Efficacy and Safety of Sebetralstat for On-demand Treatment of Hereditary Angioedema in Pooled Analysis of Placebo-controlled Clinical Trials

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Background

- The World Allergy Organization/European Academy of Allergy and Clinical Immunology (WAO/EAACI) guidelines recommend that all hereditary angioedema (HAE) attacks are considered for treatment regardless of severity or location, and to treat as early as possible[1,2]
- Parenterally administered on-demand therapies for HAE are associated with side effects and administration burden, leading to delay or withholding of treatment[2-4]
- Sebetralstat was the first orally administered on-demand therapy to be evaluated in phase 2 and 3 clinical trials (**Figure 1**) whose designs were consistent with the WAO/EAACI guideline recommendations[1,5,6]
  - Efficacy endpoints 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[5,6] (**Figure 2**)
  - Similarities in endpoints and trial designs allowed for pooling of efficacy and safety data to evaluate sebetralstat in a larger cohort of attacks

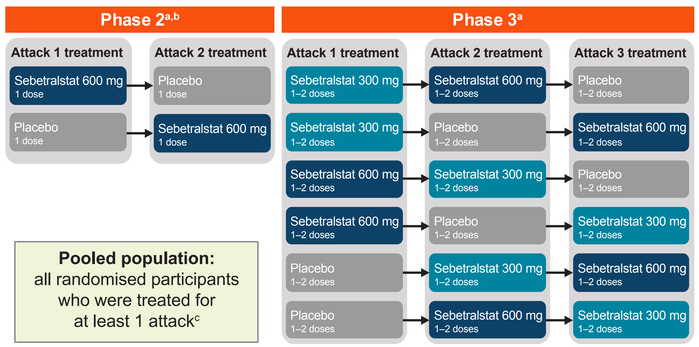
Objective

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

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)

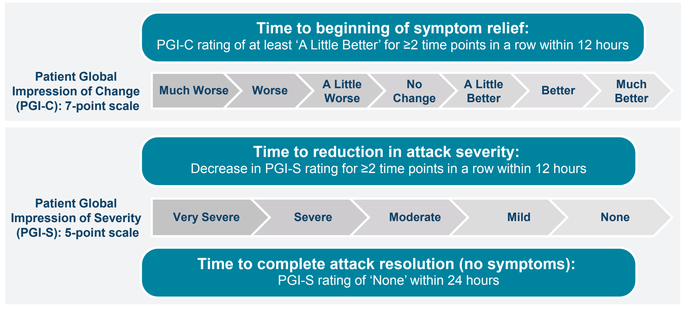
Figure 1. Trial designs



[a]A minimum 48-hour 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 analysed based on the planned treatment; 1 participant randomised to receive sebetralstat 300 mg and 1 participant randomised to placebo each received sebetralstat 600 mg; the pooled safety population was analyzed based on the actual treatment participants received.

- 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
- *P*-values were calculated using Gehan score transformation test and not adjusted for multiplicity

Figure 2. Efficacy outcome measures



Results

Table 1. Pooled characteristics of participants treated with sebetralstat or placebo[a]

	Sebetralstat 300 mg n=87	Sebetralstat 600 mg n=151	Placebo n=139	Participants in Italy n=16[b]
Age, mean (SD) years	37.2 (14.7)	38.0 (14.1)	38.5 (14.5)	46.8 (12.9)
Age group, n (%)				
Adolescent, ≥12 to <18 years	10 (11.5)	11 (7.3)	9 (6.5)	0
Adult, ≥18 to <65 years	75 (86.2)	136 (90.1)	126 (90.6)	15 (93.8)
Geriatric, ≥65 years	2 (2.3)	4 (2.6)	4 (2.9)	1 (6.3)
Sex, female, n (%)	54 (62.1)	86 (57.0)	82 (59.0)	5 (31.3)
Race, n (%)				
White	73 (83.9)	138 (91.4)	128 (92.1)	15 (93.8)
Black	1 (1.1)	0	0	0
Asian	9 (10.3)	8 (5.3)	7 (5.0)	0
Other or not reported	4 (4.6)	5 (3.3)	4 (2.9)	1 (6.3)
BMI, mean (SD) kg/m²	27.4 (6.4)	27.1 (5.5)	27.1 (5.4)	24.8 (3.1)
Time since diagnosis, years				
Mean (SD)	14.8 (10.3)	17.1 (12.0)	17.7 (12.3)	16.7 (11.4)
Current treatment regimen, n (%)				
On-demand only	68 (78.2)	130 (86.1)	121 (87.1)	16 (100)
On-demand plus prophylaxis	19 (21.8)	21 (13.9)	18 (12.9)	0

BMI, body mass index; SD, standard deviation. Participants in the overall population based on treatment group assigned during crossover may be represented in multiple columns. [a]The pooled efficacy population was analyzed based on the planned treatment; 1 participant randomised to receive sebetralstat 300 mg and 1 participant randomised to placebo each received sebetralstat 600 mg. [b]Trial participants in Italy included 5 from phase 3 and 11 from phase 2.

