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On-demand Treatment Patterns of Hereditary Angioedema Attacks with Sebetralstat in the KONFIDENT-S Study

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Background

- International treatment guidelines recommend that all hereditary angioedema (HAE) attacks, regardless of severity or location, are considered for treatment with on-demand therapy[1,2]
- People living with HAE who delay or withhold on-demand treatment report increased morbidity and diminished quality of life[3,4]
- In prospective observational real-world studies, only 50% to 79% of HAE attacks were treated when the only treatment options that were available required subcutaneous or intravenous injection[5-7]
  - Administration by injection can introduce significant barriers (eg, storing/carrying injection-related paraphernalia, potential pain and injection site reactions, finding a discreet and hygienic location) that result in delay or withholding of treatment[8-11]
- Sebetralstat, an oral plasma kallikrein inhibitor, has recently been approved for on-demand treatment of HAE attacks in patients ≥12 years old in the US, Europe, Japan and other countries[12-15]

Objective

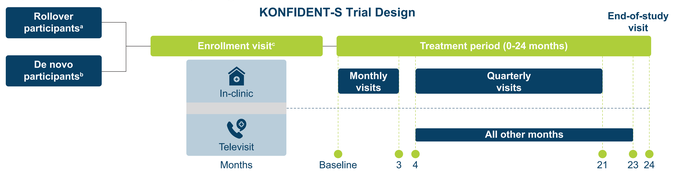
- This analysis evaluated treatment patterns among participants experiencing HAE attacks in the open-label KONFIDENT-S study

Methods

KONFIDENT-S Study Design

- The ongoing, open-label extension KONFIDENT-S study[16] (NCT05505916, EudraCT: 2021-001176-42; **Figure 1**) enrolled adults and adolescents (aged ≥12 years) with a confirmed diagnosis of type 1 or type 2 hereditary angioedema due to C1 inhibitor deficiency (HAE-C1INH)
  - Participants must have either completed the KONFIDENT trial (rollover) or have experienced ≥2 documented attacks within 3 months (de novo)
  - Patients receiving long-term prophylaxis (LTP) must have been on a stable dose and regimen for ≥3 months immediately before and during the study

Figure 1. KONFIDENT-S Study Design



[a]Completed the phase 3 KONFIDENT trial.
[b]All other participants, including those who participated in the phase 2 trial.
[c]For de novo participants, the enrollment visit is a screening visit.

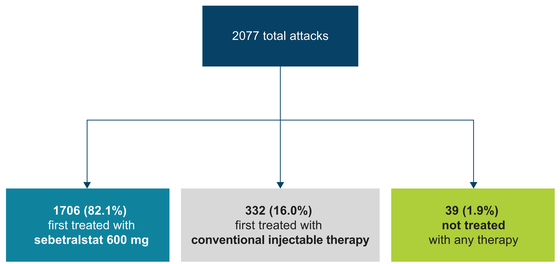
Study Treatment

- Participants were instructed to self-administer a single 600-mg dose of sebetralstat as early as possible for each attack
  - All attack severities and locations were eligible
  - No attack qualification by investigators was required
  - Participants were provided portable wallets of blistered tablets
- If warranted, a second administration of sebetralstat was permitted ≥3 hours after the first administration
- Conventional injectable on-demand treatment could be used after sebetralstat administration if symptoms were deemed severe enough by the participant
- If preferred by the participant, HAE attacks in KONFIDENT-S could be treated with conventional injectable on-demand treatment instead of with sebetralstat

Results

- As of September 14, 2024, participants reported experiencing 2077 attacks of which 98.1% were treated
  - In total, 1706 (82.1%) attacks were treated with sebetralstat and 332 (16.0%) were treated with conventional injectable on-demand therapy (**Figure 2**)
  - Untreated attacks were slightly more likely to affect subcutaneous tissues (vs. abdominal; OR, 1.24) or to occur in participants initially using on-demand treatment only (vs. participants receiving LTP; OR, 1.25)

Figure 2. Proportion of HAE Attacks Treated in KONFIDENT-S



Data cutoff date: September 14, 2024.

