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.
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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

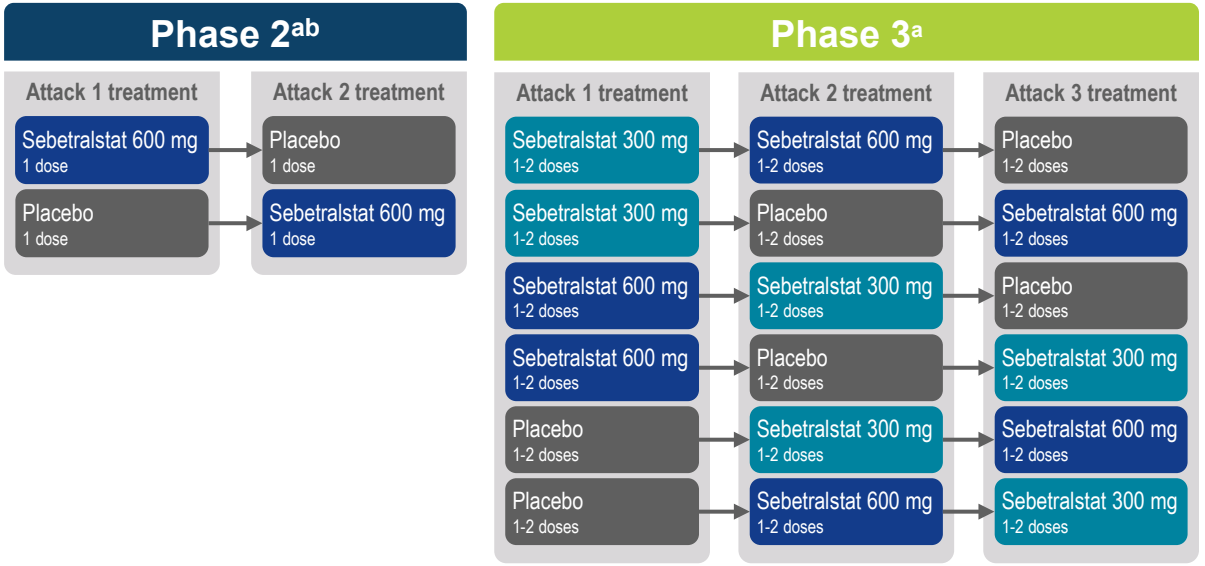
To evaluate the safety (ie, adverse events) of sebetralstat, an investigational oral plasma kallikrein inhibitor for on-demand treatment of HAE attacks, in the phase 2 and 3 trials[1–4]

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.

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