

Report on the Deliberation Results

December 3, 2025

Pharmaceutical Evaluation Division, Pharmaceutical Safety Bureau
Ministry of Health, Labour and Welfare

Brand Name	Ekterly Tablets 300 mg
Non-proprietary Name	Sebetralstat (JAN*)
Applicant	KalVista Pharmaceuticals Ltd.
Date of Application	January 15, 2025

Results of Deliberation

In its meeting held on November 27, 2025, the Second Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Council.

The product is not classified as a biological product or a specified biological product. The re-examination period is 10 years. The drug substance is classified as a powerful drug. The drug product is not classified as a poisonous drug or a powerful drug.

Approval Condition

The applicant is required to develop and appropriately implement a risk management plan.

**Japanese Accepted Name (modified INN)*

Review Report

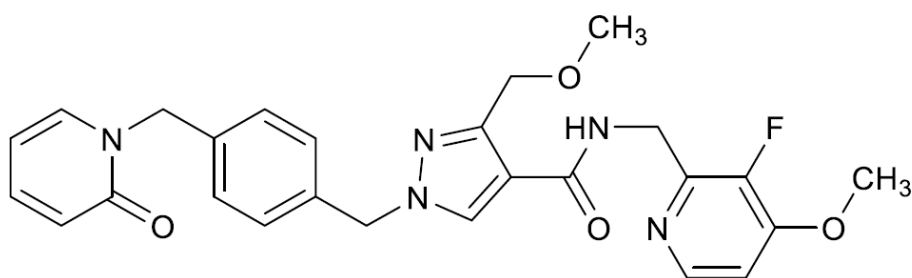
November 11, 2025

Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following pharmaceutical product submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Brand Name	Ekterly Tablets 300 mg
Non-proprietary Name	Sebetralstat
Applicant	KalVista Pharmaceuticals Ltd.
Date of Application	January 15, 2025
Dosage Form/Strength	Each tablet contains 300 mg of sebetralstat.
Application Classification	Prescription drug, (1) Drug with a new active ingredient

Chemical Structure



Molecular formula: $C_{26}H_{26}FN_5O_4$

Molecular weight: 491.51

Chemical name: *N*-[(3-fluoro-4-methoxypyridin-2-yl)methyl]-3-(methoxymethyl)-1-({4-[(2-oxopyridin-1(2*H*)-yl)methyl]phenyl}methyl)-1*H*-pyrazole-4-carboxamide

Items Warranting Special Mention

Orphan drug (Orphan Drug Designation No. 654 of 2024 [*R6 yaku*]; PSB/PED Notification No. 1225-6 dated December 25, 2024, by the Pharmaceutical Evaluation Division, Pharmaceutical Safety Bureau, Ministry of Health, Labour and Welfare)

Reviewing Office Office of New Drug IV

This English translation of this Japanese review report is intended to serve as reference material made available for the convenience of users. In the event of any inconsistency between the Japanese original and this English translation, the Japanese original shall take precedence. PMDA will not be responsible for any consequence resulting from the use of this reference English translation.

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has efficacy in the treatment of acute attacks of hereditary angioedema, and that the product has acceptable safety in view of its benefits (see Attachment).

As a result of its review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following condition. The product is not classified as a biological product or a specified biological product. The drug substance is classified as a powerful drug. The drug product is not classified as a poisonous drug or a powerful drug.

Safety of the product in clinical use warrants further evaluation in post-marketing surveillance, etc.

Indication

Acute attacks of hereditary angioedema

Dosage and Administration

The usual dosage for adults and children aged 12 years and older is one dose of 300 mg of sebetralstat administered orally. A second dose of 300 mg may be administered at least 2 hours after the first dose if response is inadequate or if symptoms recur. However, no more than 2 doses should be administered in a 24-hour period.

Approval Condition

The applicant is required to develop and appropriately implement a risk management plan.

Review Report (1)

October 17, 2025

The following is an outline of the data submitted by the applicant and content of the review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Product Submitted for Approval

Brand Name	Ekterly Tablets 300 mg
Non-proprietary Name	Sebetralstat
Applicant	KalVista Pharmaceuticals Ltd.
Date of Application	January 15, 2025
Dosage Form/Strength	Each tablet contains 300 mg of sebetralstat.

Proposed Indication

Acute attacks of hereditary angioedema

Proposed Dosage and Administration

The usual dosage for adults and children aged 12 years and older is one dose of 300 mg of sebetralstat administered orally at the earliest recognition of an attack. A second dose may be administered as appropriate if response is inadequate or if symptoms recur. However, no more than 2 doses should be administered in a 24-hour period.

Table of Contents

1. Origin or History of Discovery, Use in Foreign Countries, and Other Information.....	3
2. Quality and Outline of the Review Conducted by PMDA.....	4
3. Non-clinical Pharmacology and Outline of the Review Conducted by PMDA.....	6
4. Non-clinical Pharmacokinetics and Outline of the Review Conducted by PMDA.....	8
5. Toxicology and Outline of the Review Conducted by PMDA.....	15
6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA	26
7. Clinical Efficacy and Safety and Outline of the Review Conducted by PMDA.....	34
8. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA	57
9. Overall Evaluation during Preparation of the Review Report (1).....	57
10. Others	57

List of Abbreviations

See Appendix.

1. Origin or History of Discovery, Use in Foreign Countries, and Other Information

Sebetralstat, the active ingredient of Ekterly Tablets 300 mg, is a low-molecular-weight plasma kallikrein (PKa) inhibitor discovered by the applicant.

Hereditary angioedema (HAE) is one of the diseases included in the designated intractable disease “Primary immunodeficiency syndrome” (Designation No. 65 under Public Notice No. 393 of the Ministry of Health, Labour and Welfare dated October 21, 2014) and a congenital disease characterized by recurrent episodic angioedema attacks (HAE attacks) involving various sites such as skin, larynx, and gastrointestinal tract. HAE is caused by an abnormality in the gene encoding complement 1 esterase inhibitor (C1-INH) and is classified into HAE type 1 and HAE type 2, which are characterized by C1-INH deficiency or dysfunction (HAE with C1-INH deficiency [HAE-C1-INH]), and HAE type 3, which is characterized by normal C1-INH blood concentrations and functions without C1-INH abnormalities (HAE with normal C1-INH [HAEnCI]). In HAE type 3 (HAEnCI), pathogenic mutations of multiple genes encoding proteins other than C1-INH such as blood coagulation factor XII (FXII) and plasminogen (PLG) are identified. The estimated prevalence of HAE type 1 or 2 (HAE-C1-INH) is 1 in 50,000 people, and of patients affected by HAE-C1-INH, approximately 85% have HAE type 1, and approximately 15% have HAE type 2 (Guideline for hereditary angioedema [HAE] by the Japanese Association for Complement Research: The 2023 revision and update [*Journal of Japanese Association for Complement Research*. 2023;60:103-31] [hereinafter referred to as Japanese guideline]). On the other hand, the prevalence of HAE type 3 (HAEnCI) remains unknown (*Allergy Asthma Proc.* 2024;45:147-57).

Bradykinin is the primary inflammatory mediator potentially responsible for HAE attacks. In patients with HAE type 1 or 2 (HAE-C1-INH), C1-INH deficiency or dysfunction results in excessive activation of the kallikrein-kinin pathway, which leads to the production of bradykinin. The produced bradykinin enhances vascular permeability, causing clinical symptoms of angioedema. For HAE type 3 (HAEnCI), information on the pathophysiology is limited; however, some reports suggest that certain genetic mutations may lead to angioedema mediated by bradykinin (Japanese guideline).

HAE adversely affects physical function, mental health, etc., if laryngeal oedema occurs, it may result in fatal outcome by asphyxia in some cases, which may determine survival, and thus HAE needs to be appropriately treated (Japanese guideline). Treatment of HAE is provided for 2 major purposes, management of symptoms during an attack and prophylaxis of attacks. Drugs approved for use in patients with HAE in Japan are icatibant acetate (icatibant), a bradykinin B2 receptor antagonist, for the treatment of HAE attacks; human plasma-derived C1-inactivator (for intravenous use) for the treatment of HAE attacks and short-term prophylaxis of HAE attacks during an invasive procedure; and berotralstat hydrochloride (berotralstat) and lanadelumab, PKa inhibitors, human C1-inactivator (for subcutaneous use), and garadacimab, an activated blood coagulation factor XII inhibitor, for long-term prophylaxis of HAE attacks.

PKa cleaves high molecular weight kininogen (HK), releasing bradykinin, and sebetralstat inhibits PKa, thereby suppressing production of bradykinin responsible for HAE attacks. Sebetralstat is thus expected

to have efficacy in the treatment of HAE attacks. While the drugs approved for the treatment of HAE attacks are all injections, sebetralstat has been developed as an orally administered drug.

The applicant initiated clinical development of sebetralstat for the treatment of acute attacks of HAE in July 2019 and has submitted the application for marketing approval based on the results of global clinical studies including Japan. Regarding use in foreign countries, sebetralstat has been approved for the indication of acute attacks of HAE in the US in July 2025 and in Europe in September 2025.

Sebetralstat was designated as an orphan drug (Orphan Drug Designation No. 654 of 2024 [*R6 yaku*]) with the intended indication of “Acute attacks of hereditary angioedema” in December 2024.