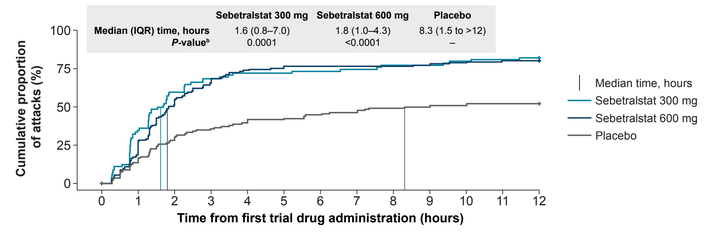
- Use of conventional treatment within 12 hours of study drug administration was lower with sebetralstat (13.8% and 10.6% of attacks treated with sebetralstat 300 mg and 600 mg, respectively) compared with placebo (27.3% of attacks treated with placebo)

Table 2. Characteristics of attacks treated with at least 1 dose of trial drug

	All attacks N=377	Attacks in Italy n=32
Baseline pooled attack location, n (%)[a]		
Mucosal (abdomen, larynx/throat)[b]	156 (41.4)	13 (40.6)
Subcutaneous (all others)	219 (58.1)	19 (59.4)
Baseline PGI-S category, n (%)[a,c]		
Mild	174 (46.2)	18 (56.3)
Moderate	153 (40.6)	14 (43.8)
Severe/very severe	48 (12.7)	0
Time from onset of attack to first administration, median (IQR), minutes	32.5 (8–94)	30.0 (17.5–45.0)
Attacks treated in <60 minutes, n (%)[d]	249 (66.0)	29 (90.6)

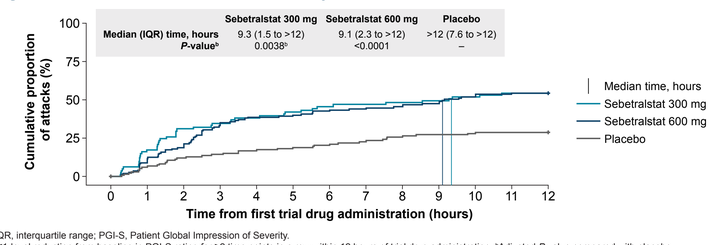
IQR, interquartile range; PGI-S, Patient Global Impression of Severity. [a]Baseline PGI-S rating and baseline attack location are missing for 2 attacks in the sebetralstat 300-mg group. [b]Among mucosal attacks, 8 involved the larynx: 2 attacks in the sebetralstat 300-mg group, 2 attacks in the sebetralstat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

Figure 3. Time to beginning of symptom relief[a]



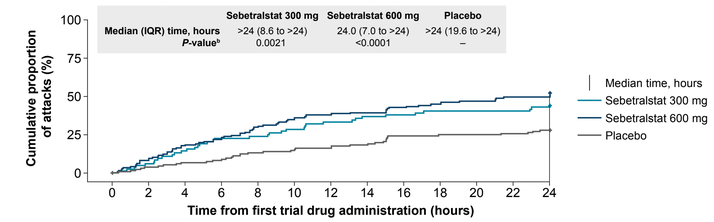
IQR, interquartile range; PGI-C, Patient Global Impression of Change. [a]Rating of ≤'A Little Better' on the PGI-C scale for ≥2 time points in a row within 12 hours of trial drug administration. [b]Adjusted *P* value compared with placebo.

Figure 4. Time to reduction in attack severity[a]



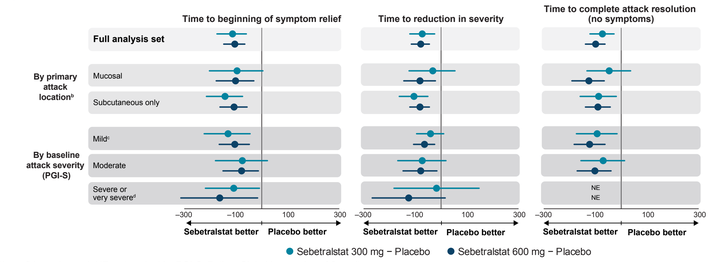
IQR, interquartile range; PGI-S, Patient Global Impression of Severity. [a]≤1-level reduction from baseline in PGI-S rating for ≥2 time points in a row within 12 hours of trial drug administration. [b]Adjusted *P* value compared with placebo.

