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

Marc A. Riedl,[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] William R. Lumry,[13] Michael E. Manning,[14,15] Jason Raasch,[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]University of California, San Diego, La Jolla, CA, 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; [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, Vienna, Austria; [12]Institute for Asthma and Allergy, Wheaton, MD, USA; [13]AARA Research Center, Dallas, TX, USA; [14]Allergy, Asthma and Immunology Associates, Ltd., Scottsdale, Arizona, USA; [15]University of Arizona College of Medicine-Phoenix, Phoenix, Arizona, USA; [16]Midwest Immunology Clinic, Plymouth, MN, 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, USA; [19]Washington University School of Medicine, St. Louis, MO, USA; [20]KalVista Pharmaceuticals, Salisbury, United Kingdom, and Cambridge, MA, USA; [21]IRCCS Policlinico San Donato, San Donato Milanese, Milan, Italy; [22]University of Milan, Milan, Italy

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Background

- HAE-C1INH is a rare genetic disorder commonly caused by deficiency or dysfunction of the C1INH, manifesting as unpredictable tissue swelling caused by uncontrolled activation of the KKS[1,2]
- Long-term prophylaxis should be individualized and considered in all HAE-C1INH patients taking into consideration the disease activity, patient's quality of life, availability of health care resources, and failure to achieve adequate control by appropriate on-demand therapy[2]
- However, patients who receive LTP may experience breakthrough attacks of all levels of severity and in any anatomical location[3]

C1INH, C1 inhibitor; HAE-C1INH, hereditary angioedema with C1-inhibitor deficiency; KKS, kallikrein-kinin system; LTP, long-term prophylaxis.

1. Busse PJ et al. *J Allergy Clin Immunol Pract*. 2021;9(1):132-150.e3. 2. Maurer M et al. *Allergy*. 2022;77(7):1961-1990. 3. Longhurst HJ et al. *Clin Rev Allergy Immunol*. 2024;67(1-3):83-95.

Objective

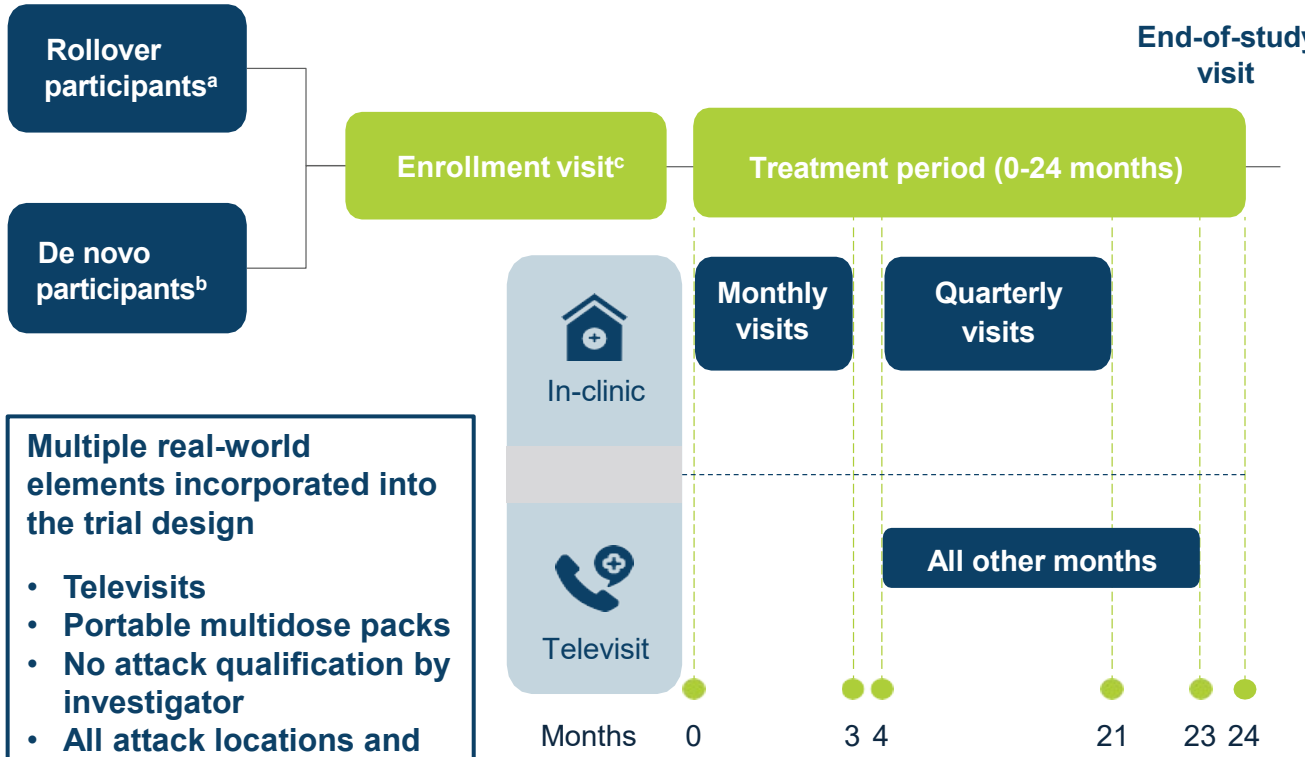
- Sebetralstat, an investigational plasma kallikrein inhibitor, is the first orally administered therapy to be evaluated in a phase 3 trial for on-demand treatment of HAE-C1INH attacks
- In the phase 3 KONFIDENT trial, compared with placebo, the use of sebetralstat resulted in faster times to beginning of symptom relief, to reduction in attack severity, and to complete attack resolution; sebetralstat was also well-tolerated[1]
- KONFIDENT-S is an ongoing, 2-year, multicenter, OLE study to evaluate sebetralstat as an on-demand treatment for HAE attacks

