L15

Effectiveness of Sebetralstat for the On-demand Treatment of Laryngeal Hereditary Angioedema Attacks: Interim Analysis from KONFIDENT-S

Jonathan A. Bernstein,[1] Emel Aygören-Pürsün,[2] Vesna Grivcheva-Panovska,[3] Inmaculada Martinez-Saguer,[4] Danny M. Cohn,[5] William R. Lumry,[6] Marc A. Riedl,[7] Andrea Zanichelli,[8,9] James Hao,[10] Michael D. Smith,[10] Christopher M. Yea,[10] Paul K. Audhya,[10] Henriette Farkas[11]

[1]University of Cincinnati College of Medicine and Bernstein Clinical Research Center, Cincinnati, OH, USA; [2]University Hospital Frankfurt, Goethe University Frankfurt, Frankfurt, Germany; [3]University Clinic of Dermatology, School of Medicine, University Saints Cyril and Methodus, Skopje, North Macedonia; [4]HZRM Haemophilia Center Rhein Main, Frankfurt, Germany; [5]Amsterdam University Medical Center, University of Amsterdam, Amsterdam, Netherlands; [6]AARA Research Center, Dallas, TX, USA; [7]University of California, San Diego, La Jolla, CA, USA; [8]IRCCS Policlinico San Donato Milanese, Milan, Italy; [9]University of Milan, Milan, Italy; [10]KalVista Pharmaceuticals, Salisbury, United Kingdom, and Cambridge, MA, USA; [11]Hungarian Angioedema Center of Reference and Excellence, Semmelweis University, Budapest, Hungary

Background

- Although they represent roughly 1% of all swelling attacks, attacks involving the larynx occur in >50% of people living with hereditary angioedema (HAE) type 1 or type 2 due to C1-inhibitor deficiency (HAE-C1INH) at least once in their lifetime[1-3]
- These attacks may be fatal without prompt administration of an appropriate on-demand treatment[1-3]
  - In a previously reported case series, laryngeal attacks were rarely noted to be lethal in less than 10 minutes; death occurred within 20 minutes in 4 of 32 fatal laryngeal attacks (11%)[4]
- Currently approved therapies for on-demand treatment of HAE-C1INH attacks must be administered parenterally; the treatment burden of parenteral administration is associated with delays and/or withholding of treatment[5-7]
- In a recent survey of people living with HAE in the United States, the mean time to treatment of attacks involving the larynx and/or tongue was 2.5 hours; 25% of respondents reported waiting 5 hours or more[8]
- Sebetralstat, an investigational oral plasma kallikrein inhibitor, is being evaluated as on-demand treatment for HAE attacks in the ongoing, 2-year, multicenter, open-label extension (OLE) study KONFIDENT-S (NCT05505916, EudraCT: 2021-001176-42) that was designed to align with guidelines recommending early treatment[9]

Objective

- The objectives of this interim analysis of KONFIDENT-S are to assess the tolerability, safety, and effectiveness of sebetralstat as an on-demand treatment for HAE attacks involving the larynx

Methods

Study Design

- Eligible participants were adults (≥18 years of age) and adolescents (≥12 years of age) with HAE-C1INH and ≥2 documented attacks within 3 months or who completed the phase 3 KONFIDENT trial
  - Participants receiving long-term prophylaxis (LTP) were required to be on a stable dose and regimen for ≥3 months immediately before and during the study
- Consistent with the EAACI/WAO treatment guideline recommendations for HAE,[9] participants were instructed to self-administer treatment (sebetralstat 600 mg) as early as possible after attack onset
  - Participants were instructed to treat immediately with conventional on-demand treatment if laryngeal attack symptoms worsened after the initial administration of sebetralstat
- Effectiveness endpoints were as follows:
  - Time to beginning of symptom relief (Patient Global Impression of Change rating of at least “A Little Better” for ≥2 consecutive time points) within 12 hours
  - Time to reduction in attack severity (≥1 level decrease on the Patient Global Impression of Severity [PGI-S] for ≥2 consecutive time points) within 12 hours
  - Time to complete attack resolution (PGI-S rating of “None”) within 24 hours
- Conventional treatment administration was censored to the end of the analysis window

Results

Participant Characteristics

- From October 21, 2022, to September 14, 2024 (data cutoff), 134 participants treated 1706 attacks with sebetralstat 600 mg (**Table 1**)
  - 32 of these 1706 attacks (1.9%) involved the larynx (**Table 2**)
  - The median time from attack onset to treatment was 11.5 minutes (IQR, 1.0 to 34.0) for attacks involving the larynx

Table 1. Participant Demographics

	All participants N=134	Participants experiencing attacks involving the larynx n=16
Age, median (IQR), years	35.0 (21.0 to 49.0)	44.5 (29.5 to 59.5)
Age group, n (%)		
≥12 to <18 years	23 (17.2)	2 (12.5)
≥18 to <65 years	107 (79.9)	13 (81.3)
≥65 years	4 (3.0)	1 (6.3)
Sex, female, n (%)	87 (64.9)	10 (62.5)
Race, n (%)		
White	99 (73.9)	13 (81.3)
Asian	17 (12.7)	2 (12.5)
Other or multiple	11 (8.2)	–
Not reported	7 (5.2)	1 (6.3)
BMI, median (IQR), kg/m^2	25.4 (22.3 to 30.6)	29.6 (26.4 to 32.2)
HAE-C1INH type, n (%)		
Type 1	125 (93.3)	16 (100)
Type 2	9 (6.7)	–
Current treatment regimen, n (%)		
On-demand only	99 (73.9)	9 (56.3)
LTP + on-demand	35 (26.1)[a]	7 (43.8)

BMI, body mass index; HAE-C1INH, hereditary angioedema type 1 or type 2 due to C1-inhibitor deficiency; IQR, interquartile range; LTP, long-term prophylaxis.
[a]Of the 35 participants using LTP, 29 (21.6%) used kallikrein inhibitors (berotralstat or lanadelumab) and 6 (4.5%) used C1INH replacement.

