Sebetralstat for On-demand Treatment of Hereditary Angioedema Attacks in European Participants: Interim Analysis from KONFIDENT-S

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Background

- Sebetralstat—a small molecule plasma kallikrein inhibitor—is an orally administered, on-demand treatment for hereditary angioedema (HAE) attacks in adults and adolescents aged ≥12 years[1,2]
- In the phase 3 KONFIDENT trial in patients with HAE, sebetralstat compared with placebo resulted in shorter times to beginning of symptom relief, reduction in attack severity, and complete attack resolution; sebetralstat was well tolerated[3]
- Here we present safety and efficacy data from an interim analysis of the European subgroup of KONFIDENT-S, an ongoing, 2-year, open-label extension study of sebetralstat for the on-demand treatment of HAE

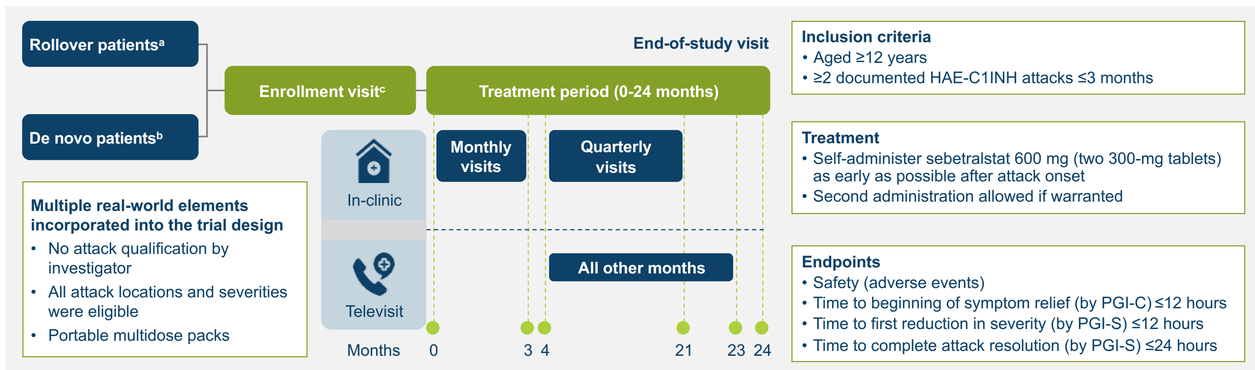
Methods

- KONFIDENT-S (NCT05505916) is a multicenter, open-label extension trial (**Figure 1**)
- Participants aged ≥12 years with HAE due to C1-inhibitor deficiency (HAE-C1INH) deficiency and with ≥2 documented HAE attacks within the past 3 months were eligible
- Participants self-administered sebetralstat 600 mg (two 300-mg tablets) as soon as possible after recognizing an HAE attack for up to 24 months

KONFIDENT-S endpoints evaluated

- Time to beginning of symptom relief, defined as at least "a little better" at 2 consecutive time points within 12 hours of the first dose, measured by the Patient Global Impression of Change (PGI-C)
- Time to first reduction in severity, defined as a ≥1-level decrease on the Patient Global Impression-Severity (PGI-S) scale for ≥2 consecutive time points within 12 hours of the first dose of sebetralstat
- Time to complete attack resolution, defined as a PGI-S rating of "None" (ie, no symptoms) within 24 hours
- Safety, including treatment-emergent adverse events (TEAEs)

Figure 1. KONFIDENT-S OLE trial design



NCT05505916, EudraCT: 2021-001176-42.
[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.
HAE-C1NH, hereditary angioedema due to C1 inhibitor deficiency; OLE, open-label extension; PGI-C, Patient Global Impression of Change; PGI-S, Patient Global Impression of Severity.

Results

Participants and Attacks

Table 1. Baseline characteristics with ≥1 sebetralstat-treated attack[a]

	Overall n=69
Age, median (IQR), years	35.0 (22.0–48.0)
≥18 years of age, n (%)	57 (82.6)
Sex, female, n (%)	39 (56.5)
White race, n (%)	64 (92.8)
BMI, median (IQR), kg/m²	25.5 (22.4–30.8)
HAE-C1INH type, n (%)	
Type 1	66 (95.7)
Type 2	3 (4.3)
Treatment, n (%)	
On-demand only	60 (87.0)
LTP	9 (13.0)
Attacks treated during study, median (IQR)	10 (5–20)