2. Quality and Outline of the Review Conducted by PMDA

2.1 Drug substance

2.1.1 Characterization

The drug substance occurs as a white solid. The general properties of the drug substance, including description, solubility, hygroscopicity, melting point, acid dissociation constant, and partition coefficient, were determined. Although the drug substance can exist in at least 6 crystalline forms (Forms 1-6), including solvates, the commercial manufacturing process has been demonstrated to produce the drug substance in Form 1 (anhydrous form) only, which is confirmed to be stable at room temperature.

The chemical structure was elucidated using mass spectrometry, elemental analysis, nuclear magnetic resonance spectroscopy (^1H -NMR, ^{13}C -NMR), infrared absorption spectroscopy (IR), differential scanning calorimetry (DSC), and X-ray powder diffraction (XRPD).

2.1.2 Manufacturing process

The drug substance is synthesized using [REDACTED], [REDACTED], and [REDACTED] as starting materials.

[REDACTED], [REDACTED], [REDACTED], and [REDACTED] have been defined as critical steps. [REDACTED], [REDACTED]

[REDACTED], and [REDACTED] have been controlled as critical intermediates.

2.1.3 Control of drug substance

The proposed specifications for the drug substance include content, description, identification (IR and high performance liquid chromatography [HPLC]), crystalline polymorphism (XRPD and DSC), purity (related substances [HPLC and gas chromatography (GC)], elemental impurities [inductively coupled plasma-mass spectrometry (ICP-MS)], and residual solvents [GC]), water content, residue on ignition, microbial limit, particle size, and assay (HPLC).

2.1.4 Stability of drug substance

Table 1 shows the main stability studies conducted on the drug substance, and the results indicate that the drug substance is stable. A photostability study showed that the drug substance is photolabile.

Table 1. Stability studies of drug substance

Study	Primary batches	Temperature	Humidity	Storage form	Storage period
Long-term	3 commercial production batches	25°C	60%RH	Low density polyethylene bags (double-layered) + high density polyethylene container	■ months
Accelerated	3 commercial production batches	40°C	75%RH		6 months

Based on the above, a retest period of ■ months has been proposed for the drug substance when stored in double-layered low density polyethylene bags, further placed in a high density polyethylene container, at room temperature and protected from light.

2.2 Drug product

2.2.1 Description and composition of drug product and formulation development

The drug product is immediate-release film-coated tablets each containing 300 mg of the drug substance. Excipients contained in the drug product are microcrystalline cellulose, croscarmellose sodium, povidone, magnesium stearate, ■■■■■■■■■■, and ■■■■■■■■■■.

2.2.2 Manufacturing process

The drug product is manufactured through a process comprising ■■■■■■■■■■, ■■■■■■■■■■, tableting, film coating, testing, packaging, and labeling and storage. ■■■■■■■■■■ and ■■■■■■■■■■ have been defined as critical steps, and in the processes for ■■■■■■■■■■, ■■■■■■■■■■, ■■■■■■■■■■, and ■■■■■■■■■■, process control items and process control values have been specified.

Based on the following investigations, the quality control strategy has been established (Table 2).

- Identification of critical quality attributes (CQAs)
- Quality risk assessment

Table 2. Overview of drug product control strategy

CQA	Control method
Description	Manufacturing process and specifications
Identification	Specifications
Assay	Manufacturing process and specifications
Uniformity of dosage units	Manufacturing process and specifications
Related substances	Specifications
Dissolution	Manufacturing process and specifications
■■■■■	Specifications
Microbial limit	Manufacturing process and specifications

2.2.3 Control of drug product

The proposed specifications for the drug product include strength, description, identification (HPLC and ultraviolet-visible spectroscopy [UV/VIS]), purity (related substances [HPLC]), water content, uniformity of dosage units (mass variation), microbial limit, dissolution (HPLC), and assay (HPLC).

2.2.4 Stability of the drug product

Table 3 shows the main stability studies conducted on the drug product, and the results indicate that the drug product is stable. A photostability study showed that the drug product is photostable.

Table 3. Stability studies of the drug product

Study	Primary batches	Temperature	Humidity	Storage form	Storage period
Long-term	2 commercial production batches	25°C	60%RH	Aluminum blister package	24 months
	1 commercial production batch				36 months
Accelerated	3 commercial production batches	40°C	75%RH		6 months

Based on the above results, a shelf life of 36 months has been proposed for the drug product when packaged in aluminum blister packages (3-layer forming film made of polyamide [nylon], aluminum foil, and polyvinyl chloride/lidding aluminum foil), which are stored in cartons at room temperature, according to the “Guideline on Evaluation of Stability Data” (PFSB/ELD Notification No. 0603004 dated June 3, 2003). Long-term testing will be continued up to 36 months.

2.R Outline of the review conducted by PMDA

Based on the submitted data, PMDA has concluded that the quality of the drug substance and the drug product is adequately controlled.

3. Non-clinical Pharmacology and Outline of the Review Conducted by PMDA

The applicant submitted primary pharmacodynamic data in the form of results from studies evaluating PKa inhibition and effects on the carrageenan-induced footpad oedema model. The applicant also submitted secondary pharmacodynamic data in the form of results from studies evaluating effects on various enzymes and receptors as well as non-clinical safety pharmacology data in the form of results from studies evaluating effects of sebetralstat on the central nervous, respiratory, and cardiovascular systems. No pharmacodynamic drug interaction studies were conducted.

Unless otherwise specified, the pharmacological parameters are expressed as the arithmetic mean $\pm$ standard deviation (SD).

3.1 Primary pharmacodynamics

3.1.1 Inhibition against human PKa (CTD 4.2.1.1-1, 4.2.1.1-5, and 4.2.1.1-10 to 4.2.1.1-13)

The *in vitro* inhibitory effect of sebetralstat on human PKa was measured by a fluorescence assay¹⁾ using PKa prepared from human plasma, and the inhibitory constant (K_i) of sebetralstat was determined to be 3.02 ± 0.33 nmol/L. In a fluorescence assay using undiluted human plasma with the kallikrein-kinin pathway activated by dextran sulfate, sebetralstat inhibited human PKa with a half-maximal inhibitory concentration (IC_{50}) of 54.0 ± 19.6 nmol/L.

Inhibitory effect of sebetralstat²⁾ on human PKa's HK cleavage was investigated using undiluted plasma samples from healthy adults and patients with HAE in which the kallikrein-kinin pathway was

¹⁾ D-prolyl-phenylalanyl-arginine aminotrifluoro methyl coumarin was used as the fluorogenic substrate.

²⁾ 50 to 1,000 nmol/L for plasma samples from healthy adults and 50 to 300 nmol/L for those from patients with HAE

preactivated with dextran sulfate, and the results were visualized by Western blotting. At ≥ 200 nmol/L and ≥ 100 nmol/L, respectively, sebetralstat inhibited HK cleavage.

Furthermore, undiluted plasma samples from healthy adults before and after oral administration of sebetralstat (600 mg) were activated with dextran sulfate, and plasma protein concentrations (HK, cleaved high molecular weight kininogen [cHK], plasma prekallikrein, FXII, and activated blood coagulation factor XII [FXIIa]) were measured by immunoassay. The results showed that sebetralstat prevented plasma concentrations of prekallikrein and FXII from decreasing, suggesting that sebetralstat inhibits PKa-mediated conversion of FXII to FXIIa, thereby blocking conversion of prekallikrein to PKa in plasma.

3.1.2 Inhibition against PKa derived from various animals (CTD 4.2.1.1-14 to 4.2.1.1-19)

Using recombinant PKa proteins (mouse, rabbit) and diluted plasma samples from various animals (rat, dog, pig, and cynomolgus monkey) in which the kallikrein-kinin pathway was activated with dextran sulfate, the inhibitory effect of sebetralstat on PKa was investigated by a fluorescence assay. K_i values of sebetralstat against mouse and rat PKa proteins were 6.94 and 37.15 nmol/L, and IC_{50} values of sebetralstat against mouse, rat, rabbit, dog, pig, and cynomolgus monkey PKa were 13.91, 69.76, $>40,000$, 8,670, $>40,000$, and 5.07 nmol/L, respectively. In addition, using diluted plasma samples from rats and cynomolgus monkeys in which the kallikrein-kinin pathway was activated with ellagic acid, the inhibitory effect of sebetralstat on PKa was investigated by a fluorescence assay. IC_{50} values were 68.4 ± 23.6 and 9.46 ± 17.5 nmol/L, respectively.

3.1.3 Effects in rat carrageenan-induced footpad oedema model (CTD 4.2.1.1-22)

To Sprague Dawley (SD) rats, sebetralstat at 30, 100, or 300 mg/kg or vehicle (D- α -tocopherol polyethylene glycol 1,000 succinate [TPGS]) was orally administered, and 1 hour later 0.1 mL of a 1% carrageenan solution was subcutaneously administered into the foot sole of the right hindlimb to induce oedema. Compared with the vehicle group, the sebetralstat 300 mg/kg group showed suppression of the increase in right hindlimb volume at 2, 4, and 6 hours after the carrageenan administration, and similar suppression was observed at 2 and 4 hours in the sebetralstat 30 mg/kg group and at 4 hours in the sebetralstat 100 mg/kg group.

