Abstract #34

Sebetralstat for Treatment of Hereditary Angioedema Attacks in Patients Receiving Berotralstat: Interim Analysis from the KONFIDENT-S Open-label Study

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Background

- People living with hereditary angioedema type 1 or 2 (HAE-C1INH) consistently report a clear preference for oral compared with parenteral medication[1-3]
  - All currently approved on-demand treatments must be administered parenterally and are associated with delays and/or withholding of treatment[4]
  - Long-term prophylactic (LTP) agents that are parenterally administered at regular intervals[5-8] have a substantial treatment burden that makes it challenging for patients with HAE-C1INH to adhere to over the long-term[1,9]
- The reduced treatment burden of oral on-demand and LTP agents has the potential to improve compliance with international HAE treatment guidelines by people living with HAE-C1INH[9]
- Berotralstat, a plasma kallikrein inhibitor, is the only orally administered non-androgen LTP agent approved by the US Food and Drug Administration and the European Medicines Agency in adults and adolescents with HAE-C1INH[10,11]
- 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 the subgroup of participants receiving concurrent oral berotralstat as 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,[12,13] 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 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), 16 participants receiving berotralstat as LTP experienced a total of 239 attacks, of which 178 (74.5%) were treated with sebetralstat (**Table 1, Table 2**)
- Mean (standard deviation) attack frequency was 1.8 (1.4) attacks/month for participants receiving berotralstat

Table 1. Participant Demographics

	Participants receiving berotralstat[a] n=16
Age, median (IQR), years	38.5 (21.0 to 48.0)
Age group, n (%)	
≥12 to <18 years	4 (25.0)
≥18 years	12 (75.0)
Sex, female, n (%)	13 (81.3)
Race, n (%)	
White	10 (62.5)
Asian	4 (25.0)
Other or multiple	1 (6.3)
Not reported	1 (6.3)
BMI, median (IQR), kg/m^2	27.1 (21.6 to 33.8)
HAE-C1INH type, n (%)	
Type 1	15 (93.8)
Type 2	1 (6.3)

BMI, body mass index; C1INH, C1 inhibitor; HAE-C1INH, hereditary angioedema with C1-inhibitor deficiency; IQR, interquartile range; LTP, long-term prophylaxis.
[a]Of the 16 participants in the berotralstat group, 1 participant was receiving LTP with C1INH replacement at study entry and switched to berotralstat during the study, and 1 participant was receiving LTP with berotralstat at study entry and switched to C1INH replacement during the study.

Table 2. Baseline Attack Characteristics

	Attacks treated with sebetralstat n=178
Baseline PGI-S category,[a] n (%)	
Mild	58 (32.6)
Moderate	64 (36.0)
Severe/very severe	53 (29.8)
Missing	2 (1.1)
Baseline attack locations, n (%)	
Mucosal[b]	107 (60.1)
Involving the larynx/throat	8 (4.5)
Subcutaneous[b]	69 (38.8)
Missing	2 (1.1)
Time from attack onset to treatment administration, median (IQR), minutes	20.0 (1.0 to 67.0)

IQR, interquartile range; PGI-S, Patient Global Impression of Severity.
[a]A baseline attack severity of “None” was reported for 1 attack (0.6%) by a participant who received berotralstat.
[b]Mucosal: attacks with primary location of “Abdomen” and/or “Larynx/Throat”; Subcutaneous: other attacks not involving the mucosal locations.

Safety

- 12 participants receiving berotralstat who treated attacks with sebetralstat experienced 63 treatment-emergent adverse events (TEAEs) (**Table 3**)
  - 6 TEAEs in 3 participants were considered treatment-related: myalgia (2 events), arthralgia (1 event), headache (1 event), nausea (1 event), and vomiting (1 event)
  - None of these treatment-related TEAEs were serious or severe
  - 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

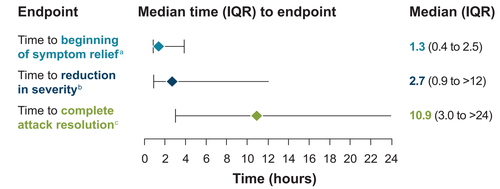
Table 3. Safety Results

TEAE, n (%)	Participants receiving berotralstat n=16
Any TEAE	12 (75.0)
Treatment-related	3 (18.8)
Serious TEAE[a]	3 (18.8)
Treatment-related	0
Severe TEAE[b]	3 (18.8)
Treatment-related	0
Any TEAE leading to permanent discontinuation	1 (6.3)
Treatment-related	1 (6.3)
Any TEAE leading to death	0

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 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.[14]

Effectiveness

Figure 1. Sebetralstat Effectiveness Among Participants Receiving Berotralstat



IQR, interquartile range; 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 38 of 178 attacks (21.3%) a second dose of sebetralstat was administered within 12 hours
  - 139 attacks (78.1%) reached beginning of symptom relief within 12 hours. Of these, 92.1% achieved this endpoint before or without a second dose of sebetralstat
- Conventional on-demand treatment was administered within 12 hours in 8 of 178 attacks (4.5%)
  - In 5 of these 8 attacks (62.5%), conventional on-demand treatment was administered after 1 dose of sebetralstat

Conclusions

- **Sebetralstat enabled rapid on-demand treatment of attacks (median: 20 minutes) and provided early symptom relief (median: 1.3 hours) in participants having attacks while on berotralstat**
- **Among attacks that reached beginning of symptom relief within 12 hours, 92.1% achieved this endpoint before or without a second dose of sebetralstat**
- **Sebetralstat was well-tolerated, and no new safety signals were observed in patients receiving berotralstat**
- **If approved, sebetralstat alone, or in combination with berotralstat, would enable management of HAE without needles**

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