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Rationale for the Short-term Prophylaxis Regimen With Sebetralstat in KONFIDENT-S

Matthew Iverson, Edward Duckworth, Erik Hansen, Sally L. Hampton, **Michael D. Smith**, Paul K. Audhya, Christopher M. Yea

KalVista Pharmaceuticals, Salisbury, UK, and Cambridge, MA, US

Disclosures and Acknowledgments

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Background

- HAE is a rare and potentially life-threatening genetic disease characterized by recurrent episodes of swelling; attacks can have a significant negative impact on patients' quality of life[1-3]
  - For many patients with HAE, guidelines recommend the use of STP prior to medical or dental procedures to reduce the risk of HAE attacks[4,5]
- All recommended STP treatments require parenteral administration, which presents significant challenges with preparation, venous access, injection-site–associated pain, and discomfort[6,7]
  - Additionally, STP treatments may not be the typical therapies used by patients for long-term prophylaxis or on-demand treatment, so there may be an additional administrative burden for the patient to obtain a prescription for recommended STP therapies[4,8]
- There remains an unmet need for a simple, safe, and effective oral STP option for HAE

HAE, hereditary angioedema; STP, short-term prophylaxis.

1. Bork K, et al. *Am J Med*. 2006;119(3):267-274. **2.** Longhurst H, Cicardi M. *Lancet*. 2012;379(9814):474-481. **3.** Banerji A, et al. *N Engl J Med*. 2017;376(8):717-728. **4.** Busse PJ, et al. *J Allergy Clin Immunol Pract*. 2021;9(1):132-150.e3. **5.** Maurer M, et al. *Allergy*. 2022;77(7):1961-1990. **6.** Berinert. Package insert. CSL Behring; 2009. **7.** Cinryze. Package insert. Takeda Pharmaceuticals USA, Inc; 2021. **8.** Nanda M, Singh U, Wilmot J, et al. *Ann Allergy Asthma Immunol*. 2014;113(2):198-203.

KONFIDENT Trials

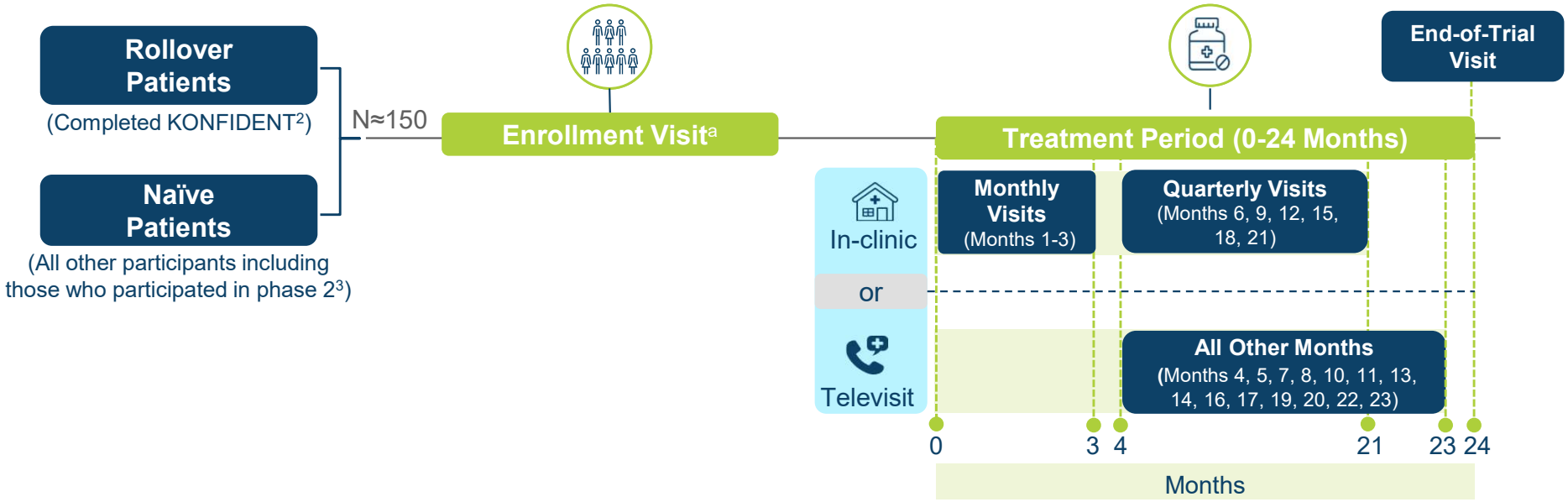
- Sebetralstat is a novel investigational oral plasma kallikrein inhibitor for the on-demand treatment of HAE attacks that showed a favorable PK and PD profile and positive efficacy and safety results in a recent phase 2 trial[1,2]
- The phase 3, randomized, double-blind, placebo-controlled trial KONFIDENT (NCT05259917) is underway to evaluate the efficacy and safety of sebetralstat in patients aged 12 years or older with HAE type I or II for the on-demand treatment of HAE attacks[3]
- An open-label extension trial, KONFIDENT-S (NCT05505916), is evaluating the safety of sebetralstat for up to 2 years[4]

HAE, hereditary angioedema; PD, pharmacodynamic; PK, pharmacokinetic.

