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Sebetralstat as Oral On-demand Treatment for Hereditary Angioedema: Interim Analysis of the Open-label KONFIDENT-S Trial

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Background

- Global treatment guidelines recommend that patients with HAE with C1-inhibitor deficiency (HAE-C1INH) consider treating all attacks, treat attacks as early as possible, and always carry a sufficient quantity of on-demand therapy to treat two attacks[1,2]
- Currently approved therapies for on-demand treatment of HAE-C1INH attacks must be administered parenterally and are associated with delays and/or withholding of treatment[3-5]
- Sebetralstat, an oral plasma kallikrein (PKa) inhibitor, was evaluated in KONFIDENT,[6] a randomized, double-blind, placebo-controlled, phase 3 crossover trial for on-demand treatment of HAE-C1INH. Compared with placebo, sebetralstat provided significantly faster symptom relief, reduction in attack severity, and complete attack resolution.

Objective

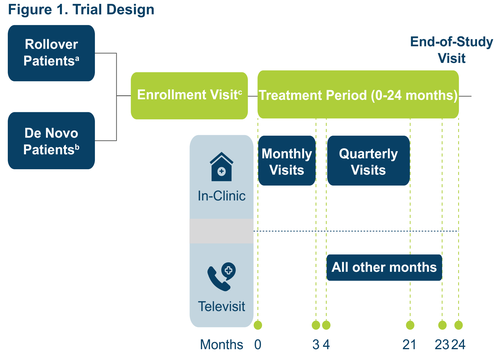
- The objective of KONFIDENT-S trial is to assess the safety and effectiveness of long-term use of sebetralstat as an on-demand treatment of HAE attacks in adolescents and adults with HAE-C1INH

Methods

Trial design

- KONFIDENT-S is a multicenter open-label extension (OLE) trial (NCT05505916, EudraCT: 2021-001176-42)
- Up to 150 adults and adolescents (≥12 years of age) with a confirmed diagnosis of HAE-C1INH (type 1 or 2) and at least two documented HAE-C1INH attacks within 3 months will be enrolled either after completing the KONFIDENT trial (rollover) or de novo (**Figure 1**)
  - Patients receiving long-term prophylaxis (LTP) must be on a stable dose and regimen for ≥3 months immediately before and during the trial
- For up to 2 years, patients self-administer sebetralstat 600 mg (2 × 300-mg tablets) as early as possible after recognizing the start of an attack
  - If needed, an optional second administration of sebetralstat is permitted ≥3 hours after the first administration (as determined by the participant)
- Interim safety was primarily assessed by adverse event reporting, supplemented by laboratory tests and vital sign measurement
- Interim effectiveness was assessed using the following endpoints:
  - Time to beginning of symptom relief (Patient Global Impression of Change rating of at least "A Little Better" 2 time points in a row) within 12 hours
  - Time to reduction in attack severity from baseline (≥1 level decrease on Patient Global Impression of Severity [PGI-S] 2 time points in a row) within 12 hours
  - Time to complete attack resolution (PGI-S rating of "None") within 24 hours

Figure 1. Trial Design



[a]Completed the phase 3 KONFIDENT trial.
[b]All other participants, including those who participated in the phase 2 trial.
[c]For de novo participants, the enrollment visit is a screening visit.

Real-world Elements Used in the Trial Design

- Real-world elements included in the KONFIDENT-S trial design were as follows:
  - "Tele-visits" were allowed and were conducted via telephone or an interactive audio/video system
  - It was not a requirement to contact a call center or investigator before, during, or after attacks
  - Participants were given a portable multidose pack

Results

Participant Characteristics

- From October 21, 2022 to January 31, 2024, 113 participants were enrolled from 50 trial sites in 19 countries (Europe, 50.0%; United States, 27.7%; other, 22.3%)
  - The safety and full analysis sets included 84 participants who treated at least one attack with sebetralstat (**Table 1**)

Table 1. Patient Demographics and Disease-specific History

	All participants (N=84)
Age, median, years (IQR)	35.0 (22.0, 47.0)
Age group, n (%)	
<18 years	12 (14.3)
≥18 years	72 (85.7)
Sex, female, n (%)	54 (64.3)
Race, n (%)	
White	63 (75.0)
Asian	12 (14.3)
Other	2 (2.4)
Not reported	7 (8.3)
BMI, median, kg/m^2 (IQR)	25.6 (22.3, 31.1)
HAE-C1INH type, n (%)	
Type 1	77 (91.7)
Type 2	7 (8.3)
Current treatment regimen, n (%)	
On-demand only	59 (70.2)
LTP[a] + on-demand	25 (29.8)

