Sebetralstat for On-demand Treatment of Hereditary Angioedema Attacks in European Participants: Interim Analysis from KONFIDENT-S

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Background and Objective

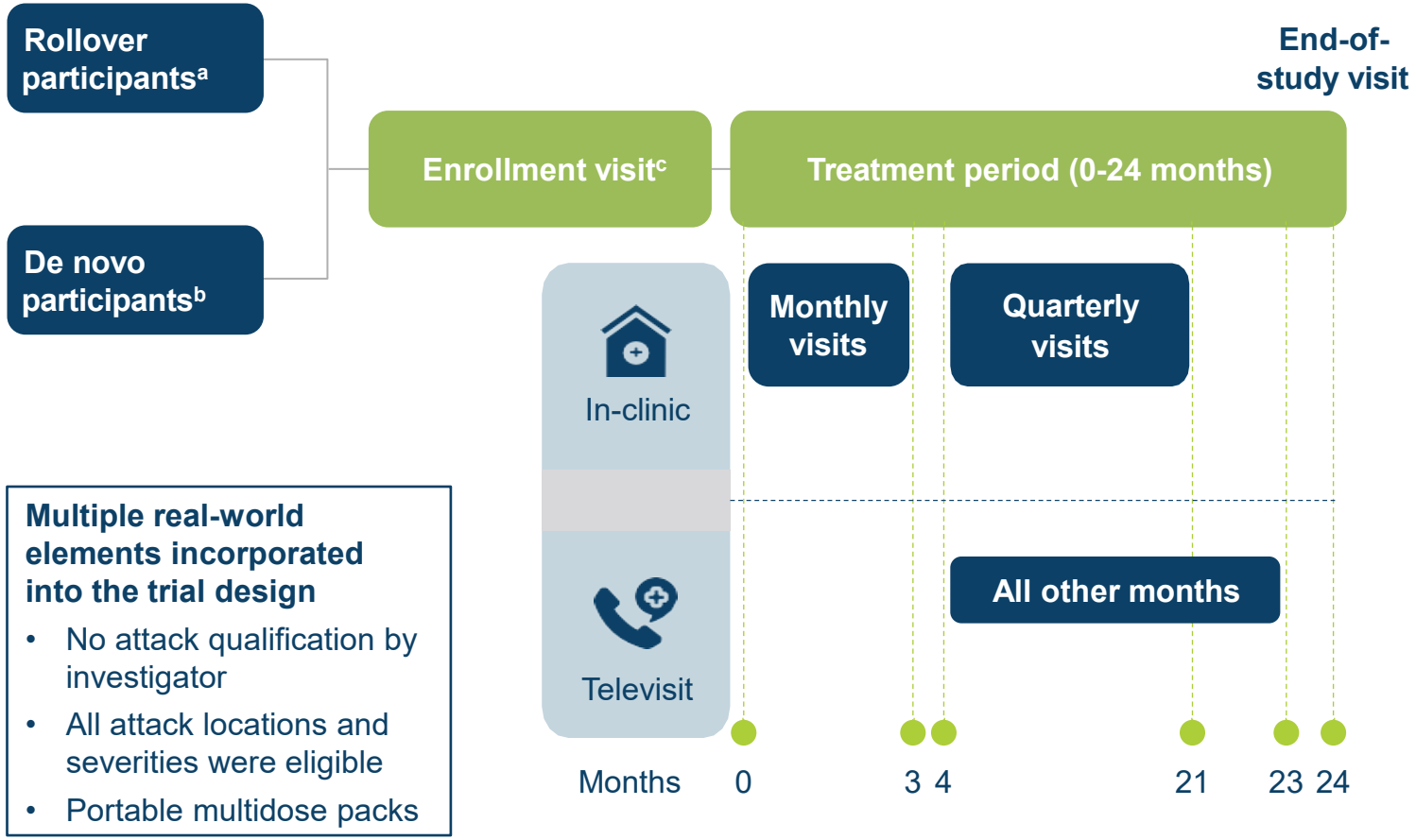
- Sebetralstat—a small molecule plasma kallikrein inhibitor—is an orally administered, on-demand treatment for HAE attacks in adults and adolescents aged ≥12 years[1,2]
- In the phase 3 KONFIDENT trial in patients with HAE, sebetralstat compared with placebo resulted in shorter times to beginning of symptom relief, reduction in attack severity, and complete attack resolution; sebetralstat was well tolerated[3]

Herein, we present safety and efficacy data from an interim analysis of the European subgroup of KONFIDENT-S, an ongoing, 2-year, open-label extension study of sebetralstat for the on-demand treatment of HAE

HAE, hereditary angioedema.