1. Aygören-Pürsün E, et al. *Lancet*. 2023;401(10375):458-469. **2.** Maetzel A, et al. *J Allergy Clin Immunol*. 2022;149(6):2034-2042. **3.** ClinicalTrials.gov identifier**:** NCT05259917**.** Updated March 28, 2023. Accessed April 6, 2023. https://clinicaltrials.gov/ct2/show/NCT05259917. **4.** ClinicalTrials.gov identifier: NCT05505916. Updated March 27, 2023. Accessed April 6, 2023. https://clinicaltrials.gov/ct2/show/NCT05505916

KONFIDENT-S Includes Rollover Patients From KONFIDENT and Naïve Patients

KONFIDENT-S (NCT05505916)[1]



On-Demand Treatment of HAE attacks:

- 1 × 600 mg sebetralstat to treat each HAE attack
- Second 1 × 600 mg sebetralstat dose is permitted at least 3 hours following the first dose if symptoms persist without improvement

[a]For naïve patients, the Enrollment Visit is a screening visit.

HAE, hereditary angioedema.

1. ClinicalTrials.gov identifier: /NCT05505916. Updated March 27, 2023. Accessed April 6, 2023. https://clinicaltrials.gov/ct2/show/NCT05505916

2. ClinicalTrials.gov identifier: NCT05259917. Updated March 28, 2023. Accessed April 6, 2023. https://clinicaltrials.gov/ct2/show/NCT05259917

3. Aygören-Pürsün E, et al. *Lancet*. 2023;401(10375):458-469.

Evaluation of Short-term Prophylaxis in KONFIDENT-S Trial

- During KONFIDENT-S, participants may use sebetralstat for on-demand treatment or, on a case-by-case basis, after consultation with the investigator and the patient, as STP therapy for a surgical, medical, or dental procedure
- To support the rationale for the STP regimen in KONFIDENT-S, we report PK, PD, and safety data from a phase 1 trial that evaluated three doses of sebetralstat q8h compared with dosing q2h or q4h

STP, short-term prophylaxis; PD, pharmacodynamic; PK, pharmacokinetic; q2h, every 2 hours; q4h, every 4 hours; q8h, every 8 hour.

Methods

- This phase 1, double-blind, placebo-controlled, multiple-dose, multiple-cohort study evaluated the safety, tolerability, and PK of multiple doses of 600 mg sebetralstat in healthy adults under fasted conditions[1]

Participants were assigned to three cohorts with different dosing schedules

Cohort 1	**Randomized to receive 600 mg sebetralstat or placebo q8h at 0, 8, and 16 hours**
Cohort 2	**Randomized to receive 600 mg sebetralstat or placebo q4h at 0, 4, and 8 hours**
Cohorts 3/4	**Randomized to receive 600 mg sebetralstat or placebo q2h at 0, 2, and 4 hours**

- Venous blood was collected for PK and PD measurements at prespecified intervals following the first and third doses, up to 40 hours postdose
- An exploratory PD assessment was performed to measure the effect of sebetralstat on PKa enzyme activity
- All participants receiving sebetralstat and having any measurable plasma concentrations were included in the PK analysis; all participants receiving at least one dose of sebetralstat or matching placebo were included in the PD and safety evaluations
- Safety was measured by the assessment of vital signs and the collection of adverse events
- Results are presented using descriptive statistics

PD, pharmacodynamic; PK, pharmacokinetic; PKa, plasma kallikrein; q2h, every 2 hours; q4h, every 4 hours; q8h, every 8 hours.

