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Substantial Reduction of Hereditary Angioedema Attack Symptom Burden in the Sebetralstat Phase 3 KONFIDENT Trial

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Background

- Early treatment has been shown to lead to a shorter attack duration and reduces the risk for progression[1-5]
- On-demand therapies require injections and are associated with delays, which may lead to progression and thereby increased symptom burden[3, 6-9]
- Sebetralstat, an investigational oral plasma kallikrein inhibitor, was studied in the phase 3 KONFIDENT trial (NCT05259917)[10,11]
  - Despite early treatment of most attacks (median time to treatment, 41 minutes [IQR, 6-140]), >50% of attacks progressed to a rating of "Moderate" to "Very Severe" on the Patient Global Impression of Severity (PGI-S) scale prior to treatment[11]

Objective

- This post hoc analysis evaluated the impact of sebetralstat on attacks that had progressed in severity prior to treatment

Methods

Trial Design

- The phase 3 KONFIDENT trial was a double-blind, randomized, placebo-controlled, 3-way crossover trial[11]
  - Adults and adolescents (≥12 years) with HAE-C1INH and ≥2 documented attacks within 3 months were randomly assigned to 1 of 6 treatment sequences in which 3 eligible attacks were treated with 1 to 2 doses of sebetralstat 300 mg, sebetralstat 600 mg, or placebo[6]
  - All attack locations and severity levels were included except for laryngeal attacks that were considered severe at onset
- PGI-S ratings from “None” to “Very Severe” were recorded at time of treatment and every 0.5 hours during the first 4 hours after first taking the trial agent, every hour from 5 to 12 hours, and every 2 hours from 14 to 24 hours

Statistical Analysis

- Time to substantial reduction of symptom burden within 12 hours was defined as time to a decrease in PGI-S rating to “Mild” for 2 consecutive time points within 12 hours for attacks that had reached the rating of “Moderate” to “Very Severe” prior to treatment (baseline)
  - “Moderate” or worse attacks at baseline were right-censored at 12 hours if they did not reach PGI-S rating of “Mild” or lower (2 time points in a row). Attacks were treated as right-censored at 0 hour if a time-to-event result could not be derived
  - Conventional treatment administration was censored to the end of analysis window

Results

Participants and Attacks

Table 1. Demographics and Disease Characteristics

	Participants with at least 1 attack with PGI-S "Moderate" or worse at baseline n=84	All participants N=110
Age, median, years (IQR)	40.0 (25.5-49.0)	39.5 (25.0-49.0)
Sex, female, n (%)	48 (57.1)	66 (60.0)
BMI, median, kg/m^2 (IQR)	26.51 (22.96-31.83)	26.24 (22.85-31.65)
Race, n (%)		
White	72 (85.7)	92 (83.6)
Asian	5 (6.0)	10 (9.1)
Black or African American	1 (1.2)	1 (0.9)
Other	1 (1.2)	1 (0.9)
Not reported	5 (6.0)	6 (5.5)
HAE-C1INH type, n (%)		
Type 1	76 (90.5)	101 (91.8)
Type 2	8 (9.5)	9 (8.2)
Time since HAE-C1INH diagnosis, median, years (IQR)	12 (6.5-22)	12 (7-22)
Current treatment regimen, n (%)		
On-demand only	69 (82.1)	86 (78.2)
On-demand + LTP[a]	15 (17.9)	24 (21.8)

BMI, body mass index; HAE-C1INH, hereditary angioedema due to deficiency or dysfunction of the C1 inhibitor; IQR, interquartile range; LTP, long-term prophylaxis.
[a]Of the 24 patients receiving LTP, 10 (42%) received berotralstat, 8 (33%) received lanadelumab, and 7 (29%) received C1INH.

