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Clinical Outcomes of Sebetralstat On-demand Treatment of Hereditary Angioedema in Pediatric (2-11 Years) Patients from Interim Analysis of KONFIDENT-KID

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Background

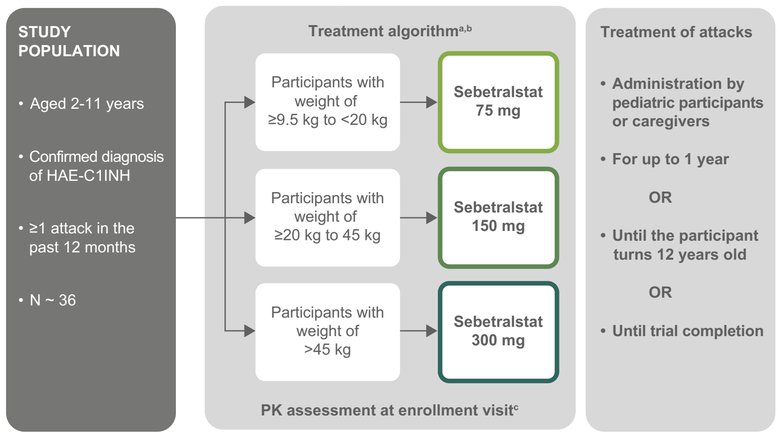
- Approximately 40% of patients with hereditary angioedema (HAE) experience their first attack by age of 5, with potential age of onset as early as infancy[1,2]
- Earlier onset is associated with more severe course of disease and increased attack burden[1]
  - Children with HAE attacks experience significant anxiety, social isolation, and academic disruption[2,3] and there is a multifaceted psychosocial impact on their caregivers[3-5]
- On-demand options for children with HAE require intravenous (IV) infusion or subcutaneous (SC) injection and are associated with substantial burden, including anxiety and pain, leading to treatment avoidance, denial or delays[5,6]
  - HAE in children (<12 years old) is primarily managed with on-demand treatment
  - International pediatric guidelines recommend the use of SC icatibant, IV pdC1INH, or IV recombinant human C1INH in children aged 2 years and older[7]
- 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, EU and other countries[8-10]

Objective

- This open-label, multicenter phase 3 KONFIDENT-KID trial was designed to evaluate the safety, pharmacokinetics (PK), and efficacy of sebetralstat orally disintegrating tablets (ODT) in children with hereditary angioedema with C1INH deficiency (HAE-C1INH) who are 2-11 years old

Methods

Figure 1. KONFIDENT-KID Trial Design



[a]All doses are equivalent to the 300-mg FCT dose in adults; provided as ODT.
[b]Trial was amended in the US to treat with the equivalent of sebetralstat 600 mg.
[c]PK samples were collected at 0.5, 2, and 4 hours. Simulated models were generated based on key parameters from each participant; 500 simulations were run for each participant.
FCT, film-coated tablet; HAE-C1INH, hereditary angioedema with C1 inhibitor deficiency; ODT, orally disintegrating tablet; PK, pharmacokinetics.

Trial Design

- The trial design of the phase 3 KONFIDENT-KID trial (NCT06467084) is shown in **Figure 1**

Objectives and Endpoints

- The primary objective was to evaluate the safety of sebetralstat in this patient population
- Secondary objectives were to assess PK and efficacy
- Population pharmacokinetic (popPK) analyses included sebetralstat plasma concentrations from ten clinical trials
  - The final popPK model used to perform simulations was created from sex-specific age-matched body weights from NHANES 2017-2018
- Efficacy endpoints were assessed using Caregiver Global Impression of Change (CaGI-C) and Severity (CaGI-S)
  - Time to beginning of symptom relief was defined as CaGI-C ratings of at least 'A Little Better' for ≥2 time points in a row within 12 hours
  - Time to reduction in severity was defined as a decrease in CaGI-S rating from baseline for ≥2 time points in a row within 12 hours
  - Time to complete attack resolution was defined as a CaGI-S rating of 'None' within 24 hours

Results

Participant Demographics

- As of June 5, 2025, 36 pediatric participants were enrolled in KONFIDENT-KID (**Table 1**)