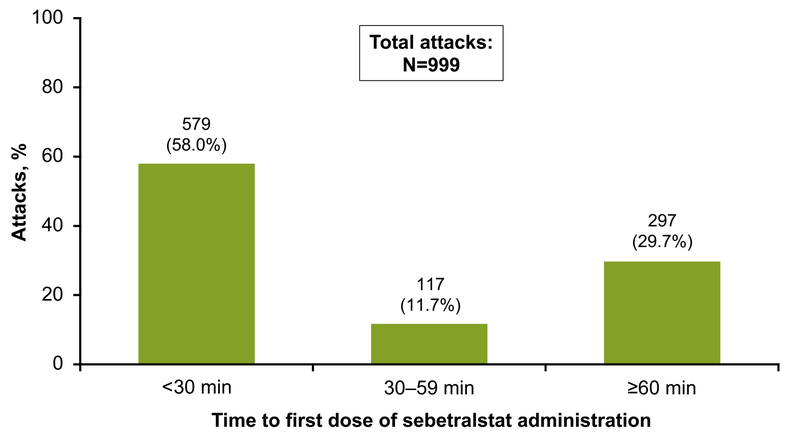
Data cutoff: September 14, 2024.
[a]Safety analysis population from 15 European countries.
BMI, body mass index; HAE-C1NH, hereditary angioedema due to C1 inhibitor deficiency; IQR, interquartile range; LTP, long-term prophylaxis.

Table 2. Attack characteristics

	Total attacks: N=999
Baseline severity (PGI-S),[a] n (%)	
Mild[b]	355 (35.5)
Moderate	395 (39.5)
Severe/very severe	229 (22.9)
Missing	20 (2.0)
Primary pooled attack location, n (%)	
Mucosal[c]	410 (41.0)
Involving the larynx	23 (2.3)
Subcutaneous only[c]	567 (56.8)
Missing	22 (2.2)

Data cutoff: September 14, 2024.
[a]PGI-S score was transformed into numeric values: 0=none, 1=mild, 2=moderate, 3=severe, 4=very severe. [b]"None" was reported for 12 attacks (1.2%). [c]Mucosal: attacks with primary location of "Abdomen" and/or "Larynx/Throat"; subcutaneous: other attacks not involving the mucosal locations. PGI-S, Patient Global Impression of Severity.

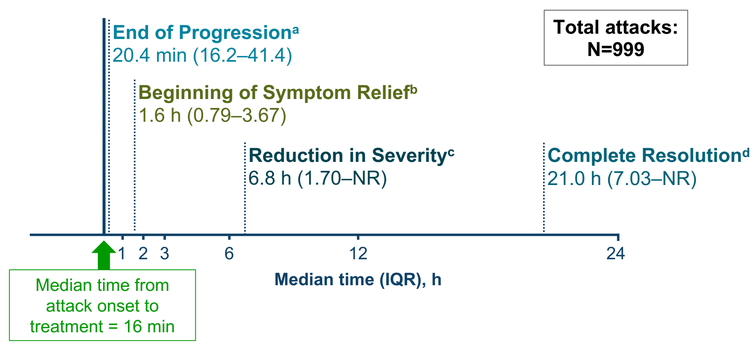
Figure 2. Time from attack onset to sebetralstat administration



Data cutoff: September 14, 2024.

