Anxiety Associated with HAE Attacks: Results from the Phase 3 KONFIDENT Trial of Oral Sebetralstat

Timothy Craig,[1] Emel Aygören-Pürsün,[2] Jonathan A. Bernstein,[3] Paula J. Busse,[4] Teresa Caballero,[5] Danny M. Cohn,[6] Mar Guilarte,[7] Henriette Farkas,[8] Douglas H. Jones,[9] Sorena Kiani-Alikhan,[10] Michael E. Manning,[11,12] Marcus Maurer,[13,14] Marc A. Riedl,[15] Sinisa Savic,[16] H. James Wedner,[17] Patrick F. K. Yong,[18] Andrea Zanichelli,[19,20] Erik Hansen,[21] James Hao,[21] Michael D. Smith,[21] Christopher M. Yea,[21] Paul K. Audhya,[21] William R. Lumry[22]

[1]Pennsylvania State University, Hershey, PA, USA; Vinmec International Hospital, Times City, Hanoi, Vietnam; [2]University Hospital Frankfurt, Goethe University Frankfurt, Frankfurt, Germany; [3]University of Cincinnati College of Medicine, and Bernstein Clinical Research Center, Cincinnati, OH, USA; [4]Icahn School of Medicine at Mount Sinai School of Medicine, New York, NY, USA; [5]Hospital Universitario La Paz, Hospital La Paz Health Research Institute (IdiPAZ), Biomedical Research Network on Rare Diseases (CIBERER), Madrid, Spain; [6]Amsterdam University Medical Center, University of Amsterdam, Amsterdam, Netherlands; [7]Hospital Universitari Vall d'Hebron, Vall d'Hebron Research Institute (VHIR), Barcelona, Spain; [8]Hungarian Angioedema Center of Reference and Excellence, Semmelweis University, Budapest, Hungary; [9]Rocky Mountain Allergy, Asthma, and Immunology, Layton, UT, USA; [10]University College London, London, UK; [11]Medical Research of Arizona, Scottsdale, AZ, USA; [12]University of Arizona College of Medicine-Phoenix, Phoenix, AZ, USA; [13]Institute of Allergology, Charité-Universitätsmedizin Berlin, corporate member of Freie Universitätsmedizin Berlin and Humboldt-Universität zu Berlin, Berlin, Germany; [14]Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Immunology and Allergology, Berlin, Germany; [15]University of California, San Diego, La Jolla, CA, USA; [16]The Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, UK; [17]Washington University School of Medicine, St. Louis, MO, USA; [18]Frimley Health NHS Foundation Trust, Frimley, UK; [19]Operative Unit of Medicine, Angioedema Center, IRCCS Policlinico San Donato, San Donato Milanese, Milan, Italy; [20]University of Milan, Milan, Italy; [21]KalVista Pharmaceuticals, Salisbury, United Kingdom, and Cambridge, MA, USA; [22]AARA Research Center, Dallas, TX, USA

Presented at the 14th C1-inhibitor Deficiency and Angioedema Workshop; 29 May-1 June, 2025; Budapest, Hungary

Disclosures

- Timothy Craig has received grants, consulting fees, honoraria, and/or served as an advisory boards and/or data safety monitoring for KalVista Pharmaceuticals, Astria, Takeda, BioMarin Pharmaceuticals, BioCryst, CSL Behring, Grifols, GSK, Intellia Therapeutics, Ionis Pharmaceuticals, Pharming, and Pharvaris; serves as the director for ACARE International Hereditary Angioedema Center and Alpha-1 Resource Center; and is a member of the Medical Advisory Board for the HAE-A\
- This study was funded by KalVista Pharmaceuticals

Background

Anxiety in people living with HAE is underappreciated

- The unpredictable, painful, and life-threatening nature of HAE attacks is associated with substantial psychological burden[1-5]
- Nearly one-third of respondents from a recent international survey of HAE patients (n=284) experienced moderate to extreme anxiety due to anticipated use of parenteral on-demand treatment (see our associated poster presentation)[6]

