Abstract 000329

Results From a Randomized, Double-Blind, Placebo-Controlled, Phase 1 Trial Evaluating Sebetralstat Pharmacokinetics, Pharmacodynamics, and Safety/Tolerability in Healthy Japanese, Chinese, and White Adults

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Background

- Hereditary angioedema (HAE) is a genetic disorder that manifests as unpredictable attacks of tissue swelling caused by uncontrolled activation of the kallikrein-kinin system[1]
- Globally, the prevalence of HAE type 1 or type 2 is estimated to be 1/50,000 to 1/100,000[2,3]
- It is assumed that there are 2000 to 3000 people living with HAE type 1 or type 2 in Japan[4]
- Similarly, it is assumed that there are around 28,000 people living with HAE type 1 or type 2 in China[5,6]
- Sebetralstat, a novel oral plasma kallikrein (PKa) inhibitor that has shown promising clinical activity in a randomized phase 2 trial, is being investigated in a phase 3 trial as on-demand treatment for patients experiencing HAE attacks[7,8]
- Most participants in a recent sebetralstat phase 2 trial were White (Caucasian).[8] This trial was designed to evaluate whether the pharmacokinetics (PK), pharmacodynamics (PD), and safety profiles in individuals of Asian descent (specifically Japanese or Chinese ancestry) were similar to those in White (Caucasian) individuals

Objective

- This phase 1 trial was designed to determine whether the PK, PD, and safety profiles of sebetralstat were similar in healthy Japanese adults, healthy Chinese adults, and healthy White (Caucasian) adults (as defined according to the study definition of Japanese, Chinese, and White)

Methods

Study Design

- In this single-center, randomized, double-blind, placebo-controlled, phase 1 trial, healthy Japanese, Chinese, and White (Caucasian) adults were enrolled
  - Definition of Japanese: a participant for whom both parents and all grandparents were Japanese (verbally self-reported) and the participant had not lived outside of Japan for >10 years
  - Definition of Chinese: a participant for whom both parents and all grandparents were Chinese (verbally self-reported) and the participant had not lived outside of China (including Hong Kong, Macau, and Taiwan) for >10 years
  - Definition of White: a participant who confirmed that all parents and grandparents were White (verbally self-reported)
- Participants received a single dose of oral sebetralstat administered at a dosage of 300 mg, 600 mg, or 1200 mg, or placebo after fasting

Key Eligibility Criteria

- Eligible participants were healthy male or female nonsmokers aged 18-55 years with a body mass index (BMI) between 18.5 and 32.0 kg/m^2
- No over-the-counter or prescription medications were allowed within 14 days, no pharmaceutical agents that affect drug metabolism were allowed within 30 days, and no angiotensin-converting enzyme inhibitors were allowed within 93 days of study drug administration

Endpoints

- Plasma concentrations of sebetralstat were determined using a validated liquid chromatography with tandem mass spectrometry method
- Concentration-time curves were assessed for the following parameters:
  - Area under the concentration-time curve from time 0 to the last observed nonzero concentration (AUC_{0-t}) or extrapolated to infinity (AUC_{0-inf})
  - Maximum observed plasma concentration (C_{max})
  - Time to maximum observed plasma concentration (T_{max})
- PD was assessed by measuring dextran sulfate (DXS)–stimulated PKa activity levels in plasma using a fluorogenic substrate
- Safety was evaluated through collection of treatment-emergent adverse events (TEAEs)

Analysis Populations

- The safety analysis population (N=74) consisted of all randomly assigned participants who received at least 1 dose of study drug (sebetralstat or placebo)
- The PK analysis population (n=54) consisted of all participants in the safety analysis population with at least 1 quantifiable sebetralstat plasma concentration and no major protocol deviations that affect PK
- The PD analysis population (n=73) consisted of all participants in the safety analysis set with at least 1 measured PD assessment in the predose sample

Results

Patients

- The mean (SD) age of participants was 39.3 (9.29) years; 47 participants (64%) were male, and 27 participants (36%) were female
  - Baseline characteristics were balanced across the 3 populations in each cohort (**Table 1**)