3.2 Secondary pharmacodynamics (4.2.1.2-1 to 4.2.1.2-2)

The inhibitory activity of sebetralstat against serine proteases³⁾ was investigated by a fluorescence assay, and its inhibitory activity against major ion channels, receptors, transporters, and enzymes⁴⁾ was investigated by radioactive ligand binding assay, and other methods. Of the targets investigated, none was inhibited by $\geq 50\%$ in the presence of sebetralstat (10 μ mol/L).

3.3 Safety pharmacology

Table 4 shows results from safety pharmacology studies. In the human ether-à-go-go-related gene (hERG) study, the hERG current was inhibited by up to 8.33% in the presence of sebetralstat at

³⁾ Tissue kallikrein 1, plasmin, thrombin, trypsin, FXIIa, activated blood coagulation factor XI (FXIa)

⁴⁾ 124 types of proteins including proteases (thrombin, activated blood coagulation factor X [FXa], activated blood coagulation factor VII [FVIIa], β secretase 1, cathepsin D, cathepsin G, renin, tissue plasminogen activator, and tryptase).

30 µmol/L. In an electrocardiogram (ECG) study in cynomolgus monkeys, no QT prolongation was observed at a maximum blood concentration of 5,920 ng/mL achieved following administration of the highest dose (300 mg/kg).

Table 4. Summary of safety pharmacology studies

Item	Test system	Endpoints and methods	Dose	Route of administration	Findings	CTD
Cardiovascular system	hERG-transfected HEK293 cells	hERG current	3, 30 µmol/L	<i>In vitro</i>	30: Inhibited by 8.33%	4.2.1.3-2
	Cynomolgus monkey (4 males)	Blood pressure, heart rate, ECG, body temperature, motor activity	30, 100, 300 mg/kg	Oral	No effects	4.2.1.3-3
Central nervous system	Wistar (Han) rat (6 males/group)	Modified Irwin's test, body temperature	100, 350, 1,000 mg/kg	Oral	No effects	4.2.1.3-4
Respiratory system		Respiratory rate, tidal volume, minute ventilation, peak inspiratory/expiratory flow, inspiratory/expiratory time, airway constriction index	100, 350, 1,000 mg/kg	Oral	No effects	4.2.1.3-5

3.R Outline of the review conducted by PMDA

Based on the submitted data, PMDA concluded that sebetralstat inhibits PKa and thus can be expected to have efficacy in treatment of bradykinin-mediated HAE attacks in humans.

4. Non-clinical Pharmacokinetics and Outline of the Review Conducted by PMDA

The applicant submitted data on the absorption, distribution, metabolism, and excretion in the form of results from oral and intravenous dose studies in mice, rats, rabbits, dogs, and monkeys. Plasma sebetralstat concentrations were determined by liquid chromatography with tandem mass spectrometry (LC-MS/MS) (lower limit of quantification, 1.0-10 ng/mL), and radioactivity concentrations in samples were determined by quantitative whole-body autoradiography and a liquid scintillation counting method.

4.1 Absorption

4.1.1 Single dose studies (CTD 4.2.2.2-2 to 4.2.2.2-3 and 4.2.2.2-6 to 4.2.2.2-7)

Table 5 shows pharmacokinetic parameters of sebetralstat in mice, rats, dogs, and monkeys after a single oral or intravenous administration. The exposure (AUC) in mice increased approximately dose-proportionally across the dose range studied, but that in rats increased more than dose-proportionally from 30 to 300 mg/kg.

Table 5. Pharmacokinetic parameters after single administration of sebetralstat

Animal species	Route of administration	Dose (mg/kg)	n	C _{max} (µg/mL)	AUC _{last} (µg·h/mL)	AUC _{inf} (µg·h/mL)	t _{max} (h)	CL (mL/min/kg)	V _{ss} (L/kg)	t _{1/2} (h)	F (%)
Mouse	Intravenous	1	3 males ^{a)}	-	0.60	0.60	-	23.9	0.725	0.33	-
	Oral	10		1.7	1.7	1.7	0.25	-	-	-	28.7
		25		6.6	4.4	4.4	0.083	-	-	-	27.0
Rat	Intravenous	1	3 males	-	1.6 ± 0.36	1.6 ± 0.36	-	11.7 ± 2.8	0.51 ± 0.15	1.03 ± 0.02	-
	Oral	10		1.9 ± 0.56	7.4 ± 1.0	7.4 ± 1.0	1.0 [0.5, 2.0]	-	-	-	49.5 ± 6.4
		30		4.5 ± 1.9	14.5 ± 7.2	14.6 ± 7.2	1.0 [1.0, 1.0]	-	-	-	29.8 ± 14.7
		100		21.5 ± 11.8	100.2 ± 74.6	100.4 ± 74.6	2.0 [1.0, 2.0]	-	-	-	66.5 ± 49.3
		300		61.8 ± 21.3	619.8 ± 314.9	620.3 ± 315.1	6.0 [4.0, 6.0]	-	-	-	129.7 ± 65.0
Dog	Intravenous	1	2 males	-	2.1, 2.1	2.1, 2.1	-	8.6, 8.8	0.62, 0.69	0.80, 1.3	-
	Oral	1		0.23, 0.34	0.55, 0.77	0.57, 0.77	0.5, 1.0	-	-	-	27.4, 40.3
Monkey	Intravenous	1	3 males	-	0.58 ± 0.12	0.59 ± 0.12	-	32.7 ± 6.9	1.5 ± 0.22	0.98 ± 0.14	-
	Oral	1 ^{b)}		0.12 ± 0.05	0.15 ± 0.04	0.15 ± 0.04	0.5 [0.5, 0.5]	-	-	-	29.5 ± 12.6
		10 ^{b)}		2.2 ± 1.3	2.4 ± 0.41	2.42 ± 0.40	0.25 [0.25, 1.0]	-	-	-	49.2 ± 3.7
		2.4 ^{c)}		0.167 ± 0.11	0.28 ± 0.11	0.30 ± 0.11	1.0 [1.0, 1.0]	-	-	-	23.7 ± 5.8
		25 ^{c)}		1.28 ± 0.23	2.7 ± 0.50	2.8 ± 0.43	1.0 [1.0, 1.0]	-	-	-	21.7 ± 1.6

Mean or mean ± SD, individual values in the case of n = ≤2; t_{max}, Median or median [minimum, maximum]; -, Not applicable or calculated

a) Number of animals per sampling point; b) Liquid preparation (vehicle, 10% dimethyl sulfoxide [DMSO] in water); c) Capsules filled with powder

4.1.2 Repeated-dose studies (CTD 4.2.3.2-5 and 4.2.3.2-13)

Table 6 shows pharmacokinetic parameters of sebetralstat in rats and monkeys after repeated oral administration. The exposure after repeated administration of sebetralstat did not clearly differ between males and females in rats or monkeys. Accumulation was observed in rats after repeated administration, and it tended to be greater in males than in females. In monkeys, accumulation was not observed after repeated administration. In rats, C_{max} and AUC_{0-24h} increased more than dose-proportionally from 30 to 100 mg/kg/day and less than dose-proportionally from 100 to 300 mg/kg/day. In monkeys, C_{max} and AUC_{0-24h} tended to increase with dose.

Table 6. Pharmacokinetic parameters after repeated oral administration of sebetralstat

Animal species	Duration of administration (interval)	Sampling point	Dose (mg/kg/day)	n	C _{max} (µg/mL)		AUC _{0-24h} (µg·h/mL)		t _{max} (h)	
					Male	Female	Male	Female	Male	Female
Rat	26 weeks (once daily)	Day 1	30	3/sex ^{a)}	4.1	10.4	9.2	27.0	1	0.5
			100		11.1	29.6	50.6	182.0	0.5	0.5
			300		23.4	54.4	168.0	547.0	4	0.5
		Day 177	30		10.1	16.4	24.8	48.3	0.5	0.5
			100		78.6	78.7	427.0	386.0	2	2
			300		94.2	106.0	942.0	1,030.0	4	1
Monkey	26 weeks (twice weekly)	Day 1	15	4/sex	0.78 ± 0.17	1.7 ± 1.3	1.3 ± 0.31	2.3 ± 1.1	0.5 [0.5, 0.5]	0.5 [0.5, 1]
			50	6/sex	2.8 ± 1.3	1.8 ± 0.72	7.2 ± 3.7	6.1 ± 1.8	0.5 [0.5, 1]	0.5 [0.5, 1]
			150		3.2 ± 2.7	2.9 ± 1.5	17.6 ± 15.0	10.3 ± 3.5	2 [2, 4]	2 [1, 2]
			300		7.4 ± 3.8	7.5 ± 2.6	36.6 ± 18.4	32.8 ± 17.2	2 [0.5, 4]	2 [2, 2]
		Day 176	15	4/sex	0.22 ± 0.09 ^{b)}	1.7 ± 0.09 ^{b)}	0.87 ± 0.33 ^{b)}	2.5 ± 0.44 ^{b)}	1 [0.5, 1] ^{b)}	1 [0.5, 1] ^{b)}
			50	6/sex	1.4 ± 0.53	3.5 ± 0.62	5.6 ± 1.8	7.5 ± 3.5	1 [1, 2]	0.75 [0.5, 2]
			150		5.3 ± 2.6	2.7 ± 1.3 ^{c)}	31.7 ± 11.5	13.0 ± 2.9 ^{c)}	3 [1, 6]	2 [2, 2] ^{c)}
			300		11.0 ± 6.1	8.4 ± 3.4	48.6 ± 16.8	36.2 ± 21.5	3 [2, 6]	2 [2, 2]