The **objective** of this analysis is to assess the safety and effectiveness of oral sebetralstat in patients receiving concurrent LTP with berotralstat, lanadelumab, or C1INH replacement in KONFIDENT-S

C1INH, C1 inhibitor; HAE, hereditary angioedema; HAE-C1INH, hereditary angioedema with C1-inhibitor deficiency; LTP, long-term prophylaxis; OLE, open-label extension.

1. Riedl MA et al. *New Engl J Med.* 2024;391:32-43.

KONFIDENT-S OLE Trial Design



Multiple real-world elements incorporated into the trial design

- **Televisits**
- **Portable multidose packs**
- **No attack qualification by investigator**
- **All attack locations and severities were eligible**

Inclusion criteria (up to 150 participants)

- Age ≥12 years
- ≥2 documented HAE-C1INH attacks within 3 months

Treatment

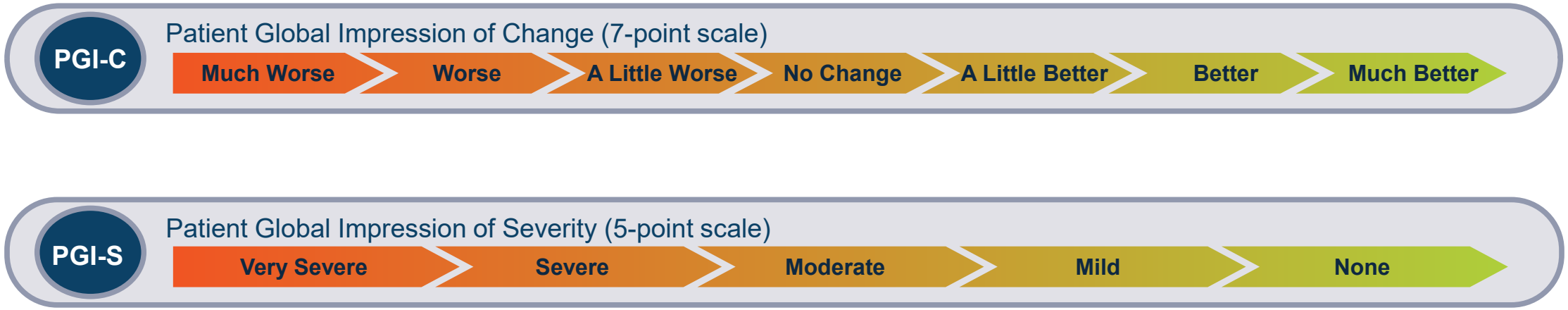
- Participants instructed to self-administer sebetralstat 600 mg (2 × 300-mg tablets) as early as possible after attack onset
- A second administration allowed if warranted