Table 2. Baseline Attack Characteristics

	All attacks treated with sebetralstat N=1706	Attacks involving the larynx treated with sebetralstat n=32
Baseline PGI-S category,[a] n (%)		
Mild	589 (34.5)	7 (21.9)
Moderate	685 (40.2)	15 (46.9)
Severe/very severe	330 (19.3)	9 (28.1)
Time from attack onset to treatment administration, median (IQR), minutes	10.0 (1.0 to 68.5)	11.5 (1.0 to 34.0)

IQR, interquartile range; PGI-S, Patient Global Impression of Severity.
[a]Missing: n (%) = 73 (4.3) for all attacks; None: n (%) = 29 (1.7) for all attacks, 1 (3.1) for attacks involving the larynx treated with sebetralstat.

Tolerability and Safety

- No participants reported difficulty swallowing sebetralstat during an attack involving the larynx
- 7 participants treating attacks involving the larynx with sebetralstat experienced treatment-emergent adverse events (TEAEs) (**Table 3**)
- 2 TEAEs were considered treatment-related: 1 instance each of grade 2 nausea and grade 2 vomiting in the same participant, who experienced an attack involving the larynx and abdomen
- 2 TEAEs of "laryngeal HAE attack" in 1 adolescent resulted in hospitalization (precautionary) and were not considered related to treatment

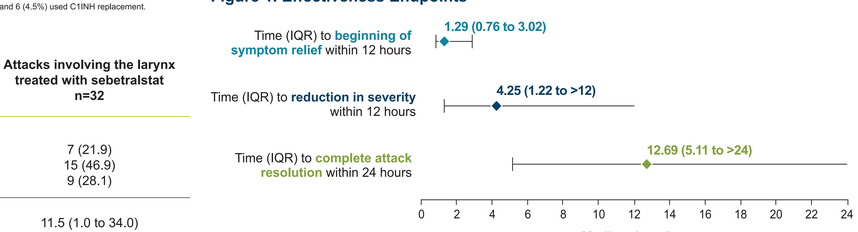
Table 3. Safety

TEAE, n (%)	Participants treating attacks involving the larynx n=16
Any TEAE	7 (43.8)
Treatment-related	**1 (6.3)**
Serious TEAE	2 (12.5)[a]
Treatment-related	**0**
Severe TEAE	3 (18.8)
Treatment-related	**0**
Any TEAE leading to permanent discontinuation	1 (6.3)
Any TEAE leading to death	0
Treatment-related TEAEs	
Gastrointestinal disorders	
Nausea	1 (6.3)[b]
Vomiting	1 (6.3)[b]

E, number of events; TEAE, treatment-emergent adverse event.
[a]Serious TEAEs were 1 event of grade 3 viral meningitis occurring in 1 participant and 2 events of laryngeal HAE attack occurring in 1 participant.
[b]Grade 2 nausea and vomiting occurred in the same participant.

Effectiveness

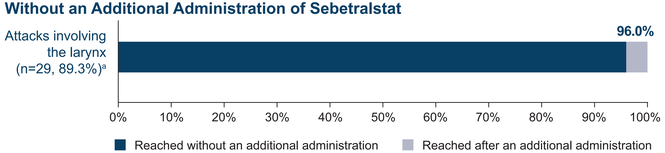
Figure 1. Effectiveness Endpoints



IQR, interquartile range.
Error bars represent IQR.

- 4 of the 32 attacks involving the larynx (12.5%) were treated with a second administration of sebetralstat within 12 hours and 3 (9.4%) were treated with conventional treatment within 12 hours; the time of conventional treatment administration was not recorded for 1 attack
  - Conventional treatment was administered after a single administration of sebetralstat in 2 attacks; 1 participant reported administering conventional on-demand treatment 1 minute after sebetralstat administration (PGI-S at the time of treatment was rated as very severe)
  - For 1 attack, conventional treatment was administered after 2 administrations of sebetralstat, 11.7 hours after the first administration of sebetralstat
- Most of the attacks (96%) affecting the larynx which achieved beginning of symptom relief did so without an additional administration of sebetralstat (**Figure 2**)

Figure 2. Proportion of Attacks Achieving Beginning of Symptom Relief Prior to or Without an Additional Administration of Sebetralstat



[a]Proportion of attacks reaching the endpoint within 12 hours.

Conclusions

- **Sebetralstat was well-tolerated for attacks involving the larynx**
  - **No participants reported trouble swallowing sebetralstat**
- **Oral sebetralstat enabled early treatment (median 11.5 minutes) and resulted in early symptom relief (median 1.29 hours)**
- **A second administration of sebetralstat was used in 12.5% of attacks; conventional treatment was used in 9.4%**
- **Most of the attacks (96%) involving the larynx that achieved beginning of symptom relief did so without an additional administration of sebetralstat**

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Contact Information

Contact the author at bernstja@ucmail.uc.edu for questions or comments.

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