Unpredictable timing of attacks

- Fear associated with the anticipation of the next attack

Attack-associated anxiety

- Impact of attack symptoms

Treatment-associated anxiety

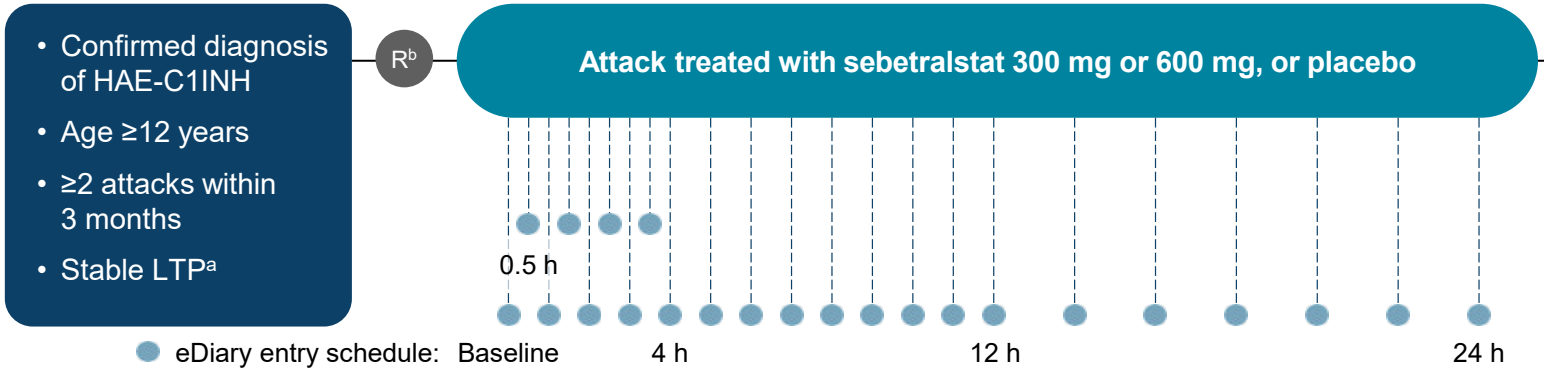
- Stress of injecting or infusing on-demand therapy

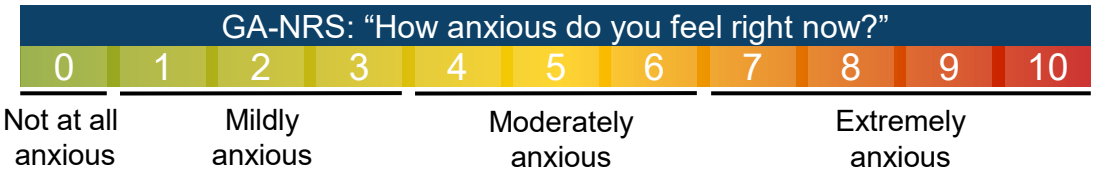
The **objective** of this analysis was to assess the impact of sebetralstat, an investigational oral plasma kallikrein inhibitor for the on-demand treatment of HAE attacks, on attack-related anxiety

HAE, hereditary angioedema.

1. Lumry WR et al. *Allergy*. 2021;76(4):1188-1198; 2. Hews-Girard J et al. *Allergy Asthma Clin Immunol*. 2021;17(1):61; 3. US Food and Drug Administration. The Voice of the Patient. 2018:31. Accessed 22 Apr 2025. https://www.fda.gov/files/about%20fda/published/The-Voice-of-the-Patient---Hereditary-Angioedema.pdf. 4. Christiansen S et al. *Ann Allergy Asthma Immunol.* 2024:S1081-1206(24)01732-0; 5. Betschel SD et al. *Allergy Asthma Clin Immunol*. 2024;20(1):43; 6. Cancian M et al. Presented at: 14th C1-inhibitor Deficiency and Angioedema Workshop; 29 May-1 June 2025; Budapest, Hungary.

