Effectiveness of Sebetralstat for Severe or Very Severe Hereditary Angioedema Attacks in KONFIDENT-S

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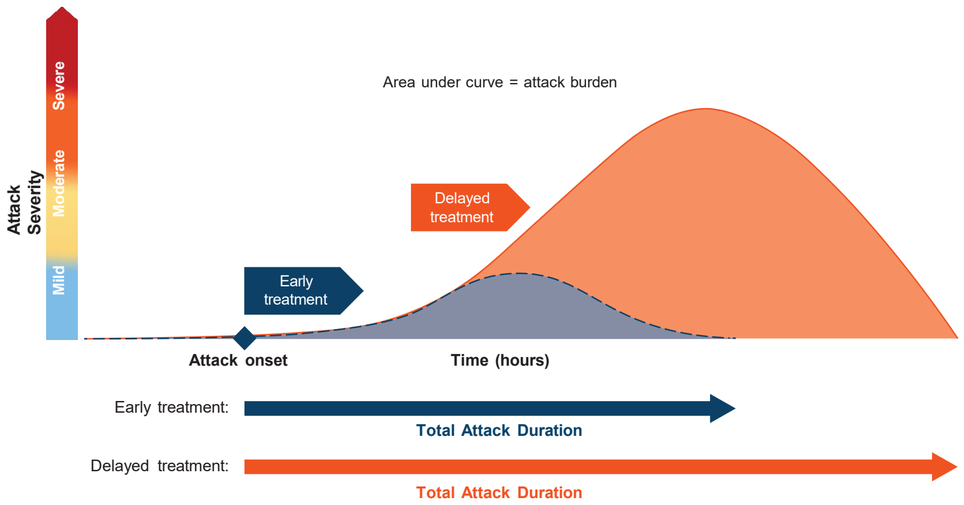
Background

- Early treatment of hereditary angioedema (HAE) has been demonstrated to arrest progression of swelling (reducing severity and morbidity), limit potential spread from the initial site, shorten the total attack duration as well as reduce attack burden, and reduce disruption to daily activities (**Figure 1**)[1–4]
- In a recent survey of people living with HAE in the US, the median time to treatment administration was reported as 3.6 hours[5]; however, 97% of respondents agreed it was important to recover quickly from an HAE attack[6]
- Sebetralstat, an investigational oral plasma kallikrein inhibitor, is being evaluated as an on-demand treatment for HAE due to C1-inhibitor deficiency (HAE-C1INH) attacks in the ongoing, 2-year, multicenter, KONFIDENT-S open-label extension study (NCT05505916)

Figure 1. Hereditary Angioedema Attack Progression



Objective

- The objective of this post hoc interim analysis was to evaluate the effectiveness of sebetralstat in the subset of attacks for which treatment administration was delayed (≥1 hour after attack onset) and had progressed to severe or very severe

Methods

Study Design

- Eligible participants were adults and adolescents ≥12 years of age with HAE-C1INH and at least 2 documented attacks within 3 months before enrollment or had completed the phase 3 KONFIDENT trial
  - Participants receiving long-term prophylaxis were required to be on a stable dose and regimen for ≥3 months immediately before and during the study
- Participants were instructed to self-administer sebetralstat 600 mg (2 × 300 mg tablets) as early as possible after attack onset, regardless of severity or anatomical location
  - If warranted, an optional second administration of sebetralstat was permitted ≥3 hours after the first administration (as determined by the participant)
- Effectiveness endpoints were as follows:
  - Time to beginning of symptom relief (Patient Global Impression of Change [PGI-C] rating of at least “A Little Better” at ≥2 consecutive time points) within 12 hours
  - Time to reduction in severity (≥1-level decrease on the Patient Global Impression of Severity [PGI-S] scale at ≥2 consecutive time points) within 12 hours
  - Time to complete attack resolution (PGI-S rating of “None”) within 24 hours
  - Time to substantial reduction of symptom burden (PGI-S rating of “Mild” for ≥2 consecutive time points) within 24 hours
- Conventional treatment administration was censored at the end of the analysis window

