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Correlation of Time to Treatment with Attack Duration in the Sebetralstat KONFIDENT Phase 3 Trial

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Background

- International treatment guidelines recommend that people living with hereditary angioedema (HAE) treat attacks early after onset,[1,2] because previous trials evaluating on-demand treatments in HAE demonstrated that early treatment was associated with reduced attack duration[3,4]
- Despite these data, delays are common due to challenges associated with parenterally administered on-demand treatments (eg, anxiety surrounding injections, transport/portability of treatment, disruption of important activities, and fear of injection site reactions)
  - In a recently published survey, the average time to treatment in people living with HAE was 2.4 hours[5]
- Sebetralstat, an oral plasma kallikrein (PKa) inhibitor, provided significantly faster times to beginning of symptom relief, reduction in attack severity, and complete attack resolution compared with placebo in the phase 3 KONFIDENT trial[6]

Objective

- The objective of this analysis was to assess the relationship between the time from attack onset to sebetralstat administration and the time to complete attack resolution in KONFIDENT

Methods

Participants

- The phase 3 KONFIDENT trial (NCT05259917) was a double-blind, randomized, placebo-controlled, 3-way crossover trial
  - Adults and adolescents 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 1-2 doses of sebetralstat 300 mg, sebetralstat 600 mg, or placebo
  - Patients were instructed to treat their attacks as early as possible
- For this analysis, attacks treated with sebetralstat 300 mg or 600 mg were grouped into those that received treatment "earlier" (first quartile of time to treatment) versus "later" (fourth quartile of time to treatment)

Assessments

- Patient Global Impression of Severity, ranging in ratings from "None" to "Very Severe," was recorded at attack onset 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
  - Complete attack resolution was defined as a rating of "None" on the PGI-S scale within 24 hours after the first administration of treatment

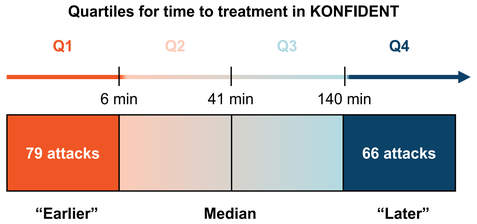
Statistical Analysis

- The relationship between time of attack onset to treatment and time from treatment to complete attack resolution was evaluated in sebetralstat-treated attacks using Cox proportional hazards models adjusted for sequence, period, and baseline attack severity

Results

Time to Treatment Administration

Figure 1. Time from Attack Onset to Treatment in KONFIDENT



Q1, first quartile; Q2, second quartile; Q3, third quartile, Q4, fourth quartile.

Data shown is for all attacks treated in KONFIDENT (N=264). All attack locations and severities were included in KONFIDENT except for laryngeal attacks that were considered severe at baseline.

Participants and Attacks

Table 1. Demographics and Disease Characteristics of Participants Treating Attacks with Sebetralstat Earlier and Later

	"Earlier"[a] n=39	"Later"[a] n=29
Age, median, years (IQR)	35 (23-48)	35 (21-49)
Sex, female, n (%)	26 (66.7)	16 (55.2)
BMI, median, kg/m^2 (IQR)	27.7 (23.68-34.58)	26.8 (23.05-31.65)
Race, n (%)		
White	32 (82.1)	23 (79.3)
Asian	5 (12.8)	3 (10.3)
Black or African American	0	1 (3.4)
Other or not reported	2 (5.1)	2 (6.9)
HAE-C1INH type, n (%)		
Type 1	36 (92.3)	27 (93.1)
Type 2	3 (7.7)	2 (6.9)
Time since HAE-C1INH diagnosis, median, years (IQR)	12.0 (7.0-24.0)	12.1 (6.2-18.0)
Current treatment regimen, n (%)		
On-demand only	30 (76.9)	25 (86.2)
On-demand + LTP	9 (23.1)	4 (13.8)

BMI, body mass index; HAE-C1INH, hereditary angioedema due to deficiency or dysfunction of C1 inhibitor; IQR, interquartile range; LTP, long-term prophylaxis.

[a]Due to the crossover design of the study, participants may be represented in both categories for different attacks.

Table 2. Characteristics of Sebetralstat-treated Attacks

	"Earlier" n=55	"Later" n=44
Baseline PGI-S category, n (%)[a,b]		
Mild	28 (50.9)	11 (25.0)
Moderate	15 (27.3)	25 (56.8)
Severe/very severe	11 (20.0)[c]	8 (18.2)
Baseline pooled attack location, n (%)[a,c,d]		
Mucosal	23 (41.8)	17 (38.6)
Larynx/throat	2 (3.6)	2 (4.5)
Subcutaneous	43 (78.2)	35 (79.5)

PGI-S, Patient Global Impression of Severity.

[a]Participants who had multiple attack locations were counted once in each reported location.

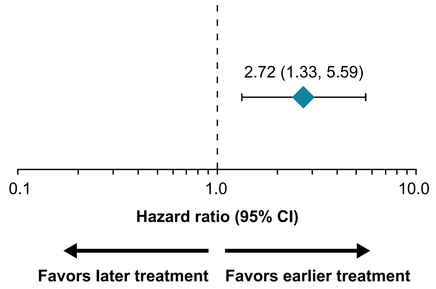
[b]None, n (%) = 0 earlier, 1 (1.3) later; Missing, n (%) = 1 (1.8) earlier, 0 later.

[c]All attack locations and severities were included in KONFIDENT except for laryngeal attacks that were considered severe at baseline.

[d]Missing, n (%) = 1 (1.8) earlier, 0 later.

- The largest proportion of sebetralstat-treated attacks treated "earlier" were mild at baseline, whereas the largest proportion of attacks treated "later" were moderate at baseline (**Table 2**)

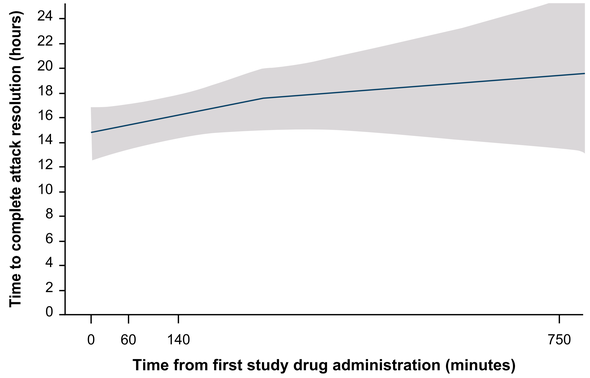
Figure 2. Probability for Faster Complete Attack Resolution



h, hours; HR, Hazard ratio; IQR, interquartile range.

- The probability for shorter attack duration was higher when attacks were treated earlier versus later in KONFIDENT (**Figure 2**)
- When modeled as a continuous variable, the relationship between time to treatment and time to complete attack resolution was 0.88 (95% CI, 0.79-0.97)

Figure 3. LOESS Regression Curve Fitting Time to Complete Attack Resolution within 24 hours Versus Time to Treatment



Conclusions

- **In KONFIDENT, attacks that were treated earlier were more likely to be mild than attacks treated later**
- **Complete attack resolution was reached faster (HR: 2.72 [1.33, 5.59]) in attacks that were treated "earlier" with sebetralstat compared with those that were treated "later" (at a time similar to parenteral on-demand treatments)**
- **When modeled as a continuous variable, the relationship between time to treatment and time to complete attack resolution was 0.88 (95% CI, 0.79-0.97)**

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

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