Pooled Sebetralstat Placebo-controlled Efficacy for On-demand Treatment of Hereditary Angioedema

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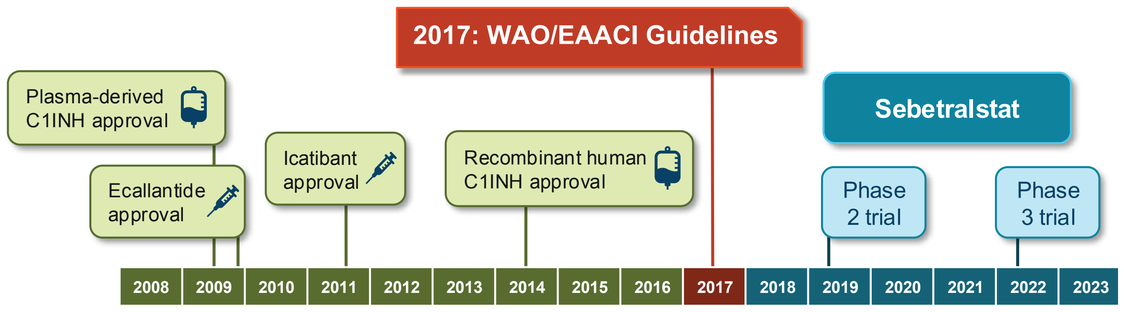
Background

- Data from clinical trials and real-world evidence for parenteral on-demand hereditary angioedema (HAE) treatments (**Figure 1**) were the basis for the 2017 World Allergy Organization/European Academy of Allergy and Clinical Immunology (WAO/EAACI) guidelines, which recommended considering the treatment of all attacks regardless of severity or location, and to treat as early as possible[1]

Figure 1. Timeline of HAE Treatments



C1INH, C1 inhibitor.

- Sebetralstat was the first orally administered on-demand therapy to be evaluated in phase 2 and 3 clinical trials (**Figure 2**),[2–5] which were consistent with the WAO/EAACI guideline recommendations
- Endpoints assessed in both trials included beginning of symptom relief on the Patient Global Impression of Change (PGI-C) scale as well as reduction in severity and complete attack resolution on the Patient Global Impression of Severity (PGI-S) scale (**Figure 3**)
- Similarities in endpoints and trial designs allowed for a pooled analysis of the efficacy data to evaluate sebetralstat in a larger pool of attacks

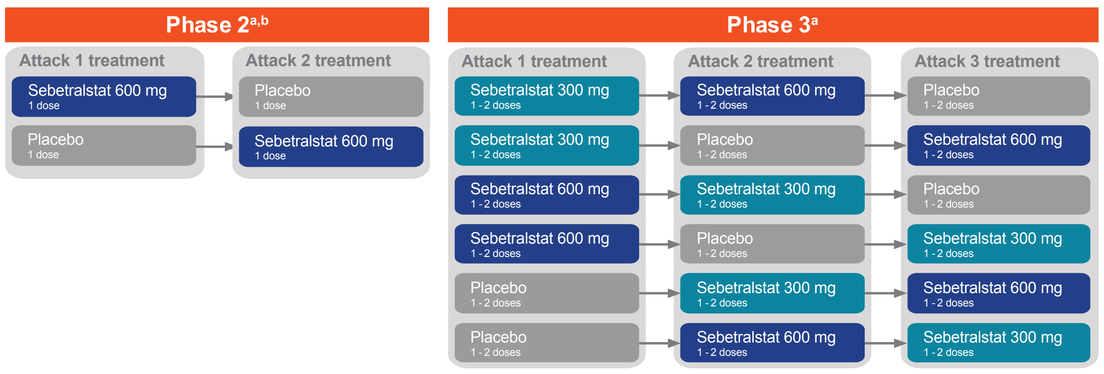
Objective

- To evaluate the efficacy of sebetralstat for the on-demand treatment of HAE attacks in the pooled, randomised, double-blind, placebo-controlled, crossover components of the phase 2 and phase 3 trials[2–5]

Methods

- Participants had confirmed HAE-C1INH, were aged ≥18 years (phase 2) or ≥12 years (phase 3), received ≥1 dose of study drug, had ≥3 (phase 2; mild to moderate; neck and above excluded) or ≥2 (phase 3; mild to very severe; all locations; excluding severe laryngeal only) attacks in the past 3 months, and had a stable dose of long-term prophylaxis (phase 3)

