Abstract #44

Safety and Effectiveness of Sebetralstat in Patients with Hereditary Angioedema Receiving Long-term Prophylaxis: Interim Analysis from the KONFIDENT-S Open-label Study

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Background

- Long-term prophylaxis (LTP) has been shown to reduce the frequency of attacks in patients with hereditary angioedema type 1 or 2 (HAE-C1INH)[1]; however, patients who receive LTP may continue to experience attacks of all severities and in all anatomical locations, including the larynx[2]
- International treatment guidelines recommend that patients with HAE consider treating all attacks regardless of LTP use[3,4]
- Sebetralstat, an investigational oral plasma kallikrein inhibitor, is being evaluated as an on-demand treatment for HAE-C1INH attacks in the ongoing, 2-year, multicenter, open-label extension KONFIDENT-S study (NCT05505916, EudraCT: 2021-001176-42)

Objective

- This interim analysis of the KONFIDENT-S study evaluated the tolerability, safety, and effectiveness of oral sebetralstat for HAE-C1INH attacks in participants receiving concurrent LTP

Methods

Study Design

- Eligible participants were adults and adolescents (≥12 years of age) with HAE-C1INH and at least 2 documented attacks within 3 months before enrollment or had completed the phase 3 KONFIDENT trial
  - Participants receiving LTP were required to be on a stable dose and regimen for ≥3 months immediately before and during the study
- Consistent with international HAE treatment guideline recommendations,[3,4] participants were instructed to self-administer treatment (sebetralstat 600 mg) as early as possible after attack onset, regardless of severity or anatomical location
  - If warranted, an optional second administration of sebetralstat was permitted ≥3 hours after the first administration (as determined by the participant)
- Effectiveness was assessed using the following endpoints:
  - Time to beginning of symptom relief (defined as a Patient Global Impression of Change response of at least "A Little Better" for ≥2 consecutive time points) within 12 hours
  - Time to reduction in attack severity (defined as ≥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 (defined as PGI-S rating of "None" [ie, no symptoms]) within 24 hours
- Conventional treatment administration was censored to the end of the analysis window (12 or 24 hours)

Results

Participants and Attacks

- From October 21, 2022, to September 14, 2024 (data cutoff), 35 of 134 participants (26.1%) were receiving LTP and experienced a total of 504 attacks, of which 382 (75.8%) were treated with sebetralstat (**Table 1, Table 2**)
  - Of these, 16 participants receiving berotralstat treated 178 attacks, 13 participants receiving lanadelumab treated 80 attacks, and 6 participants receiving C1-inhibitor (C1INH) replacement treated 124 attacks
- The mean (standard deviation [SD]) attack frequency was 1.7 (1.5) attacks/month for participants receiving LTP
  - The mean (SD) attack frequency was 1.8 (1.4) attacks/month with berotralstat, 1.2 (1.1) with lanadelumab, and 2.5 (2.2) with C1INH replacement

Table 1. Participant Demographics

	Participants receiving LTP[a,b] n=35
Age, median (IQR), years	44.0 (28.0 to 56.0)
Age group, n (%)	
≥12 to <18 years	5 (14.3)
≥18 years	30 (85.7)
Sex, female, n (%)	27 (77.1)
Race, n (%)	
White	25 (71.4)
Asian	8 (22.9)
Other or multiple	1 (2.9)
Not reported	1 (2.9)
BMI, median (IQR), kg/m^2	26.6 (22.1 to 33.1)
HAE-C1INH type, n (%)	
Type 1	31 (88.6)
Type 2	4 (11.4)

BMI, body mass index; HAE-C1INH, hereditary angioedema with C1-inhibitor deficiency; IQR, interquartile range; LTP, long-term prophylaxis.
[a]Of the 35 participants receiving LTP, 16 used berotralstat, 13 used lanadelumab, and 6 used C1INH replacement.
[b]Four participants who were receiving LTP at baseline switched to a different LTP agent during the study. One participant switched from C1INH replacement to lanadelumab and was included in the lanadelumab group, 1 participant switched from C1INH replacement to berotralstat and was included in the berotralstat group, 1 participant switched from lanadelumab to C1INH replacement and was included in the lanadelumab group, and 1 participant switched from berotralstat to C1INH replacement and was included in the berotralstat group.

