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

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Introduction

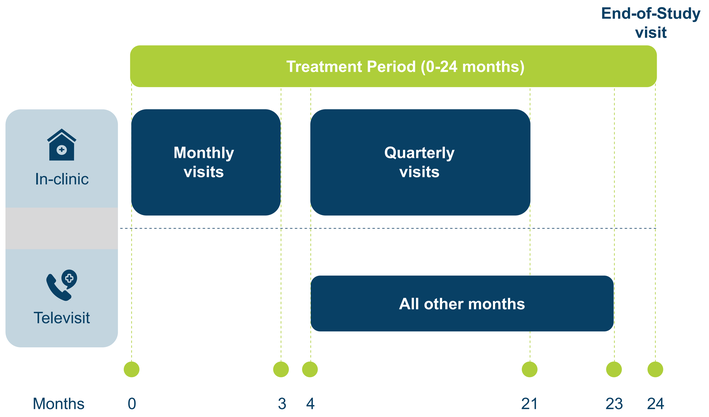
- Attacks caused by hereditary angioedema (HAE) type 1 or type 2 due to C1-inhibitor deficiency (HAE-C1INH) involving gastrointestinal and laryngeal tissues share an underlying pathophysiology because they affect the mucosal lining of internal surfaces[1-8]
- Mucosal attacks may progress rapidly and are associated with substantial morbidity[9,10]
  - Gastrointestinal attacks lead to severe pain, nausea, vomiting, and in some cases, may result in circulatory shock due to hypovolemia or temporary obstruction due to the thickening of the bowel wall[9,11]
  - In the larynx, even minor edema can rapidly progress to life-threatening airway compromise[3-5]
- Sebetralstat, an oral plasma kallikrein inhibitor, is being evaluated as an on-demand treatment of 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[1,12]
- The objective of this interim analysis of KONFIDENT-S was to assess the safety and effectiveness of sebetralstat as an on-demand treatment for mucosal attacks

Methods

Trial Design

- Eligible participants were ≥12 years of age with HAE-C1INH and ≥2 documented attacks within 3 months or completed the phase 3 KONFIDENT (NCT05259917) trial (**Figure 1**)
  - 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
- Participants were instructed to self-administer sebetralstat 600 mg (2 x 300-mg tablets) as early as possible after HAE attack onset
  - Participants were instructed to treat their attacks involving the larynx immediately with conventional on-demand therapy if the attack symptoms worsened after the initial sebetralstat administration
- Endpoints were as follows:
  - Safety assessed by adverse event monitoring throughout the study
  - Time to beginning of symptom relief (Patient Global Impression of Change [PGI-C] 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

Figure 1. 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.

Results

Participant and Attack Characteristics

- From October 21, 2022, to September 14, 2024 (data cutoff), 16 participants experienced 32 of 1706 (1.9%) laryngeal attacks and 102 participants experienced 533 (31.2%) abdominal attacks (**Tables 1** and **2**)

Table 1. Participant Demographics

	Participants Experiencing	
	Laryngeal Attacks[a] n=16	Abdominal Attacks n=102[b]
Age, mean (range), years	43.4 (15-67)	36.8 (12-77)
Age group, <18 years, n (%)	2 (12.5)	17 (16.7)
Sex, female, n (%)	10 (62.5)	71 (69.6)
Race, n (%)[c]		
White	13 (81.3)	76 (74.5)
Asian	2 (12.5)	13 (12.7)
Other	-	6 (5.9)
BMI, mean (range), kg/m^2	29.7 (19.5-41.5)	25.9 (16.7-41.5)
HAE-C1INH-Type 1, n (%)	16 (100)	95 (93.1)
Current treatment regimen, n (%)		
On-demand only	9 (56.3)	77 (75.5)
On-demand + LTP	7 (43.8)	25 (24.5)
Kallikrein-inhibiting agent[d]	6 (85.7)	21 (84.0)
C1INH	1 (14.3)	4 (16.0)
Time since diagnosis, median (IQR), years	16.6 (6.1-25.0)	12.6 (6.0-22.5)

BMI, body mass index; HAE-C1INH, hereditary angioedema with C1-inhibitor protein deficiency; IQR, interquartile range; LTP, long-term prophylaxis.
[a]Attacks reported by participants as affecting components of the upper aerodigestive tract (ie, including larynx/throat, pharynx, and tongue edema).
[b]Of 134 participants in KONFIDENT-S.
[c]Not reported, 1 (6.3%) for laryngeal attacks, 7 (6.9%) for abdominal attacks.
[d]Lanadelumab or berotralstat.

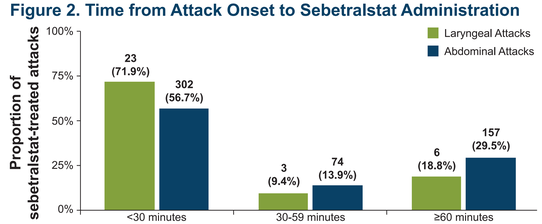
Table 2. Sebetralstat-treated Attack Characteristics

	Laryngeal Attacks n=32[a]	Abdominal Attacks n=533
Baseline PGI-S rating, n (%)		
Mild[b]	8 (25.0)	158 (29.7)
Moderate	15 (46.9)	227 (42.6)
Severe/very severe	9 (28.1)	148 (27.7)

PGI-S, Patient Global Impression of Severity.
[a]Attacks reported by participants as affecting components of the upper aerodigestive tract (ie, including larynx/throat, pharynx, and tongue edema).
[b]PGI-S none: 1 (3.1%) for laryngeal attacks; 4 (0.8%) for abdominal attacks.

