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

Emel Aygören-Pürsün,[1] Jonathan A. Bernstein,[2] Danny Cohn,[3] Henriette Farkas,[4] William Lumry,[5] Marc Riedl,[6] Andrea Zanichelli,[7,8] Samuel Owiredu-Yeboa,[9] James Hao,[9] Michael D. Smith,[9] Christopher M. Yea,[9] Paul K. Audhya,[9] Sorena Kiani-Alikhan,[10] Marcus Maurer[11,12]

[1]University Hospital Frankfurt, Goethe University, Frankfurt, Germany; [2]University of Cincinnati College of Medicine, Cincinnati, OH, US; [3]Amsterdam UMC, University of Amsterdam, Amsterdam, Netherlands; [4]Hungarian Angioedema Center of Reference and Excellence, Semmelweis University, Budapest, Hungary; [5]AARA Research Center, Dallas, TX, US; [6]University of California – San Diego, La Jolla, California, US; [7]IRCCS Policlinico San Donato, San Donato Milanese, Milan, Italy; [8]University of Milan, Milan, Italy; [9]KalVista Pharmaceuticals, Inc., Salisbury, UK, and Cambridge, Massachusetts, US; [10]Royal Free London NHS Foundation Trust, London, United Kingdom; [11]Institute of Allergology, Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany; [12]Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Immunology and Allergology, Berlin, Germany

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. **SO-Y**, **JH, MDS, CMY,** and **PKA** are employees of KalVista Pharmaceuticals. **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.
- This work was supported by KalVista Pharmaceuticals, Inc.

Background

The unpredictability and potential lethality of HAE attacks calls for patients to:

- consider treating **all** attacks[1]
- treat attacks as **early** as possible[1]
- **always** carry on-demand medication for at least 2 attacks[1]

Early treatment is associated with less severe and shorter attacks[1,2]

Parenterally administered on-demand therapies for treatment of HAE attacks are associated with side effects, which may lead to delays and/or withholding of treatment[1,3,4]

C1-INH, C1 inhibitor; HAE, hereditary angioedema.

References: **1**. Maurer M, et al. *Allergy*. 2022;77:1961-1990. **2.** Longhurst H. *Front Med (Lausanne)*. 2018;4:245. **3.** Mendivil J et al. *Orphanet J Rare Dis*. 2021;16(1):94. **4.** Burton AE, et al. *Int Emerg Nurs*. 2023;71:101339.

Adverse Drug Reactions of On-demand Therapies

- Approved subcutaneously administered on-demand HAE therapies may be associated with injection site adverse drug reactions such as pain, swelling, erythema, itching, and burning sensation[1–2]
- Other commonly reported adverse reactions including headache, nausea, and dizziness can occur, which may also limit adherence to guidelines[1–7]

On-demand Treatment Label Information[a]						
Adverse events (frequency)	**Icatibant[2]** Subcutaneous 		**Recombinant human C1INH[4]** Intravenous 		**Plasma-derived C1INH[6]** Intravenous 	
Very common (≥1/10)	**Injection site reaction**				**Injection site reaction**	
Common (≥1/100 to <1/10)	**Transaminase increase** **Headache** **Nausea** **Dizziness**	**Pyrexia** **Rash** **Erythema** **Pruritus**	**Nausea**		**Hypersensitivity**	**Dizziness**
Uncommon (≥1/1000 to <1/100)			**Headache** **Vertigo** **Hypoaesthesia** **Dizziness** **Auricular swelling** **Throat irritation**	**Diarrhoea** **Abdominal discomfort** **Oral paraesthesia** **Urticaria** **Anaphylaxis**		

[a]Adverse events of on-demand treatments available in both the EU and US, per EMA-approved Summary of Product Characteristics. This excludes Kalbitor (ecallantide) and Cinryze (plasma-derived C1INH).