Results

Participants and Attacks

- From October 21, 2022 to September 14, 2024 (data cutoff), 30 participants treated 76 attacks rated severe to very severe with sebetralstat 600 mg ≥1 hour after attack onset (**Table 1, Table 2**)

Table 1. Participant Demographics

	Participants treating attacks rated severe to very severe (n=30)
Age, median mean (range), years	31.1 (12 to 64)
Age group, n (%)	
≥12 to <18 years	7 (23.3)
≥18 years	23 (76.7)
Sex, female, n (%)	20 (66.7)
Race, n (%)	
White	22 (73.3)
Asian	2 (6.7)
Other or multiple	3 (10.0)
Not reported	3 (10.0)
BMI, mean (range), kg/m²	27.0 (16.7 to 39.8)
HAE-C1INH type, n (%)	
Type 1	29 (96.7)
Type 2	1 (3.3)
Treatment paradigm, n (%)	
LTP + on-demand	5 (16.7)
On-demand only	25 (83.3)

BMI, body-mass index; HAE-C1INH, hereditary angioedema due to C1-inhibitor deficiency; LTP, long-term prophylaxis; n, number of participants.

Table 2. Baseline Attack Characteristics

	Attacks rated severe to very severe (n=76)
Baseline PGI-S category, n (%)	
Severe	70 (92.1)
Very severe	6 (7.9)
Baseline attack locations, n (%)[a]	
Mucosal[b]	37 (48.7)
Involving the larynx/throat	1 (1.3)
Subcutaneous[b]	39 (51.3)
Time from attack onset to treatment administration, median (IQR), minutes	129.5 (95.5 to 241.5)

IQR, interquartile range; n, number of attacks; PGI-S, Patient Global Impression of Severity.
[a]Participants with multiple attack locations were counted once in each reported location.
[b]Mucosal attacks include attacks with primary location of ‘Abdomen’ and/or ‘Larynx/Throat’. Subcutaneous attacks include other attacks not involving the mucosal locations.

Interim Effectiveness

Table 3. Interim Effectiveness in Attacks Treated with Sebetralstat 600 mg Rated Severe to Very Severe

Effectiveness Endpoint	Attacks rated severe to very severe (n=76)
Time to beginning of symptom relief[a] Median (IQR), hours	1.36 (0.76 to 3.97)
Time to reduction in attack severity[b] Median (IQR), hours	1.77 (0.76 to 3.84)
Time to complete attack resolution[c] Median (IQR), hours	>24 (11.08 to >24)
Time to substantial reduction in symptom burden[d] Median (IQR), hours	9.15 (2.54 to >24)

IQR, interquartile range; n, number of attacks; PGI-C, Patient Global Impression of Change; PGI-S, Patient Global Impression of Severity.
[a]Defined as a PGI-C rating of at least “A Little Better” at ≥2 consecutive time points within 12 hours.
[b]Defined as a ≥1-level decrease on the PGI-S scale at ≥2 consecutive time points within 12 hours.
[c]Defined as a PGI-S rating of “None” within 24 hours.
[d]Defined as a PGI-S rating of “Mild” or lower for ≥2 consecutive time points within 24 hours.

- Overall, 63.4% of attacks rated severe to very severe achieved a substantial reduction of symptom burden within 24 hours
- In 23 of 76 attacks (30.3%) rated severe to very severe, a second dose of sebetralstat was administered within 12 hours (**Table 3**)
  - 56 attacks (73.7%) rated severe to very severe reached beginning of symptom relief within 12 hours; of those, all of which achieved this endpoint before or without a second dose of sebetralstat
- Conventional on-demand treatment was administered within 12 hours for 9 of 76 attacks (11.8%) rated severe to very severe

Conclusions

- **Although treatment guidelines recommend early treatment to minimize HAE attack progression, a subset of attacks in KONFIDENT-S treated ≥1 hour had progressed to severe or very severe**
- **In these severe or very severe attacks, sebetralstat demonstrated early symptom relief as well as a rapid reduction in attack severity and symptom burden**

References

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