Table 1. Baseline Characteristics

	Sebetralstat 300 mg			Sebetralstat 600 mg			Sebetralstat 1200 mg			Pooled Placebo		
	Japanese n=7	Chinese n=6	White n=7	Japanese n=6	Chinese n=6	White n=6	Japanese n=6	Chinese n=6	White n=6	Japanese n=6	Chinese n=6	White n=6
Age, mean (SD)	42.6 (11.9)	35.2 (6.2)	43.4 (10.4)	37.0 (11.3)	45.5 (7.9)	37.7 (9.8)	40.8 (6.5)	39.3 (7.0)	33.8 (7.5)	40.2 (9.8)	37.3 (9.0)	37.7 (12.2)
Female, n (%)	4 (57.1)	1 (16.7)	2 (28.6)	4 (66.7)	1 (16.7)	4 (66.7)	1 (16.7)	1 (16.7)	2 (33.3)	4 (66.7)	0	3 (50.0)
Height, mean (SD), cm	164.7 (10.3)	175.0 (4.8)	167.9 (10.1)	163.8 (10.7)	169.3 (6.9)	165.0 (7.0)	169.2 (4.6)	169.3 (9.7)	173.7 (13.5)	162.7 (6.9)	170.2 (7.6)	174.2 (7.9)
Weight, mean (SD), kg	62.23 (8.50)	82.58 (13.40)	76.54 (16.77)	62.00 (14.98)	70.00 (11.98)	71.80 (12.35)	71.23 (8.32)	74.78 (14.85)	75.65 (14.80)	60.02 (11.12)	73.63 (14.16)	78.47 (12.09)
BMI, mean (SD), kg/m^2	23.14 (4.41)	26.87 (3.52)	26.89 (4.01)	22.83 (3.51)	24.23 (2.31)	26.27 (3.10)	24.87 (2.59)	25.87 (3.77)	25.08 (4.08)	22.60 (3.57)	25.32 (4.02)	25.85 (3.59)

BMI, body mass index.

Pharmacokinetics

- Although variability was observed due to the small population sizes, PK parameters were overall consistent across healthy Japanese, Chinese, and White adults after administration of a single dose of sebetralstat 300 mg, 600 mg, or 1200 mg (**Table 2**)
- Geometric mean (SD) plasma concentrations for sebetralstat 600 mg in Japanese, Chinese, and White participants are shown in **Figure 1** and **Table 2**

Figure 1. Mean Plasma Concentration of Sebetralstat 600 mg

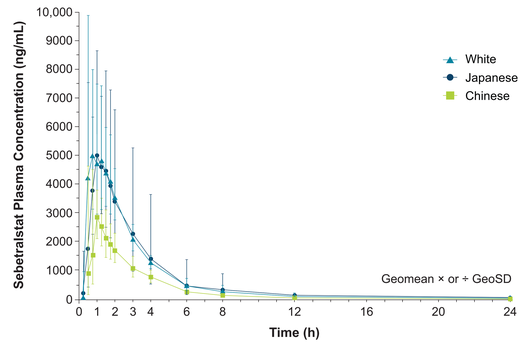


Table 2. Summary of Plasma PK Parameters of Sebetralstat After a Single Oral Dose

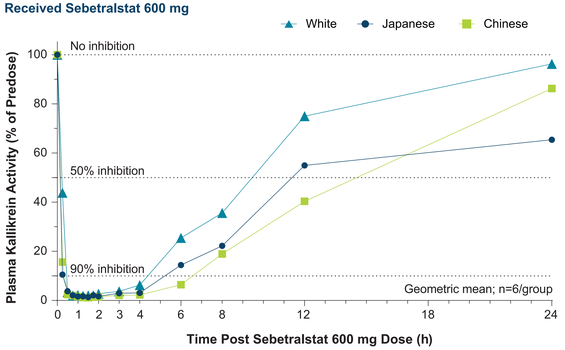
	Sebetralstat 300 mg			Sebetralstat 600 mg			Sebetralstat 1200 mg		
	Japanese n=6	Chinese n=6	White n=6	Japanese n=6	Chinese n=6	White n=6	Japanese n=6	Chinese n=6	White n=6
AUC_{0-t}, geometric mean (CV%), ng·h/mL	7458 (51.2)	7712 (22.7)	8162 (22.3)	16,410 (66.8)	15,590 (39.3)	16,200 (28.2)	23,490 (62.8)	30,100 (50.1)	23,690 (35.2)
AUC_{0-inf}, geometric mean (CV%), ng·h/mL	7495 (50.4)	7725 (22.7)	8190 (22.2)	16,600 (64.8)	16,120[a] (42.9)	16,400[a] (31.8)	21,800[b] (39.0)	30,530 (49.2)	24,450 (35.5)
C_{max}, geometric mean (CV%), ng/mL	2832 (90.4)	3173 (20.6)	2243 (53.7)	6178 (51.8)	5197 (92.0)	5961 (41.4)	7736 (111.8)	7645 (78.8)	5746 (31.6)
T_{max}, median (range), h	1.26 (0.55-1.75)	1.00 (0.62-1.25)	1.29 (0.95-1.6)	0.99 (0.50-1.50)	0.64 (0.27-1.48)	1.00 (0.50-1.25)	0.75 (0.50-4.00)	1.16 (0.73-3.00)	1.02 (1.00-1.50)

AUC_{inf}, area under the concentration-time curve from time 0 extrapolated to infinity; AUC_{0-t}, area under the concentration-time curve from time 0 to the last observed nonzero concentration; C_{max}, maximum observed plasma concentration; CV, coefficient of variation; PK, pharmacokinetics; T_{max}, time to maximum observed plasma concentration.
[a]n=5.
[b]n=4.