Mean (rat), mean ± SD or median [range] (t_{max}) (monkey)

a) Number of animals per sampling point, b) n = 3, c) n = 5

4.1.3 In vitro membrane permeability (CTD 4.2.2.6-1)

Membrane permeability of sebetralstat was investigated using human colorectal adenocarcinoma (Caco-2) cells. The apical-to-basolateral and basolateral-to-apical apparent permeability coefficients (P_{app A→B}

and $P_{app\ B \rightarrow A}$) of sebetralstat at 10 to 50 $\mu\text{mol/L}$ were 1.51 to 3.75×10^{-6} cm/s and 30.3 to 46.1×10^{-6} cm/s , and in the presence of a P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) inhibitor (elacridar), the $P_{app\ A \rightarrow B}$ and $P_{app\ B \rightarrow A}$ were 13.9 to 15.3×10^{-6} cm/s and 12.2 to 13.3×10^{-6} cm/s , respectively. In view of $P_{app\ A \rightarrow B}$ values of the low membrane permeability reference compound (atenolol) and high membrane permeability one (propranolol), which were 0.179 to 0.268×10^{-6} cm/s and 10.0 to 31.0×10^{-6} cm/s , respectively,⁵⁾ it was suggested that sebetralstat has moderate membrane permeability.

4.2 Distribution

4.2.1 Tissue distribution (CTD 4.2.2.2-4)

Tissue distribution of the radioactivity⁶⁾ was investigated following administration of a single oral dose of 30 mg/kg of ^{14}C -sebetralstat to male albino Wistar (Han) rats and male pigmented Lister Hooded rats.

In male albino Wistar (Han) rats, the radiolabeled sebetralstat was rapidly distributed throughout the body except for the brain and spinal cord, and the radioactivity concentration peaked at 0.5 to 1 hour post-dose in most of the tissues. In all tissues except for the liver, kidney, and adrenal gland, the radioactivity concentration decreased to below the lower limit of quantitation by 72 hours post-dose.

In male pigmented Lister Hooded rats, radioactivity was not detected in most of the tissues at 24 hours post-dose (the first sampling point). Although radioactivity was measurable in the uvea, eye, liver, kidney, non-pigmented skin, pigmented skin, and small intestine wall, radioactivity concentrations in these tissues decreased within 336 hours post-dose.

The radioactivity concentrations in melanin-containing tissues such as pigmented skin and uvea were higher in pigmented rats than in albino rats, suggesting that sebetralstat may bind to melanin. However, the radioactivity concentrations in such tissues decreased with time. Therefore, the applicant explained that the binding of sebetralstat to melanin is likely to be reversible.

4.2.2 Plasma protein binding and distribution in blood cells (CTD 4.2.2.3-1 to 4.2.2.3-2)

Table 7 shows plasma protein binding (equilibrium dialysis method, 5 $\mu\text{mol/L}$) and blood/plasma concentration ratios (1 $\mu\text{mol/L}$) of sebetralstat determined in various animal species.

Table 7. Plasma protein binding and blood/plasma concentration ratios of sebetralstat

Animal species	Mouse	Rat	Rabbit	Pig	Dog	Monkey	Human
Plasma protein binding	94.1%	96.1%	87.5%		65.9%	62.4%	76.8%
Blood/plasma concentration ratio	0.60	0.56		0.93	0.80	0.90	0.80

⁵⁾ Including results from measurements in the presence and absence of a P-gp or BCRP inhibitor.

⁶⁾ Tissues subjected to the measurements were adrenal gland, adrenal cortex, adrenal medulla, blood, bone marrow, brain (whole), brown fat, epididymis, lacrimal gland, eye, Harderian gland, kidney, renal cortex, renal medulla, renal cone, colon wall, eye lens, liver, lung, lymph node, myocardium, skeletal muscle, pancreas, non-pigmented skin, pigmented skin, pineal gland, pituitary gland, preputial gland, prostate gland, salivary gland, vesicular gland, rectum wall, small intestine wall, spinal cord, spleen, gastric wall (glandular stomach), gastric wall (other than glandular stomach), testis, thymus, thyroid, bladder wall, uvea, and white fat.

4.2.3 Placental transfer (CTD 4.2.2.3-4)

A single dose of ^{14}C -sebetralstat 100 mg/kg was orally administered to pregnant rats, and at 1 hour post-dose, the radioactivity concentration was 17.77 $\mu\text{g equiv/g}$ and 29.44 $\mu\text{g equiv/g}$ in maternal blood and plasma, respectively, and 1.46 $\mu\text{g equiv/g}$ in fetuses.

4.3 Metabolism

4.3.1 *In vitro* study (CTD 4.2.2.4-5 to 4.2.2.4-7)

Incubation of sebetralstat (1 or 5 $\mu\text{mol/L}$) with hepatocytes from mice, rats, rabbits, pigs, dogs, monkeys, or humans revealed that a major metabolic pathway of sebetralstat is oxidation of the pyridone ring, and various metabolites, including products of O-demethylation and N-dealkylation, were detected (Figure 1). No metabolites unique to humans were identified.

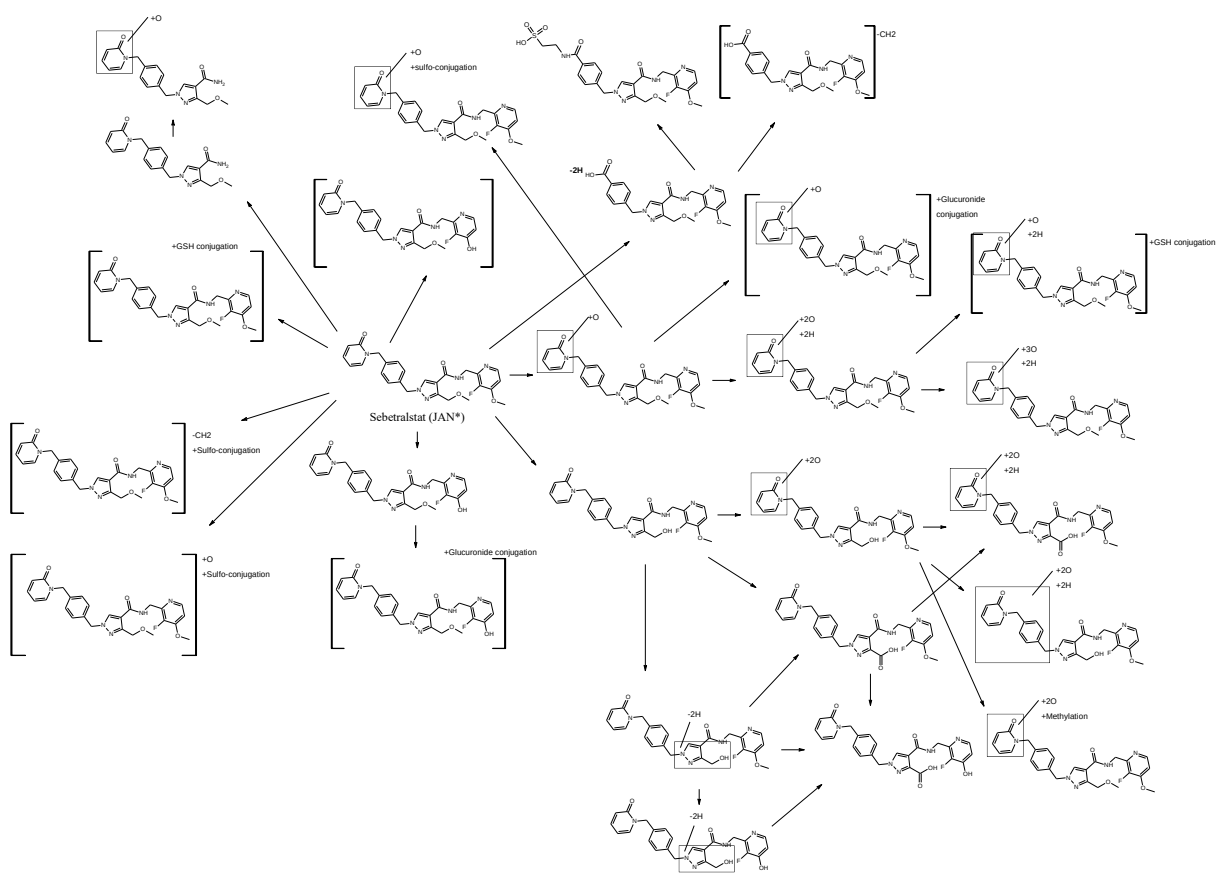


Figure 1. Putative metabolic pathways of sebetralstat

A study using human liver microsomes and inhibitors selective for specific cytochrome P450 (CYP) isoforms⁷⁾ suggested that sebetralstat is metabolized primarily by CYP3A4 and partially by CYP2C8 (contribution rate to metabolism [f_m], 59% and 21%, respectively).

