Sebetralstat for Treatment of HAE Attacks in Patients Receiving Berotralstat, Lanadelumab, or C1 Inhibitor for Long-term Prophylaxis: Interim Analysis from KONFIDENT-S

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Background

- Long-term prophylaxis (LTP) should be individualised and considered in all patients with hereditary angioedema with C1-inhibitor deficiency (HAE-C1INH) based on the disease activity, patient's quality of life, availability of healthcare resources, and failure to achieve adequate control by appropriate on-demand therapy[1]
- However, patients who receive LTP may still experience breakthrough attacks of all severity levels and in any anatomical location[2]
- Sebetralstat, an oral plasma kallikrein inhibitor, has recently been approved for the on-demand treatment of acute attacks in patients with HAE ≥12 years old in the United States, United Kingdom, and European Union[3-5]

Objective

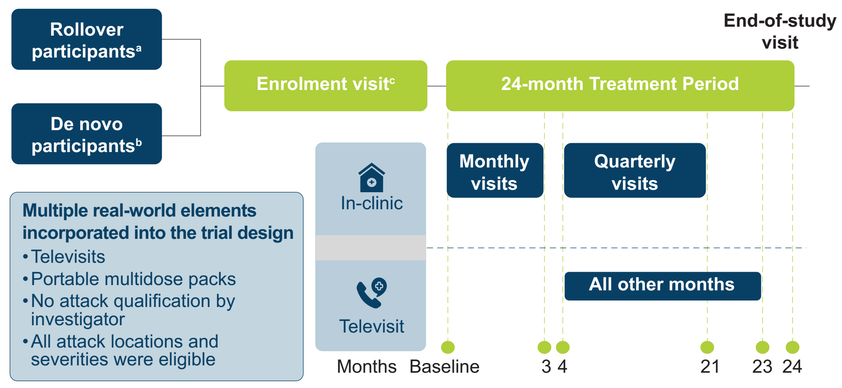
- To assess the safety and effectiveness of oral sebetralstat in patients receiving concurrent LTP with berotralstat, lanadelumab, or C1INH replacement in an ongoing open-label extension study (KONFIDENT-S)

Methods

Study Design

- KONFIDENT-S is a multicentre open-label extension (OLE) trial (NCT05505916; EudraCT: 2021-001176-42)
- Eligible participants were ≥12 years of age with HAE-C1INH and ≥2 documented attacks within 3 months (de novo) or who completed the phase 3 KONFIDENT (NCT05259917) trial (rollover; **Figure 1**)
  - Participants receiving LTP were required to be on a stable dose and regimen for ≥3 months immediately before the study
- Participants self-administered sebetralstat 600 mg (two 300-mg tablets) as early as possible after HAE attack onset; a second administration was allowed if warranted
- Endpoints were as follows:
  - Safety, assessed by adverse event monitoring
  - Time to beginning of symptom relief (Patient Global Impression of Change [PGI-C] rating of at least "A Little Better" for ≥2 consecutive time points) within 12 hours
  - Time to reduction in attack severity (≥1 level decrease on the Patient Global Impression of Severity [PGI-S] for ≥2 consecutive time points) within 12 hours
  - Time to complete attack resolution (PGI-S rating of "None") within 24 hours

Figure 1. KONFIDENT-S OLE Trial 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 enrolment visit is a screening visit.

Results

Participant and Attack Characteristics

- As of September 14, 2024 (data cutoff), 35 participants receiving LTP (berotralstat: 16; lanadelumab 13; C1INH: 6 [5 subcutaneous, 1 intravenous]) treated at least 1 HAE attack with sebetralstat (**Table 1**)
  - 382 attacks were treated with sebetralstat by participants receiving LTP (**Table 2**)

Table 1. Characteristics of Participants with ≥1 Sebetralstat-treated Attack

	Any LTP[a] n=35	Berotralstat n=16	Lanadelumab n=13	C1INH n=6
Age, median (IQR), years	44.0 (28.0 – 56.0)	38.5 (21.0 – 48.0)	44.0 (31.0 – 60.0)	48.5 (28.0 – 54.0)
Sex, female, n (%)	27 (77.1)	13 (81.3)	11 (84.6)	3 (50.0)
Race, n (%)				
Asian	8 (22.9)	4 (25.0)	3 (23.1)	1 (16.7)
White	25 (71.4)	10 (62.5)	10 (76.9)	5 (83.3)
Other	1 (2.9)	1 (6.3)	—	—
Not reported	1 (2.9)	1 (6.3)	—	—
Region, n (%)				
North America	19 (54.3)	7 (43.8)	7 (53.8)	5 (83.3)
Europe	9 (25.7)	5 (31.3)	3 (23.1)	1 (16.7)
Asia-Pacific	7 (20.0)	4 (25.0)	3 (23.1)	—
BMI, median (IQR), kg/m^2	26.6 (22.1 – 33.1)	27.1 (21.6 – 33.8)	25.3 (24.2 – 27.3)	32.1 (30.6 – 37.7)
HAE-C1INH type, n (%)				
Type 1	31 (88.6)	15 (93.8)	13 (100)	3 (50.0)
Type 2	4 (11.4)	1 (6.3)	—	3 (50.0)