Endpoints:

- Safety (adverse events)
- Time to beginning of symptom relief (by PGI-C)[d]
- Time to first reduction in severity (by PGI-S)[d]
- Time to complete attack resolution (by PGI-S)[e]

PGI-C, Patient Global Impression of Change; PGI-S, Patient Global Impression of Severity.
NCT05505916, EudraCT: 2021-001176-42. [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. [d]Within 12 hours. [e]Within 24 hours.

Efficacy Assessments[a]



[a]The KONFIDENT-S study is not designed for evaluation of differences in the effectiveness in the subgroup of participants who received LTP or by the specific LTP agent received.

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/m²	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)

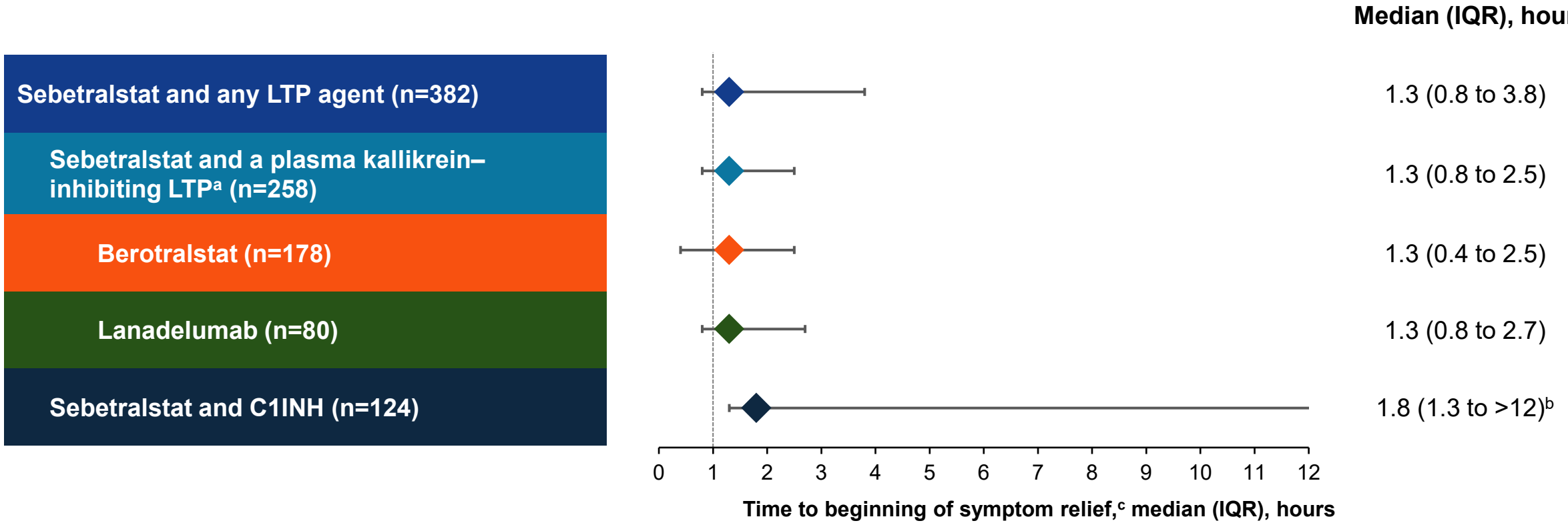
BMI, body mass index; C1INH, C1 inhibitor; IQR, interquartile range.
[a]Four participants receiving LTP at baseline switched to a different LTP agent during the study: 1 participant switched from C1INH replacement to lanadelumab and was included in the lanadelumab group, 1 participant switched from C1INH 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.
KONFIDENT-S data cutoff: September 14, 2024.