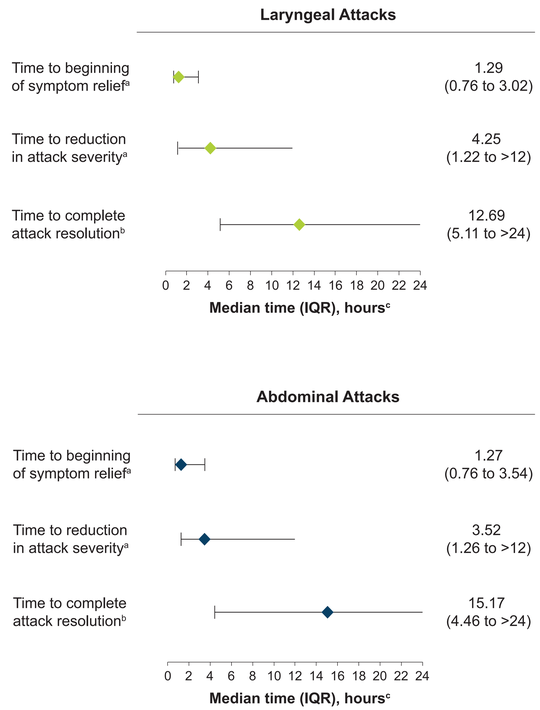
- The median time from attack onset to sebetralstat administration was 11.5 minutes (interquartile range [IQR], 1.0 to 34.0) for laryngeal attacks and 20.0 minutes (IQR, 1.0-61.0) for abdominal attacks (**Figure 2**)
  - 81.3% of laryngeal attacks and 70.5% of abdominal attacks were treated within <1 hour of onset

Figure 2. Time from Attack Onset to Sebetralstat Administration



Effectiveness

Figure 3. Effectiveness Endpoints



IQR, interquartile range.
[a]Within 12 hours.
[b]Within 24 hours.
[c]Error bars display IQR.

- Of attacks reaching beginning of symptom relief within 12 hours (89.3% laryngeal; 85.7% abdominal), 96.0% and 95.8%, respectively, did so before or without an additional sebetralstat administration (**Table 3**)

Table 3. Sebetralstat Administrations and Use of Conventional Treatment in Laryngeal and Abdominal Attacks

	Laryngeal Attacks n=32	Abdominal Attacks n=533
Attacks treated with an additional dose within 12 hours, n (%)	4 (12.5)	95 (17.8)
Attacks treated with conventional treatment within 12 hours, n (%)	3 (9.4)	43 (8.1)
Proportion of attacks reaching beginning of symptom relief within 12 hours before or without an additional dose[a]	96.0%	95.8%

[a]Among the attacks that reached this endpoint (89.3% of laryngeal attacks; 85.7% of abdominal).

Safety

- No participants reported difficulty swallowing sebetralstat during laryngeal or abdominal attacks
- 7 and 36 participants treating attacks involving the larynx and abdomen, respectively, experienced treatment-emergent adverse events (TEAEs) (**Table 4**)
  - TEAEs were deemed treatment related in 1 participant (6.3%) experiencing a laryngeal attack and in 6 participants (5.9%) experiencing an abdominal attack

Table 4. Safety

	Laryngeal Attacks n=16	Abdominal Attacks n=102
Any TEAE, n (%)	7 (43.8)	36 (35.3)
Treatment related	**1 (6.3)[a]**	**6 (5.9)[a,b]**
Serious TEAE, n (%)	2 (12.5)[c]	2 (2.0)
Treatment related	**0**	**0**
Severe TEAE, n (%)	3 (18.8)	2 (2.0)
Treatment related	**0**	**0**
Any TEAE leading to permanent discontinuation, n (%)	1 (6.3)	2 (2.0)
Any TEAE leading to death, n (%)	0	0

AE, adverse event; n, number of participants; TEAE, treatment-emergent adverse event.
[a]Treatment-related nausea and vomiting (grade 2) occurred in the same participant who experienced an attack involving the larynx and abdomen.
[b]Treatment-related flu-like symptoms, cutaneous burning, diarrhea (3 events), headaches, myalgia (bilateral arm and bilateral leg [1 event each]; all grade 2), and vomiting (2 events, grade 1) occurred in 6 participants who experienced an attack involving the abdomen only.
[c]Serious AEs resulting in hospitalization (but considered unrelated to treatment) were 1 event of grade 3 viral meningitis occurring in 1 participant and 2 events of laryngeal HAE attack occurring in 1 participant.

Discussion

- **Sebetralstat demonstrated similar effectiveness for laryngeal and abdominal mucosal HAE attacks**
- **Oral sebetralstat enabled rapid self-administration, resulting in early symptom relief and shorter attack duration in patients with HAE-C1INH**
- **Sebetralstat has demonstrated a favorable safety profile across multiple clinical studies and analyses and was well-tolerated as treatment for mucosal attacks**

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