⁷⁾ Chemical compounds used as inhibitors against each isoform are as follows: α -naphthoflavone for CYP1A2, 8-methoxypsoralen for CYP2A6, thio-TEPA for CYP2B6, quercetin for CYP2C8, sulfaphenazole for CYP2C9, tranilcypromine for CYP2C19, quinidine for CYP2D6, diethylthiocarbamate for CYP2E1, and ketoconazole for CYP3A4/5.

4.3.2 *In vivo* study (CTD 4.2.2.2-4 and 4.2.2.2-13)

Table 8 shows metabolites identified in samples from rats and monkeys following a single oral dose of sebetralstat. In a mass balance study [see Section 6.2.1.2], no metabolites unique to humans were identified.

Table 8. Metabolite profile in each animal species

Animal species	Dose	Plasma	Feces	Bile ^{a)}	Urine	Attached document CTD
Rat ^{b)}	30 mg/kg	Up to 24 hours post-dose Unchanged sebetralstat, M10, m/z 508	Up to 48 hours post-dose Unchanged sebetralstat, M10, m/z 508, M3, ^{c)} M6, ^{c)} M22 ^{c)}	Up to 24 hours post-dose Unchanged sebetralstat, M10, m/z 508, M3, M6, M19, M20, M21, m/z 815, m/z 526, m/z 588	Up to 24 hours post-dose Unchanged sebetralstat, M10, m/z 508, M3, M6, M19, M20	4.2.2.2-4
Monkey ^{d)}	10 mg/kg	Up to 8 hours post-dose Unchanged sebetralstat, M3, M19, M6, M10, M23, M24, M29	Male: Up to 72 hours post-dose Female: Up to 120 hours post-dose Unchanged sebetralstat, M3, M19, M6, M10, M27, M23, M24, M28		Up to 24 hours post-dose Unchanged sebetralstat, M3, M19, M6, M10, M23, M24, M25, ^{c)} M26, M29	4.2.2.2-13

a) Males only

b) Unchanged sebetralstat, M10, and m/z 508 were co-eluted.

c) Detected only in samples from females.

d) M3 and M19 were co-eluted, and M6, M10, and M27 were also co-eluted.

Figure 2 shows putative metabolic pathways of sebetralstat in humans based on the above metabolism study results.

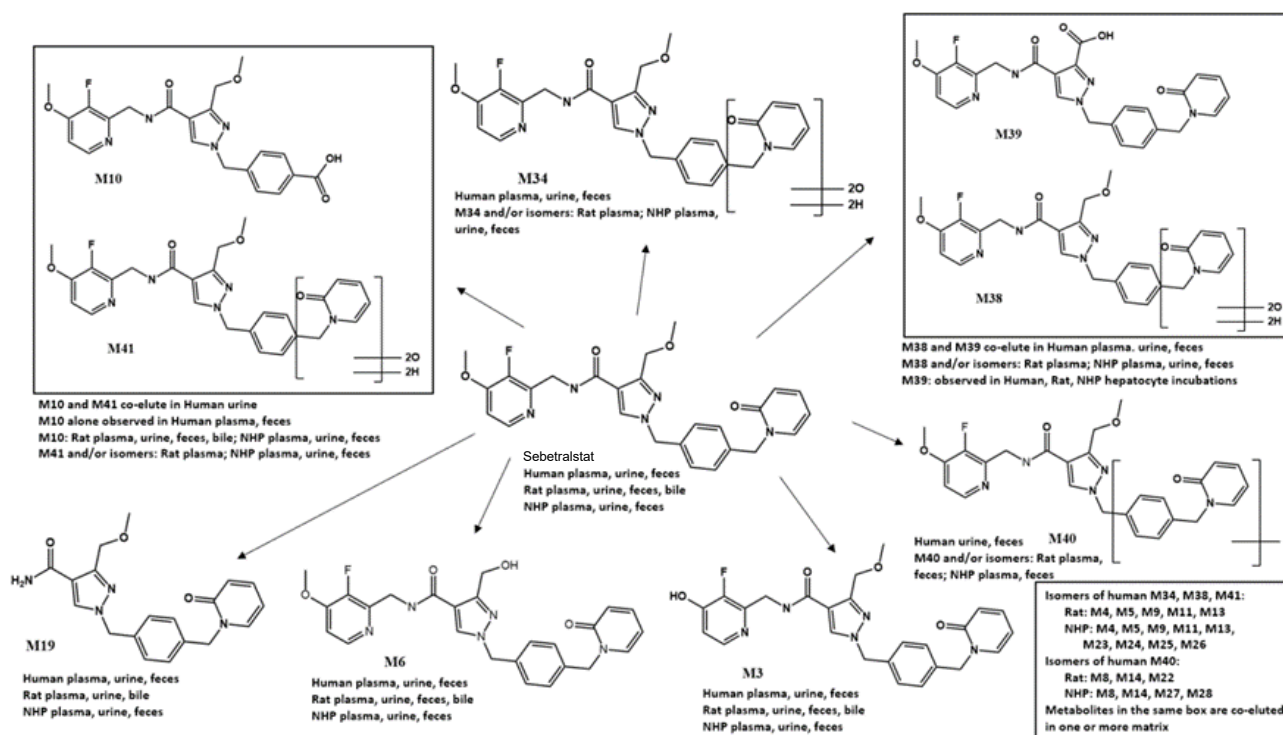


Figure 2. Putative metabolic pathways of sebetralstat in humans

4.4 Excretion

4.4.1 Excretion in urine, feces, and bile (CTD 4.2.2.2-4 and 4.2.2.2-13)

Following administration of a single oral dose of ^{14}C -sebetralstat 30 mg/kg to rats, 6.5% and 91.0% of the administered radioactivity were excreted in urine and feces, respectively, in males, and 7.3% and 91.2%, respectively, in females up to 168 hours post-dose. In bile-duct-cannulated male rats, 55.1% of the administered radioactivity was excreted in bile up to 48 hours post-dose.

Following administration of a single oral dose of ^{14}C -sebetralstat 10 mg/kg to monkeys, 10.8% and 84.5% of the administered radioactivity were excreted in urine and feces, respectively, in males, and 9.8% and 78.7% were excreted in urine and feces, respectively, in females up to 168 hours post-dose.

4.4.2 Excretion in milk (CTD 4.2.2.3-4)

A single dose of ^{14}C -sebetralstat 100 mg/kg was orally administered to lactating female rats. Table 9 shows radioactivity concentrations in plasma and milk, indicating transfer of sebetralstat into milk.

Table 9. Radioactivity concentrations in plasma and milk in lactating female rats which orally received a single dose of ^{14}C -sebetralstat 100 mg/kg ($\mu\text{g equiv/mL}$)

Sample	n	Time after administration (h)		
		1	8	24
Plasma	3	28.17 $\pm$ 10.33	4.18 $\pm$ 1.79	0.37 $\pm$ 0.28
Milk	3	22.03, 29.70	5.02 $\pm$ 2.61	0.36 $\pm$ 0.39

Mean $\pm$ SD, individual values in the case of $n = \leq 2$

4.5 Pharmacokinetic interactions

4.5.1 Enzyme inhibition and induction (CTD 4.2.2.6-1 to 4.2.2.6-3)

The inhibitory effect of sebetralstat on CYP isoforms (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4) was investigated using human liver microsomes.⁸⁾ Sebetralstat reversibly inhibited CYP3A4 and CYP2C9, with IC_{50} values of 120 to 121 and 30.1 $\mu\text{mol/L}$, respectively, whereas the IC_{50} values for the other isoforms were $>200 \mu\text{mol/L}$. Sebetralstat did not exhibit time-dependent inhibition of any CYP isoform.

The inhibitory effect of sebetralstat on uridine diphosphate-glucuronosyltransferase (UGT) isoforms was investigated using microsomes prepared from insect cells expressing human hepatic UGT isoforms (UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A9, or UGT2B7).⁹⁾ Sebetralstat weakly inhibited UGT1A1, UGT1A3, UGT1A4, and UGT1A9, with IC_{50} values of 87.9, 90.1, 57.5, and 31.3 $\mu\text{mol/L}$, respectively. IC_{50} values of sebetralstat against UGT1A6 and UGT2B7 were $>100 \mu\text{mol/L}$.

Using human hepatocytes, induction of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP3A4 by sebetralstat (1-100 $\mu\text{mol/L}$) were investigated. Increased messenger ribonucleic acid (mRNA) expression was observed for CYP2C9 and CYP2C19 at sebetralstat concentrations of 1 to 100 $\mu\text{mol/L}$, for CYP3A4 at 10 to 100 $\mu\text{mol/L}$, and for CYP2B6 and CYP2C8 at 100 $\mu\text{mol/L}$.

⁸⁾ Chemical compounds used as substrates of each isoform are as follows:

Phenacetin for CYP1A2, bupropion for CYP2B6, paclitaxel for CYP2C8, tolbutamide for CYP2C9, S-mephenytoin for CYP2C19, bufuralol for CYP2D6, and testosterone and midazolam for CYP3A4.

⁹⁾ Chemical compounds used as substrates of each isoform are as follows:

Estradiol for UGT1A1, sulindac sulfone for UGT1A3, trifluoperazine for UGT1A4, naphthol for UGT1A6, propofol for UGT1A9, and naloxone for UGT2B7.