1. Maetzel A, et al. *J Allergy Clin Immunol*. 2022;149(6):2034-2042.

Maximum Plasma Concentrations of Sebetralstat Were Similar After Dose 1

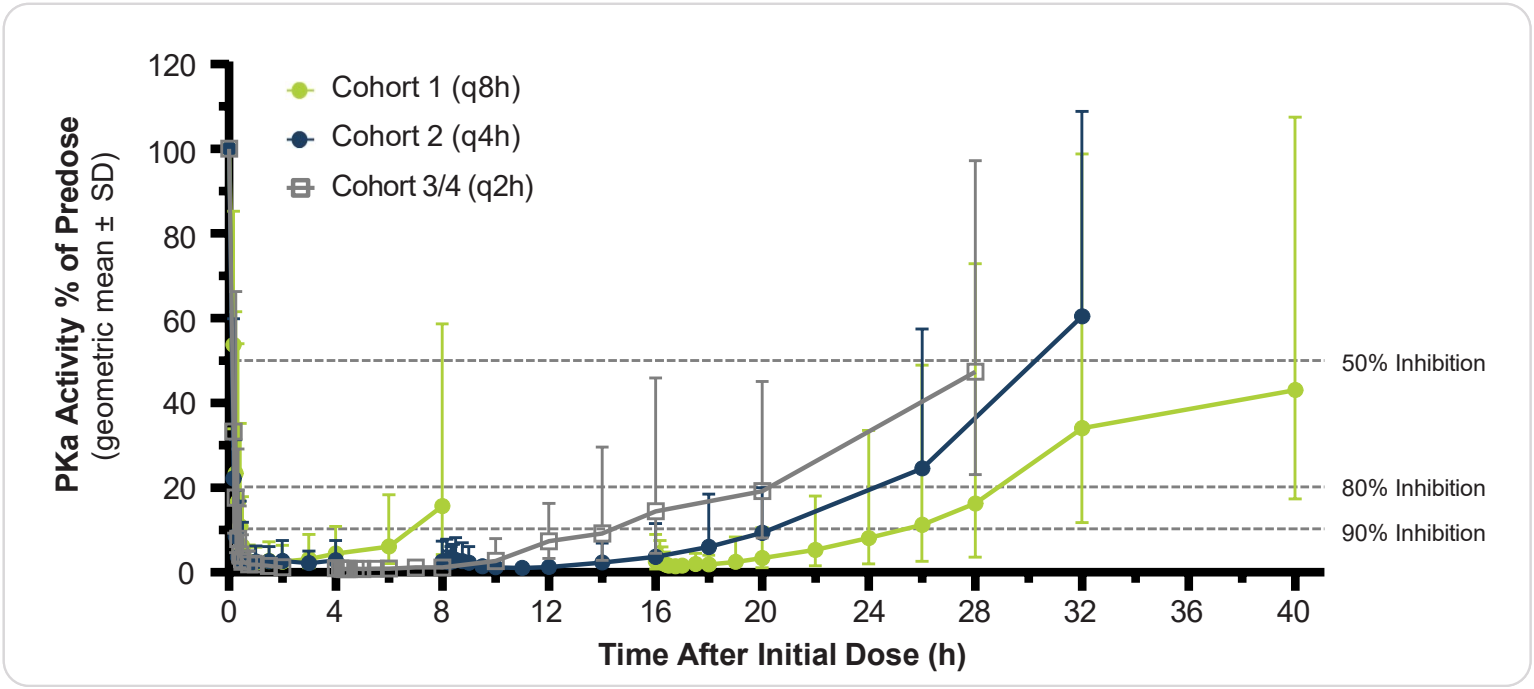
Maximum Plasma Concentrations After Dose 1 and Dose 3

			Dose 1	Dose 3
Cohort 1; q8h (n=6)	C_{max}	Geometric mean (CV%)	3916 ng/mL (104.7%)	8838 ng/mL (92.8%)
Cohort 2; q4h (n=6)	C_{max}	Geometric mean (CV%)	4412 ng/mL (54.3%)	7136 ng/mL (32.8%)
Cohorts 3/4; q2h (n=18)	C_{max}	Geometric mean (CV%)	5035 ng/mL (54.2%)	15,627 ng/mL (32.2%)

- The lowest arithmetic mean plasma concentrations in the q8h cohort were 758.5 ng/mL at 8 hours prior to the second dose and 749.8 ng/mL at 28 hours and thereafter
- For q4h and q2h dosing schedules, arithmetic mean plasma sebetralstat remained >1000 ng/mL between the first and third doses

C_{max}, maximum plasma concentration; CV, coefficient of variation; q2h, every 2 hours; q4h, every 4 hours; q8h, every 8 hours.