References: **1**. FIRAZYR (icatibant) injection. USPI. 2024. **2.** FIRAZYR (icatibant) injection [package insert]. SmPC. 2013. **3.** RUCONEST (C1 esterase inhibitor [recombinant]). USPI. 2020. **4.** RUCONEST (C1 esterase inhibitor [recombinant]) [package insert]. SmPC. 2015. **5.** BERINERT (C1 esterase inhibitor [human]). USPI. 2021. **6**. BERINERT (C1 esterase inhibitor [human]) [package insert]. SmPC. 2021. **7**. CINRYZE (C1 esterase inhibitor [human]) [package insert]. SmPC. 2016.

Objective

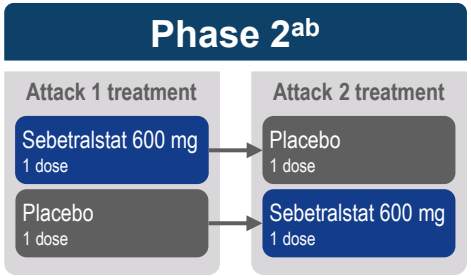
To evaluate the safety (ie, adverse events) of sebetralstat, an investigational oral plasma kallikrein inhibitor for on-demand treatment of HAE attacks, in the phase 2 and 3 trials[1–4]

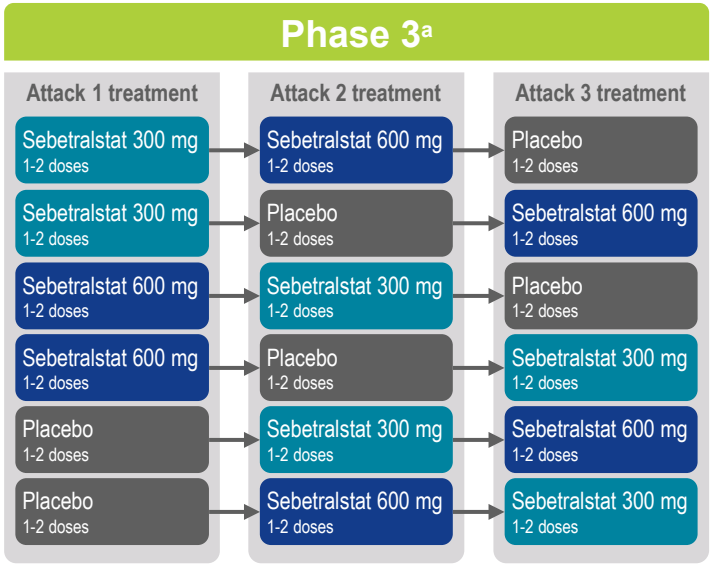
References: **1**. ClinicalTrials.gov. A phase II, cross-over clinical trial evaluating the efficacy and safety of KVD900 in the on-demand treatment of angioedema attacks in adult subjects with hereditary angioedema Type I or II. Accessed July 18, 2024. https://clinicaltrials.gov/study/NCT04208412. **2.** 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. **3.** Aygören-Pürsün E, et al. *Lancet.* 2023;401:458-469. **4.** Riedl MA, et al. *New Engl J Med.* 2024;391:32-43.

Trial Designs

Eligibility:

- Confirmed diagnosis of HAE-C1INH
- Aged ≥18 years (phase 2); ≥12 years (phase 3)
- ≥3 (phase 2); ≥2 (phase 3) attacks in the past 3 months
  - Phase 2: mild to moderate; neck and above excluded
  - Phase 3: mild to very severe; all locations; excluding severe laryngeal only
- Stable dose of LTP (phase 3)





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

LTP, long-term prophylaxis.
[a]Minimum 48-h washout period required between each eligible attack (ie, 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 safety population is based on the actual treatment patients received.

