On-demand Treatment of HAE Attacks with Sebetralstat in Adolescents: Pooled Analysis from KONFIDENT and KONFIDENT-S

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Background

*"…my school hasn't really been all that understanding with me being diagnosed with HAE, especially because they've never heard of it, and we've actually been **struggling for like a few months, trying to even have my emergency medicine at the school**. So, if I have an attack, I have to be checked out of school and go get my medicine from somewhere else. Instead of being able to have it on me right away."*

- 17-year-old US male with HAE-C1INH[1]

*"**I'm just scared like you know, one day my medicine will be too far [away]**, and I'll have like a life-threatening attack and like I know it could kill me."*

- 17-year-old US male with HAE-C1INH[1]

*"…how long it takes to do. … I'm prescribed 3 boxes like per dose, so like we have to push all those vials of the medicine and then do another saline. So that the thing itself usually take about half an hour… Yeah, so **the whole thing is about an hour**. ."*

- 17-year-old US male with HAE-C1INH[1]

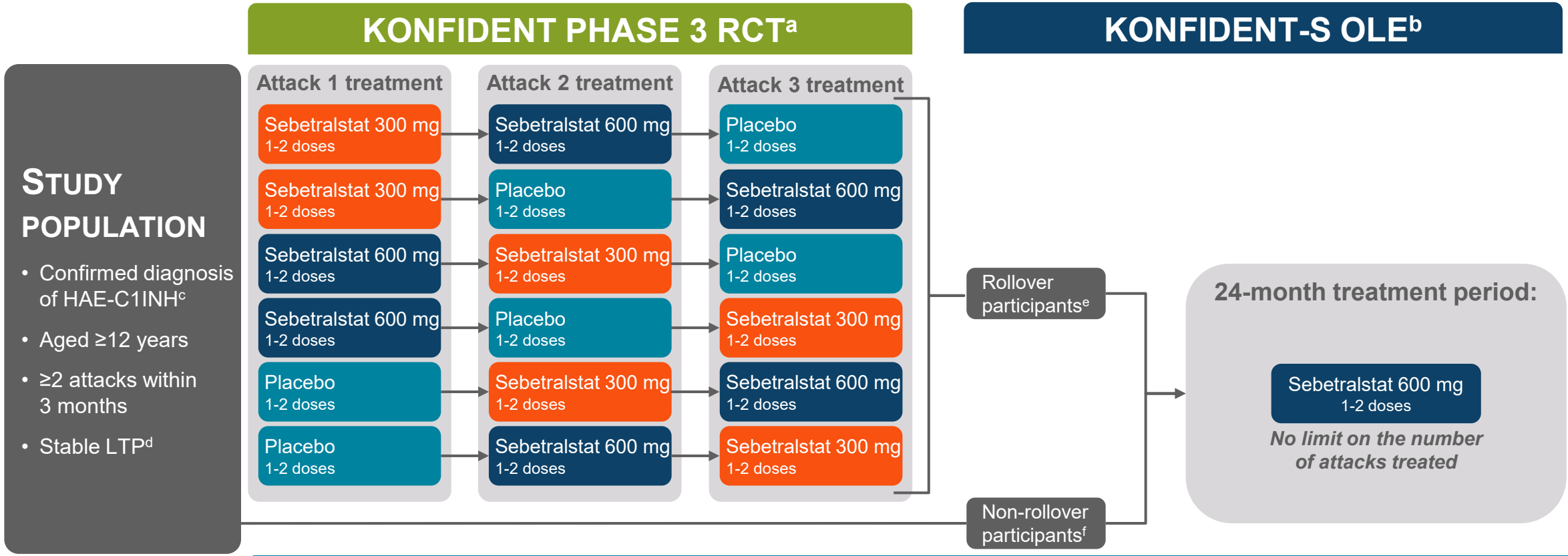
- Consistent with this feedback, a recent survey revealed that adolescents with HAE-C1INH in the US (n=14) had a mean (SD) time to treatment of 7.7 hours (13.0 hours) for their most recent treated attack (vs 3.2 hours [4.0 hours] in 80 adults)[2,a]
- Sebetralstat, an investigational oral plasma kallikrein inhibitor, was evaluated in a phase 3 clinical trial (KONFIDENT)[3] and is being further assessed in a 2-year OLE study (KONFIDENT-S) for on-demand treatment of HAE attacks in participants ≥12 years of age

HAE, hereditary angioedema; HAE-C1INH, HAE due to C1 inhibitor deficiency; IV, intravenous; OLE, open-label extension; SD, standard deviation.

[a]In the USA, all approved on-demand treatment options for adolescents require IV administration (C1INH replacement) or require administration by a health care provider (ecallantide).

