Sebetralstat for On-demand Treatment of Hereditary Angioedema Attacks: US Subgroup Analysis From the Double-blind, Placebo-controlled Phase 3 KONFIDENT Trial

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Background

- Global treatment guidelines for patients with hereditary angioedema caused by deficiency or dysfunction of the C1 inhibitor protein (HAE-C1INH) recommend considering treatment for all attacks, treating attacks as early as possible, and always carrying a sufficient quantity of on-demand therapy to treat two attacks[1,2]
- All approved therapies for on-demand treatment of HAE-C1INH attacks must be administered parenterally and are associated with delays and/or withholding of treatment[2-5]
- Sebetralstat, a plasma kallikrein inhibitor, is the first orally administered therapy being evaluated in a phase 3 trial for the on-demand treatment of HAE-C1INH attacks across 20 countries, including the United States (US)

Objective

- To determine the efficacy and safety of sebetralstat compared with placebo as on-demand treatment in adults and adolescents with HAE-C1INH

Methods

Study design

- KONFIDENT (NCT05259917) was a phase 3, randomized, double-blind, placebo-controlled, three-way crossover trial[6]
- Adults and adolescents with a confirmed diagnosis of HAE-C1INH (type 1 or 2) and ≥2 documented attacks within 3 months were randomly assigned to one of six treatment sequences in which up to three eligible attacks were treated
- Patients self-administered a single dose of sebetralstat 300 mg, 600 mg, or placebo as early as possible after recognizing the start of an attack
  - If needed, an optional second administration of sebetralstat was permitted ≥3 hours after the first administration (as determined by the patient)
  - Severe laryngeal attacks were excluded and were treated with conventional therapy
- The primary endpoint was time to beginning of symptom relief, defined as a rating of at least "A Little Better" on the Patient Global Impression of Change (PGI-C) scale ≥2 time points in a row within 12 hours of the first dose of study drug
- Key secondary endpoints were tested hierarchically in the following order:
  - Time to reduction in attack severity, defined as a decrease in Patient Global Impression of Severity (PGI-S) rating for ≥2 time points in a row within 12 hours of the first dose of study drug
  - Time to complete attack resolution, defined as a PGI-S rating of "None" within 24 hours of the first dose of study drug
- Primary and key secondary endpoints were tested in the full analysis set (FAS) using a fixed sequence and were adjusted for multiplicity
- Analyses in the US subgroup of participants were not powered

Results

Patients and attacks

- A total of 136 patients recruited from 66 study sites across 20 countries were randomly assigned to one of six treatment sequences
  - A total of 34 patients from 24 study sites in the United States were randomized to a treatment sequence
- The FAS contained 110 patients (**Table 1**) who treated 264 attacks (**Table 2**)
  - A total of 34 US patients treated 78 attacks (29.5%)

Table 1. Patient Demographics

	All patients (N=110)	US patients (n=34)
Age, median, yrs (Q1, Q3)	39.5 (25.0, 49.0)	39.5 (28.0, 51.0)
Sex, female, n (%)	66 (60.0)	27 (79.4)
Race, n (%)		
White	92 (83.6)	31 (91.2)
Asian	10 (9.1)	2 (5.9)
Black or African American	1 (0.9)	1 (2.9)
Other	1 (0.9)	0
Not reported	6 (5.5)	0
BMI, median, kg/m^2 (Q1, Q3)	26.2 (22.8, 31.7)	29.3 (25.2, 35.4)
HAE-C1INH type, n (%)		
Type 1	101 (91.8)	28 (82.4)
Type 2	9 (8.2)	6 (17.6)
Current treatment regimen, n (%)		
On-demand only	86 (78.2)	18 (52.9)
LTP + on-demand	24 (21.8)	16 (47.1)

BMI, body mass index; HAE-C1INH, hereditary angioedema with C1 inhibitor deficiency; LTP, long-term prophylaxis; yrs, years.
Of the 24 patients receiving LTP, 10 (42%) received berotralstat, 8 (33%) received lanadelumab, and 7 (29%) received C1INH.
Of the 16 US patients receiving LTP, 5 (31%) received berotralstat, 7 (44%) received lanadelumab, and 5 (31%) received C1INH.

Table 2. Characteristics of Treated Attacks

	All attacks (N=264)	Attacks treated by US patients (n=78)
Pooled attack locations, n (%)[a]		
Mucosal[b]	120 (45.5)	43 (55.1)
Subcutaneous[c]	142 (53.8)	34 (43.6)
Baseline PGI-S category, n (%)[a]		
Mild[d]	115 (43.6)	36 (46.2)
Moderate	102 (38.6)	33 (42.3)
Severe or very severe	45 (17.0)	8 (10.3)
Time from onset of attack to first administration, median, min (Q1, Q3)	41 (6, 140)	38 (5, 124)
Attacks treated in <60 min, n (%)	147 (55.7)	44 (56.4)

min, minutes; PGI-S, Patient Global Impression of Severity.
[a]Baseline PGI-S score and baseline location were missing for 2 attacks (1 attack in a US patient).
[b]Affecting the abdomen or larynx/throat.
[c]Affecting the arms/hands, legs/feet, head/face/neck, torso, or genitals.
[d]Two attacks in the placebo group (1 from a US patient) had a baseline PGI-S category of "None."

