Phase 3 KONFIDENT Trial of Oral Sebetralstat for Treatment of Hereditary Angioedema Attacks: Analysis of the European and US Patient Subgroups

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Rationale

- International treatment guidelines recommend that patients with hereditary angioedema with C1-inhibitor deficiency (HAE-C1INH) consider treating all attacks, treat attacks as early as possible, and always carry sufficient on-demand therapy with them to treat 2 attacks[1,2]
- Currently approved on-demand treatments must be administered parenterally[3-7] and are associated with delays and/or withholding of treatment[8-13]
- Sebetralstat, a plasma kallikrein inhibitor, is the first orally administered therapy to have been evaluated in a phase 3 trial for the on-demand treatment of HAE-C1INH attacks[14]

Objective

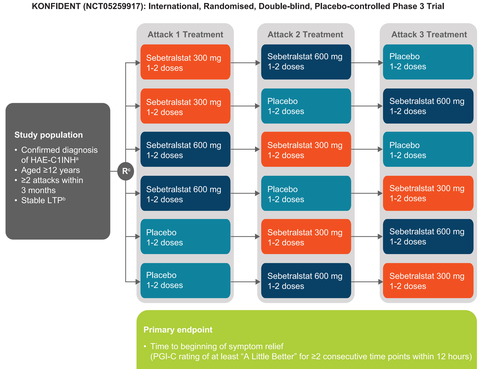
- The objective of the phase 3 KONFIDENT trial was to determine the safety and efficacy of sebetralstat in adults and adolescents with HAE-C1INH. This analysis assessed consistency between US participants and European participants (ie, the two largest geographic subgroups)

Methods

- The phase 3 KONFIDENT trial (NCT05259917) was a double-blind, randomised, placebo-controlled, 3-way crossover trial[15]
- 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 or 600 mg or with placebo (**Figure 1**)
  - All attack locations and severity were included except for laryngeal attacks that were considered severe at onset
- The primary endpoint was time to beginning of symptom relief, defined as a Patient Global Impression of Change (PGI-C) rating of at least "A Little Better" for 2 consecutive time points within 12 hours
- Subgroup analyses are not powered for efficacy and must be interpreted with caution

Figure 1. Study Design

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



HAE-C1INH, hereditary angioedema due to deficiency of C1 inhibitor; LTP, long-term prophylaxis, PGI-C, Patient Global Impression of Change.
[a]Participants must have had access to conventional on-demand treatment.
[b]Participants receiving LTP were required to be on a stable dose for ≥3 months prior to screening.
[c]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.

Results

Participants and Attacks

- The full analysis set included 110 participants (**Table 1**) who treated 264 attacks (**Table 2**)

Table 1. Participant Demographics and Disease Characteristics

	All participants[a] N=110	US participants[a] n=34	European participants[a,b] n=58
Age, median (IQR), years	39.5 (25.0 to 49.0)	39.5 (28.0 to 51.0)	40.0 (25.0 to 48.0)
Sex, female, n (%)	66 (60.0)	27 (79.4)	28 (48.3)
BMI, median (IQR), kg/m^2	26.2 (22.8 to 31.7)	29.3 (25.2 to 35.4)	25.4 (22.9 to 30.7)
Race, n (%)			
White	92 (83.6)	31 (91.2)	50 (86.2)
Asian	10 (9.1)	2 (5.9)	1 (1.7)
Black or African American	1 (0.9)	1 (2.9)	0
Other or not reported	7 (6.4)	0	7 (12.1)
HAE-C1INH type, n (%)			
Type 1	101 (91.8)	28 (82.4)	55 (94.8)
Type 2	9 (8.2)	6 (17.6)	3 (5.2)
Time since HAE diagnosis, median (IQR), years	12 (7 to 22)	13 (5 to 29)	13 (8 to 20)
Current treatment regimen, n (%)			
On-demand only	86 (78.2)	18 (52.9)	54 (93.1)
On-demand + LTP[c]	24 (21.8)	16 (47.1)	4 (6.9)