1. Broderick L, et al. *Orphanet J Rare Dis*. 2025;20(1):16. 2. Christiansen S, et al. *Ann Allergy Asthma Immunol*. 2024.doi:10.1016/j.anai.2024.12.012. 3. Riedl M et al. *New Engl J Med.* 2024;391:32-43.

Study Designs



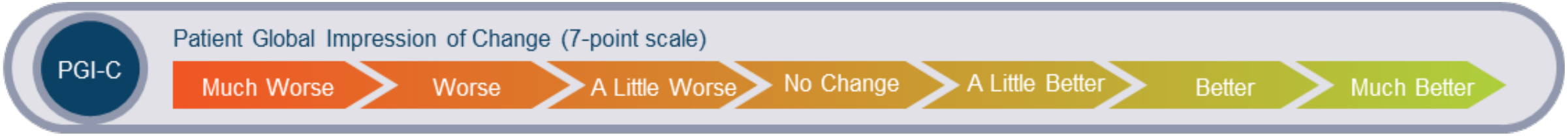
Pooled populations in this analysis to assess safety and effectiveness:

- Adolescents (12 to 17 years) who treated attacks with sebetralstat 600 mg (1-2 doses)
- Adults (≥18 years) who treated attacks with sebetralstat 600 mg (1-2 doses)

HAE-C1INH, hereditary angioedema due to C1 inhibitor deficiency; LTP, long-term prophylaxis; OLE, open-label extension; RCT, randomized controlled trial.
[a]NCT05259917. [b]NCT05505916, EudraCT: 2021-001176-42. [c]Participants must have had access to conventional on-demand treatment. [d]Participants receiving LTP were required to be on a stable dose for ≥3 months prior to screening.
[e]Completed the phase 3 KONFIDENT trial. [f]All other participants, including those who participated in the phase 2 RCT (NCT04208412).

Effectiveness Endpoints

- **Time to beginning of symptom relief** defined as a rating of at least ‘A Little Better’ on the PGI-C scale for ≥2 consecutive time points within 12 hours
- **Time to reduction in attack severity** defined as a decrease in PGI-S rating for ≥2 consecutive time points within 12 hours
- **Time to complete attack resolution** defined as a PGI-S rating of “None” within 24 hours

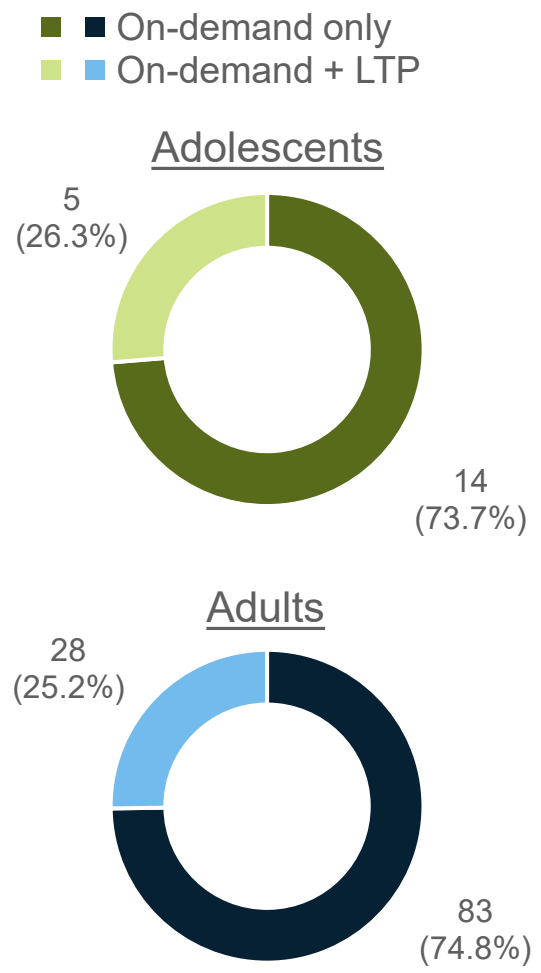


PGI-C, patient global impression of change; PGI-S, patient global impression of severity.

Participant Demographics

	Adolescents n=19	Adults n=111
Age, mean (range), years	15.3 (13-17)	40.0 (18-77)
Sex, male, n (%)	10 (52.6)	41 (36.9)
Race, n (%)		
White	16 (84.2)	90 (81.1)
Black or African American	0	0
Asian	0	13 (11.7)
Other	0	2 (1.8)
Not reported	3 (15.8)	6 (5.4)
BMI, mean (range), kg/m^2	23.6 (16.7-35.6)	27.5 (17.2-42.8)
HAE-C1INH-Type 1, n (%)	19 (100)	102 (91.9)
Time since diagnosis, median (IQR), years	10.0 (5.0-12.8)	13.0 (6.2-22.2)

Current Treatment Paradigm



BMI, body-mass index; HAE-C1INH, hereditary angioedema due to C1 inhibitor deficiency; IQR, interquartile range; LTP, long-term prophylaxis; OLE, open-label extension.
Note: Data cutoff date of January 31, 2024.