4.5.2 Potential as a substrate of drug transporters (CTD 4.2.2.6-7 to 4.2.2.6-8)

A study using Madin-Darby canine kidney (MDCK) cells expressing human P-gp or BCRP¹⁰⁾ suggested that sebetralstat is a substrate of P-gp and BCRP.

A study using human embryonic kidney 293 (HEK293) cells expressing human organic anion transporting polypeptide (OATP) 1B1, OATP1B3, organic anion transporter (OAT) 1, OAT3, OCT2, or multidrug and toxin extrusion protein (MATE) 1 or MDCK cells expressing MATE2-K¹¹⁾ suggested that sebetralstat is unlikely to be a substrate for transporters other than MATE2-K. The applicant explained that a clinical evaluation of sebetralstat as a substrate of MATE2-K was not considered necessary because the mass balance study [see Section 6.2.1.2] showed that renal clearance of sebetralstat in humans accounted for <10% of the total clearance.

4.5.3 Inhibition against drug transporters (CTD 4.2.2.6-5 to 4.2.2.6-6)

The inhibitory effect of sebetralstat on drug transporters was investigated using MDCK cells expressing human P-gp, BCRP, or MATE2-K or HEK293 cells expressing human bile salt export pump (BSEP), OATP1B1, OATP1B3, OAT1, OAT3, organic cation transporter (OCT) 2, or MATE1.¹²⁾ The results are shown in Table 10. The inhibitory effect of sebetralstat on BCRP, BSEP, OATP1B1, OATP1B3, OAT3, OCT2, MATE1, and MATE2-K was observed.

Table 10. Inhibitory effect of sebetralstat against drug transporters

Transporter	Concentration (μmol/L)	IC ₅₀ (μmol/L) (maximum inhibition rate)	Transporter	Concentration (μmol/L)	IC ₅₀ (μmol/L) (maximum inhibition rate)
P-gp	0.1-100	>100 (6.47%)	OAT1	0.1-100	>100 (14.4%)
BCRP	0.1-100	82.3 (50%)	OAT3	0.1-100	19.2 (74.6%)
BSEP	0.01-100	76.9 (45.3%)	OCT2	0.1-100	5.29 (97.1%)
OATP1B1	0.1-100	95.4 (53.1%)/86.3 (44.4%) ^{a)}	MATE1	0.1-100	8.05 (115%)
OATP1B3	0.1-100	60.1 (54.9%)/51.3 (64.1%) ^{a)}	MATE2-K	0.1-100	7.76 (90.2%)

a) Result from investigation of time-dependent inhibition employing 30-minute pre-incubation

4.R Outline of the review conducted by PMDA

In vitro studies suggested that sebetralstat may inhibit and induce CYP isoforms, inhibit UGT isoforms, and inhibit drug transporters.

The applicant's explanation about the above findings:

Sebetralstat is intended for the treatment of HAE attacks at the time of onset and is not intended for long-term use. Because plasma concentrations of sebetralstat rapidly decrease after administration, no clinical drug interaction studies have been conducted. Sebetralstat is considered unlikely to affect the pharmacokinetics of the other drugs through inhibition or induction of metabolic enzymes or transporters.

¹⁰⁾ Inhibitors against each transporter are as follows:

Cyclosporin A, valspodar, and verapamil against P-gp; cyclosporin A, elacridar, and Ko143 against BCRP.

¹¹⁾ Inhibitors against each transporter are as follows:

Cyclosporin A against OATP1B1 and OATP1B3; probenecid against OAT1 and OAT3; quinidine against OCT2; cimetidine against MATE1; and pyrimethamine against MATE2-K.

¹²⁾ Chemical compounds used as substrates of each transporter are as follows:

Vinblastine for P-gp, prazosin for BCRP, ³H-taurocholate for BSEP, ³H-estradiol-β-glucuronide for OATP1B1, ³H-cholecystokinin-8 for OATP1B3, ³H-p-aminohippuric acid for OAT1, ³H-estrone-3-sulphate for OAT3, and ¹⁴C-metformin for OCT2, MATE1, and MATE2-K.

PMDA accepted the above explanation. PMDA also considered that the submitted study results provide an adequate understanding of the *in vivo* disposition of sebetralstat. Whether sebetralstat may be subject to clinically relevant pharmacokinetic interactions in clinical use should be discussed in view of the clinical study results [see Section 6.2.3].

5. Toxicology and Outline of the Review Conducted by PMDA

The applicant submitted toxicity data of sebetralstat in the form of results from repeated-dose toxicity, genotoxicity, carcinogenicity, reproductive and developmental toxicity, juvenile animal studies, and other toxicity studies (phototoxicity and impurity-related studies). Unless otherwise specified, 20% TPGS solution or 0.5% hydroxypropyl methylcellulose (HPMC) solution¹³⁾ was used as vehicle.

5.1 Single-dose toxicity

No single-dose toxicity studies of sebetralstat have been conducted. In repeated oral dose toxicity studies of sebetralstat in mice, rats, dogs, and cynomolgus monkeys [see Section 5.2] (CTD 4.2.3.2-1, 4.2.3.2-6, 4.2.3.2-8 and 4.2.3.4.1-1), no acute signs of toxicity or death were observed after the first dose. The approximate lethal oral dose was determined to be >1,500 mg/kg in mice and >1,000 mg/kg in the other animal species.

5.2 Repeated-dose toxicity

Repeated oral dose toxicity studies were conducted in rats for 28 days, 13 weeks, and 26 weeks, in mice for 28 days,¹⁴⁾ in dogs for 4 weeks as well as in cynomolgus monkeys for 35 days, 13 weeks, and 26 weeks (Tables 11 and 12). Abnormal findings related to sebetralstat were mainly observed in the liver, including hypertrophic changes of hepatocytes, degeneration and necrosis of hepatocytes, inflammatory cell infiltration, brown pigmentation, and bile duct hyperplasia in mice, rats, or cynomolgus monkeys. In rats, changes considered to be associated with enzyme induction and hormone alterations related to sebetralstat were observed in the thyroid (increased thyroid weight and follicular epithelial cell hypertrophy), submandibular gland (degranulation), kidney (decreased hyaline droplets), adrenal gland (cortical hypertrophy), ovary (luteal hypertrophy accompanied by vacuolation of interstitial cells), and vagina (increased vaginal mucus production related to abnormal estrus), and hematological changes (anemia-like changes) were also observed. Changes observed at ≤ 300 mg/kg/day across repeated-dose toxicity studies were minor and were adaptive in nature or were not associated with cellular injury or functional impairment, and were therefore considered of little toxicological significance. In the 26-week repeated oral dose toxicity study in rats, the no observed adverse effect level (NOAEL) was determined to be 300 mg/kg/day (both sexes). In rats receiving repeated doses of sebetralstat at the NOAEL, $C_{\max}$ and AUC_{0-24h} on Day 177 were 96,400 ng/mL and 983,000 ng·h/mL (mean in both sexes), respectively, corresponding to approximately 17- and 50-fold the respective clinical exposures in humans.¹⁵⁾

¹³⁾ In toxicity studies at the early development stage, 20% TPGS solution was used as vehicle, but was subsequently replaced with 0.5% HPMC solution.

¹⁴⁾ Repeated-dose toxicity of sebetralstat was evaluated mainly based on findings in rats and cynomolgus monkeys. In mice, a short-term repeated-dose toxicity study was conducted to support dose selection for carcinogenicity studies.

¹⁵⁾ $C_{\max}$ = 5,640 ng/mL and AUC_{inf} = 19,500 ng·h/mL (clinical exposures [arithmetic mean] in healthy adults who received a single dose of sebetralstat 600 mg [white film-coated tablets 300 mg $\times$ 2] in a foreign phase I study [Study KVD900-108])