BMI, body mass index; HAE-C1INH, hereditary angioedema due to deficiency of C1 inhibitor; IQR, interquartile range; LTP, long-term prophylaxis.
[a]Participant characteristics are reported for patients who experienced ≥1 treated attack.
[b]European countries with participants who treated ≥1 attack included Greece (n=9), the United Kingdom (n=8), France (n=6), Germany (n=5), Italy (n=5), Poland (n=5), Bulgaria (n=4), Spain (n=4), the Netherlands (n=3), Portugal (n=3), Hungary (n=2), Macedonia (n=2), and Slovakia (n=2).
[c]Of the 24 participants receiving LTP, 10 (42%) received berotralstat, 8 (33%) received lanadelumab, and 7 (29%) received C1INH.

Table 2. Attack Characteristics

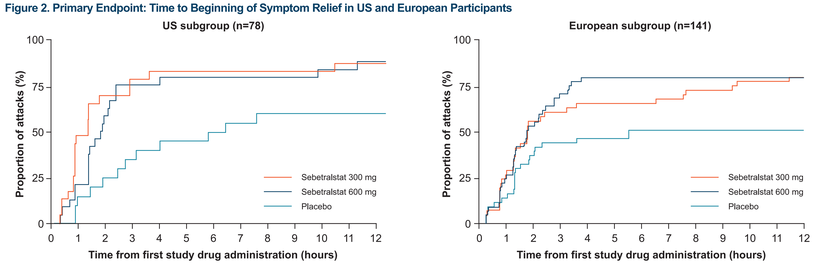
	All attacks N=264	Attacks treated by US participants n=78	Attacks treated by European participants n=141
Baseline PGI-S category, n (%)[a,b]			
Mild	113 (42.8)	35 (44.9)	45 (31.9)
Moderate	102 (38.6)	33 (42.3)	59 (41.8)
Severe/very severe	45 (17.0)	8 (10.3)	35 (24.8)
Baseline pooled attack location, n (%)[a,c]			
Mucosal (abdomen, larynx/throat)	120 (45.5)	43 (55.1)	57 (40.4)
Larynx/throat	8 (3.0)	5 (6.4)	2 (1.4)
Subcutaneous (all others)	142 (53.8)	34 (43.6)	83 (58.9)
Time from onset of attack to first administration, median (IQR), minutes[d]	41 (6 to 140)	38 (5 to 124)	48 (6 to 205)
Attacks treated in <60 minutes, n (%)[d]	147 (55.7)	44 (56.4)	74 (52.5)
Second administration of study drug, n (%)[e]			
Sebetralstat 300 mg	34 (39.1)	13 (48.1)	16 (36.4)
Sebetralstat 600 mg	37 (39.8)	12 (42.9)	20 (40.8)
Placebo	47 (56.0)	11 (47.8)	26 (54.2)

IQR, interquartile range; PGI-S, Patient Global Impression of Severity.
[a]Baseline PGI-S rating and baseline attack location are missing for 2 attacks in the sebetralstat 300-mg group (1 attack in a US participant and 1 attack in a European participant).
[b]Two attacks in the placebo group (1 from a US participant and 1 from a European participant) had a baseline PGI-S category of "None".
[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]The time from attack onset to first administration of study drug was missing for 1 attack treated by a European participant.
[e]Participants were instructed to administer the optional second dose of study drug ≥3 hours after the administration of the first dose.

- 78 (29.5%) attacks occurred among US participants and 140 (53%) attacks occurred among European participants. Baseline attack severity tended to be higher in European participants than in US participants
- A higher proportion of attacks with mucosal involvement (including laryngeal attacks) occurred in US participants than in European participants

Efficacy

Figure 2. Primary Endpoint: Time to Beginning of Symptom Relief in US and European Participants



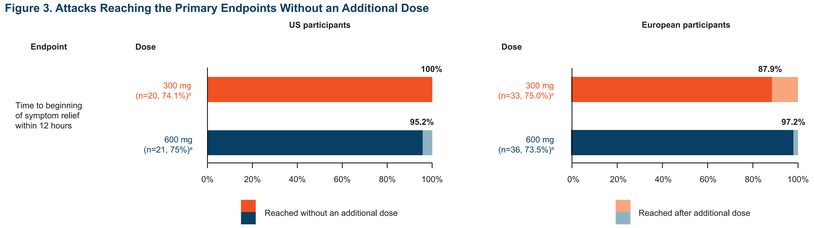
Time to beginning of symptom relief was defined as a PGI-C of "A Little Better" for 2 consecutive time points within 12 hours.