KONFIDENT Trial Design and Anxiety Endpoints as Measured by Generalized Anxiety Numeric Rating Scale (GA-NRS)





Anxiety was recorded by use of GA-NRS at the time points above and analysed as the following endpoints

- Cumulative GA-NRS score: Area under the curve (AUC) from treatment administration to 12 or 24 hours (AUC_{0-12} or AUC_{0-24})[c]
- Least squares mean (LSM) change from baseline at 4- and 12-hours post-baseline
- Time to a ≥2-point reduction in GA-NRS score at ≥2 consecutive time points and agreement with time to beginning of symptom relief within 12 hours (the primary endpoint of the KONFIDENT trial)[d,e,f]
- Correlation between GA-NRS rating and baseline demographics and attack characteristics[g]

AUC, area under the curve; GA-NRS, Generalized Anxiety Numeric Rating Scale; LSM, least squares mean; LTP, long-term prophylaxis; PGI-C, Patient Global Impression of Change; R, randomization.
[a]Participants receiving LTP were required to be on a stable dose for ≥3 months prior to screening. [b]Participants were randomly assigned 1:1:1:1:1:1 to a treatment sequence using a permuted-block method, stratified by the use of LTP at enrolment. [c]Pre-specified exploratory endpoint. [d]In attacks with baseline GA-NRS score ≥2. [e]Cohen's kappa analysis was used to determine the agreement between time to ≥2-point reduction in GA-NRS score and time to beginning of symptom relief. [f]Beginning of symptom relief was defined as a PGI-C rating of "A Little Better" for ≥2 consecutive time points. [g]Pearson correlation was used to determine the coefficients.

Attacks Inducing Moderate to Extreme Anxiety

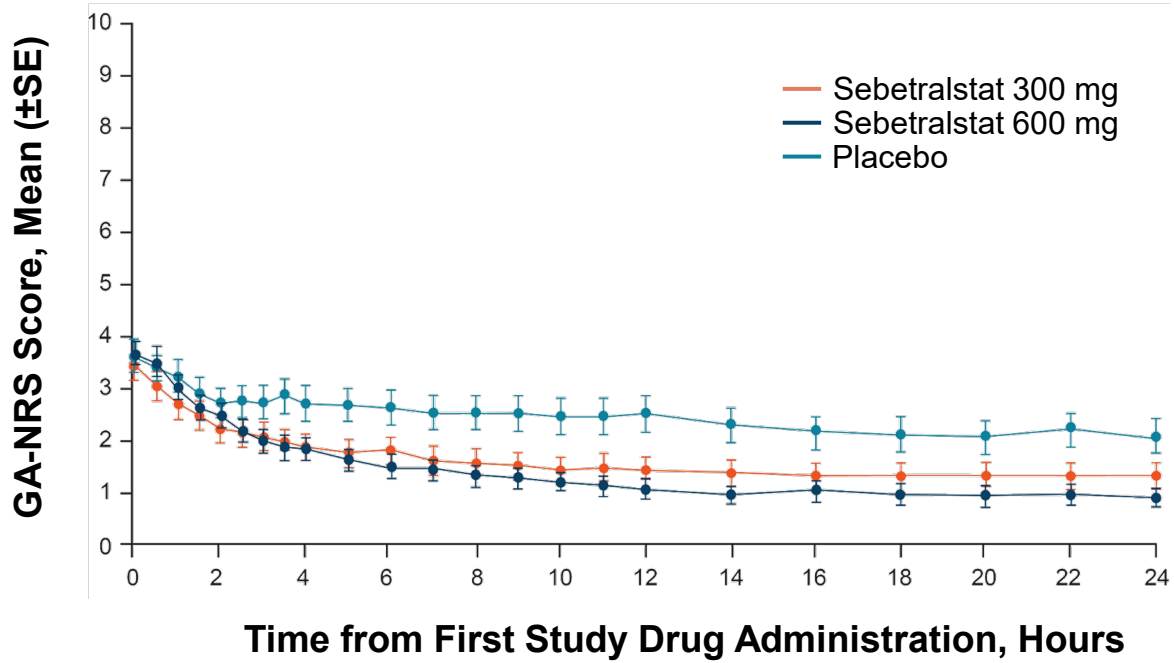
- In 261 attacks for which there are GA-NRS records in KONFIDENT, the median GA-NRS score was 3.0 at baseline
  - **115 attacks (44%)** induced moderate to extreme anxiety[a] at baseline
- Factors associated with increased anxiety at the onset of an attack included
  - Female sex (vs male, *P*=0.0034)
  - Shorter time since HAE diagnosis (vs longer time, *P*=0.0014)
  - Moderate or severe/very severe baseline attack severity
    - Moderate (vs mild, *P*=0.0030)
    - Severe/very severe (vs mild, *P*<0.0001)