1. Sebetralstat (EKTERLY) prescribing information. KalVista Pharmaceuticals, Inc. 2025. 2. Sebetralstat (EKTERLY) Summary of Product Characteristics. KalVista Pharmaceuticals (Ireland), Ltd; 2025. 3. Riedl MA et al. *New Engl J Med.* 2024;391(1):32-43.

KONFIDENT-S OLE Trial Design



Multiple real-world elements incorporated into the trial design

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

Inclusion criteria

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

Treatment

- Self-administer sebetralstat 600 mg (2 × 300-mg tablets) as early as possible after attack onset
- Second administration allowed if warranted

Endpoints

- Safety (adverse events)
- Time to beginning of symptom relief (by PGI-C) ≤12 hours
- Time to first reduction in severity (by PGI-S) ≤12 hours
- Time to complete attack resolution (by PGI-S) ≤24 hours

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.
HAE-C1NH, hereditary angioedema due to C1 inhibitor deficiency; OLE, open-label extension; PGI-C, Patient Global Impression of Change; PGI-S, Patient Global Impression of Severity.

Baseline Characteristics of European Participants with ≥1 Sebetralstat-treated Attack[a]

	Overall n=69
Age, median (IQR), years	35.0 (22.0–48.0)
≥18 years of age, n (%)	57 (82.6)
Sex, female, n (%)	39 (56.5)
White race, n (%)	64 (92.8)
BMI, median (IQR), kg/m²	25.5 (22.4–30.8)
HAE-C1INH type, n (%)	
Type 1	66 (95.7)
Type 2	3 (4.3)
Treatment, n (%)	
On-demand only	60 (87.0)
LTP	9 (13.0)

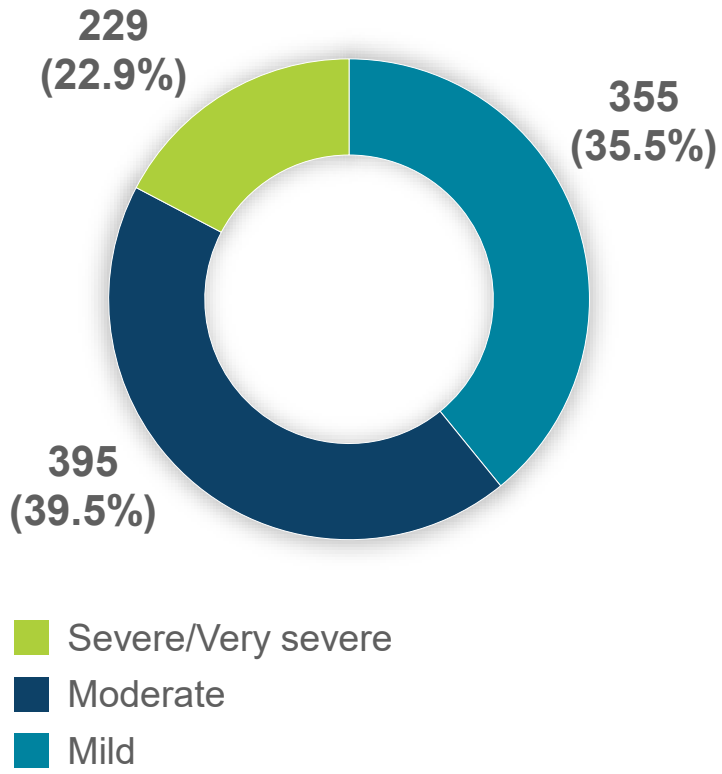
- Participants treated a median of 10 attacks (IQR, 5-20) during the study

Data cutoff: September 14, 2024.
[a]Safety analysis population from 15 European countries.
BMI, body mass index; HAE-C1NH, hereditary angioedema due to C1 inhibitor deficiency; IQR, interquartile range; LTP, long-term prophylaxis.