Table 3. Primary Endpoint

	Sebetralstat 300 mg	Sebetralstat 600 mg	Placebo
Time to beginning of symptom relief[a]			
Attacks treated with study drug by US participants, n	27	28	23
P value versus placebo[b]	0.0007	0.0242	—
Median (IQR), hours	1.28 (0.77 to 3.12)	1.77 (1.31 to 3.89)	6.23 (2.28 to >12)
Attacks treated with study drug by European participants, n	44	49	48
P value versus placebo[b]	0.0219	0.0071	—
Median (IQR), hours	1.78 (0.98 to 9.36)	1.77 (1.02 to 3.33)	5.54 (1.32 to >12)

IQR, interquartile range; PGI-C, Patient Global Impression of Change.
[a]Defined as a PGI-C of "A Little Better" for 2 consecutive time points within 12 hours.
[b]Nominal *P* value compared with placebo.

Figure 3. Attacks Reaching the Primary Endpoints Without an Additional Dose



[a]Proportion of attacks reaching endpoint within 12 hours.

- In both US and European participants, most attacks treated with sebetralstat that reached beginning of symptom relief did so without an additional dose of study drug (**Figure 3**)

Safety

- The observed safety profiles of sebetralstat in US participants and in European participants were consistent with that of the overall population and were no different to that of placebo (**Table 4**)

Table 4. Safety

	Sebetralstat 300 mg	Sebetralstat 600 mg	Placebo
US participants, n (%)	n=27	n=28	n=23
Any TEAE **Treatment-related**	7 (25.9) **2 (7.4)**	8 (28.6) **1 (3.6)**	6 (26.1) **1 (4.3)**
Serious TEAE **Treatment-related**	0 **0**	2 (7.1)[b] **0**	0 **0**
Severe TEAE **Treatment-related**	 **0**	0 **0**	0 **0**
TEAEs leading to study discontinuation	0	0	0
TEAEs leading to death	0	0	0
European participants, n (%)	n=43	n=49	n=47
Any TEAE **Treatment-related**	9 (20.9) **0**	6 (12.2) **2 (4.1)**	9 (19.1) **3 (6.4)**
Serious TEAE **Treatment-related**	1 (2.3)[a] **0**	0 **0**	0 **0**
Severe TEAE **Treatment-related**	1 (2.3)[a] **0**	0 **0**	0 **0**
TEAEs leading to study discontinuation	0	0	0
TEAEs leading to death	0	0	0

TEAE, treatment-emergent adverse event.
Values are in n (%) unless otherwise noted.
[a]The severe TEAE and serious TEAEs listed are the same event: lumbar disc herniation that necessitated hospitalization and was deemed severe by the investigator.
[b]The serious TEAEs were 1 event of anisocoria related to lisdexamfetamine use and 1 event of exacerbation of an HAE attack, in which the participant did not have the study drug.

Conclusions

- **Sebetralstat, an oral plasma kallikrein inhibitor, enabled early treatment of HAE-C1INH attacks among US and European participants. Compared with placebo, attacks treated with sebetralstat exhibited faster times to beginning of symptom relief in both subgroups**
  - **Although certain demographic factors (eg, LTP use) and attack characteristics (eg, baseline attack severity) differed, the efficacy and safety of sebetralstat were comparable between the US and European subgroups**
- **Long-term safety and efficacy are being studied in the KONFIDENT-S (NCT05505916, EudraCT: 2021-001176-42) 2-year open-label extension trial**
  - **As of 13 September 2024, XX US participants have treated XXX attacks and XX European participants have treated XXX attacks with sebetralstat**

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

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