Pooled Characteristics of Participants Treated with Sebetralstat or Placebo

	Sebetralstat 300 mg (n=86)	Sebetralstat 600 mg (n=151)	Placebo (n=138)
Age, mean (SD) years	37.0 (14.6)	38.0 (14.1)	38.3 (14.4)
Age group, n (%)			
Adolescent (≥12 to <18 years)	10 (11.6)	11 (7.3)	9 (6.5)
Adult (≥18 to <65 years)	74 (86.0)	136 (90.1)	125 (90.6)
Geriatric (≥65 years)	2 (2.3)	4 (2.6)	4 (2.9)
Sex, female, n (%)	54 (62.8)	86 (57.0)	81 (58.7)
Race, n (%)			
White	72 (83.7)	138 (91.4)	127 (92.0)
Black	1 (1.2)	0	0
Asian	9 (10.5)	8 (5.3)	7 (5.1)
Other or not reported	4 (4.7)	5 (3.3)	4 (2.9)
BMI, mean (SD) kg/m^2	27.4 (6.4)	27.1 (5.5)	27.1 (5.4)
Current treatment regimen, n (%)			
On-demand only	67 (77.9)	130 (86.1)	120 (87.0)
On-demand plus prophylaxis	19 (22.1)	21 (13.9)	18 (13.0)

BMI, body mass index; SD, standard deviation.

Pooled Safety

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

AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent AE.
[a]Sebetralstat 300 mg: one event each of dyspepsia and fatigue; 600 mg: one event each of dyspepsia, nausea, hot flush, abdominal pain, back pain, and 2 events of headache; placebo: one event each of nausea, anal incontinence, dysgeusia, menstruation irregular, 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 AE 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.

Pooled Safety

Preferred Term, n (%) E[a]	Sebetralstat 300 mg (n=86)	Sebetralstat 600 mg (n=151)	Placebo (n=138)
Treatment-related TEAE	**2 (2.3) 2**	**6 (4.0) 7**	**6 (4.3) 7**
Dyspepsia	1 (1.2) 1	1 (0.7) 1	0
Upper abdominal pain	0	1 (0.7) 1	0
Nausea	0	1 (0.7) 1	1 (0.7) 1
Anal incontinence	0	0	1 (0.7) 1
Fatigue	1 (1.2) 1	0	0
Back pain	0	1 (0.7) 1	0
Headache	0	2 (1.3) 2	2 (1.4) 2
Dysgeusia	0	0	1 (0.7) 1
Hot flush	0	1 (0.7) 1	0
Irregular menstruation	0	0	1 (0.7) 1
Rash	0	0	1 (0.7) 1

E, number of events; n, number of participants with at least one AE.
[a]Preferred term coded using MedDRA, version 26.0.

Conclusions

- Adverse drug reactions associated with subcutaneous and intravenous administration may cause patients to delay or withhold treatment[1–7]
- Other commonly reported adverse reactions of parenteral therapies for HAE include headache, nausea, and dizziness[1–7]
- In this pooled safety analysis, sebetralstat was well-tolerated with a safety profile no different than placebo
  - Common (≥1/100 to <1/10) TEAEs reported in pooled participants treated with sebetralstat[a] were dyspepsia and fatigue (1.2% each)
  - No occurrences of dysphagia or TEAEs related to swallowing were reported
  - No treatment-related TEAEs were ≥ grade 3, serious, or resulted in death or discontinuation
- As an oral on-demand treatment, sebetralstat has the potential to improve compliance with guidelines by avoiding treatment-limiting adverse events of parenteral treatments in people with HAE

[a]Only events different to placebo are summarized.

References: **1**. FIRAZYR (icatibant) injection. USPI. 2024. **2.** FIRAZYR (icatibant) injection [package insert]. SmPC. 2013. **3.** RUCONEST (C1 esterase inhibitor [recombinant]). USPI. 2020. **4.** RUCONEST (C1 esterase inhibitor [recombinant]) [package insert]. SmPC. 2015. **5.** BERINERT (C1 esterase inhibitor [human]). USPI. 2021. **6**. BERINERT (C1 esterase inhibitor [human]) [package insert]. SmPC. 2021. **7**. CINRYZE (C1 esterase inhibitor [human]) [package insert]. SmPC. 2016.

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.