Pharmacodynamics

- PD parameters were consistent across healthy Japanese, Chinese, and White adults after administration of a single dose of sebetralstat 300 mg, 600 mg, or 1200 mg
- ≥95% geometric mean inhibition of PKa was observed within 30 minutes and was maintained out to 4 hours in all participant groups after receiving sebetralstat 600 mg (**Figure 2**)

Figure 2. Plasma Kallikrein Activity in Healthy Japanese, Chinese, and White Adults Who Received Sebetralstat 600 mg



Safety

- Sebetralstat was well tolerated in Japanese, Chinese, and White individuals (**Table 3**)
  - In the Japanese population, 3 TEAEs (abdominal pain upper, headache, and epistaxis) were reported in 2 participants who received sebetralstat and 1 TEAE (dysmenorrhea) was reported in 1 participant who received placebo
  - In the Chinese population, 4 TEAEs (dizziness, diarrhea, nausea, and abdominal pain upper) were reported in 2 participants who received sebetralstat and no TEAEs were reported in participants who received placebo
  - In the White population, 2 TEAEs (headache) were reported in 2 participants who received sebetralstat and 1 TEAE (dysmenorrhea) was reported in 1 participant who received placebo
- No deaths, serious AEs, or discontinuations owing to AEs occurred during the trial

Table 3. Safety

Event, n (%)	Sebetralstat 300 mg			Sebetralstat 600 mg			Sebetralstat 1200 mg			Pooled Placebo		
	Japanese n=7	Chinese n=6	White n=7	Japanese n=6	Chinese n=6	White n=6	Japanese n=6	Chinese n=6	White n=6	Japanese n=6	Chinese n=6	White n=6
Any TEAE	1 (14.3)	0	0	0	2 (33.3)	2 (33.3)	1 (16.7)	0	0	1 (16.7)	0	1 (16.7)
Headache	0	0	0	0	0	2 (33.3)	1 (16.7)	0	0	0	0	0
Abdominal pain upper	1 (14.3)	0	0	0	1 (16.7)	0	0	0	0	0	0	0
Diarrhea	0	0	0	0	1 (16.7)	0	0	0	0	0	0	0
Dizziness	0	0	0	0	1 (16.7)	0	0	0	0	0	0	0
Dysmenorrhea	0	0	0	0	0	0	0	0	0	1 (16.7)	0	1 (16.7)
Epistaxis	0	0	0	0	0	0	1 (16.7)	0	0	0	0	0
Nausea	0	0	0	0	1 (16.7)	0	0	0	0	0	0	0

AE, adverse event; TEAE, treatment-emergent AE.
Safety analysis set.
Participants with multiple events in the same category are counted only once in that category.
Only on-treatment period TEAEs were considered. AEs were coded to system organ class and preferred term using Medical Dictionary for Regulatory Activities (MedDRA), version 25.0.

Conclusions

- **Sebetralstat PK, PD, and safety profiles were comparable in healthy Japanese, Chinese, and White adults**
- **Near-complete (≥95% geometric mean) inhibition of stimulated PKa was rapidly achieved (ie, within 30 minutes) and maintained through to the 4-hour time point in all 3 cohorts; more than 50% inhibition was observed through 8 hours**
- **These findings support the continued global expansion of the KONFIDENT phase 3 trial (NCT05259917) to assess sebetralstat for use as on-demand treatment of HAE attacks**

References

1. Busse P, Kaplan A. *J Allergy Clin Immunol Pract*. 2022;10:716-722.
2. Lumry WR, Settipane RA. *Allergy Asthma Proc*. 2020;41(suppl 1):S08-S13.
3. Aygören-Pürsün E et al. *Orphanet J Rare Dis*. 2018;13:73.
4. Ohsawa I et al. *Intern Med*. 2018;57:319-324.
5. Li PH et al. *J Allergy Clin Immunol Pract*. 2023;11(4):1253-1260.
6. Cui Q et al. *World Allergy Organ J*. 2021;15:100620.
7. Maetzel A et al. *J Allergy Clin Immunol*. 2022;149:2034-2042.
8. Aygören-Pürsün E et al. *Lancet*. 2023;401:458-469.

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