	All attacks[1] N=264	Attacks inducing moderate to extreme anxiety n=115/261[b] (44%)
Baseline PGI-S category[c]		
Mild[d]	115 (43.6)	38 (33.0)
Moderate	102 (38.6)	47 (40.9)
Severe/very severe	45 (17.0)	30 (26.1)
Baseline primary attack location[c]		
Abdomen	114 (43.2)	57 (49.6)
Legs/feet	62 (23.5)	33 (28.7)
Arms/hands	76 (28.8)	30 (26.1)
Head/face/neck	29 (11.0)	12 (10.4)
Larynx/throat	8 (3.0)	4 (3.5)
Genitals	9 (3.4)	3 (2.6)
Time from onset to first administration, median (IQR), minutes	41 (6-140)	45 (6-155)

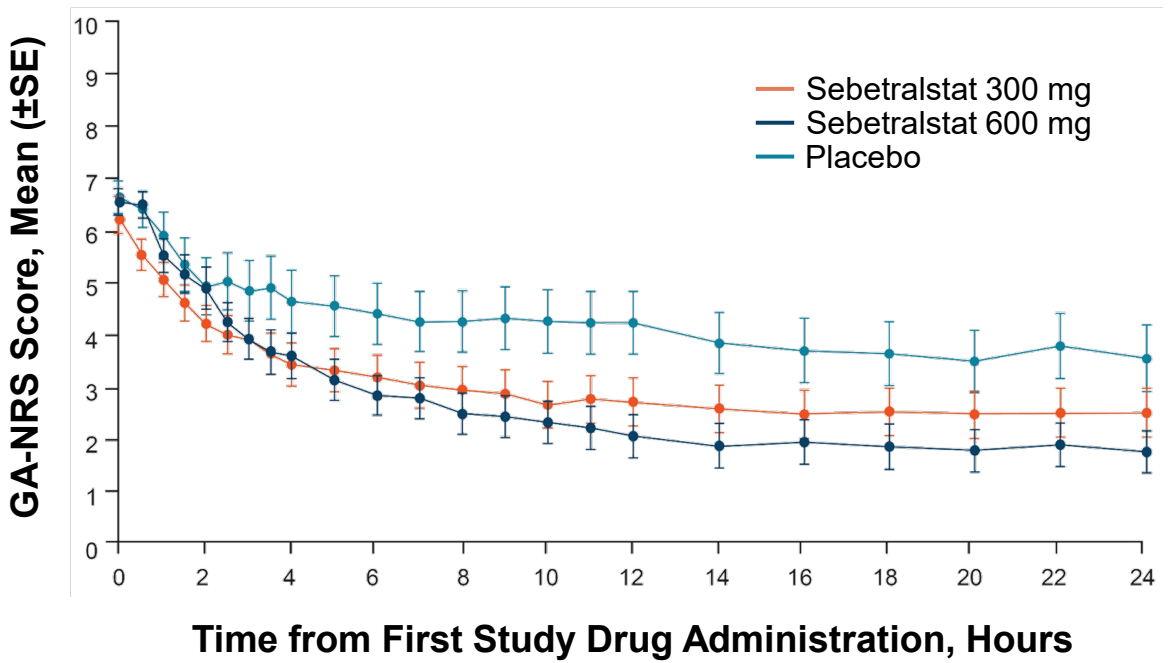
IQR, interquartile range; PGI-S, Patient Global Impression of Severity.
[a]Moderate to extreme anxiety defined as a GA-NRS score of ≥4. [b]Of 261 attacks for which there were GA-NRS ratings at baseline. [c]The score on the PGI-S scale and attack location at baseline are missing for 2 attacks in the 'All attacks' category. [d]Includes 2 attacks in the 'All attacks' category and 1 attack in the 'Attacks inducing moderate to extreme anxiety' category with a baseline PGI-S category of 'None'.
1. Riedl MA et al. *N Engl J Med*. 2024;391:32-43.