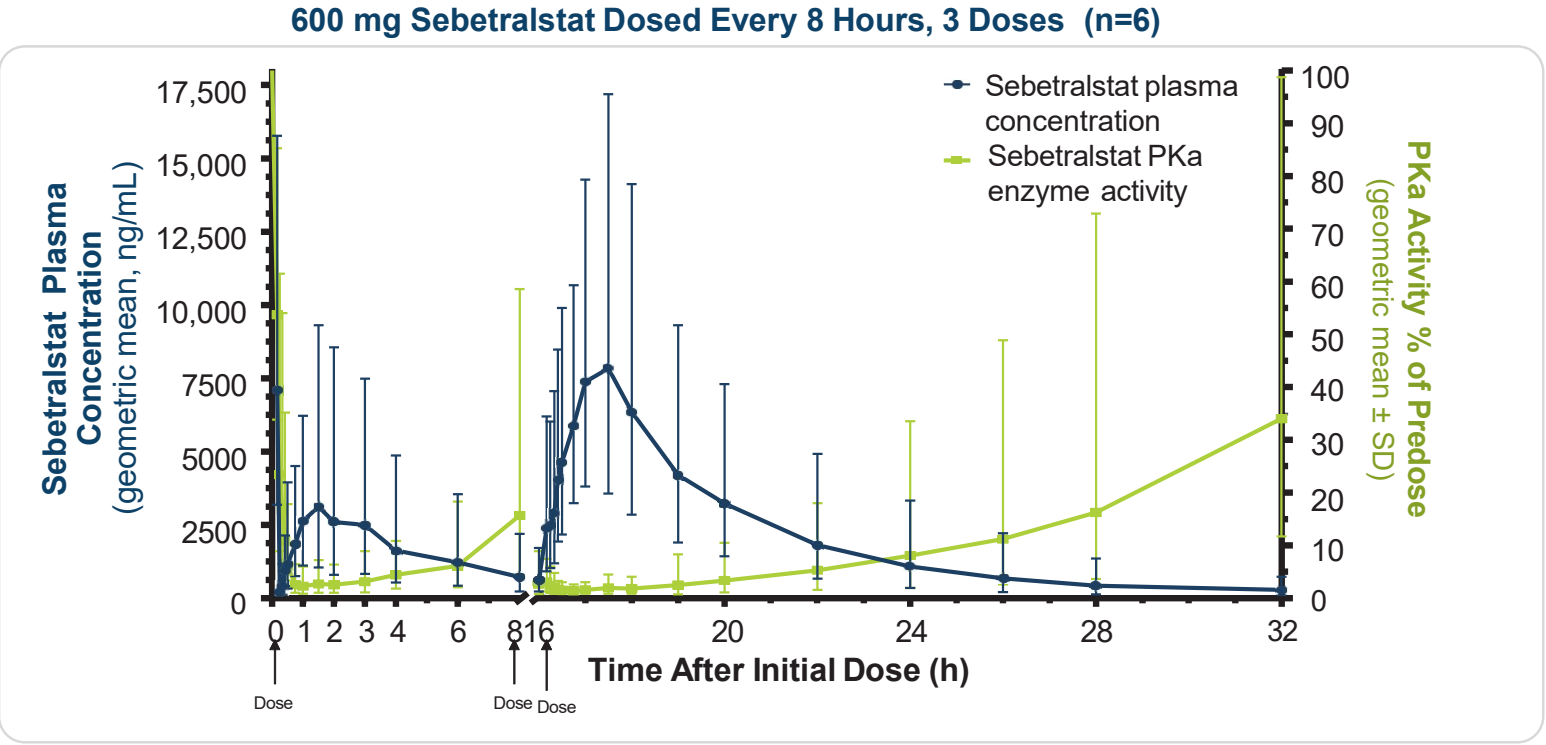
A Geometric Mean PKa Inhibition of >90% Was Achieved Within 30 Minutes of Dose 1 in All Cohorts



PKa inhibition in the q8h cohort (cohort 1; n=6), q4h cohort (cohort 2; n=6) and q2h cohort (cohort 3/4; n=18) (geometric mean ± SD, linear scale)

PKa, plasma kallikrein activity; q2h, every 2 hours; q4h, every 4 hours; q8h, every 8 hours.