Figure 2. Trial Designs

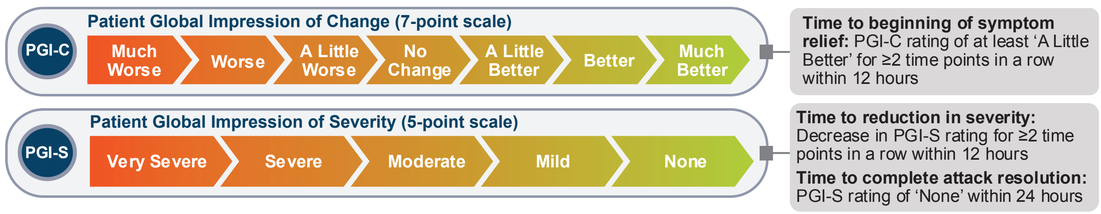


Pooled population: all randomised participants who treated at least 1 attack[c]

[a]A minimum 48-h washout period was required between each eligible attack and, therefore, each dose of trial drug. [b]Only the randomised, double-blind, placebo-controlled part 2 of the phase 2 trial is included in the pooled analysis. [c]The pooled efficacy population was analyzed based on the planned treatment; 1 patient randomised to receive 300mg and 1 patient randomised to receive placebo each received sebetralstat 600 mg.

- Assessments were recorded in both trials every 0.5 hours for the first 4 hours after first taking the study drug. After which:
  - For phase 2, every hour from 4–12 hours, every 3 hours from 12–24 hours, and once at 36 and 48 hours
  - For phase 3, every hour from 5–12 hours, every 2 hours from 14–24 hours, and once at 36 and 48 hours

Figure 3. Efficacy Outcome Measures



Results

Table 1. Pooled Characteristics of Participants Treated with Sebetralstat or Placebo

	Sebetralstat 300 mg n=87	Sebetralstat 600 mg n=151	Placebo n=139
Age, mean (SD) years	37.2 (14.7)	38.0 (14.1)	38.5 (14.5)
Age group, n (%)			
Adolescent, ≥12 to <18 years	10 (11.5)	11 (7.3)	9 (6.5)
Adult, ≥18 to <65 years	75 (86.2)	136 (90.1)	126 (90.6)
Geriatric, >65 years	2 (2.3)	4 (2.6)	4 (2.9)
Sex, female, n (%)	54 (62.1)	86 (57.0)	82 (59.0)
Race, n (%)			
White	73 (83.9)	138 (91.4)	128 (92.1)
Black	1 (1.1)	0	0
Asian	9 (10.3)	8 (5.3)	7 (5.0)
Other or not reported	4 (4.6)	5 (3.3)	4 (2.9)
BMI, mean (SD) kg/m²	27.4 (6.4)	27.1 (5.5)	27.1 (5.4)
Time since diagnosis, mean (SD) years	14.8 (10.3)	17.1 (12.0)	17.7 (12.3)
Current treatment regimen, n (%)			
On-demand only	68 (78.2)	130 (86.1)	121 (87.1)
On-demand plus prophylaxis	19 (21.8)	21 (13.9)	18 (12.9)

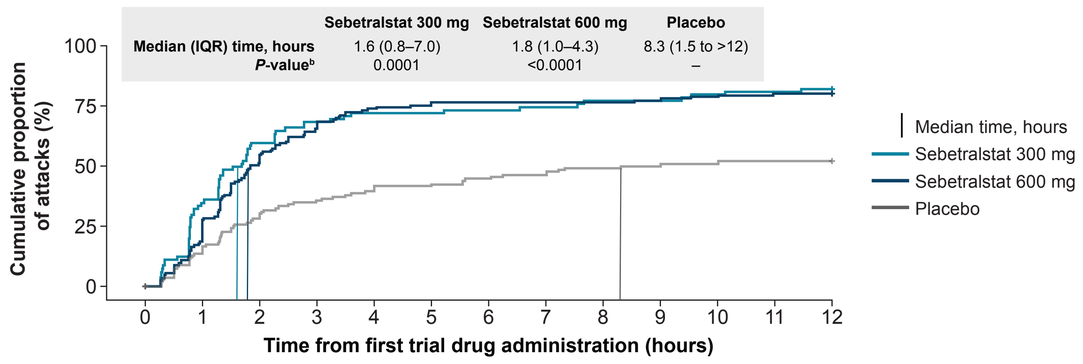
BMI, body mass index; SD, standard deviation.