Reduction in Cumulative GA-NRS Scores

All attacks



Attacks inducing moderate to extreme anxiety



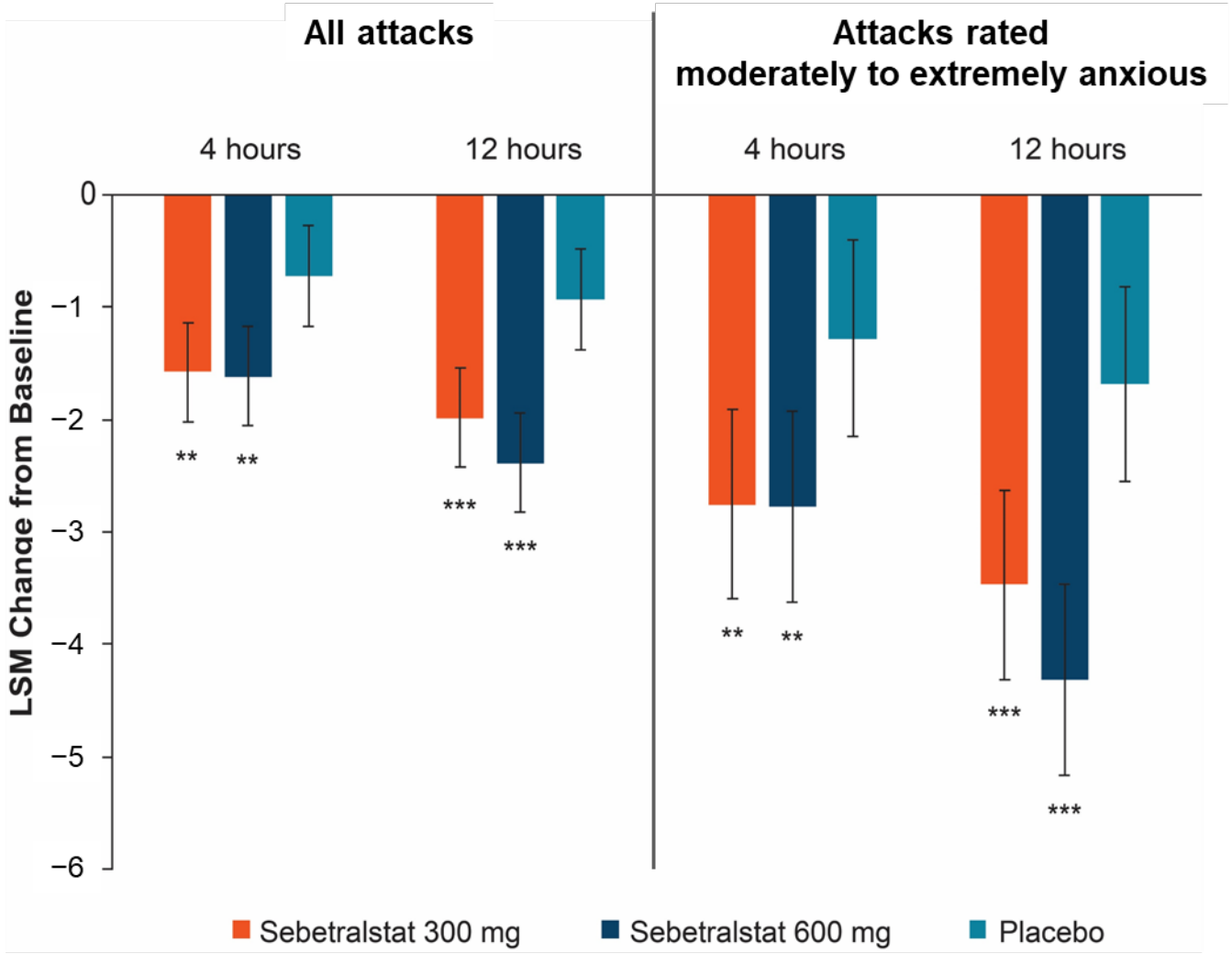
Compared with placebo for all attacks, on-demand treatment with sebetralstat significantly reduced the $AUC_{0\text{-}12}$ (300 mg, P=0.0040; 600 mg, P=0.0008) and $AUC_{0\text{-}24}$ (300 mg, P=0.0220; 600 mg, P=0.0012)