BMI, body mass index; HAE-C1INH; hereditary angioedema with C1-inhibitor deficiency; IQR, interquartile range; LTP, long-term prophylaxis.
[a]Of the 25 participants using LTP, 13 (52%) used berotralstat, 5 (20%) used lanadelumab, and 7 (28%) used C1-inhibitor agents.

- From October 21, 2022 to January 31, 2024, 640 attacks were treated with sebetralstat (**Table 2**)

Table 2. Baseline Attack Characteristics

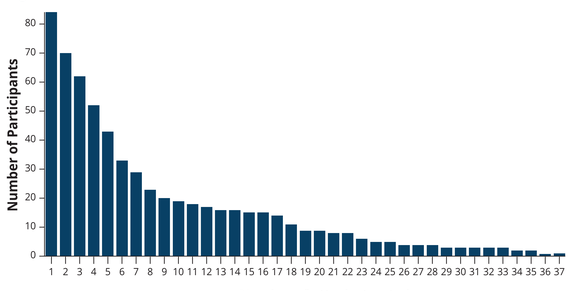
	Sebetralstat-treated attacks (N=640)
Primary attack locations,[a,b] n (%)	
Abdomen	244 (38.1)
Arms/hands	190 (29.7)
Legs/feet	154 (24.1)
Head/face/neck	56 (8.8)
Torso	43 (6.7)
Genitals	37 (5.8)
Larynx/throat	14 (2.2)
Primary pooled attack locations, n (%)	
Mucosal	257 (40.2)
Laryngeal	14 (2.2)
Subcutaneous	376 (58.8)
Baseline PGI-S category,[c] n (%)	
Mild	192 (30.0)
Moderate	277 (43.3)
Severe / Very severe	160 (25.0)

IQR, interquartile range; PGI-S, Patient Global Impression of Severity.
[a]Patients who had multiple attack locations were counted once in each reported location.
[b]Missing, n (%) = 7 (1.1).
[c]None, n (%) = 4 (0.6); Missing, n (%) = 7 (1.1).

Sebetralstat Exposure

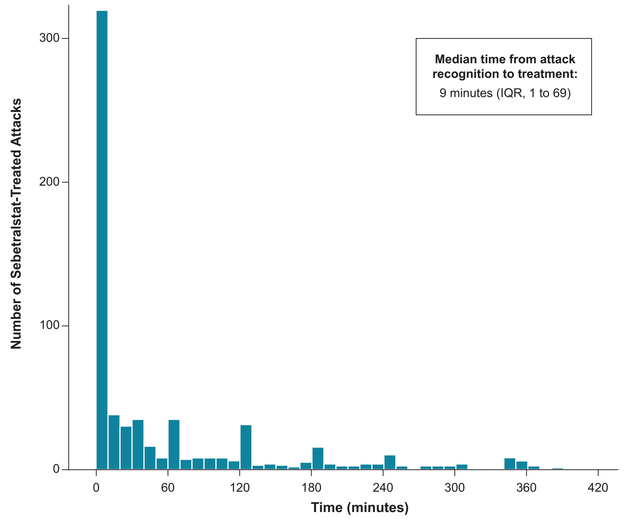
- Participants treated a median of five attacks with sebetralstat (IQR, 2 to 8; **Figure 2**; range, 1 to 37)
  - Twenty participants treated at least nine attacks

Figure 2. Number of Sebetralstat-treated Attacks in KONFIDENT-S



- The median time from attack recognition to treatment was 9 minutes (IQR, 1 to 69; **Figure 3**)
  - Fourteen laryngeal attacks (2.2%) were treated with sebetralstat, with a median time from onset of attack to first administration of 8.0 minutes (IQR, 1.0 to 27.0)

Figure 3. Time From Attack Recognition to Sebetralstat Administration



Two of the 640 attacks (0.3%) were treated >420 minutes after attack recognition.

