Impact of Oral Sebetralstat on Anxiety Associated with Hereditary Angioedema Attacks in the Phase 3 KONFIDENT Trial

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Background

- People living with hereditary angioedema with C1-inhibitor deficiency (HAE-C1INH) experience unpredictable, painful, and potentially life-threatening attacks that are associated with substantial psychological burden[1-3]
- All currently approved on-demand treatments must be administered parenterally[4-7]
  - Due in part to anxiety associated with parenteral treatments, including injection-site reactions or fear of needles, people living with HAE-C1INH reported delaying or withholding their on-demand treatment[5,8]
- Sebetralstat, an investigational oral plasma kallikrein inhibitor for on-demand treatment of HAE attacks, met primary and key secondary endpoints in the phase 3, randomised, double-blind, placebo controlled KONFIDENT (NCT05259917) trial and was well-tolerated[9]

Objective

- This analysis assessed whether orally-administered sebetralstat could reduce anxiety due to HAE attacks as compared to placebo

Methods

Trial Design

- In KONFIDENT, participants with HAE-C1INH (≥12 years old) were randomised to 1 of 6 sequences to treat ≤3 attacks with oral sebetralstat 300 mg, 600 mg, or placebo
  - Participants reported the baseline attack severity at attack onset using the Patient Global Impression of Severity (PGI-S) scale, ranging from "None" to "Very Severe"
- Participants completed a Modified Generalized Anxiety Numeric Rating Scale (GA-NRS; "How anxious do you feel right now?") from 0 (not at all anxious) to 10 (extremely anxious) at attack onset and for 24 hours after to record levels of anxiety (**Figure 1**)

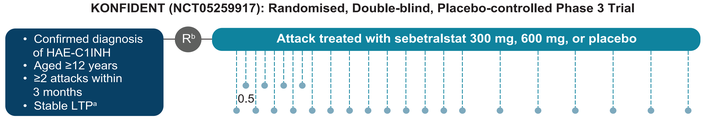
Figure 1. GA-NRS Scale

Prespecified Exploratory Endpoints

- Cumulative GA-NRS score, calculated as the area under the curve over 12 hours (AUC_{0-12}) or 24 hours (AUC_{0-24}) from administration
- Least squares mean change from baseline at 4 hours post-baseline and 12 hours post-baseline (**Figure 2**)
- Time to reductions of ≥2 points in GA-NRS score with a baseline GA-NRS score of ≥2

Figure 2. Anxiety Assessments

KONFIDENT (NCT05259917): Randomised, Double-blind, Placebo-controlled Phase 3 Trial



HAE-C1INH, hereditary angioedema due to C1 inhibitor deficiency; LTP, long-term prophylaxis; R, randomisation.
[a]Participants receiving LTP were required to be on a stable dose for ≥3 months prior to screening.
[b]Participants were randomised 1:1:1:1:1:1 to a treatment sequence using a permuted-block method, stratified by the use of LTP at enrolment.

Statistical Considerations

- Outcomes were assessed in all attacks and attacks rated moderately-to-extremely anxious (baseline GA-NRS score of 4-10)
- Pearson correlation was used to determine the coefficients between GA-NRS rating at baseline and baseline demographics and attack characteristics
- Cohen's kappa analysis was used to determine the agreement between time to ≥2-point reduction in GA-NRS rating and time to beginning of symptom relief

Results

Table 1. Participant Demographics and Disease Characteristics

	All participants[a] N=110
Age, median, years (IQR)	39.5 (25.0-49.0)
Sex, female, n (%)	66 (60.0)
Race, n (%)	
White	92 (83.6)
Asian	10 (9.1)
Black or African American	1 (0.9)
Other or not reported	7 (6.4)
Time since HAE diagnosis, median, years (IQR)	12 (7-22)
Medical history of anxiety, n (%)	8 (7.3)
Current treatment regimen, n (%)	
On-demand only	86 (78.2)
On-demand + LTP[b]	24 (21.8)

HAE, hereditary angioedema; IQR, interquartile range; LTP, long-term prophylaxis.
[a]Characteristics are reported for participants who experienced ≥1 treated attack.
[b]Of the 24 participants receiving LTP, 10 (42%) received berotralstat, 8 (33%) received lanadelumab, and 7 (29%) received C1INH.