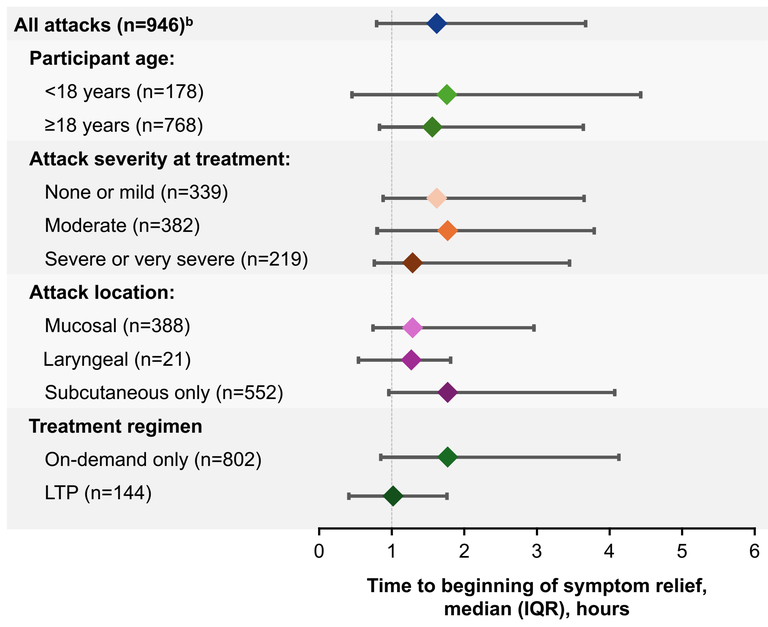
Efficacy

Figure 3. Effectiveness in sebetralstat-treated attacks



Data cutoff: September 14, 2024.
[a]End of progression was analyzed post hoc as the time when the worst HAE attack severity was recorded within 4 hours on the PGI-S scale for attacks treated with sebetralstat.
[b]Defined as a PGI-C rating of at least "A little better" for 2 consecutive time points (with missing data entries in between) within 12 hours of the first dose of sebetralstat (7-point scale: "Much worse," "Worse," "A little worse," "No change," "A little better," "Better," "Much better").
[c]Defined as a ≥1-level decrease on the PGI-S scale for ≥2 consecutive time points within 12 hours of the first dose of sebetralstat.
[d]Defined as a PGI-S rating of "None" (ie, no symptoms) within 24 hours.
HAE, hereditary angioedema; IQR, interquartile range; NR, not reached; PGI-C, Patient Global Impression of Change; PGI-S, Patient Global Impression of Severity.

Figure 4. Time to beginning of symptom relief in subgroups[a]



Data cutoff: September 14, 2024.
Diamonds are the medians met within time window. Error bars are IQR.
[a]Defined as a PGI-C rating of at least "A little better" for 2 consecutive time points within 12 hours of the first dose of sebetralstat. [b]Excluding attacks that lacked post-baseline assessments.
IQR, interquartile range; LTP, long-term prophylaxis; PGI-C, Patient Global Impression of Change.

Table 3. Sebetralstat administration and use of conventional treatment in KONFIDENT-S

	Total attacks: N=999
Attacks treated with a second dose within 12 hours of the first dose of sebetralstat, n (%)	174 (17.4)
Attacks reaching beginning of symptom relief within 12 hours before or without an additional dose[a], %	97.0
Attacks treated with conventional treatment within 12 hours of the first dose of sebetralstat, n (%)	60 (6.0)

Data cutoff: September 14, 2024.
[a]Among the 803 attacks that reached this endpoint (80.4%).

Safety

- 40 participants (58%) experienced any TEAE and 6 participants (8.7%) experienced a treatment-related TEAE (**Table 4**)
  - No grade ≥3 or serious TEAEs were considered treatment-related

Table 4. Safety

Participants experiencing TEAE, n (%)	Total n=69
Any TEAE	40 (58.0)
Treatment related[a]	6 (8.7)
Any TEAE within 3 days of sebetralstat administration	27 (39.1)
Any grade ≥3 TEAE	6 (8.7)
Treatment related	0
Any serious TEAE	6 (8.7)
Treatment related	0
Any TEAE leading to hospitalization	5 (7.2)
Any TEAE leading to study discontinuation	2 (2.9)[b]
Any TEAE leading to death	0

Data cutoff: September 14, 2024.
[a]Six patients reported treatment-related TEAEs, including headache (n=3), influenza-like illness (n=3), vomiting (n=3), skin burning sensation (n=2), myalgia (n=2), and tremor (n=1). [b]TEAEs leading to discontinuations included intracranial mass (n=1) and skin burning sensation (n=1).
TEAE, treatment-emergent adverse event.

Conclusions

- **In KONFIDENT-S, sebetralstat enabled early treatment of HAE attacks in European participants (median time, 16 minutes)**
- **Sebetralstat resulted in rapid end of attack progression, early symptom relief, reduction in attack severity, and attack resolution, consistent with data reported in the KONFIDENT trial**
- **Median time to beginning of symptom relief was consistent across all subgroups, including by age, attack severity at onset, attack location at onset, and LTP use**
- **Sebetralstat was well tolerated, and safety results were consistent with the phase 3 KONFIDENT trial[3]**

References
1. Sebetralstat (EKTERLY) prescribing information. KalVista Pharmaceuticals, Inc. 2025.
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3. Riedl MA et al. *New Engl J Med*. 2024;391(1):32-43.

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