Table 1. Participant Demographics

	Participants in sebetralstat ODT dosing group[a]			
	75 mg n=3	150 mg n=27	300 mg n=6	All participants N=36
Age, mean (range), years	5.0 (4-5)	8.0 (6-11)	9.5 (8-10)	8.0 (4-11)
Sex, male, n (%)	1 (33.3)	14 (51.9)	3 (50.0)	18 (50.0)
Race, n (%)				
White	3 (100)	20 (74.1)	3 (50.0)	26 (72.2)
Other[b]	0	3 (11.1)	2 (33.3)	5 (13.9)
Not reported	0	4 (14.8)	1 (16.7)	5 (13.9)
Weight, mean (range), kg	19.4 (19.0-19.5)	28.0 (20.2-43.2)	50.6 (47.2-70.0)	28.8 (19.0-70.0)
HAE-C1INH-Type 1, n (%)	3 (100)	24 (88.9)	5 (83.3)	32 (88.9)

[a]No participants have received 600 mg sebetralstat.
[b]Includes Asian (n=2; 5.6%), Black or African American (n=1; 2.8%), American Indian/Native Alaskan (n=1; 2.8%), other (n=1; 2.8%).
Data cutoff date: June 5, 2025.
HAE-C1INH, hereditary angioedema with C1 inhibitor deficiency; ODT, orally disintegrating tablet.

Part 1: Pharmacokinetics

- Observed sebetralstat plasma concentrations from 35 patients reliably fit within predicted simulated exposures
- Sebetralstat concentrations in pediatric participants 30 minutes post-dose were comparable to plasma concentrations in adults following a 300-mg film-coated tablet (FCT) dose
  - Pediatric plasma concentration 30 minutes after dosing (C_{30}) (geomean): 1364 ng/mL
  - Adult C_{30} (geomean): 1810 ng/mL[11]

Attack Characteristics

- Participants treated a mean of 0.8 (SD, 0.56) attacks/month with sebetralstat ODT
- Sixty-five attacks were treated with sebetralstat (**Table 2**) by 26 pediatric participants
  - The baseline severity of most (86.1%) attacks was mild or moderate; 48% of attacks were mucosal (**Table 2**)

Table 2. Baseline Attack Characteristics

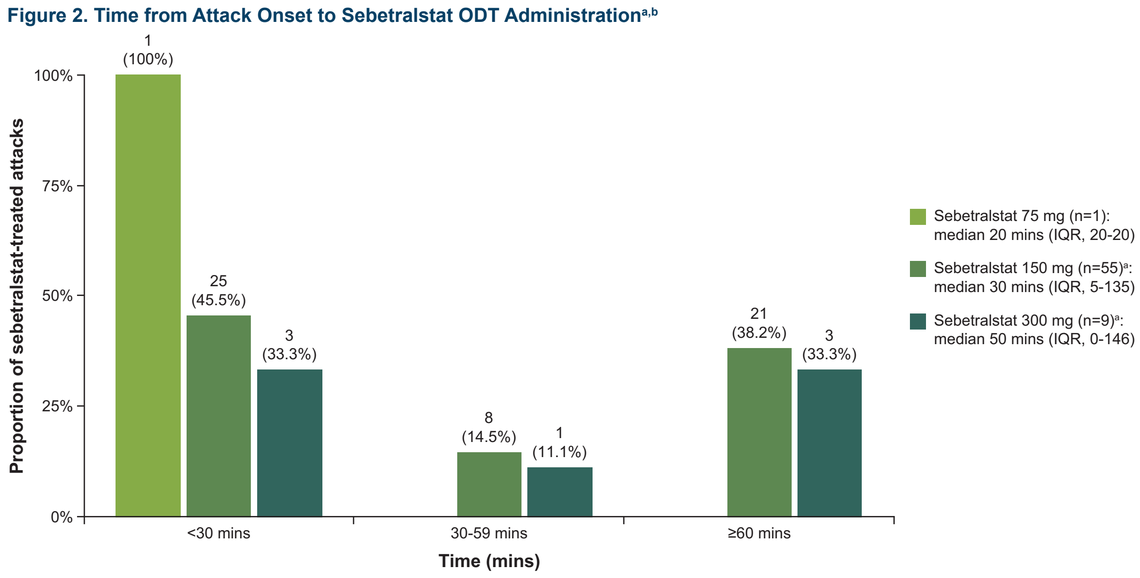
	Attacks in sebetralstat ODT dosing group			
	75 mg n=1	150 mg n=55	300 mg n=9	All attacks N=65
Severity[a,b]				
Mild[c]	1 (100)	16 (29.1)	4 (44.4)	21 (32.3)
Moderate	0	31 (56.4)	4 (44.4)	35 (53.8)
Severe	0	5 (9.1)	0	5 (7.7)
Very Severe	0	0	0	0
Primary pooled attack location[d]				
Laryngeal	0	2 (3.6)	1 (11.1)	3 (4.6)
Abdominal only	0	23 (41.8)	1 (11.1)	24 (36.9)
Subcutaneous only	1 (100)	25 (45.5)	5 (55.6)	31 (47.7)
Abdominal and subcutaneous	0	3 (5.5)	1 (11.1)	4 (6.2)