Table 11. Summary of repeated-dose toxicity studies in mice and rats

Test system	Route of administration	Duration of administration	Dose (mg/kg/day)	Main findings	NOAEL (mg/kg/day)	Attached document CTD
Male and female wild-type mouse (CB6F1-Tg rasH2)	Oral gavage	10 days (once daily)	0, 100, 300, 1,000, 1,500	10-day treatment ≥300: Hepatocyte hypertrophy (both sexes) ≥1,000: Increased liver weight, individual hepatocyte necrosis (both sexes), and decreased body weight (male)	Not evaluated	4.2.3.4.1-1
		28 days (once daily)	Males: 0, 300, 600, 1,000 Females: 0, 300, 750, 1,500	28-day treatment ≥300 ⁹⁾ : Increased liver weight, hepatocyte hypertrophy, hepatic mixed-cell inflammation, individual hepatocyte necrosis (both sexes), and reduced body weight gain (male) ≥600/750: Increased blood ALT and AST (both sexes), decreased body weight, increased fibrinogen, increased monocyte count (male), reduced body weight gain, and increased blood cholesterol (female) 1,000/1,500: Dehydration; increased platelet count; increased blood ALP; decreased blood total bilirubin and glucose (both sexes); increased monocyte count; decreased neutrophil count; increased blood creatinine phosphokinase, cholesterol, and creatine (male); decreased body weight; respiratory changes; hunched posture; coarse fur; cool to touch; hypoactivity; decreased white blood cell, lymphocyte, and eosinophil counts; increased fibrinogen; and prolonged activated partial thromboplastin time (female)	300	
Male and female rat (Wistar [Han])	Oral gavage	28 days (once daily) + 4 weeks for recovery	0, 30, 100, 300, 1,000	≥30: Mouth rubbing (both sexes), increased urine volume (male), and salivation (female) ≥100: Salivation (male), increased urine volume, increased liver weight, centrilobular hepatocyte hypertrophy, and splenic extramedullary hematopoiesis (female) ≥300: Elevated hemoglobin distribution, increased blood cholesterol, decreased blood potassium, adrenocortical hypertrophy, adrenal inflammatory cell foci (both sexes), reduced body weight gain, increased adrenal weight, mammary lobular atrophy, decreased hyaline droplets in renal tubules (male), increased body weight gain, increased water intake, increased reticulocyte count and red cell distribution width, decreased blood total protein and albumin, increased kidney and spleen weights, and renal tubule hypertrophy (female) 1,000: Increased white blood cell, lymphocyte, and monocyte counts and fibrinogen; decreased hemoglobin, red blood cell count, and hematocrit; increased blood phosphate; decreased blood albumin and calcium; increased heart weight; vacuolation of periportal hepatocytes in the liver; thyroid follicular epithelial cell hypertrophy (both sexes); increased water intake; increased reticulocyte count and red cell distribution width; decreased blood total protein and globulin; increased liver, kidney, and spleen weights; centrilobular hepatocyte hypertrophy; renal tubular hypertrophy; degranulation of the submandibular gland; splenic extramedullary hematopoiesis (male); increased thyroid/parathyroid gland, adrenal gland, and ovary weights; increased mitotic figures in hepatocytes; luteal hypertrophy in the ovary, vacuolation of ovarian interstitial cells; increased vaginal mucification; and abnormal anestrus in the uterus (female) Reversible	300	4.2.3.2-3

Male and female rat (Wistar [Han])	Oral gavage	13 weeks (once daily) + 4 weeks for recovery	0, 30, 100, 300	≥30: Salivation, mouth rubbing (both sexes), reduced body weight gain, decreased blood calcium, tremors, decreased blood total protein, decreased blood albumin (female) ≥100: Increased urine volume (both sexes), tremors, piloerection, increased white blood cell and lymphocyte counts, shortened prothrombin time, increased adrenal weight, vacuolation of the adrenal cortex (male), increased reticulocytes, and decreased mean corpuscular hemoglobin concentration (female) 300: Increased blood cholesterol, decreased blood potassium (both sexes), increased reticulocyte and monocyte counts, increased blood sodium and phosphate, decreased blood globulin, increased thyroid/parathyroid gland weight, decreased hyaline droplets in the kidney (male), increased red cell distribution, increased liver weight, centrilobular hepatocyte hypertrophy in the liver, vacuolation of the adrenal cortex, and vacuolation of interstitial cells in the ovary (female) Reversible	300	4.2.3.2-4
Male and female rat (Wistar [Han])	Oral gavage	26 weeks (once daily) + 4 weeks for recovery	0, 30, 100, 300	≥30: Salivation (male), increased blood phosphate, and increased kidney weight (female) ≥100: Increased blood A/G ratio, vacuolation of the adrenal cortex, thyroid follicular epithelial cell hypertrophy (both sexes), increased white blood cell count, increased blood phosphate, decreased blood globulin (male), salivation, increased urine volume, increased liver weight, and centrilobular hepatocyte hypertrophy in the liver (female) 300: Increased reticulocyte count; increased lymphocyte count; increased blood cholesterol; decreased blood potassium (both sexes); reduced body weight gain; increased monocyte count; increased blood urea; decreased blood total protein and glucose; increased urine volume; decreased urine specific gravity; increased thyroid/parathyroid gland and adrenal weights; decreased hyaline droplets in the kidney (male); increased red cell distribution width, white blood cell count, and fibrinogen; decreased blood creatinine; vacuolation of interstitial cells in the ovary; and renal tubular cell hypertrophy (female) Reversible	300	4.2.3.2-5

a) In view of incidence and severity and changes in hepatic enzymes (no statistically significant differences), histopathological findings were not considered toxic findings. For body weight, only decreased gain was observed, and the mean body weight was not affected.

During the early development stage, the dog was selected as a non-rodent animal species, but sebetralstat had effects on the gastrointestinal tract and was poorly tolerated. The dog was thus not considered as a non-rodent animal species suitable for evaluation of sebetralstat, and thus the cynomolgus monkey was subsequently used instead. In cynomolgus monkeys receiving sebetralstat at ≥300 mg/kg/day once daily for 5 weeks, effects on the liver were observed, and at a higher dose of 500 mg/kg/day, some animals were found moribund due to hepatotoxicity. In animals receiving sebetralstat 300 mg/kg/dose twice weekly, no hepatotoxicity was observed. In cynomolgus monkeys receiving oral doses of sebetralstat twice weekly for 26 weeks, the NOAEL was determined to be 300 mg/kg/dose for both sexes. In animals receiving repeated doses of sebetralstat at the NOAEL, $C_{\max}$ and AUC_{0-24h} on Day 176 were 9,710 ng/mL (mean in both sexes) and 42,400 ng·h/mL (mean in both sexes), respectively, corresponding to approximately 1.7- and 2.2-fold the respective clinical exposures in humans.¹⁵⁾ In cynomolgus monkeys receiving oral doses of sebetralstat once daily for 5 weeks, the NOAEL was determined to be 50 mg/kg/day for both sexes. In animals receiving repeated doses of sebetralstat at the NOAEL, $C_{\max}$ and AUC_{0-24h} on Day 35 were 2,795 ng/mL (mean in both sexes) and 8,155 ng·h/mL (mean in both sexes), respectively, corresponding to approximately 0.5- and 0.4-fold the respective clinical exposures in humans.¹⁵⁾

Table 12. Summary of repeated-dose toxicity studies in dogs and cynomolgus monkeys

Test system	Route of administration	Duration of administration	Dose (mg/kg/day or mg/kg/dose)	Main findings ^{a)}	NOAEL (mg/kg/day or mg/kg/dose)	Attached document CTD
Male and female dog (beagle)	Oral gavage	4 weeks (once daily) + 4 weeks for recovery	0, 25, 50, 100	Animals prematurely subjected to necropsy^{b)} 100: 3 of 5 males, 3 of 5 females Poor clinical condition; tremor; decreased body weight and food consumption; decreased reticulocyte count; prolonged prothrombin time and activated partial thromboplastin time; increased white blood cell count; increased blood urea and creatine; and red or dark stomach, small intestine, and large intestine;^{c)} etc. Surviving animals ≥50^{d)}: Decreased reticulocyte count and increased fibrinogen 100: Prolonged activated partial thromboplastin time; increased neutrophil, lymphocyte, monocyte, platelet, white blood cell counts, and mean platelet volume; increased blood urea and creatinine; and red or dark stomach, small intestine, and large intestine^{c)} Reversible	50	4.2.3.2-7
Male and female cynomolgus monkey	Oral gavage	5 weeks (once daily) + 4 weeks for recovery	0, 50, 100, 300, 500/300 ^{e)}	Animals prematurely subjected to necropsy^{f)} 300: 1 of 3 males 500/300: 1 of 5 males, 1 of 5 females Poor general condition; decreased body weight; symptoms of dehydration; pale skin; yellow or light-colored oral mucosa and skin; increased blood total bilirubin, ALT, AST, γ-GT, and GLDH; increased adrenal and liver weights; hepatocyte hypertrophy, vacuolation, individual cell necrosis, inflammatory cell infiltration, and pigmentation; bile duct hyperplasia; thymus atrophy; and inflammatory cell infiltration and basophilic tubules in the kidney, etc. Surviving animals ≥50^{g)}: Increased blood ALT and GLDH ≥100: Vomiting, soft feces, watery stool, and decreased body weight and food consumption 300 and 500/300: Prolonged activated partial thrombin time and prothrombin time; increased blood AST, γ-GT, creatinine, and inorganic phosphate; decreased albumin, cholesterol, triglyceride, glucose, sodium, chloride, and potassium; increased liver and adrenal weights; hepatocyte hypertrophy; vacuolation of hepatocytes; individual hepatocyte necrosis; inflammatory cell infiltration; pigmentation in the liver; bile duct hyperplasia; adrenocortical hypertrophy; basophilic tubules in the kidney; thymus atrophy; and irregular menstrual cycle Reversible	50	4.2.3.2-10
Male and female cynomolgus monkey	Oral gavage	13 weeks (once daily) + 4 weeks for recovery	0, 10, 25, 50	10^{h)}: Mononuclear cell infiltration in the liver and increased blood ALT 25^{h)}: Increased blood GLDH 50^{h)}: Increased blood AST, hepatocyte degeneration, and hepatocyte necrosis	50	4.2.3.2-11
Male and female cynomolgus monkey	Oral gavage	13 weeks (twice weekly) + 4 weeks for recovery	0, 50, 100, 200, 300	≥50ⁱ⁾: Hepatocyte degeneration, vacuolation of hepatocytes, pigmentation in the liver, and inflammatory cell infiltration	300	4.2.3.2-12
Male and female cynomolgus monkey	Oral gavage	26 weeks (twice weekly) + 8 weeks for recovery	0, 15, 50, 150, 300	Animals prematurely subjected to necropsy 15: 1 of 4 males, 1 of 4 females 100^{j)}: 1 of 6 females Decreased body weight, dehydration, and watery stool Surviving animals No effects	300	4.2.3.2-13