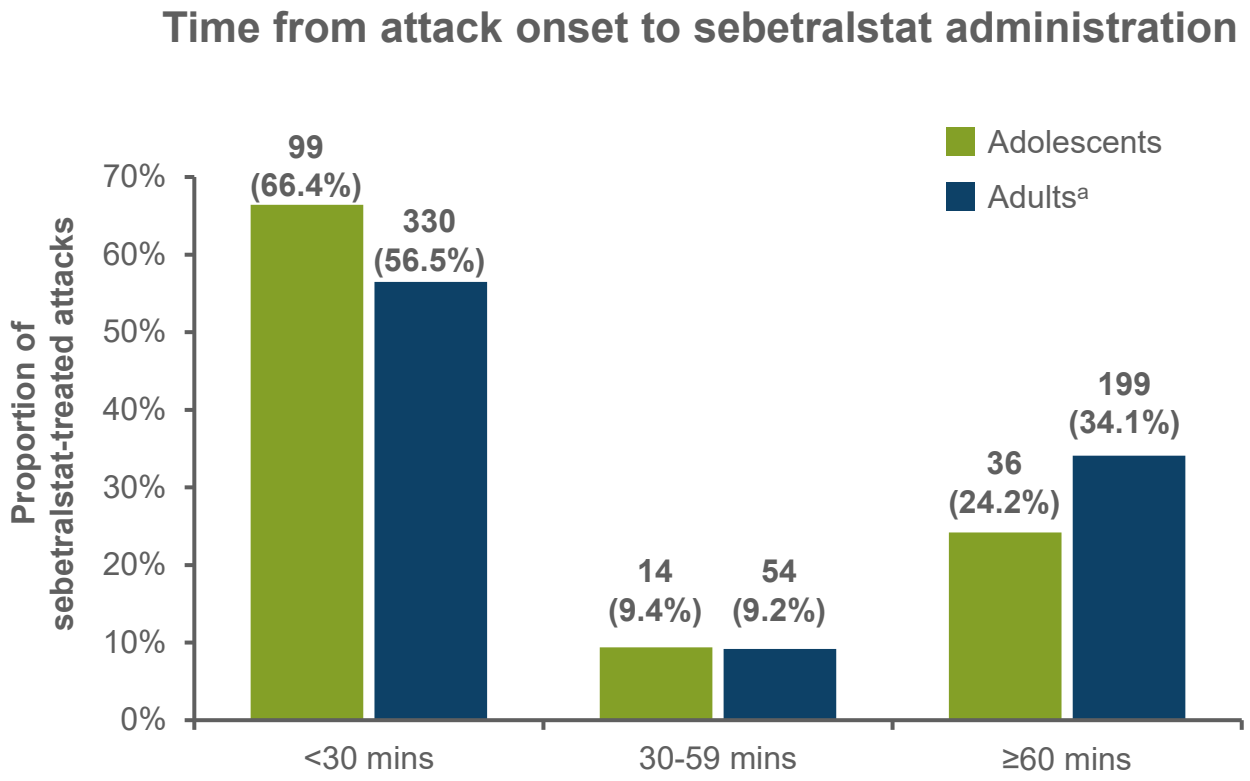
Sebetralstat-treated Attack Characteristics

	Attacks in adolescents n=149	Attacks in adults[b] n=584
Attack locations, n (%)		
Laryngeal	1 (0.7)	15 (2.6)
Subcutaneous	81 (54.4)	344 (58.9)
Abdominal	54 (36.2)	171 (29.3)
Subcutaneous and abdominal	13 (8.7)	47 (8.0)
Baseline PGI-S rating, n (%)		
Mild	34 (22.8)[a]	203 (34.8)[b]
Moderate	50 (33.6)	261 (44.7)
Severe/very severe	65 (43.6)	113 (19.3)

- Adolescents treated a median of 4 attacks (IQR, 1-8; range, 1-34)
- Adults treated a median of 2 attacks (IQR, 1-6; range 1-38)

IQR, interquartile range; OLE, open-label extension; PGI-S, Patient Global Impression of Severity.
[a]PGI-S none: 1 (0.7%). [b]Missing: 7 (1.2%); PGI-S none: 3 (0.5%).
Note: Data cutoff date of January 31, 2024.

