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Sebetralstat KONFIDENT Is the First Phase 3 On-demand HAE Trial to Include Japanese Sites

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Background

- People living with hereditary angioedema (HAE), a rare genetic disease most commonly caused by deficiency or dysfunction in the C1 inhibitor (C1INH) protein (HAE-C1INH), experience unpredictable, painful, and debilitating attacks of tissue swelling that can be life-threatening if the upper airways are affected[1-3]
  - The estimated minimal prevalence of HAE in Japan is 0.4 per 100,000 persons, but the true prevalence is assumed to be higher due to underdiagnosis and delayed detection of HAE[4-6]
- Per global treatment guidelines, it is recommended that all patients with HAE-C1INH consider on-demand treatment for all attacks, treat attacks as early as possible, and always carry 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 due to associated complexity[7-9]
  - In Japan, icatibant and plasma-derived C1INH are the only approved therapies for on-demand treatment of HAE-C1INH attacks[8,10]
- In a phase 2 trial, sebetralstat 600 mg increased the time to and decreased the use of conventional attack treatment versus placebo, as well as reduced time to beginning of symptom relief and time to attack resolution[11]
  - A phase 1 ethnobridging trial demonstrated comparable pharmacokinetic, pharmacodynamic, and safety profiles in healthy Japanese and White adults[12]
- Sebetralstat, a plasma kallikrein (PKa) inhibitor, is the first orally administered therapy being investigated in a phase 3 trial for the on-demand treatment of HAE-C1INH attacks across 20 countries, including Japan

Objective

- To determine the efficacy and safety of sebetralstat 300 mg or 600 mg compared with placebo as on-demand treatment in adults and adolescents with HAE-C1INH

Methods

Study Design

- KONFIDENT (NCT05259917) is a phase 3, randomized, double-blind, placebo-controlled, 3-way crossover trial[13]
- Adults and adolescents with a confirmed diagnosis of HAE-C1INH (type 1 or 2) and at least two documented HAE-C1INH attacks within 3 months were randomly assigned to one of six treatment sequences in which up to three eligible attacks were treated with sebetralstat 300 mg, 600 mg, or placebo (**Supplementary Figure 1**)
  - Patients must have had access to and the ability to use conventional on-demand treatment (eg, plasma-derived C1INH, icatibant)
  - Patients receiving long-term prophylaxis (LTP) must have been on a stable dose and regimen for ≥3 months immediately before and during the trial
- 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
  - A second dose of study drug was permitted ≥3 hours after the first dose, as determined by the patient
  - Attacks of any severity and in any location of the body were eligible for treatment
    - Only severe laryngeal attacks were excluded
- 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 for ≥2 time points in a row within 12 hours of the first dose of study drug (**Supplementary Figure 2**)
- 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 (**Supplementary Figure 2**)
  - 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 a fixed sequence and were adjusted for multiplicity

Results

Participants and Attacks

- A total of 136 participants recruited from 66 study sites across 20 countries were randomly assigned to one of six treatment sequences
  - Seven patients from four study sites in Japan were randomized
- The Full Analysis Set contained 110 patients who treated 264 attacks (87 treated with sebetralstat 300 mg, 93 treated with sebetralstat 600 mg, and 84 treated with placebo)
  - Seven Japanese patients treated 17 attacks (six treated with sebetralstat 300 mg, six treated with sebetralstat 600 mg, and five treated with placebo)

Table 1. Patient Demographics

	All patients (N=110)	Japanese patients (n=7)
Age, median, years (Q1, Q3)	39.5 (25.0, 49.0)	48.0 (35.0, 50.0)
Sex, female, n (%)	66 (60.0)	6 (85.7)
Race, n (%)		
White	92 (83.6)	0
Asian	10 (9.1)	7 (100.0)
Black or African American	1 (0.9)	0
Other	1 (0.9)	0
Not reported	6 (5.5)	0
Body mass index, median, kg/m^2 (Q1, Q3)	26.2 (22.8, 31.7)	23.6 (22.8, 34.6)
HAE-C1INH type, n (%)		
Type 1	101 (91.8)	7 (100.0)
Type 2	9 (8.2)	0
Time since HAE-C1INH diagnosis, median, years (Q1, Q3)	12 (7, 22)	10 (9, 19)
Current treatment regimen, n (%)		
On-demand only	86 (78.2)	3 (42.9)
LTP + on-demand	24 (21.8)	4 (57.1)

HAE-C1INH, hereditary angioedema with C1 inhibitor mutation; LTP, long-term prophylaxis.
Of the 24 patients receiving LTP, 11 (46%) received berotralstat, 8 (33%) received lanadelumab, and 5 (21%) received C1INH. All four (100%) Japanese patients receiving LTP were using berotralstat.

Table 2. Characteristics of Treated Attacks

	All attacks (N=264)	Attacks treated by Japanese patients (n=17)
Baseline attack locations, n (%)[a]		
Abdomen	114 (43.2)	5 (29.4)
Arms/hands	76 (28.8)	5 (29.4)
Legs/feet	62 (23.5)	3 (17.6)
Head/face/neck	29 (11.0)	2 (11.8)
Torso	15 (5.7)	3 (17.6)
Genitals	9 (3.4)	0
Larynx/throat	8 (3.0)	1 (5.9)
Baseline PGI-S category, n (%)[b]		
Mild	113 (42.8)	14 (82.4)
Moderate	102 (38.6)	3 (17.6)
Severe/very severe	45 (17.0)	0
Missing	2 (0.8)	0
Time from onset of attack to first administration, median, minutes (Q1, Q3)	41 (6, 140)	30 (4, 136)
Attacks treated in <60 minutes, n (%)	147 (55.7)	10 (58.8)

NA, not available; PGI-S, Patient Global Impression of Severity.
[a]One attack can be summarized in several attack locations.
[b]Baseline PGI-S score was "None" for two attacks and missing for two attacks.