Table 2. Attack Characteristics

	Sebetralstat 300 mg n=87	Sebetralstat 600 mg n=151	Placebo n=139	All attacks N=377
Baseline pooled attack location, n (%)[a]				
Mucosal (abdomen, larynx/throat[b])	36 (41.4)	62 (41.1)	58 (41.7)	156 (41.4)
Subcutaneous (all others)	49 (56.3)	89 (58.9)	81 (58.3)	219 (58.1)
Baseline PGI-S category, n (%)[a,c]				
Mild	36 (41.4)	67 (44.4)	67 (48.2)	170 (45.1)
Moderate	35 (40.2)	62 (41.1)	56 (40.3)	153 (40.6)
Severe/very severe	14 (16.1)	20 (13.2)	14 (10.1)	48 (12.7)
Time from onset of attack to first administration, median (IQR), minutes	35.0 (6–130)	32.0 (7–85)	32.0 (13–82)	32.5 (8–94)
Attacks treated in <60 minutes, n (%)[d]	53 (60.9)	103 (68.2)	93 (66.9)	249 (66.0)
Conventional treatment within 12 hours of first study drug administration, n (%)				
Yes	12 (13.8)	16 (10.6)	38 (27.3)	N/A
No	75 (86.2)	135 (89.4)	101 (72.7)	N/A

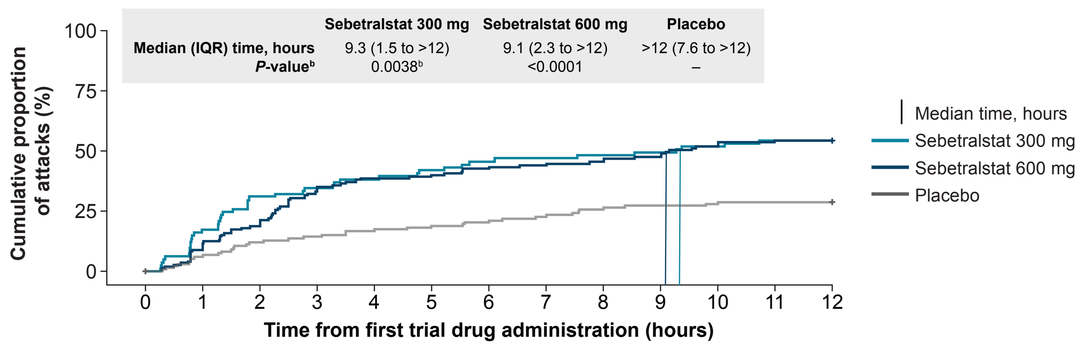
IQR, interquartile range; PGI-S, Patient Global Impression of Severity.
[a]Baseline PGI-S rating and baseline attack location are missing for two attacks in the sebetralstat 300-mg group. [b]Among mucosal attacks, 8 involved the larynx: 2 attacks in the sebetralstat 300-mg group, 2 attacks in the sebetralstat 600-mg group, and 4 attacks in the placebo group. [c]Baseline PGI-S score was 'None' for 2 attacks in the sebetralstat 600-mg group and 2 attacks in the placebo group. [d]Time from onset of attack to first administration was missing for 1 attack in the sebetralstat 300-mg group.

Figure 4. Time to Beginning of Symptom Relief (PGI-C)[a]



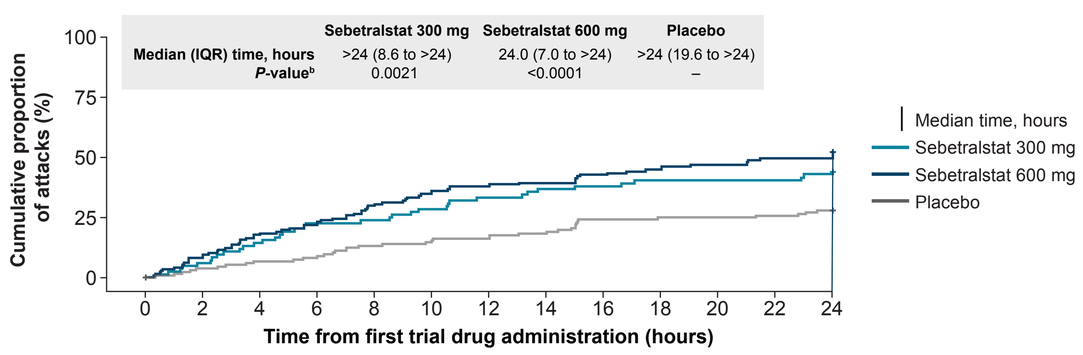
IQR, interquartile range; PGI-C, Patient Global Impression of Change.
[a]Beginning of symptom relief was defined as a rating of at least 'A Little Better' on the PGI-C scale for ≥2 time points in a row within 12 hours of trial drug administration.
[b]Adjusted *P* value compared with placebo.