[a]Four participants receiving LTP at baseline switched to a different LTP agent during the study: 1 participant switched from C1INH replacement to lanadelumab and was included in the lanadelumab group, 1 participant switched from C1INH replacement to berotralstat and was included in the berotralstat group, 1 participant switched from lanadelumab to C1INH replacement and was included in the lanadelumab group, and 1 participant switched from berotralstat to C1INH replacement and was included in the berotralstat group.
BMI, body-mass index; HAE-C1INH, hereditary angioedema due to C1 inhibitor deficiency; IQR, interquartile range; LTP, long-term prophylaxis; n, number of participants.

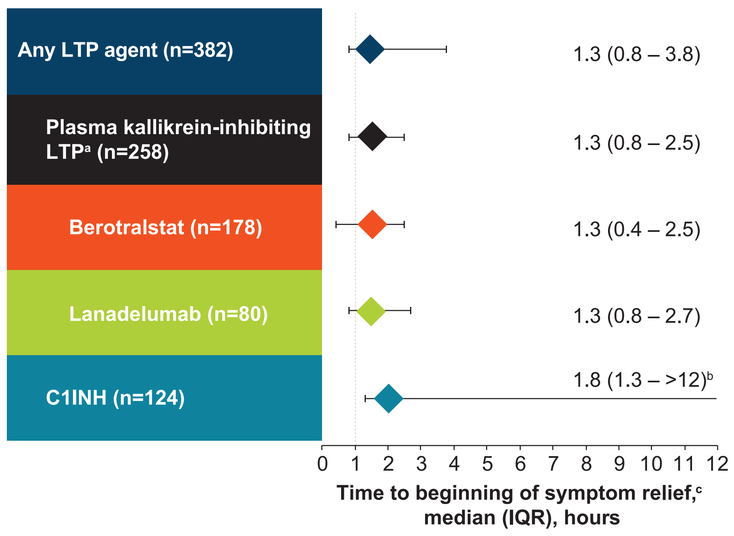
Table 2. Sebetralstat-treated Attack Characteristics

	Any LTP n=382	Berotralstat n=178	Lanadelumab n=80	C1INH n=124
Baseline PGI-S category, n (%)				
Mild[a]	113 (29.6)	59 (33.1)	24 (30.0)	30 (24.2)
Moderate	141 (36.9)	64 (36.0)	48 (60.0)	29 (23.4)
Severe/very severe	94 (24.6)	53 (29.8)	6 (7.5)	35 (28.2)
Missing	34 (8.9)	2 (1.1)	2 (2.5)	30 (24.2)
Primary pooled attack location, n (%)				
Mucosal[b]	189 (49.5)	107 (60.1)	55 (68.8)	27 (21.8)
Involving the larynx	17 (4.5)	8 (4.5)	7 (8.8)	2 (1.6)
Subcutaneous only[b]	159 (41.6)	69 (38.8)	23 (28.8)	67 (54.0)
Missing	34 (8.9)	2 (1.1)	2 (2.5)	30 (24.2)
Time from attack onset to treatment, median (IQR), minutes	6 (1 – 40)	20 (1 – 67)	11 (1 – 50)	1 (0 – 7)
Monthly attack frequency,[c] mean (SD)	1.7 (1.5)	1.8 (1.4)	1.2 (1.1)	2.5 (2.2)

[a]Includes 1 attack with a baseline severity of "None" reported by a participant who was receiving LTP with berotralstat.
[b]Mucosal: attacks with primary location of "Abdomen" and/or "Larynx/Throat"; subcutaneous: other attacks not involving the mucosal locations.
[c]Includes all attacks, including those not treated with sebetralstat.
C1INH, C1 inhibitor; IQR, interquartile range; LTP, long-term prophylaxis; n, number of attacks; PGI-S, Patient Global Impression of Severity; SD, standard deviation.