Figure 5. Time to complete attack resolution (no symptoms)[a]



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

Figure 6. Efficacy outcomes in subgroups, treatment differences (95% CI)[a]



CI, confidence interval; NE, not evaluable; PGI-S, Patient Global Impression of Severity. [a]Least square means differences from placebo in Gehan scores. [b]Baseline primary pooled attack locations: mucosal: an attack with larynx/throat, abdominal only, or abdominal and subcutaneous; 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 PGI-S score was 'None' for 2 attacks in the placebo group. [d]Treatment difference for time to beginning of symptom relief shown for the severe or very severe subgroup treated with the sebetralstat 300 mg dose are for the phase 3 trial only. NE is indicated where pooled statistics were not possible due to small sample size.

Table 3. Treatment-emergent adverse events

Number of participants, n (%)	Sebetralstat 300 mg (n=86)	Sebetralstat 600 mg (n=151)	Placebo (n=138)
Any TEAE	17 (19.8)	28 (18.5)	24 (17.4)
Treatment-related TEAE[a]	**2 (2.3)**	**6 (4.0)**	**6 (4.3)**
Any serious TEAE	1 (1.2)[d]	2 (1.3)	0
Treatment-related serious TEAE[b]	**0**	**0**	**0**
Any severe TEAE	1 (1.2)[d]	0	0
Treatment-related severe TEAE[c]	**0**	**0**	**0**
Any TEAE leading to trial discontinuation	0	0	0
Any TEAE leading to death	0	0	0

TEAE, treatment-emergent adverse event. [a]Sebetralstat 300 mg: 1 event each of dyspepsia and fatigue; 600 mg: 1 event each of dyspepsia, nausea, hot flush, abdominal pain, back pain, and 2 events of headache; placebo: 1 event each of nausea, anal incontinence, dysgeusia, irregular menstruation, rash, and 2 events of headache. [b]Any untoward medical occurrence that at any dose resulted in death, was life threatening, required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or substantial disability/incapacity, was a congenital anomaly/birth defect, or was an important medical event by medical and scientific judgement. [c]A qualitative assessment by the investigator of an adverse event of grade 3 severity or as reported by the participants. [d]The severe TEAE and serious TEAE in the sebetralstat 300-mg group are the same event: lumbar disc herniation requiring hospitalization.

Conclusions

- **Early treatment was associated with milder attacks and therefore less morbidity**
- **Results in a large number of attacks (N=377) corroborate the efficacy and safety of sebetralstat for on-demand treatment**
  - **Attack relief was significantly faster with sebetralstat (vs placebo), with a median time to beginning of symptom relief of 1.6–1.8 hours (vs 8.3 hours) and a median time to reduction in attack severity of 9.1–9.3 hours (vs >12 hours)**
  - **Sebetralstat was efficacious for all attack locations and severity**
  - **Sebetralstat was well tolerated, with a safety profile no different than placebo**
- **As an oral on-demand treatment, sebetralstat has the potential to improve compliance with guidelines by avoiding treatment-limiting adverse events of parenteral treatments, offering a patient-preferred administration route, enabling early treatment, and providing rapid overall time to symptom relief in people living with HAE**

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 support was provided by Heather A. Mitchell, PhD, of Oxford PharmaGenesis Inc., Newtown, PA, USA, and funded by KalVista Pharmaceuticals, Inc.

Disclosures
Mauro Cancian: has received funding for research projects from or served on advisory boards for CSL Behring, BioCryst, and Shire/Takeda.
Jonathan A. Bernstein: 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).
Danny M. Cohn: 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.
Henriette Farkas: 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.
William R. Lumry: is a member of advisory boards for BioCryst, CSL Behring, and Takeda; has received research grants from BioCryst, CSL Behring, Ionis, and Takeda; consulting fees from BioCryst, CSL Behring, Fresenius Kabi, Pharming, and Takeda; payments for lectures from CSL Behring, Pharming, and Takeda; and is an advisory board member of the US Hereditary Angioedema Association.
Marc A. Riedl: 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.
Andrea Zanichelli: has received honoraria, meeting/travel support, and/or served on advisory boards for KalVista Pharmaceuticals, Astria, BioCryst, CSL Behring, Pharming, Pharvaris, and Takeda.
James Hao, Michael D. Smith, Christopher M. Yea, and Paul K. Audhya: are employees of KalVista Pharmaceuticals.
Emel Aygören-Pürsün: 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.
Sorena Kiani-Alikhan: has received speaker or consultancy fees from BioCryst, CSL Behring, Pharming, and Takeda.

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Presented at The 4th National Italian Network for Hereditary and Acquired Angioedema (ITACA) Congress; 27–29 March 2025; Palermo, Italy

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