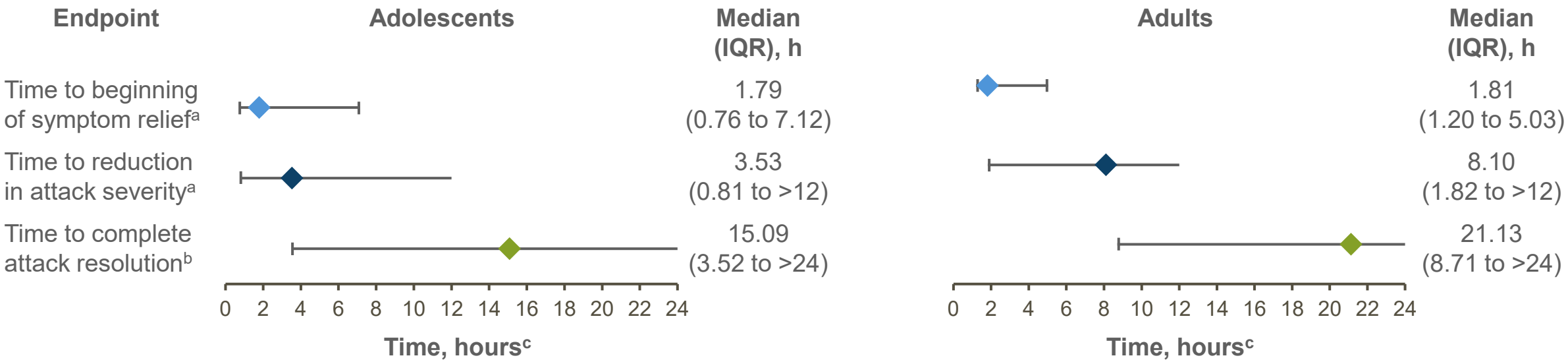
Time to Treatment



- The median time (IQR) from attack onset to sebetralstat administration was 4.0 minutes (1.0 to 52.0) for adolescents (16.0 minutes [1.0 to 93.0] in adults)
- 75.8% of attacks were treated in <1 hour of onset in adolescents (65.7% in adults)

IQR, interquartile range.
[a]Missing: 1 (0.2%).
Note: Data cutoff date of January 31, 2024.

Effectiveness of Sebetralstat



- 25 attacks (16.8%) were treated with a second administration of sebetralstat within 12 hours in adolescents (137 [23.5%] in adults)
- Among the attacks that achieved beginning of symptom relief, 93.5% of attacks[d] did so before or without a second administration of sebetralstat (94.8% in adults)
- 5 attacks (3.4%) were treated with conventional treatment within 12 hours (40 attacks [6.8%] in adults)

IQR, interquartile range; OLE, open-label extension.
[a]Within 12 hours. [b]Within 24 hours. [c]Error bars display IQR. [d]Among 108 attacks (72.5%) achieving the beginning of symptom relief within 12 hours.
Note: Data cutoff date of January 31, 2024. Analysis included 149 attacks treated with sebetralstat 600 mg.

Safety of Sebetralstat

	Adolescents n=19	Adults n=111
Any TEAE, n (%)	6 (31.6)	50 (45.0)
Treatment-related	**1 (5.3)**	**9 (8.1)**
Serious TEAE, n (%)	0	5 (4.5)
Treatment-related	**0**	**0**
Severe TEAE, n (%)	0	5 (4.5)
Treatment-related	**0**	**1 (0.9)**
Any TEAE leading to permanent discontinuation, n (%)	0	4 (3.6)
Any TEAE leading to death, n (%)	0	0

- A treatment-related TEAE of tremor was reported by 1 adolescent and resolved on the same day

TEAE, treatment-emergent adverse event.
Note: Data cutoff date of January 31, 2024.

Conclusion

- Adolescents with HAE-C1INH delay on-demand treatment due to challenges associated with injectable on-demand therapies[1]
- Oral sebetralstat enabled rapid treatment and early symptom relief in adolescents
  - The median time (IQR) to treatment was only 4.0 minutes (1.0-52.0)
  - Median time (IQR) to beginning of symptom relief was 1.79 hours (0.76-7.12)
  - 16.8% of attacks were treated with a second administration of sebetralstat
    - Among attacks that achieved beginning of symptom relief, 93.5% of attacks did so before or without a second administration of sebetralstat
  - 3.4% of attacks were treated with conventional treatment within 12 hours
- Sebetralstat was well tolerated and no adolescents discontinued treatment due to AEs

AE, adverse event; HAE-C1INH, hereditary angioedema due to C1 inhibitor deficiency; IQR, interquartile range.
Note: Data cutoff date of January 31, 2024.
1. Christiansen S, et al. *Ann Allergy Asthma Immunol*. 2024.doi:10.1016/j.anai.2024.12.012.

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HAEA, US Hereditary Angioedema Association; HAEi, HAE International.