Attack Characteristics in European Participants

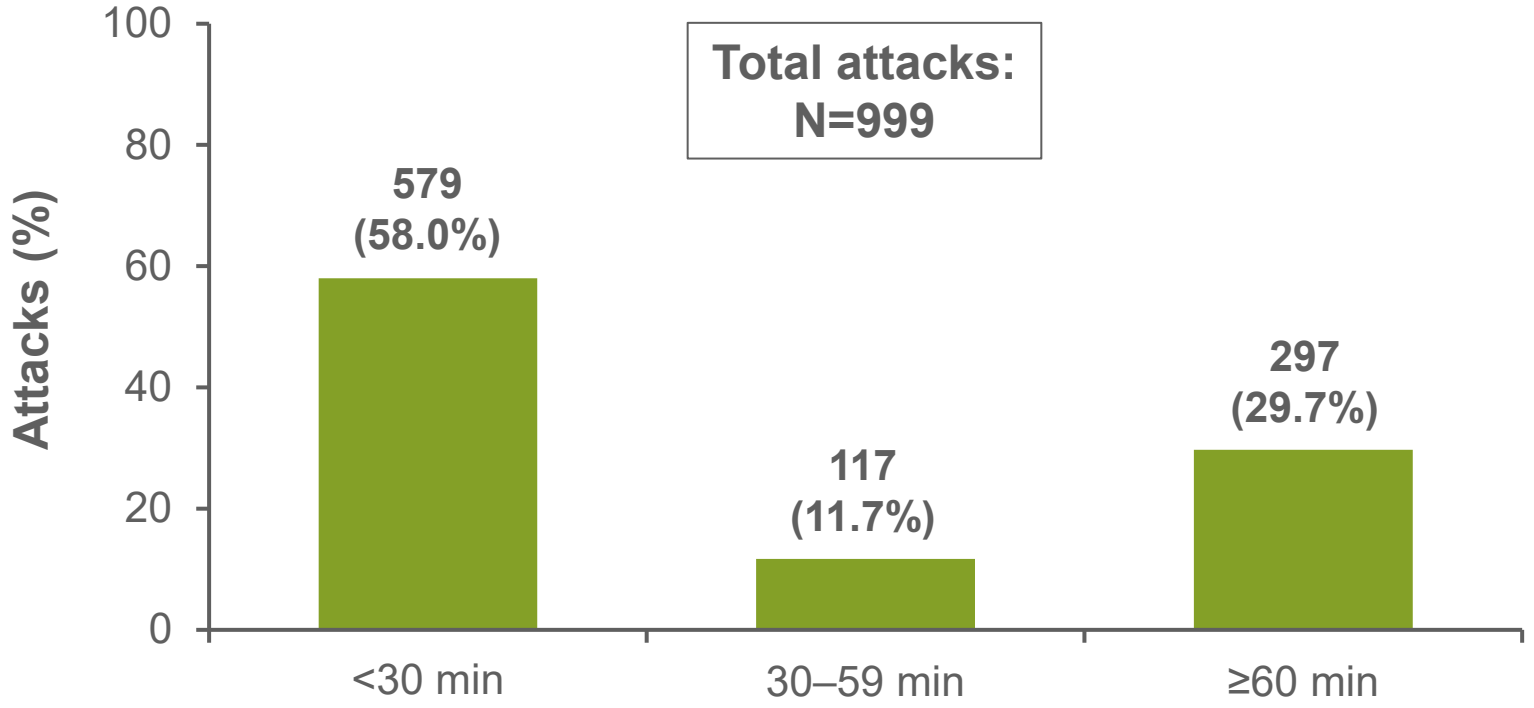
	Total attacks: N=999
Primary attack locations,[a,b] n (%)	
Abdomen	387 (38.7)
Arms/hands	308 (30.8)
Legs/feet	237 (23.7)
Genitals	60 (6.0)
Head/face/neck	54 (5.4)
Torso	44 (4.4)
Larynx/throat	23 (2.3)
Primary pooled attack location,[b,c] n (%)	
Mucosal	410 (41.0)
Subcutaneous only	567 (56.8)