When attacks with moderate to extreme anxiety were assessed, reductions in anxiety were greater than in all attacks

SE, standard error.

Changes in LSM Change from Baseline in HAE Attacks in KONFIDENT

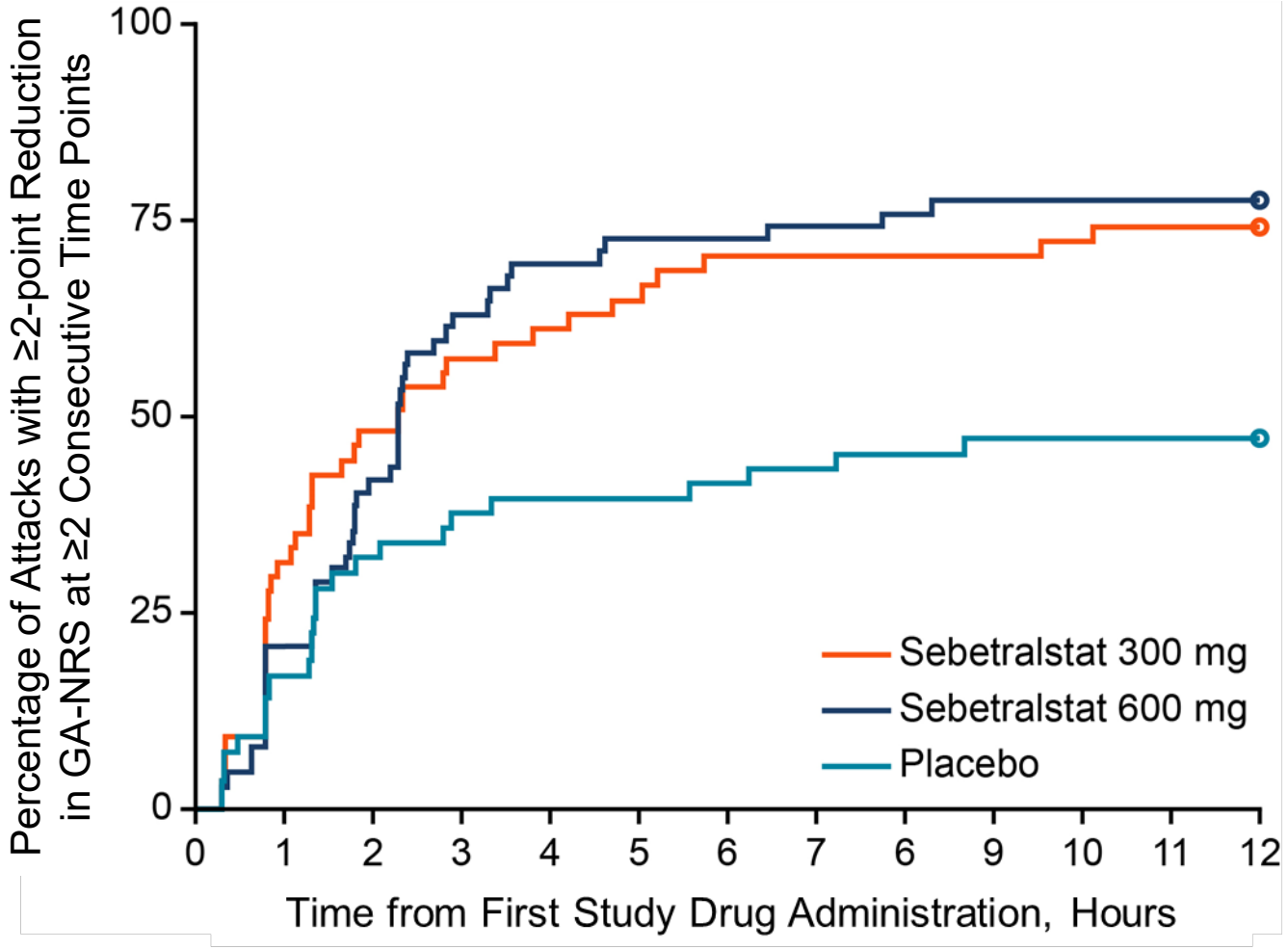
- Significantly greater changes from baseline in GA-NRS score were observed at 4 and 12 hours for attacks treated with sebetralstat compared with placebo
- LSM change from baseline was more pronounced in attacks that induced moderate to extreme anxiety than with all attacks