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)

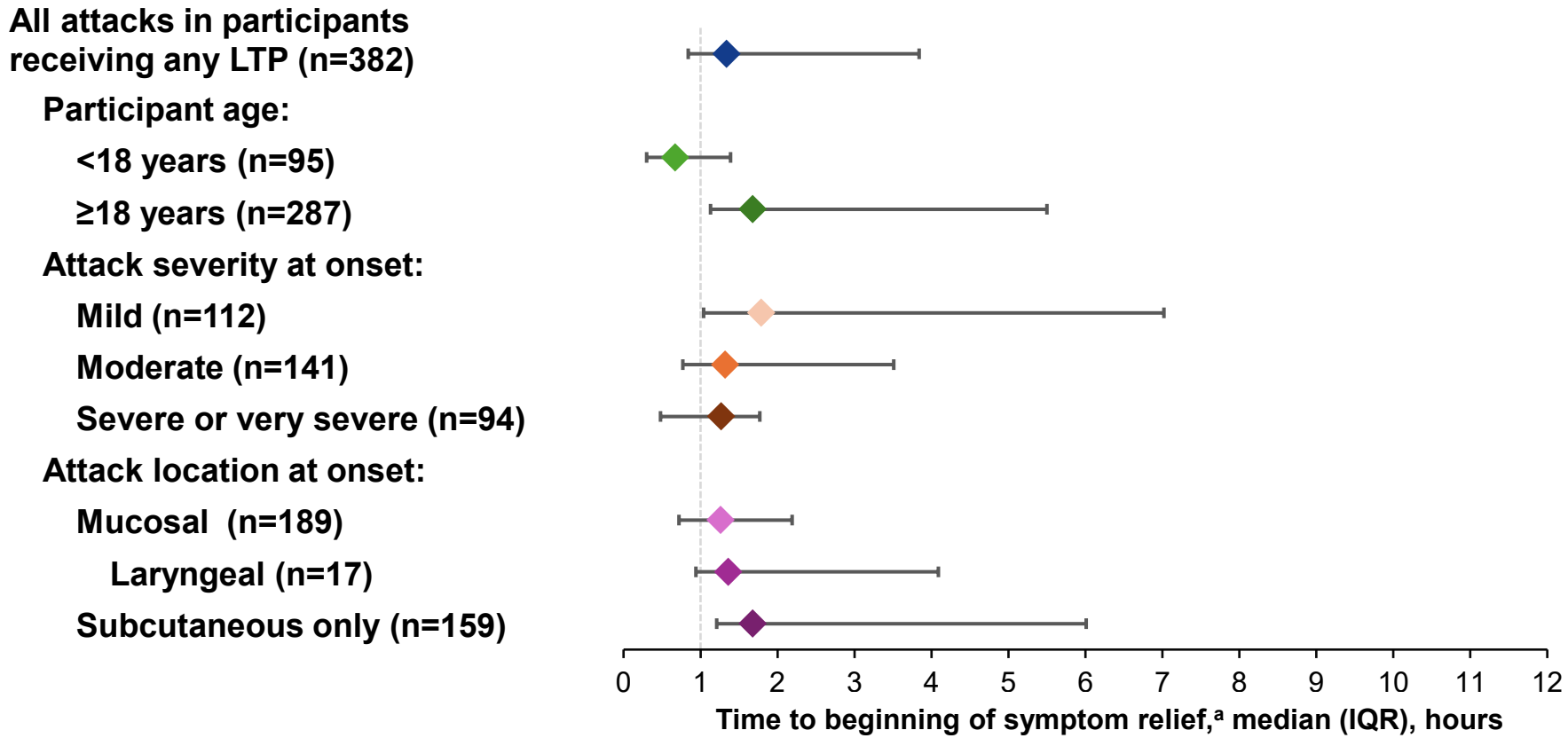
[a]Includes1 attack with a baseline severity of "None" reported by a participant who was receiving LTP with berotralstat. [b]Mucosal: attacks with primary location of "Abdomen" and/or "Larynx/Throat"; subcutaneous: other attacks not involving the mucosal locations. [c]Includes all attacks, including those not treated with sebetralstat.
KONFIDENT-S data cutoff: September 14, 2024.

