	**0**
Serious TEAE	1 (12.5)
Treatment-related	**0**
Severe TEAE	2 (25.0)
Treatment-related	**0**
Adverse event during treatment that led to study discontinuation	0
Adverse event during treatment that led to death	0

TEAE, treatment-emergent adverse event.
Values are in n (%).
[a]Includes participants who experienced an attack involving the larynx treated with sebetralstat 600 mg in KONFIDENT or KONFIDENT-S.

- There were no serious or severe treatment-related adverse events in participants who experienced an attack involving the larynx
- There were no reports of dysphagia associated with administration of study drug for any attacks involving the larynx

Conclusions

- **Sebetralstat, an oral plasma kallikrein inhibitor, enabled rapid treatment of attacks involving the larynx in patients with HAE-C1INH**
- **In the phase 3 KONFIDENT trial, on-demand treatment of HAE-C1INH attacks with orally administered sebetralstat resulted in significantly faster beginning of symptom relief versus placebo**
  - **In this pooled analysis, the efficacy of sebetralstat in attacks involving the larynx was comparable with that observed in all sebetralstat-treated attacks in KONFIDENT and KONFIDENT-S**
  - **Most attacks involving the larynx treated with sebetralstat 600 mg did not require the use of a second dose to achieve efficacy endpoints**
- **Long-term efficacy of sebetralstat in attacks involving the larynx continues to be studied in the on-going KONFIDENT-S open-label extension**
  - **As of September 14, 2024, 16 participants have treated 34 attacks involving the larynx with sebetralstat**

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Acknowledgments

Medical writing support was provided under the guidance of the authors by Bridget Healy, MBChB, MPH at ApotheCom, San Francisco, CA, USA, and was funded by KalVista Pharmaceuticals.

KalVista thanks the people living with HAE and their families, their advocates, and the investigator teams who have supported KONFIDENT and KONFIDENT-S.

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Presented at the American College of Allergy Asthma and Immunology Annual Scientific Meeting 2024; October 24-28, 2024; Boston, Massachusetts