Table 2. Baseline Attack Characteristics

	Attacks treated with sebetralstat n=382
Baseline PGI-S category,[a] n (%)	
Mild	112 (29.3)
Moderate	141 (36.9)
Severe/very severe	94 (24.6)
Missing	34 (8.9)
Baseline attack locations, n (%)	
Mucosal[b]	189 (49.5)
Involving the larynx/throat	17 (4.5)
Subcutaneous[b]	159 (41.6)
Missing	34 (8.9)
Time from attack onset to treatment administration, median (IQR), minutes	6 (1 to 40)

IQR, interquartile range; LTP, long-term prophylaxis; PGI-S, Patient Global Impression of Severity.
[a]A baseline attack severity of "None" was reported for 1 attack (0.3%) by a participant who was receiving LTP.
[b]Mucosal: attacks with primary location of "Abdomen" and/or "Larynx/Throat"; Subcutaneous: other attacks not involving the mucosal locations.

Safety

- 23 of 35 participants (65.7%) receiving LTP and treated attacks with sebetralstat experienced 104 treatment-emergent adverse events (TEAEs) (**Table 3**)
  - 8 TEAEs in 5 participants were considered treatment related: headache (3 events), myalgia (2 events), arthralgia (1 event), nausea (1 event), and vomiting (1 event)
  - There were no serious or severe treatment-related TEAEs in participants receiving LTP
  - 1 participant discontinued the study due to treatment-related TEAEs of nausea and vomiting, which occurred during an attack involving the abdomen and the larynx/throat
  - 1 participant discontinued the study due to a TEAE of increased alanine aminotransferase (not considered related to treatment)

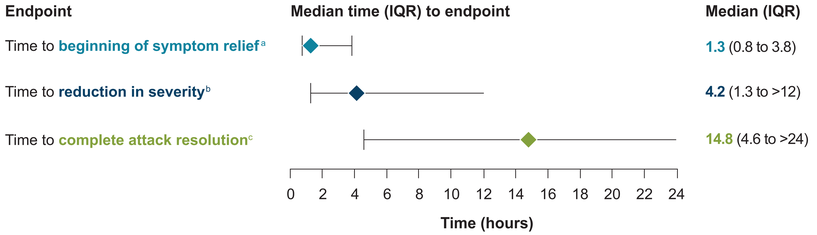
Table 3. Safety Results

TEAE, n (%)	Participants receiving LTP n=35
Any TEAE	23 (65.7)
Treatment-related	5 (14.3)
Serious TEAE[a]	5 (14.3)
Treatment-related	0
Severe TEAE[b]	7 (20.0)
Treatment-related	0
Any TEAE leading to permanent discontinuation	2 (5.7)
Treatment-related	1 (2.9)
Any TEAE leading to death	0

LTP, long-term prophylaxis; TEAE, treatment-emergent adverse event.
[a]Serious TEAE was defined as any untoward medical occurrence that at any dose resulted in death, was life-threatening, required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability/incapacity, was a congenital anomaly/birth defect, or was considered an important medical event by medical and scientific judgment.
[b]Baseline severe (grade 3 or 4) TEAEs were evaluated by investigators according to the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials.[5]

Effectiveness

Figure 1. Sebetralstat Effectiveness Among Participants Receiving LTP



IQR, interquartile range; LTP, long-term prophylaxis; PGI-C, Patient Global Impression of Change; PGI-S, Patient Global Impression of Severity.
[a]Defined as a PGI-C rating of at least "A Little Better" for 2 consecutive time points within 12 hours (with missing data entries between consecutive time points).
[b]Defined as a decrease in the PGI-S rating for 2 consecutive time points within 12 hours.
[c]Defined as a PGI-S rating of "None" within 24 hours.

- In 85 of 382 attacks (22.3%) a second dose of sebetralstat was administered within 12 hours
  - 264 attacks (69.1%) reached beginning of symptom relief within 12 hours. Of these, 90.5% achieved this endpoint before or without a second dose of sebetralstat
- Conventional on-demand treatment was administered within 12 hours in 20 of 382 attacks (5.2%)
  - In 16 of these 20 attacks (80%), conventional on-demand treatment was administered after 1 dose of sebetralstat

Conclusions

- **Sebetralstat enabled rapid on-demand treatment of attacks (median: 6 minutes) in participants with HAE-C1INH, thereby allowing participants to comply with treatment guidelines**
- **Sebetralstat was generally well tolerated, and no new safety signals were observed in participants receiving LTP with berotralstat, lanadelumab, or C1INH replacement**
- **Sebetralstat was effective in treating HAE-C1INH attacks and provided early symptom relief (median: 1.3 hours) in participants having attacks while on LTP**
- **Among attacks that reached the beginning of symptom relief within 12 hours, 90.5% achieved this endpoint before or without a second dose of sebetralstat**

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