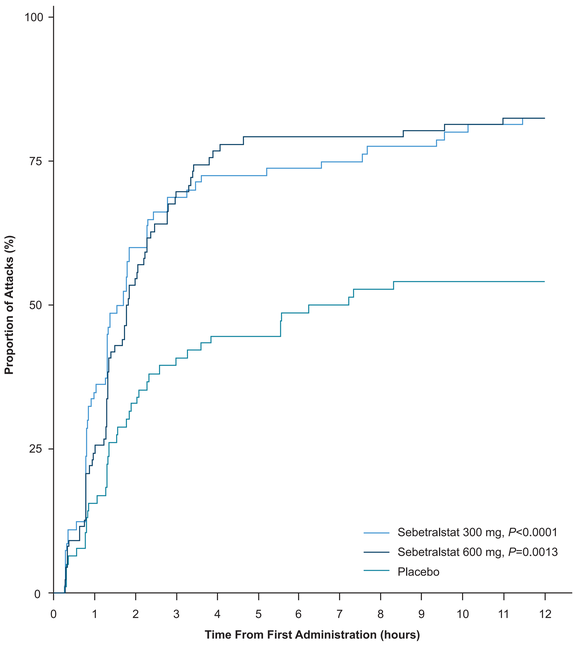
Efficacy

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 (primary)			
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)
Time to reduction in attack severity (key secondary)			
P-value versus placebo	0.0036	0.0032	—
Median time, hours (Q1, Q3)	9.27 (1.53, >12)	7.75 (2.19, >12)	>12 (6.23, >12)
Time to complete attack resolution (key secondary)			
P-value versus placebo	0.0022	<0.0001	—
Median time, hours (Q1, Q3)	>24 (8.58, >24)	24.00 (7.54, >24)	>24 (22.78, >24)

- Results in the subgroup of Japanese patients were generally consistent with those observed in the overall population
  - The median (Q1, Q3) time to beginning of symptom relief was 2.06 hours (0.91, 2.27) with sebetralstat 300 mg, 1.56 hours (1.21, 2.97) with sebestralstat 600 mg, and 7.22 hours (3.28, 8.30) with placebo
- The proportions of attacks treated with a second administration of study drug were 38.4% with sebetralstat 300 mg, 41.1% with sebetralstat 600 mg, and 55.4% with placebo
- 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 (see **Supplementary Material**)
- The proportions of attacks treated with conventional medication within 12 hours were 13.8% with sebetralstat 300 mg, 8.6% with sebetralstat 600 mg, and 25.0% with placebo

Figure 1. Primary Endpoint: Time to Beginning of Symptom Relief Within 12 Hours[14]



- Kaplan-Meier plots for time to reduction in attack severity and time to complete symptom relief (key secondary endpoints) are presented in **Supplementary Figure 4**

Safety

- Doses of sebetralstat 300 mg and 600 mg were well-tolerated, with a safety profile comparable to that of placebo (**Table 4** and **Supplementary Table 1**)

Table 4. Safety

	Sebetralstat 300 mg (n=87)	Sebetralstat 600 mg (n=93)	Placebo (n=84)
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[a]	1 (1.2)	2 (2.2)	0
Treatment-related	**0**	**0**	**0**
Any severe TEAE[b]	1 (1.2)	0	0
Treatment-related	**0**	**0**	**0**
Any TEAE leading to study discontinuation	0	0	0
Any TEAE leading to death	0	0	0

TEAE, Treatment-emergent adverse event.
Values are n (%) of patients.
[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 TEAE was defined as a qualitative assessment of an adverse event of grade 3 severity by the Investigator or as reported by the patient

- In the subgroup of Japanese patients, no TEAEs occurred with sebetralstat 300 mg or 600 mg; one TEAE of eczema occurred in one of five patients (20%) after treatment with placebo
  - No TEAEs were treatment-related, serious, or severe, and no TEAEs led to study discontinuation or death in Japanese patients

Conclusions

- **The KONFIDENT trial met primary and key secondary endpoints; beginning of symptom relief, reduction in attack severity, and complete attack resolution were significantly faster with sebetralstat 300 mg and 600 mg than with placebo**
  - **More than 90% of attacks that reached the primary endpoint did so without a second dose or before a second dose was administered**
- **Use of oral sebetralstat enabled patients to treat attacks rapidly, in line with current international and Japanese treatment guidelines**
- **Sebetralstat was well tolerated at both dose levels, and the number of treatment-related adverse events was comparable with that of placebo; there were no treatment-emergent adverse events among Japanese patients receiving sebetralstat**
- **The long-term safety and efficacy of sebetralstat is being studied in the KONFIDENT-S (NCT05505916; EudraCT 2021-001176-42) 2-year open-label extension trial including nine Japanese study sites**
- **In KONFIDENT, oral on-demand sebetralstat for HAE-C1INH attacks provided rapid symptom relief and facilitated early treatment[14]**

Contact information

Contact the author at dhonda@chiba-u.jp for questions or comments.

Please scan this QR code to view this poster and its supplementary information after the presentation.

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