*P<0.05, **P<0.01, ***P<0.001.

Time to Reduction in Anxiety in KONFIDENT

- The median time to reduction in anxiety[a] in KONFIDENT for attacks treated with sebetralstat 300 mg or 600 mg was **2.3 hours** (IQR: 0.8 to 10.1 and 1.3 to 5.5, respectively)
  - For placebo, the median was >12 hours
- The time to reduction in anxiety highly correlated with the primary and key secondary endpoints in KONFIDENT
  - Time to beginning of symptom relief (P<0.0001)[b,c]
  - Time to reduction in severity (P<0.0001)[b,c]
  - Time to complete attack resolution (P<0.0001)[b,d]



IQR, interquartile range.
[a]Defined as time to a ≥2-point reduction in GA-NRS score at ≥2 consecutive time points within 12 hours for attacks with baseline GA-NRS score ≥2 (n=176). [b]Based on Cohen's kappa analysis. [c]Within 12 hours. [d]Within 24 hours.

Agreement of ≥2-point Reduction in Anxiety with Achievement of Beginning of Symptom Relief

Characteristic	Beginning of symptom relief[a] within 12 hours Correlation to reduction in anxiety within 12 hours,[b,c] kappa (*P* value)
All attacks	0.47 (<0.0001)
Attacks that induced moderate to severe anxiety	0.49 (<0.0001)
By attack location	
Mucosal attacks	0.55 (<0.0001)
Abdominal attacks	0.44 (0.0005)
Subcutaneous attacks	0.39 (0.0002)
By treatment paradigm	
On-demand only	0.46 (<0.0001)
On-demand + LTP	0.51 (0.0013)
By age group	
≥12 to <18 years	0.42 (0.0671)
≥18 years	0.48 (<0.0001)

Participants who had attacks achieving beginning of symptom relief earlier (within 12 hours) had a greater chance to reach meaningful reductions in anxiety (≥2 points) regardless of attack location, treatment paradigm, and age

[a]Primary endpoint; defined as a PGI-C rating of 'A Little Better' for ≥2 consecutive time points; [b]Defined as a ≥2-point reduction in GA-NRS score for attacks with a baseline GA-NRS score ≥2; [c]In total, 176 attacks for which baseline GA-NRS score was ≥2 were included in this analysis.

Conclusions

- In the phase 3 KONFIDENT trial, anxiety was rated as moderate to extreme at the time of treatment in >40% of attacks
  - In the absence of injectables, anxiety was correlated with baseline attack severity
- Compared with placebo, on-demand treatment with sebetralstat reduced anxiety, especially in attacks rated as inducing moderate to extreme anxiety
- The median time to reduction in anxiety was 2.3 hours with sebetralstat and >12 hours with placebo
- The time to reduction in anxiety highly correlated with the primary and key secondary endpoints in KONFIDENT

Acknowledgments

- We thank the people living with HAE and their families; the HAEA, HAEi and member organizations, and the investigator teams who contributed to the international KONFIDENT trial
- Medical writing assistance was provided under the direction of the authors by Richard W. Davis IV, PhD, of ApotheCom (San Francisco, CA), and was supported by KalVista Pharmaceuticals

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