Table 2. Characteristics of Treated Attacks at Baseline

	Attacks rated “Moderate” or worse at baseline			All attacks treated N=264
	Sebetralstat 300 mg n=49	Sebetralstat 600 mg n=52	Placebo n=46	
Baseline PGI-S category, n (%)[a,b]				
Mild	N/A	N/A	N/A	113 (42.8)
Moderate	35 (71.4)	34 (65.4)	33 (71.7)	102 (38.6)
Severe/very severe	14 (28.6)	18 (34.6)	13 (28.3)	45 (17.0)
Baseline primary pooled attack location, n (%)				
Mucosal (abdomen, larynx/throat)	24 (49.0)	25 (48.1)	24 (52.2)	73 (49.7)
Larynx/throat	2 (4.1)	1 (1.9)	2 (4.3)	5 (3.4)
Subcutaneous (all others)	25 (51.0)	27 (51.9)	22 (47.8)	74 (50.3)
Time from onset of attack to first administration, minutes				
Median	35	79	73	41
IQR	7-201	6-180	6-223	6-140

IQR, interquartile range; n, number of attacks; N/A, not applicable; PGI-S, Patient Global Impression of Severity.
[a]Baseline PGI-S rating and baseline attack location are missing for 2 attacks in the sebetralstat 300-mg group.
[b]Two attacks in the placebo group had a baseline PGI-S category of “None”.

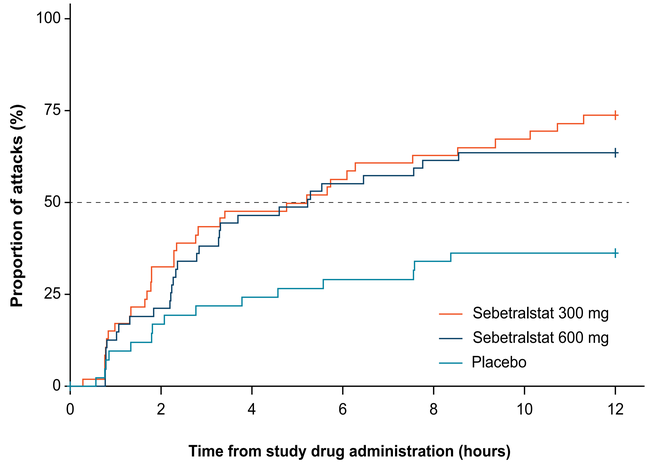
Time to Substantial Reduction of Symptom Burden within 12 hours

Table 3. Time to PGI-S Rating of “Mild” for Attacks Rated “Moderate” or Worse at Baseline

	Sebetralstat 300 mg n=49	Sebetralstat 600 mg n=52	Placebo n=46
Number of patients Events[a]	34 (69.4)	30 (57.7)	15 (32.6)
Time to PGI-S rating of “Mild” for attacks rated “Moderate” or worse at baseline,[b] hours			
Nominal *P*-Value	0.002	0.034	-
Median	5.0	5.2	>12
IQR	1.7->12	2.2->12	4.6->12

IQR, interquartile range; n, number of attacks; PGI-S, Patient Global Impression of Severity.
[a]“Moderate” or worse attacks at baseline, which achieved PGI-S rating of “Mild” within 12 hours.
[b]Kaplan-Meier estimates for time to PGI-S of “Mild” or lower within 12 hours.

Figure 1. Time to PGI-S Rating of “Mild” for Attacks Rated “Moderate” or Worse at Baseline



PGI-S, Patient Global Impression of Severity.

- The proportion of participants who experienced substantial reduction of symptom burden within 24 hours was 75.5% with sebetralstat 300 mg, 67.3% with sebetralstat 600 mg, and 54.3% with placebo

Conclusions

- **Attacks that progressed in severity were associated with a longer time to treatment**
- **The time to substantial reduction of symptom burden in attacks that had progressed to “Moderate” or worse by the time the attack was treated was significantly faster with sebetralstat 300 mg or 600 mg compared with placebo**
- **Median time to substantial reduction in symptom burden was approximately 5 hours for sebetralstat-treated attacks and >12 hours for attacks treated with placebo**
- **Approximately 70% of participants receiving sebetralstat experienced substantial reduction of symptom burden within 24 hours versus 54% with placebo**

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