Figure 5. Time to Reduction in Attack Severity (PGI-S)[a]



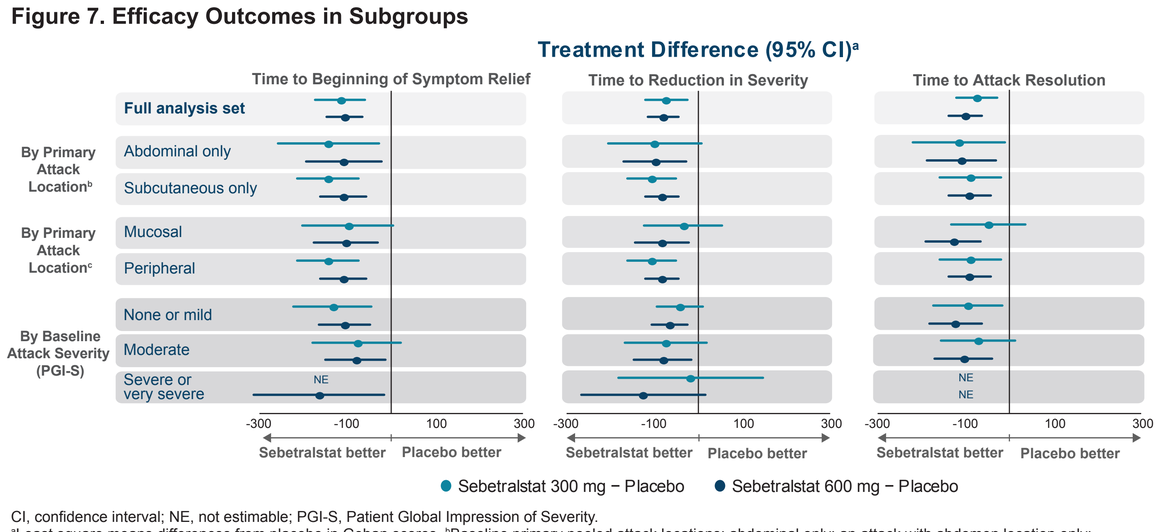
IQR, interquartile range; PGI-S, Patient Global Impression of Severity.
[a]Reduction in severity was defined as at least a one-level reduction from baseline in PGI-S rating for ≥2 time points in a row within 12 hours of trial drug administration.
[b]Adjusted *P* value compared with placebo.

Figure 6. Time to Attack Resolution (PGI-S)[a]



IQR, interquartile range; PGI-S, Patient Global Impression of Severity.
[a]Complete resolution of an attack was defined as a PGI-S rating of 'None' within 24 hours of trial drug administration. [b]Adjusted *P* value compared with placebo.

Figure 7. Efficacy Outcomes in Subgroups



CI, confidence interval; NE, not estimable; PGI-S, Patient Global Impression of Severity.
[a]Least square means differences from placebo in Gehan scores. [b]Baseline primary pooled attack locations: abdominal only: an attack with abdomen location only; subcutaneous only: an attack with arms/hands, genitals, legs/feet, head/face/neck, or torso location(s) only; a subgroup analysis of laryngeal attacks was not feasible because only 8 of these attacks occurred: the 300-mg and 600-mg doses were administered after 2 attacks each and placebo after 4. [c]Baseline primary pooled attack locations: mucosal (an attack involving larynx/throat or abdomen),or peripheral (an attack not involving larynx/throat and abdomen).

