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

William R. Lumry,[1] Emel Aygören-Pürsün,[2] Jonathan A. Bernstein,[3] Paula J. Busse,[4] Mauro Cancian,[5] Danny M. Cohn,[6] Timothy Craig,[7,8] Henriette Farkas,[9] Sorena Kiani-Alikhan,[10] Tamar Kinaciyan,[11] H. Henry Li,[12] Michael E. Manning,[13,14] Jason Raasch,[15] Marc A. Riedl,[16] Daniel F. Soteres,[17] Raffi Tachdjian[18] H. James Wedner[19] James Hao[20] Michael D. Smith,[20] Paul K. Audhya,[20] Andrea Zanichelli,[21,22]

[1]AARA Research Center, Dallas, TX, USA; [2]University Hospital Frankfurt, Goethe University, Frankfurt, Germany; [3]University of Cincinnati College of Medicine and Bernstein Clinical Research Center, Cincinnati, OH, USA; [4]The Mount Sinai Hospital, New York, NY, USA; [5]Azienda Ospedaliera, Università degli Studi di Padova, Padova, Italy; [6]Amsterdam UMC, University of Amsterdam, Amsterdam, Netherlands; [7]The Pennsylvania State University School of Medicine, State College, PA, USA; [8]Vinmec International Hospital, Times City, Hanoi, Vietnam and Vin-University, Hanoi, Vietnam; [9]Hungarian Angioedema Center of Reference and Excellence, Semmelweis University, Budapest, Hungary; [10]Royal Free London NHS Foundation Trust, London, United Kingdom; [11]Medical University of Vienna, Department of Dermatology, Vienna, Austria; [12]Institute for Asthma and Allergy, Wheaton, MD, USA; [13]Allergy, Asthma and Immunology Associates, Ltd., Scottsdale, AZ, USA; [14]University of Arizona College of Medicine-Phoenix, Phoenix, AZ, USA; [15]Midwest Immunology Clinic, Plymouth, MN, USA; [16]University of California, San Diego, La Jolla, CA, USA; [17]Asthma & Allergy Associates, PC and Research Center, Colorado Springs, CO, USA; [18]University of California, Los Angeles, School of Medicine, Los Angeles, CA, US; [19]Washington University School of Medicine, St Louis, MO, USA; [20]KalVista Pharmaceuticals, Cambridge, MA, USA; [21]IRCCS Policlinico San Donato, San Donato Milanese, Milan, Italy; [22]University of Milan, Milan, Italy.

Background

- Long-term prophylaxis (LTP) should be individualized 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 been approved for the treatment of acute HAE attacks in patients ≥12 years old in the United States and United Kingdom[3,4]

Objective

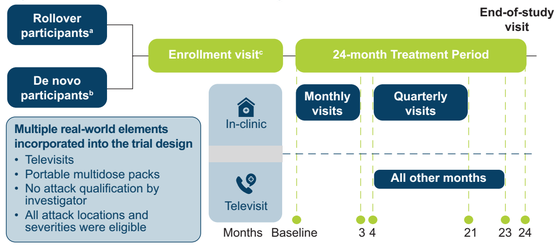
- To assess the safety and effectiveness of oral sebetralstat in patients receiving concurrent LTP with berotralstat, lanadelumab, or C1INH replacement in an ongoing open-label extension study (KONFIDENT-S)

Methods

Study Design

- KONFIDENT-S is a multicenter 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 (2 × 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 enrollment 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]) experienced HAE attacks (**Table 1**)
- Participants treated 382 attacks with sebetralstat (berotralstat: 178; lanadelumab 80; C1INH: 124; **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

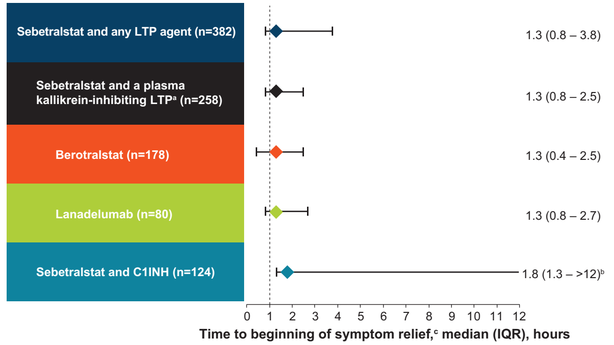
	Any LTP n=382	Berotralstat n=178	Lanadelumab n=80	C1INH n=124
Baseline PGI-S category, n (%)				
Mild[a]	113 (29.6)	59 (33.1)	24 (30.0)	30 (24.2)
Moderate	141 (36.9)	64 (36.0)	48 (60.0)	29 (23.4)
Severe/very severe	94 (24.6)	53 (29.8)	6 (7.5)	35 (28.2)
Missing	34 (8.9)	2 (1.1)	2 (2.5)	30 (24.2)
Primary 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

- The median (IQR) time to beginning of symptom relief with sebetralstat was 1.3 hours (0.8 – 3.8) for participants receiving any LTP agent (berotralstat: 1.3 hours [0.4 – 2.5]; lanadelumab: 1.3 hours [1.8 – >12]; C1INH: 1.8 hours [1.3 – >12]) (**Figure 2**)

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)

C1INH, C1 inhibitor; IQR, interquartile range; LTP, long-term prophylaxis; n, number of attacks; PGI-S, Patient Global Impression of Severity.
[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 medicine within 12 hours of the first dose of sebetralstat.

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	**5 (14.3)[a]**	**3 (18.8)[a]**	**0**	**2 (33.3)[a]**
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	**1 (2.9)[b]**	**1 (6.3)[b]**	**0**	**0**
Any TEAE leading to death	0	0	0	0

C1INH, C1 inhibitor; IQR, interquartile range; LTP, long-term prophylaxis; n, number of participants; TEAE, treatment-emergent adverse event.
[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.

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**

References

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