Interim Safety

- Sebetralstat has been generally well-tolerated (**Table 3**), with a safety profile consistent with that observed in the double-blind, randomized KONFIDENT trial[7]
  - Eighteen treatment-emergent adverse events (TEAEs) related to sebetralstat were reported for eight participants (9.5%) (**Table 4**)
  - No serious treatment-related TEAEs were reported
  - One severe TEAE was reported as related to treatment: one incident of grade 3 diarrhea that started 1 day before sebetralstat administration
  - The treatment-related TEAEs of skin burning sensation and nausea (both grade 2) led to discontinuation for two participants
  - No significant laboratory abnormalities were reported

Table 3. Interim Safety Results

Participants, n (%)	All participants (N=84)
Any TEAE	47 (56.0)
Treatment-related	**8 (9.5)**
Serious TEAE[a]	3 (3.6)
Treatment-related	**0**
Severe TEAE[b]	5 (6.0)
Treatment-related	**1 (1.2)**
Any TEAE leading to permanent discontinuation	4 (4.8)
Treatment-related	**2 (2.4)**
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]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.[8]

Table 4. Treatment-related TEAEs

Participants, n (%)	All participants (N=84)
Treatment-related TEAE	8 (9.5)
Gastrointestinal disorders	
Diarrhea	1 (1.2)
Nausea	1 (1.2)
Vomiting	1 (1.2)
General disorders	
Influenza-like illness	1 (1.2)
Musculoskeletal and connective tissue disorders	
Arthralgia	1 (1.2)
Nervous system disorders	
Headache	3 (3.6)
Tremor	1 (1.2)
Skin and subcutaneous tissue disorders	
Skin burning sensation	1 (1.2)
Urticaria	1 (1.2)

TEAE, treatment-emergent adverse event.

Interim Efficacy

- 486 attacks (75.9%) were treated with one dose of sebetralstat
- Conventional on-demand treatments were utilized for 36 attacks (5.6%) within 12 hours of the first dose of sebetralstat
- Regardless of the number of attacks treated using sebetralstat, efficacy was maintained
  - Median time to beginning of symptom relief for the first nine sebetralstat-treated attacks were 1.66, 1.77, 1.79, 2.79, 1.86, 1.93, 1.77, 2.35, and 1.77 hours
- Efficacy in the subset of laryngeal attacks (n=14) is presented in **Table 5**

Table 5. Interim Efficacy Results

	All treated attacks (N=640)	Laryngeal attacks (n=14)
Time to beginning of symptom relief within 12 hours, h		
Median	1.80	1.3
IQR	0.95 to 5.45	0.5 to 5.3
Time to reduction in attack severity within 12 hours, h		
Median	6.57	1.5
IQR	1.61 to >12	0.8 to 6.1
Time to complete resolution within 24 hours, h		
Median	21.02	6.8
IQR	7.22 to >24	1.8 to >24

IQR, interquartile range.

- 449 attacks (94.3%) reached beginning of symptom relief without a second dose or before a second dose was administered
- The proportions of attacks that reached reduction in severity and complete resolution without a second dose or before a second dose was administered were 95.5% and 85.7%, respectively

Conclusions

- **With data from 640 sebetralstat-treated attacks, this interim analysis provides important additional information to the data from 180 sebetralstat-treated attacks in the randomized phase 3 KONFIDENT trial[7]**
- **Data from this OLE trial with real-world elements show that oral sebetralstat enabled patients to treat attacks early, consistent with global HAE treatment guidelines**
  - **Median time to treatment was shorter in the KONFIDENT-S OLE trial (9 minutes [IQR, 1 to 69]) than in the phase 3 KONFIDENT trial (41 minutes [IQR, 6 to 140]),[7] potentially reflecting the real-world nature of KONFIDENT-S**
- **In this OLE trial, safety and efficacy results with sebetralstat were consistent with those observed in the randomized phase 3 KONFIDENT trial[7]**
- **Results in attacks involving the larynx were consistent with those observed across all attacks in both KONFIDENT and KONFIDENT-S[7]**
- **KONFIDENT-S OLE trial is ongoing; additional interim analyses are planned. As of May 7, 2024, 109 participants have treated over 1000 attacks with sebetralstat (including 24 laryngeal attacks)**
  - **The final analysis will be reported after all participants have used sebetralstat for 2 years as on-demand treatment for their HAE-C1INH attacks**

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