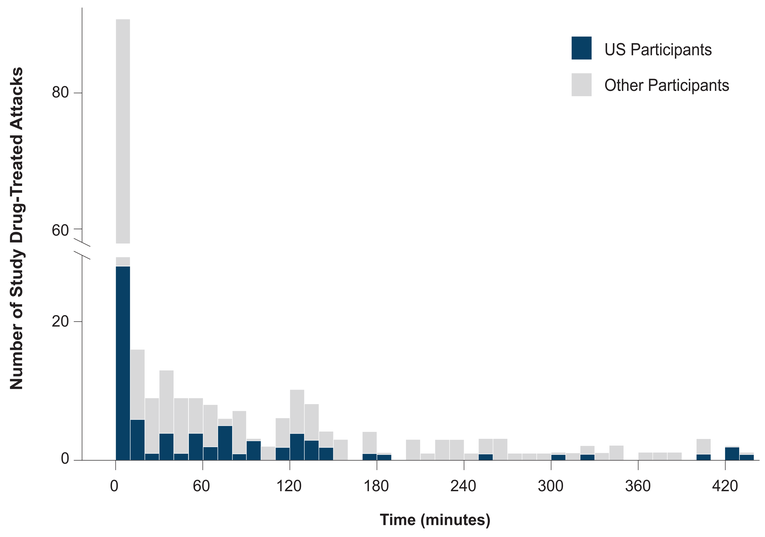
Efficacy

Table 3. Efficacy by Dosing Group

	Sebetralstat 300 mg	Sebetralstat 600 mg	Placebo
All attacks treated with study drug, n	**87**	**93**	**84**
Time to beginning of symptom relief			
P-value versus placebo	<0.0001	0.0013	--
Median time, hours (Q1, Q3)	1.61 (0.78, 7.04)	1.79 (1.02, 3.79)	6.72 (1.34, >12)
Attacks treated with study drug by US patients, n	**27**	**28**	**23**
Time to beginning of symptom relief			
Nominal *P* value versus placebo	0.0007	0.0242	--
Median time, hours (Q1, Q3)	1.28 (0.77, 3.12)	1.77 (1.31, 3.89)	6.23 (2.28, >12)

- The proportions of attacks treated with a second administration of study drug were 39.1% with sebetralstat 300 mg, 39.8% with sebetralstat 600 mg, and 56.0% with placebo
  - These proportions were 48.1% with sebetralstat 300 mg, 42.9% with sebetralstat 600 mg, and 47.8% with placebo in US patients
- Of attacks that reached beginning of symptom relief, the proportions that did so without a second dose or before a second dose was administered were 93.9% and 95.8% with sebetralstat 300 mg and 600 mg, respectively
  - These proportions were 100% with sebetralstat 300 mg and 95.2% with sebetralstat 600 mg in US patients

Figure 1. Time From Attack Recognition to Study Drug Administration



Safety

Table 4. Safety

	Sebetralstat 300 mg	Sebetralstat 600 mg	Placebo
All patients	**86**	**93**	**83**
Any TEAE	17 (19.8)	14 (15.1)	17 (20.5)
Treatment-related	2 (2.3)	3 (3.2)	4 (4.8)
Any serious TEAE	1 (1.2)	2 (2.2)	0
Treatment-related	0	0	0
Any severe TEAE	1 (1.2)	0	0
Treatment-related	0	0	0
US patients	**27**	**28**	**23**
Any TEAE	7 (25.7)	8 (28.6)	6 (26.1)
Treatment-related	2 (7.4)	1 (3.6)	1 (4.3)
Any serious TEAE	0	2 (7.1)	0
Treatment-related	0	0	0
Any severe TEAE	0	0	0
Treatment-related	0	0	0

TEAE, treatment-emergent adverse event.
Values are n (%) of patients.

- No TEAEs led to permanent discontinuation or death

Conclusions

- **The KONFIDENT trial met primary and key secondary endpoints; beginning of symptom relief, reduction in attack severity, and complete attack resolution were reached significantly faster with sebetralstat 300 mg and 600 mg than with placebo[6]**
  - **The efficacy of sebetralstat in US patients was consistent with the overall trial population**
  - **More than 93% of US participants that reached the primary endpoint did so without a second dose or before a second dose was administered**
- **Oral sebetralstat enabled patients to treat rapidly, in line with current international and US treatment guidelines**
- **Sebetralstat 300 mg and 600 mg were well-tolerated in KONFIDENT, and treatment-related adverse events, including those in the subset of US participants, were comparable with those in the placebo group**
- **The long-term safety and efficacy of sebetralstat is being studied in the KONFIDENT-S (NCT05505916) 2-year open-label extension trial including 20 US study sites**
- **In KONFIDENT, oral on-demand sebetralstat for HAE-C1INH attacks provided rapid symptom relief and facilitated early treatment**

References

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Presented at the Eastern Allergy Conference; May 30–June 2, 2024; Palm Beach, Florida