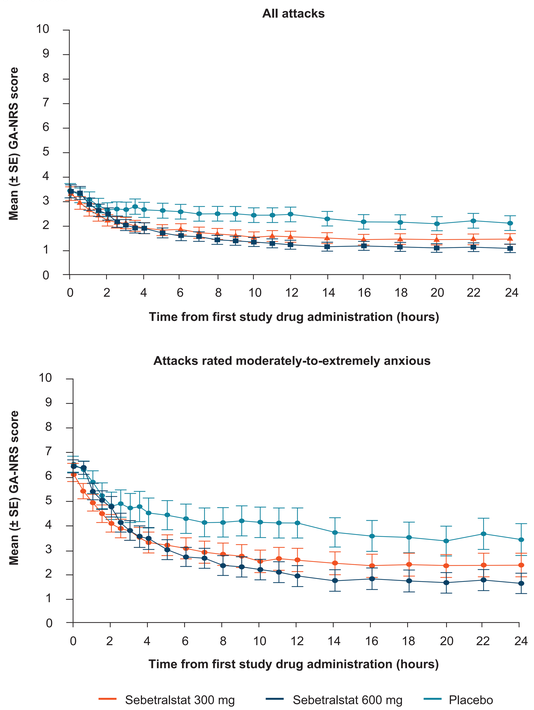
Table 2. Attack Characteristics

	All attacks N=264	Attacks rated moderately-to-extremely anxious n=115 (44%)
Baseline PGI-S category, n (%)[a,b]		
Mild	113 (42.8)	37 (32.2)
Moderate	102 (38.6)	47 (40.9)
Severe/very severe	45 (17.0)	30 (26.1)
Baseline pooled attack location, n (%)[a,c,d]		
Mucosal	120 (45.5)	61 (53.0)
Larynx/throat	8 (3.0)	4 (3.5)
Subcutaneous	142 (53.8)	86 (74.8)
Time from onset of attack to first administration, median, minutes (IQR)	41 (6-140)	45 (6-155)
Baseline GA-NRS category, n (%)[e]		
Not at all anxious (0)	53 (20.1)	N/A
Mildly anxious (1-3)	93 (35.2)	N/A
Moderately anxious (4-6)	65 (24.6)	65 (56.5)
Extremely anxious (7-10)	50 (18.9)	50 (43.5)

GA-NRS, Generalized Anxiety Numeric Rating Scale; IQR, interquartile range; N/A, not applicable; PGI-S, Patient Global Impression of Severity.
[a]Baseline PGI-S rating and baseline location are missing for 2 attacks in the sebetralstat 300-mg group.
[b]2 attacks in the placebo group had a baseline PGI-S category of "None," 1 of these attacks was in the moderate-to-severe anxiety subgroup.
[c]Among mucosal attacks, 8 involved the larynx: 2 attacks in the sebetralstat 300-mg group, 2 attacks in the sebetralstat 600-mg group, and 4 attacks in the placebo group.
[d]Participants with multiple attack locations are counted once in each reported location.
[e]Baseline GA-NRS score was missing for 3 (1.1%) attacks.

- 115 (44%) attacks were rated moderately-to-extremely anxious
  - 39 of these attacks were treated with sebetralstat 300 mg, 40 were treated with sebetralstat 600 mg, and 36 were treated with placebo
- Among baseline variables, severity of the attack (P=0.0030 for moderate and P<0.0001 for severe/very severe versus none/mild), time since HAE diagnosis (P=0.0014 for shorter versus longer time), and sex (P=0.0.0034 for female versus male) were correlated with baseline anxiety

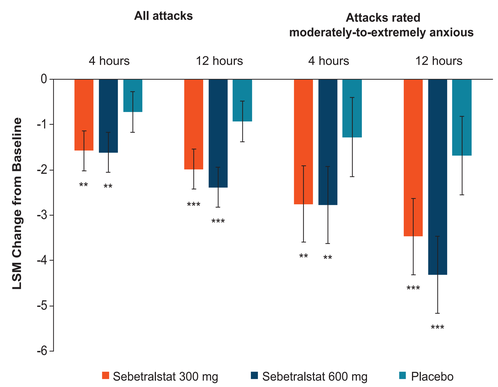
Figure 3. Changes in Anxiety over Time with Sebetralstat 300 mg, Sebetralstat 600 mg, or Placebo



GA-NRS, Generalized Anxiety Numeric Rating Scale; SE, standard error.

- AUC_{0-12} and AUC_{0-24} were significantly reduced with either dose of sebetralstat compared with placebo (**Figure 3**)

Figure 4. Least Squares Mean Change from Baseline in GA-NRS by Treatment



*P<0.05, **P<0.01, ***P<0.001
LSM, least squares mean

Correlation of Reduced Anxiety with Time to Beginning of Symptom Relief

- Participants who had attacks with an earlier time to beginning of symptom relief (defined as a Patient Global Impression of Change rating of "A Little Better" for 2 consecutive time points) reached larger anxiety reductions (defined as a GA-NRS reduction of ≥2 points) sooner than those with a later time to beginning of symptom relief
  - Cohen's kappa was 0.47 (moderate correlation)

Conclusions

- **In the phase 3 KONFIDENT trial, >40% of participants rated their anxiety as moderate to extreme at the time of treatment**
- **Greater baseline anxiety was most associated with greater attack severity**
- **Sebetralstat significantly reduced anxiety compared with placebo, especially in attacks rated moderately-to-extremely anxious**
- **Earlier times to beginning of symptom relief were associated with greater reductions in anxiety**

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Disclosures

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Please scan the QR code to view this poster after the presentation.

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