Baseline PGI-S rating[d,e]



Data cutoff: September 14, 2024.
[a]Participants who had multiple attack locations were counted once in each reported location. [b]Missing: 22 (2.2%). [c]Mucosal: abdomen, larynx/throat; subcutaneous: all other attack locations. [d]PGI-S score was transformed into numeric values: 0=none, 1=mild, 2=moderate, 3=severe, 4=very severe. [e]'None' was reported for 12 attacks (1.2%); missing: 20 (2.0%).
PGI-S, Patient Global Impression of Severity.

Time from Attack Onset to Sebetralstat Administration in European Participants

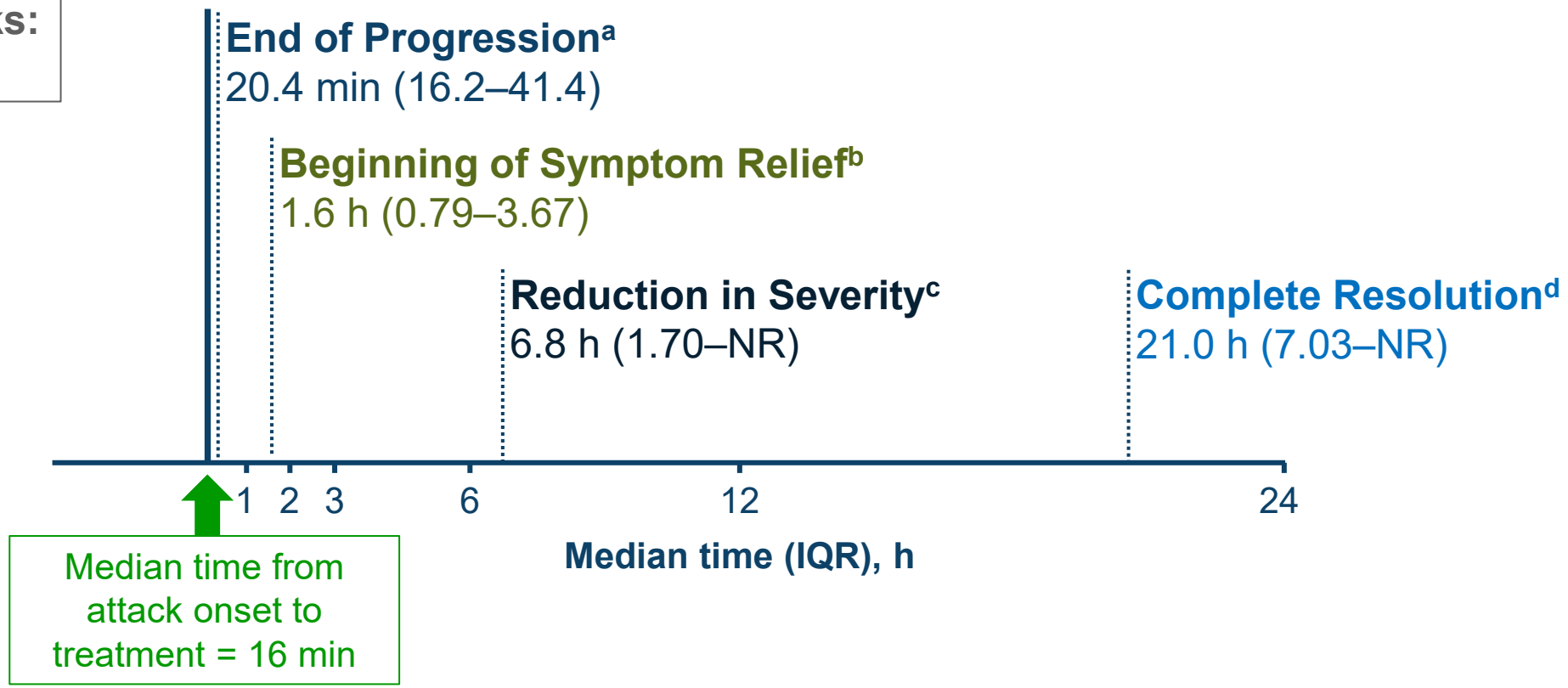


- The median time from attack onset to sebetralstat administration was 16.0 minutes (IQR, 1.0–69.0)
  - 69.7% of attacks were treated within <1 hour of onset
- For adolescents (n=12), the median time to sebetralstat administration was 10.0 minutes (IQR, 1.0-41.0)

Data cutoff: September 14, 2024.
IQR, interquartile range.