[a]Assessed by CaGI-S.
[b]Missing: 3 (5.5%) attacks in 150-mg group and 1 (11.1%) attack in the 300-mg group.
[c]Includes attacks with baseline CaGI-S rating of 'None': 1 (1.8%) attack in 150-mg group and 2 (22.2%) attacks in 300-mg group.
[d]Missing: 2 (3.6) attacks in 150-mg group and 1 (11.1%) attack in 300-mg group.
Data cutoff date: June 5, 2025.
All values are n (%).
CaGI-S, Caregiver Global Impression of Severity; ODT, orally disintegrating tablet.

Time to Treatment

- Across all attacks, the median (IQR) time to treatment was 30 minutes (5-135) (**Figure 2**)
  - 61.3% of attacks were treated in <1 hour of onset

Figure 2. Time from Attack Onset to Sebetralstat ODT Administration[a,b]



[a]Data missing for 1 (1.8%) attack in the 150-mg group and 2 (22.2%) attacks in the 300-mg group.
[b]Caregiver or child could administer treatment.
Data cutoff date: June 5, 2025.
IQR, interquartile range; ODT, orally disintegrating tablet.

Part 2: Interim Efficacy

Table 3. Efficacy of Sebetralstat in Pediatric Participants

	Attacks in sebetralstat ODT dosing group		
	75 mg n=1	150 mg n=55	300 mg n=9
Time to beginning of symptom relief within 12 hours, median (IQR), hours	**NE**	**1.50** (0.50 to 4.00)	**NE** (0.50 to >12)
Time to reduction in attack severity within 12 hours, median (IQR), hours	**NE**	**4.00** (1.50 to >12)	**NE** (1.00 to >12)
Time to complete attack resolution within 24 hours, median (IQR), hours	**NE**	**12.00** (8.00 to 24.00)	**18.00** (4.00 to >24)

Data cutoff date: June 5, 2025.
NE, not estimable; IQR, interquartile range.

- Overall, 78.9% of attacks achieved beginning of symptom relief within 12 hours (includes all attacks with post-baseline values)
- Conventional medication was utilized within 12 hours for 3.1% of attacks

Safety and Tolerability

- Fifteen adverse events occurred in 9 participants; none were serious or considered treatment-related (**Table 4**)
- No reports of difficulty swallowing sebetralstat ODT

Table 4. Safety and Tolerability

	All participants[a] N=26
Any TEAE, n (%)	9 (34.6)
Treatment-related	**0**
Serious TEAE, n (%)	0
Treatment-related	**0**
Severe TEAE, n (%)	0
Treatment-related	**0**
Any TEAE leading to discontinuation, n (%)	0
Any TEAE leading to death, n (%)	0

[a]Participants who treated at least 1 HAE attack with sebetralstat.
Data cutoff date: June 5, 2025.
TEAE, treatment-emergent adverse event.

Conclusions

- **Children with HAE aged 2-11 years have a high unmet need for non-parenteral treatment options**
- **Observed sebetralstat plasma concentrations reliably fit within predicted exposures**
  - **Sebetralstat concentrations in children 30 minutes post-dose were comparable to plasma concentrations in adults following a 300-mg dose**
- **A high number of attacks were treated with sebetralstat in this study**
  - **Participants treated a mean of 0.8 attacks/month with sebetralstat**
- **Sebetralstat enabled early treatment (median: 30 minutes) by participants or their caregivers**
  - **Attacks occurred in all locations with 32% still mild at time of treatment**
- **Sebetralstat was generally safe, well tolerated, and demonstrated rapid symptom relief, reduction in severity and complete attack resolution**
- **Sebetralstat ODT has the potential to address high unmet need for children (2-11 years) with HAE and their caregivers**

Ongoing Analyses

- **Additional data from the KONFIDENT-KID trial will be presented at the HAEi Global Angioedema Leadership Conference (March 26-29, 2026; Madrid, Spain)**

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