Effectiveness

Figure 2. Time to Beginning of Symptom Relief for Breakthrough Attacks Treated with Sebetralstat



[a]Berotralstat or lanadelumab.
[b]Size of error bars may be due to the number of patients receiving C1INH as LTP (n=6).
[c]Defined as a PGI-C rating of at least "A Little Better" for ≥2 consecutive time points, with missing data entries between consecutive time points within 12 hours of the first dose of sebetralstat.
Diamonds are the medians met within time window.
Error bars are Q1 and Q3.
C1INH, C1 inhibitor; IQR, interquartile range; LTP, long-term prophylaxis, n, number of attacks; PGI-C, Patient Global Impression of Change.

Table 3. Other Effectiveness Endpoints for Breakthrough Attacks Treated with Sebetralstat

	Time to reduction in attack severity,[b] median (IQR), hours	Time to complete resolution,[c] median (IQR), hours	Attacks treated with conventional treatment, n (%)[d]
Any LTP agent (n=382)	4.2 (1.3 – >12)	14.8 (4.6 – >24)	20 (5.2)
Plasma kallikrein-inhibiting LTP[a] (n=258)	3.3 (1.1 – >12)	12.1 (3.4 – >24)	13 (5.0)
Berotralstat (n=178)	2.7 (0.9 – >12)	10.9 (3.0 – >24)	8 (4.5)
Lanadelumab (n=80)	4.4 (1.4 – >12)	15.1 (3.7 – >24)	5 (6.3)
C1INH (n=124)	>12 (1.8 – >12)	16.6 (9.0 – 23.5)	7 (5.6)

[a]Berotralstat or lanadelumab.
[b]Defined as a time to first incidence of decrease from baseline in PGI-S score for ≥2 consecutive time points within 12 hours of the first dose of sebetralstat.
[c]Defined as a PGI-S rating of "None" (ie, no symptoms) within 24 hours of the first dose of sebetralstat.
[d]Received conventional on-demand treatment (ie, plasma-derived C1INH, recombinant human C1INH, icatibant, or ecallantide) within 12 hours of the first dose of sebetralstat.
C1INH, C1 inhibitor; IQR, interquartile range; LTP, long-term prophylaxis; n, number of attacks; PGI-S, Patient Global Impression of Severity.

Safety

- Overall, treatment-related adverse events occurred in 5 (14.3%) participants receiving sebetralstat and any LTP (**Table 4**)
- No serious treatment-related adverse events occurred

Table 4. Safety

Participants experiencing TEAE, n (%)	Any LTP n=35	Berotralstat n=16	Lanadelumab n=13	C1INH n=6
Any TEAE	23 (65.7)	12 (75.0)	6 (46.2)	5 (83.3)
Treatment related[a]	**5 (14.3)**	**3 (18.8)**	**0**	**2 (33.3)**
Serious TEAE	5 (14.3)	3 (18.8)	1 (7.7)	1 (16.7)
Treatment related	**0**	**0**	**0**	**0**
Severe TEAE	7 (20.0)	3 (18.8)	2 (15.4)	2 (33.3)
Treatment related	**0**	**0**	**0**	**0**
Any TEAE leading to discontinuation	2 (5.7)	1 (6.3)	1 (7.7)	0
Treatment related[b]	**1 (2.9)**	**1 (6.3)**	**0**	**0**
Any TEAE leading to death	0	0	0	0

[a]TEAEs in 5 participants receiving LTP were considered treatment-related: headache (berotralstat, n=1; C1INH, n=2), myalgia (berotralstat, n=1), arthralgia (berotralstat, n=1), nausea (berotralstat, n=1), and vomiting (berotralstat, n=1).
[b]1 participant receiving berotralstat discontinued sebetralstat due to treatment-related TEAEs of grade 2 nausea and grade 2 vomiting, which occurred during an attack involving the abdomen and larynx/throat.
C1INH, C1 inhibitor; IQR, interquartile range; LTP, long-term prophylaxis; n, number of participants; TEAE, treatment-emergent adverse event.

Conclusions

- **Participants receiving LTP continued to experience attacks in all anatomical locations, including laryngeal attacks**
  - **The overall attack rate for participants receiving LTP was 1.7 attacks/month**
- **Sebetralstat resulted in rapid symptom relief, reduction in attack severity, and complete attack resolution in patients receiving LTP, regardless of the individual LTP or its mechanism of action**
  - **Conventional treatment was used in 5.2% of attacks**
- **Sebetralstat was well-tolerated in participants receiving LTP and no new safety signals were observed**

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