- Sebetralstat treatment was preferred across patient subpopulations and types of attacks (**Tables 1-2**)

Table 1. Treatment Pattern by Population

Characteristic	Participants who treated ≥1 attack with sebetralstat N = 134	Participants who treated ≥1 attack with conventional injectable treatment n = 72	Participants with ≥1 untreated attack n = 19
By sex			
Female	87 (64.9)	51 (70.8)	11 (57.9)
Male	47 (35.1)	21 (29.2)	8 (42.1)
By age group			
Adolescents (12 to <18 years)	23 (17.2)	8 (11.1)	2 (10.5)
Adults (≥18 years)	111 (82.8)	64 (88.9)	17 (89.5)
By treatment paradigm			
On-demand only	99 (73.9)	51 (70.8)	15 (78.9)
On-demand + LTP	35 (26.1)	21 (29.2)	4 (21.1)
By region			
Europe	69 (51.5)	39 (54.2)	9 (47.4)
North America	30 (22.4)	14 (19.4)	4 (21.1)
Rest of world[a]	35 (26.1)	19 (26.4)	6 (31.6)

[a]Rest of world includes Australia, Canada, Israel, Japan, New Zealand, Saudi Arabia, and South Africa.
Data cutoff date: September 14, 2024.

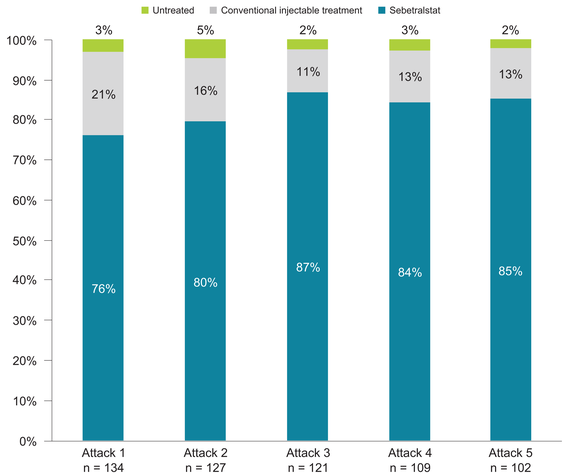
Table 2. Treatment Pattern by Attack Location and Severity

Characteristics	All attacks N = 2077	Attacks treated with sebetralstat n = 1706	Attacks treated with conventional injectable treatment n = 332	Untreated attacks n = 39
By location[a]				
Mucosal[b]	825 (39.7)	675 (39.6)	136 (41.0)	14 (35.9)
Subcutaneous[b]	1087 (53.3)	954 (55.5)	110 (33.1)	23 (59.0)
By severity[c]				
Mild[d]	718 (34.6)	618 (36.2)	84 (25.3)	16 (41.0)
Moderate	793 (38.2)	685 (40.2)	97 (29.2)	11 (28.2)
Severe/very severe	400 (19.3)	330 (19.3)	60 (18.1)	10 (25.6)

[a]Attacks with missing location data: All attacks, 165 (7.9%); Attacks treated with sebetralstat, 77 (4.5%); Attacks treated with conventional injectable treatment, 86 (25.9%); Untreated attacks, 2 (5.1%).
[b]Mucosal attacks were defined as those with primary location of 'Abdomen' and/or 'Larynx/Throat.' Subcutaneous attacks were defined as not involving the mucosal locations.
[c]Attacks with missing PGI-S rating: All attacks, 166 (8.0%); Attacks treated with sebetralstat, 73 (4.3%); Attacks treated with conventional injectable treatment, 91 (27.4%); Untreated attacks, 2 (5.1%).
[d]Includes attacks with PGI-S rating of 'None.'
Data cutoff date: September 14, 2024.

- Across the first 5 attacks treated by participants in the KONFIDENT-S study, sebetralstat was consistently used to treat 76.1% to 86.8% of attacks (**Figure 3**)

Figure 3. Initial Treatment Choice for First 5 Attacks



n represents the number of participants.
Data cutoff date: September 14, 2024.

Conclusions

- **The availability of oral sebetralstat has shifted on-demand treatment patterns in KONFIDENT-S, likely due to the reduced barriers of treatment, leading to increased willingness of participants to treat attacks**
- **Consistent with the treatment guideline recommendation that all attacks should be considered for treatment, 98.1% of HAE attacks were treated in the KONFIDENT-S study**
  - **Participants treated more mild and subcutaneous attacks than previously reported values for injectable on-demand treatments[3,6,7]**
  - **Of those attacks left untreated, more were likely to be subcutaneous (versus mucosal) or occurred in participants not receiving LTP (versus those receiving LTP)**
  - **Initial conventional injectable treatment use was most common among attacks that occurred in the beginning of the study**
- **Across the first 5 attacks treated by participants in the KONFIDENT-S study, preference for sebetralstat was high and increased after the initial attack was treated**

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