Geometric Mean PKa Inhibition Was at >90% Through 24 Hours and Then >80% Through 28 Hours After 3 Doses of Sebetralstat in Cohort 1 (q8h)



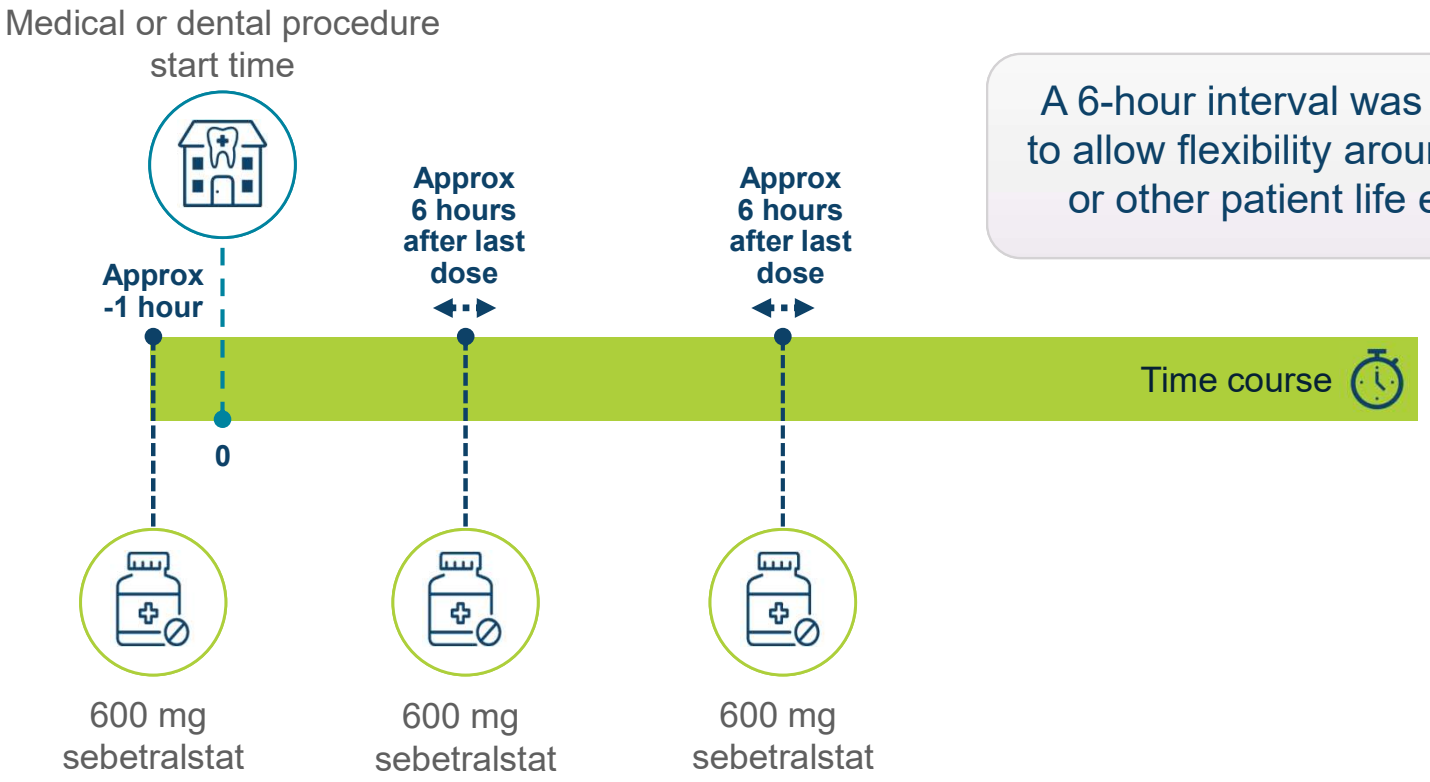
Sebetralstat plasma concentration (blue, geometric mean ± SD) and inhibition of PKa activity as a percentage of the activity in predose samples (green, geometric mean ± SD) in the q8h cohort (cohort 1, linear scale)

PKa, plasma kallikrein activity; q8h, every 8 hours.

Sebetralstat Was Well Tolerated in All Cohorts

- Adverse events were mild and comparable between treatment groups receiving sebetralstat and placebo
  - No participants discontinued the trial because of an adverse event
- No serious adverse events occurred during the trial, and all adverse events were resolved by trial exit

Administration of Sebetralstat for Short-term Prophylaxis in KONFIDENT-S Begins 1 Hour Prior to a Surgical, Medical, or Dental Procedure



A 6-hour interval was chosen to allow flexibility around sleep or other patient life events

Conclusions

- Three doses of sebetralstat within 24 hours were well tolerated and led to drug accumulation
- Geometric mean PKa inhibition of >80% was maintained for 28 hours when dosing sebetralstat q8h
- Based on these data, KONFIDENT-S will prospectively evaluate the effectiveness and safety of three doses of 600 mg sebetralstat administered before and approximately 6 hours after each previous dose in the periprocedural STP setting

PKa, plasma kallikrein activity; q8h, every 8 hours; STP, short-term prophylaxis.

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Thank You