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



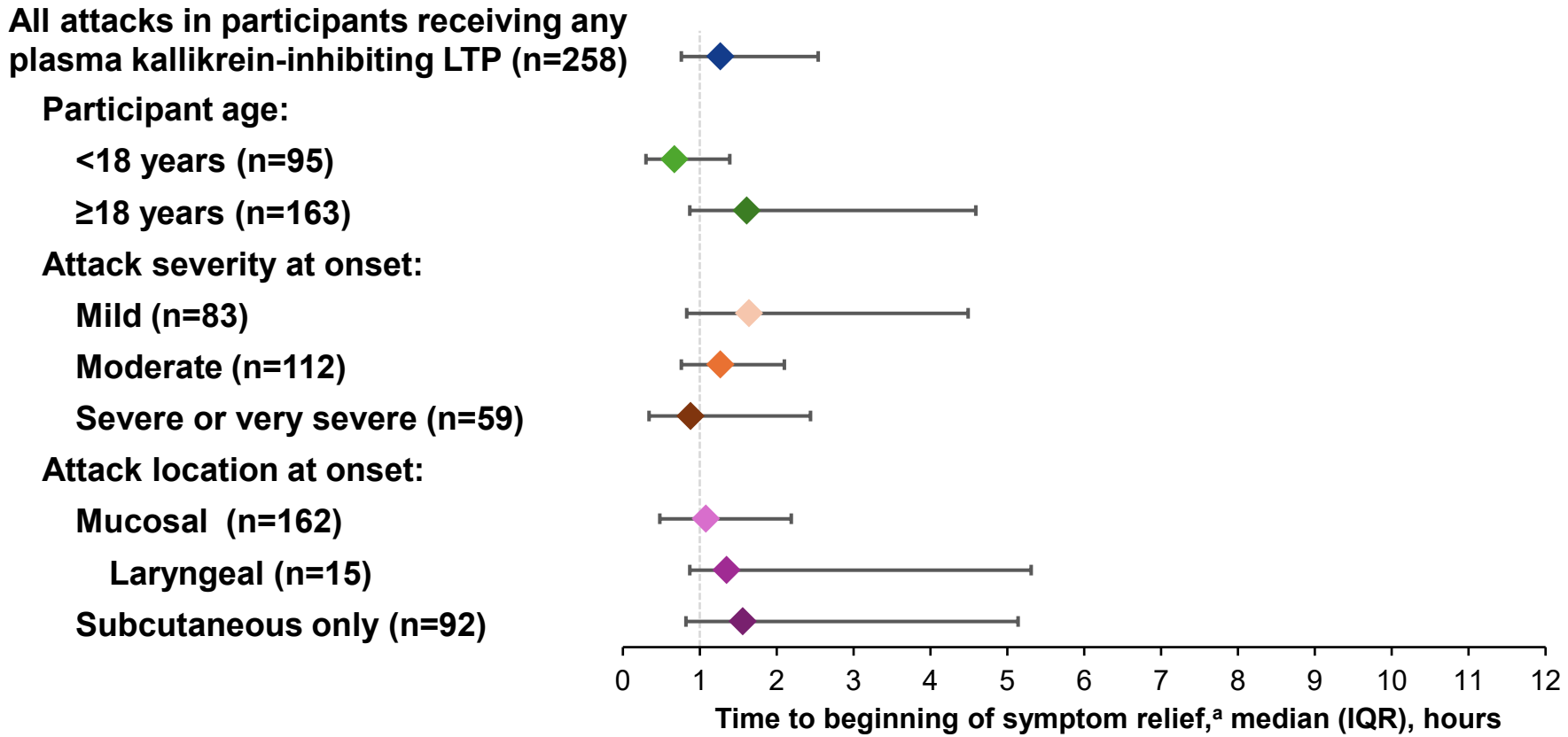
C1INH, C1 inhibitor; IQR, interquartile range; PGI-C, Patient Global Impression of Change; LTP, long-term prophylaxis.
[a]Berotralstat or lanadelumab. [b]Size of error bars may be due to the number of patients receiving C1INH as LTP (n=6), [c]Defined as a PGI-C rating of at least "A Little Better" for 2 consecutive time points, with missing data entries between consecutive time points within 12 hours of the first dose of sebetralstat.
KONFIDENT-S data cutoff: September 14, 2024. Diamonds are the medians met within time window. Error bars are Q1 and Q3.