Effectiveness in Sebetralstat-treated Attacks

Total attacks: N=999

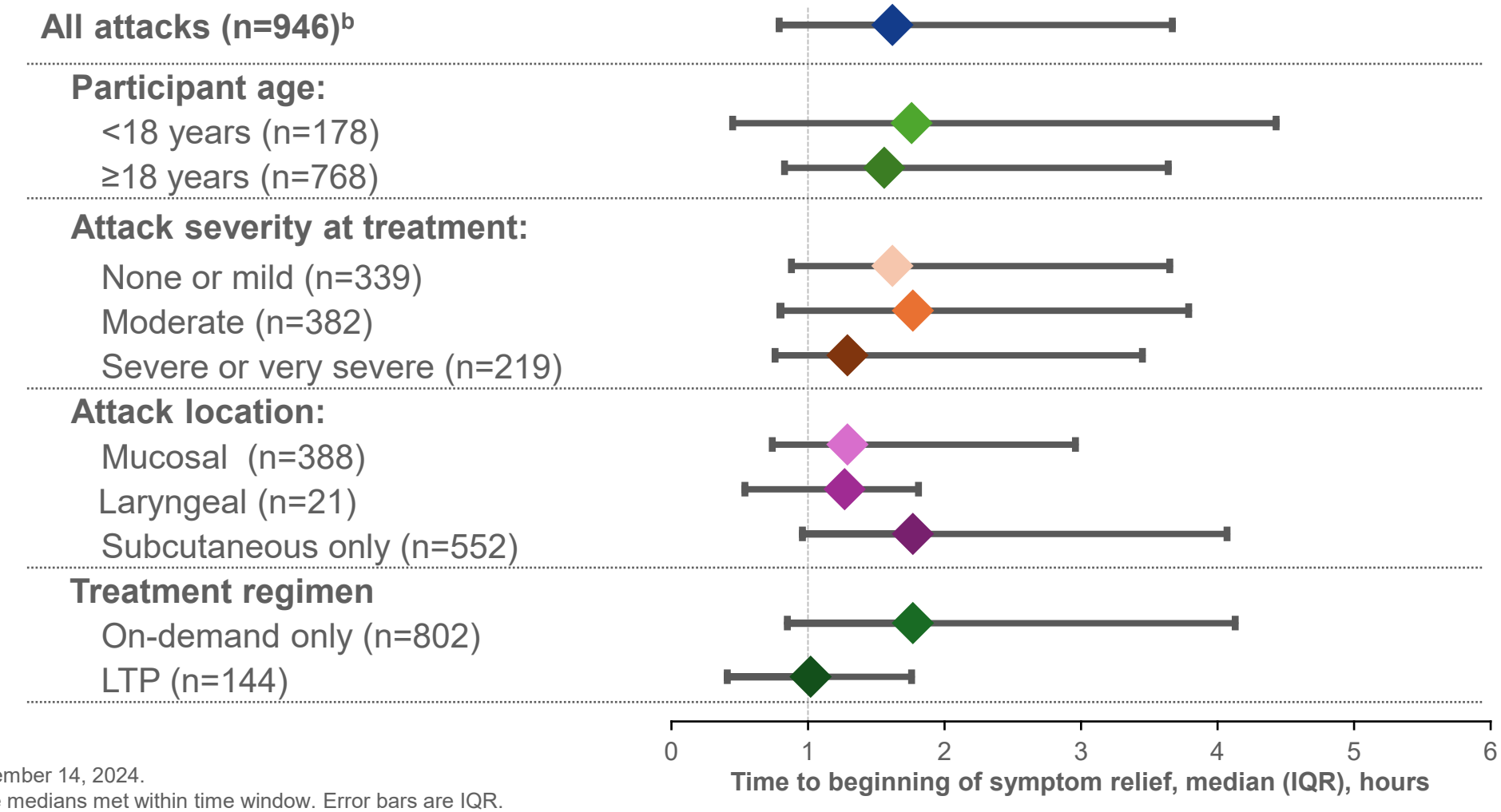


Data cutoff: September 14, 2024.

[a]End of progression was analyzed post hoc as the time when the worst HAE attack severity was recorded within 4 hours on the PGI-S scale for attacks treated with sebetralstat. [b]Defined as a PGI-C rating of at least "A little better" for ≥2 consecutive time points (with missing data entries in between) within 12 hours of the first dose of sebetralstat (7-point scale: "Much worse," "Worse," "A lttle worse," "No change," "A little better," "Better," "Much better"). [c]Defined as a ≥1-level decrease on the PGI-S scale for ≥2 consecutive time points within 12 hours of the first dose of sebetralstat. [d]Defined as a PGI-S rating of "None" (ie, no symptoms) within 24 hours.

HAE, hereditary angioedema; IQR, interquartile range; NR, not reached; PGI-C, Patient Global Impression of Change; PGI-S, Patient Global Impression of Severity.

Time to Beginning of Symptom Relief in Subgroups[a]



Data cutoff: September 14, 2024.
Diamonds are the medians met within time window. Error bars are IQR.
[a]Defined as a PGI-C rating of at least "A little better" for 2 consecutive time points within 12 hours of the first dose of sebetralstat.
[b]Excluding attacks that lacked post-baseline assessments.
IQR, interquartile range; LTP, long-term prophylaxis; PGI-C, Patient Global Impression of Change.

Sebetralstat Administration and Use of Conventional Treatment in KONFIDENT-S

	Total attacks: N=999
Attacks treated with a second dose within 12 hours of the first dose of sebetralstat, n (%)	174 (17.4)
Attacks reaching beginning of symptom relief within 12 hours before or without an additional dose[a], %	97.0