Conclusions

- **Results of the trials were highly consistent**
- **In this pooled analysis, time to beginning of symptom relief, reduction in severity, and complete attack resolution were significantly faster with sebetralstat compared with placebo**
  - **Use of conventional treatment within 12 hours of study drug administration was lower with sebetralstat compared with placebo**
  - **These results were consistent across subgroups**
- **As an oral on-demand treatment sebetralstat has the potential to offer a preferred administration route, enable early treatment, and provide rapid symptom relief for patients experiencing HAE attacks**

References

1. Maurer M, et al. *Allergy*. 2018;73(8):1575-1596. **2.** ClinicalTrials.gov. A phase II, cross-over clinical trial evaluating the efficacy and safety of KVD900 in the on-demand treatment of angioedema attacks in adult subjects with hereditary angioedema Type I or II. Accessed July 18, 2024. https://clinicaltrials.gov/study/NCT04208412. **3.** ClinicalTrials.gov. A phase III, crossover trial evaluating the efficacy and safety of KVD900 for on-demand treatment of angioedema attacks in adolescent and adult patients with hereditary angioedema (HAE). Accessed July 18, 2024. https://clinicaltrials.gov/study/NCT05259917. **4.** Aygören-Pürsün E, et al. *Lancet*. 2023;401:458-469. **5.** Riedl MA, et al. *N Engl J Med*. 2024;391:32-43.

Disclosures

EA-P has received grants, consulting fees, honoraria, fees paid to the institution, and/or personal fees from KalVista Pharmaceuticals, Astria, BioCryst, BioMarin Europe, Centogene, CSL Behring, Intellia, Pharming Technologies, Pharvaris, and Takeda/Shire. **JAB** has received grants and/or honoraria from KalVista Pharmaceuticals, BioCryst, BioMarin, CSL Behring, Intellia, Ionis, Pharming, Pharvaris, and Takeda/Shire and serves as the immediate past president of the American Academy of Allergy, Asthma & Immunology (AAAAI). **DC** has received consulting fees paid to the institution, honoraria paid to the institution, meeting/travel support, and research support; has served on advisory boards for KalVista Pharmaceuticals, Astria, BioCryst, CSL Behring, Intellia, Ionis Pharmaceuticals, Pharming, Pharvaris, and Takeda; and has a leadership role for the HAE International (HAEi) Medical Advisory panel for Central Eastern Europe and Benelux. **HF** has received grants paid to the institution, honoraria, meeting/travel support, and/or served on advisory boards for KalVista Pharmaceuticals, Astria, BioCryst, CSL Behring, Intellia, Ono Pharmaceutical, Pharming, Pharvaris, and Takeda and has served a leadership role on the Angioedema Centers of Reference and Excellence (ACARE) Steering Committee. **WL** has received grants, consulting fees, and/or honoraria from KalVista Pharmaceuticals, AstraZeneca, Astria, BioCryst, BioMarin, CSL Behring, Express Scripts/CVS, Fresenius Kabi, GlaxoSmithKline, Grifols, Intellia, Ionis, Magellan, OptiNose, Optum, Pharming, Pharvaris, Sanofi/Regeneron, Takeda/Shire, and Teva and serves on the board of the United States Hereditary Angioedema Association (HAEA) and Dallas/Fort Worth (DFW) Metroplex Allergy Society. **MR** is or recently was a speaker and/or advisor for and/or has received research funding from Astria, BioCryst, BioMarin, Celldex, CSL Behring, Cycle Pharma, Grifols, Intellia, Ionis, KalVista, Pfizer, Pharming, Pharvaris, Sanofi-Regeneron, and Takeda. **AZ** has received honoraria, meeting/travel support, and/or served on advisory boards for KalVista Pharmaceuticals, Astria, BioCryst, CSL Behring, Pharming, Pharvaris, and Takeda. **JH**, **MI**, **MDS**, **CMY**, and **PKA** are employees of KalVista Pharmaceuticals. This work was supported by KalVista Pharmaceuticals, Inc. **SKA** has received honoraria for consultations and talks sponsored by Astria, BioCryst, CSL Behring, KalVista, Pharming, Pharvaris, and Takeda. **MM** is or recently was a speaker and/or advisor for and/or has received research funding from Astria, BioCryst, CSL Behring, Intellia, Ionis, KalVista, Pharvaris, and Takeda.

Acknowledgements

KalVista thanks the people living with HAE and their families, their advocates, and the investigator teams around the world who supported these clinical trials. Medical writing assistance was provided under the direction of the authors by Marisa DeGuzman, PhD, of Oxford PharmaGenesis Inc., Newtown, PA, and was supported by KalVista Pharmaceuticals. The authors wish to acknowledge Dr. Marcus Maurer, our colleague, mentor, and friend. We join all who knew Marcus in mourning his untimely passing. He will be deeply missed.

Presented at the Bradykinin Symposium; 4–6 September 2024; Berlin, Germany