LTP Subgroups:
Time to Beginning of Symptom Relief



LTP, long-term prophylaxis.
[a]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.
KONFIDENT-S data cutoff: September 14, 2024. Diamonds are the medians met within time window. Error bars are Q1 and Q3.

Plasma Kallikrein Inhibitor LTP Subgroups:
Time to Beginning of Symptom Relief



LTP, long-term prophylaxis.
[z]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.
KONFIDENT-S data cutoff: September 14, 2024. Diamonds are the medians met within time window. Error bars are Q1 and Q3.

Other Effectiveness Endpoints for Breakthrough Attacks Treated with Sebetralstat

	Participants, n	Sebetralstat-treated attacks, n	Time to reduction in attack severity,[a] median (IQR), hours	Time to complete resolution,[b] median (IQR), hours	Attacks treated with conventional treatment, n (%)[c]
Any LTP agent	35	382	4.2 (1.3 to >12)	14.8 (4.6 to >24)	20 (5.2)
Plasma kallikrein–inhibiting LTP[a]	29	258	3.3 (1.1 to >12)	12.1 (3.4 to >24)	13 (5.0)
Berotralstat	16	178	2.7 (0.9 to >12)	10.9 (3.0 to >24)	8 (4.5)
Lanadelumab	13	80	4.4 (1.4 to >12)	15.1 (3.7 to >24)	5 (6.3)
C1INH	6	124	>12 (1.8 to >12)	16.6 (9.0 to 23.5)	7 (5.6)

[a]Defined as a time to first incidence of decrease from baseline in Patient Global Impression of Severity (PGI-S) score for at least 2 consecutive time points within 12 hours of the first dose of sebetralstat. [b]Defined as a PGI-S rating of "None" (ie, no symptoms) within 24 hours of the first dose of sebetralstat. [c]Received conventional medicine within 12 hours of the first dose of sebetralstat.
KONFIDENT-S data cutoff: September 14, 2024.

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)**	**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	**1 (2.9)**	**1 (6.3)**	**0**	**0**
Any TEAE leading to death	0	0	0	0

- 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)
- One 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

TEAE, treatment-emergent adverse event.
KONFIDENT-S data cutoff: September 14, 2024.

Conclusions

- Participants receiving LTP continued to experience attacks in all anatomical locations, including laryngeal attacks
  - Overall attack rate for participants receiving LTP was 1.7 attacks/month
- Sebetralstat resulted in rapid symptom relief in patients receiving LTP, regardless of the individual LTP or its mechanism of action
  - Sebetralstat was effective in all age groups and in attacks of any severity and location (median times to beginning of symptom relief, reduction in attack severity, and complete resolution were 1.3, 4.2, and 14.8 hours, respectively)
  - Conventional treatment was used in 5.2% of attacks
- Sebetralstat was well-tolerated in participants receiving LTP, and no new safety signals were observed

KONFIDENT-S data cutoff: September 14, 2024.

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