Attacks treated with conventional treatment within 12 hours of the first dose of sebetralstat, n (%)	60 (6)

[a]Among the 803 attacks that reached this endpoint (80.4%).
Data cutoff: September 14, 2024.

Safety

Participants experiencing TEAE, n (%)	Total n=69
Any TEAE	40 (58.0)
Treatment related[a]	6 (8.7)
Any TEAE within 3 days of sebetralstat administration	27 (39.1)
Any grade ≥3 TEAE	6 (8.7)
Treatment related	0
Any serious TEAE	6 (8.7)
Treatment related	0
Any TEAE leading to hospitalization	5 (7.2)
Any TEAE leading to study discontinuation	2 (2.9)[b]
Any TEAE leading to death	0

Data cutoff: September 14, 2024.
[a]Six patients reported treatment-related TEAEs, including headache (n=3), influenza-like illness (n=3), vomiting (n=3), skin burning sensation (n=2), myalgia (n=2), and tremor (n=1). [b]TEAEs leading to discontinuations included intracranial mass (n=1) and skin burning sensation (n=1).
TEAE, treatment-emergent adverse event.

Conclusions

- In KONFIDENT-S, sebetralstat enabled early treatment of HAE attacks in European participants (median time, 16 minutes)
- Sebetralstat resulted in rapid end of attack progression, early symptom relief, reduction in attack severity, and attack resolution, consistent with data reported in the KONFIDENT trial
- Median time to beginning of symptom relief was consistent across all subgroups, including by age, attack severity at onset, attack location at onset, and LTP use
- Sebetralstat was well tolerated, and safety results were consistent with the phase 3 KONFIDENT trial[1]

1. Riedl MA et al. *New Engl J Med.* 2024;391:32-43. HAE, hereditary angioedema; LTP, long-term prophylaxis.

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