- a) In view of the incidence of the findings, they are not described separately by sex.
- b) In the 100 mg/kg/day group, 1 male and 1 female were prematurely subjected to necropsy on Days 16 and 14, respectively, because of deterioration of general condition (moribund condition). The other animals in this group were removed from sebetralstat treatment after 16 days of dosing. Because deterioration of general condition and decreased body weight and food consumption were observed in animals other than those assigned to the recovery phase, these animals were subjected to unscheduled necropsy on Day 17.
- c) Histopathologically, these findings were observed as sites of congestion or haemorrhage. These anatomical and histopathological changes in the gastrointestinal tract were observed in many animals in the 100 mg/kg/day group, but were also observed in some animals in the control group and the other sebetralstat-treated groups.
- d) In view of the severity of the changes observed and other test results, these findings were not considered toxic.
- e) Because of poor tolerability [see note f)], the animals in this group received sebetralstat 500 mg/kg/day until Day 16 and at a reduced dose of 300 mg/kg/day from Day 17 onward.
- f) In the 500 mg/kg/day group, 1 male was prematurely subjected to necropsy on Day 16 because of deterioration of general condition (moribund condition). From Day 17 onward, the animals in the same group received sebetralstat at a reduced dose of 300 mg/kg/day (500/300 mg/kg/day group), and 2 each of males and females were additionally included in the 500/300 mg/kg/day group and continued to receive sebetralstat. Then, 1 male in the 300 mg/kg/day group and 1 female in the 500/300 mg/kg/day group were found in poor clinical (moribund) condition and prematurely subjected to necropsy on Day 29. Because the other animals in the same groups were also found in poor clinical condition, all of them were removed from sebetralstat treatment after 29 days of the treatment and subjected to unscheduled necropsy on Day 29, except for the animals assigned to the recovery period.
- g) The transiently increased alanine aminotransferase (ALT) and glutamate dehydrogenase (GLDH) in the 50 mg/kg/day group were considered of no toxicological significance because they were not accompanied by histopathological changes and returned to values close to baseline or historical values before the end of the treatment period.
- h) The histopathological changes observed were considered of no toxicological significance by the independent pathology working group because they were slight to mild, not dose-dependent, and considered to be exacerbated background lesions. The changes in clinical chemistry test parameters were not considered toxicologically significant in view of the histopathological findings.
- i) The findings were changes that did not differ between the sebetralstat-treated and control groups in terms of frequency and severity or changes that showed no dose-related worsening. In response to the remarkably increased hepatic enzyme values that were sporadic, not dose-dependent, and observed also in the control group, a test for hepatitis viruses was performed, and some animals tested positive for hepatitis A virus. These increased hepatic enzyme values were thus considered attributable to hepatitis virus infection but not to sebetralstat.
- j) In view of results in the 300 mg/kg/dose group, the findings were considered attributable to stress and unrelated to sebetralstat.

5.3 Genotoxicity

Bacterial reverse mutation assay (Ames assay), mouse lymphoma gene mutation assay, and rat bone marrow micronucleus assay were performed and yielded negative results, and sebetralstat was considered non-genotoxic (Table 13).

Table 13. Summary of genotoxicity studies

Type of study		Test system	Metabolic activation (treatment time)	Concentration or dose	Result	Attached document CTD
In vitro	Ames	Salmonella typhimurium: TA98, TA100, TA1535, TA1537, TA102	S9-/+	0, ^{a)} 5, 16, 50, 160, 500, 1,600, 5,000 µg/plate	Negative	4.2.3.3.1-2
	Gene mutation	Mouse lymphoma L5178Y/TK ^{+/+} cells	S9- (24 hours)	0, ^{a)} 50, 100, 150, 200, 250, 300, 350, 400, 450 µg/mL	Negative	4.2.3.3.1-3
			S9- (3 hours)	0, ^{a)} 50, 100, 200, 300, 400, 450 µg/mL	Negative	
			S9+ (3 hours)	0, ^{a)} 50, 100, 200, 300, 400, 450, 492 µg/mL	Negative	
In vivo	Rat micronucleus ^{b)}	Rat (Wistar [Han]) bone marrow (both sexes)		0, 30, 100, 300, 1,000 mg/kg/day (oral, repeatedly for 28 days)	Negative	4.2.3.3.2-1

a) Vehicle, DMSO; b) Performed as a part of the evaluation of the 28-day repeated oral dose toxicity study in rats (CTD 4.2.3.2-3).

5.4 Carcinogenicity

A 6-month carcinogenicity study in Tg rasH2 hemizygous (Tg rasH2) mice was conducted, and no increase in the incidence of tumors related to sebetralstat was observed (Table 14). In the 6-month carcinogenicity study in Tg rasH2 mice, the non-carcinogenic dose was determined to be 200 mg/kg/day in males and 300 mg/kg/day in females. On Day 180 of repeated administration at these dose levels, AUC_{last} of sebetralstat was 25,500 ng·h/mL in male mice and 48,800 ng·h/mL in female mice, corresponding to approximately 1.3- and 2.5-fold, respectively, the clinical exposure (AUC_{inf})¹⁵⁾ in humans.

Table 14. Summary of carcinogenicity study in Tg rasH2 mice

Test system	Route of administration	Duration of administration	Main lesion	Sex	Dose (mg/kg/day)				Non-carcinogenic dose (mg/kg/day)	Attached document CTD
					Male 0 Female 0	Male 20 Female 30	Male 65 Female 100	Male 200 Female 300		
				n	25 each	25 each	25 each	25 each		
Male and female mouse (CB6F1-Tg rasH2)	Oral	26 weeks	Neoplastic lesion	No noteworthy neoplastic development				200 (male) 300 (female)	4.2.3.4.1-2	
			Non-neoplastic lesion	200/300: Centrilobular hepatocyte hypertrophy, yellow-brown pigmentation in sinusoidal macrophages, individual hepatocyte necrosis, and mixed cell inflammation (both sexes)						

A 2-year carcinogenicity study in Wistar (Han) rats was conducted (Table 15). In Wistar (Han) rats, increased incidences of hepatocellular adenoma (300 mg/kg in females), pituitary adenoma (300 mg/kg in males), and testicular interstitial cell tumor (≥ 100 mg/kg in males) were observed. In addition, increased incidences of thyroid follicular epithelial cell adenoma (300 mg/kg in males) and ovarian granulosa cell tumor (300 mg/kg in females) exceeding the historical control range were observed but were not statistically significant. Malignant granulosa cell tumor in the ovary was observed in 1 female at 300 mg/kg, but the incidence fell within the historical control range (0%-3.3%), and even evaluation of the malignant and benign tumors combined did not show any statistically significant difference. The non-carcinogenic dose was determined to be 30 mg/kg/day in male rats and 100 mg/kg/day in female rats. On Day 178 of repeated administration at this dose, AUC_{0-24h} of sebetralstat was 74,200 ng·h/mL in male rats and 413,000 ng·h/mL in female rats, which were approximately 3.8- and 21-fold, respectively, the clinical exposure¹⁵⁾ in humans. The applicant explained that these tumors were considered attributable to hepatic enzyme induction by sebetralstat and subsequent enhanced metabolism of thyroid hormones as well as adaptive changes associated with the disturbed hypothalamic-pituitary-gonadal axis [see Section 5.R.2].

Table 15. Summary of carcinogenicity study in rats

Test system	Route of administration	Duration of administration	Main lesion	Sex	Dose (mg/kg/day)				Non-carcinogenic dose (mg/kg/day)	Attached document CTD
					Vehicle	Sebetralstat				
				0	30	100	300			
				n	50/sex	50/sex	50/sex	50/sex		
Male and female rat (Wistar [Han])	Oral gavage	104 weeks	Neoplastic lesion						30 (male) 100 (female)	4.2.3.4.1-4
			Liver/hepatocellular adenoma	Male	0	0	3	2		
				Female	2	2	2	9*		
			Pituitary gland/adenoma	Male	11	16	12	24*		
				Female	19	19	22	20		
			Testis/interstitial cell tumor	Male	1	1	4*	8*		
				Female	11	5	8	15		
			Thyroid/follicular epithelial cell adenoma	Male	2	1	6	3		
				Female	0	2	3	4		
			Ovary/granulosa cell tumor (benign)	Female	0	0	0	1		
				Female	0	2	3	5		
			Ovary/granulosa cell tumor (malignant)							
			Ovary/granulosa cell tumor (combined)							
Non-neoplastic lesion										
≥30: Localized hypertrophy and vacuolation of the anterior pituitary gland (male) and localized glandular hyperplasia in the uterus (female)										
≥100: Gastric gland dilatation (both sexes), decreased secretion from the salivary gland granular duct (male), centrilobular hepatocyte hypertrophy in the liver, localized thyroid follicular cell hyperplasia, and interstitial cell hyperplasia in the ovary (female)										
300: Cystic degeneration of the adrenal cortex, localized inflammatory cell infiltration in the adrenal gland, decreased incidence of localized cortical hypertrophy in the adrenal zona glomerulosa (both sexes), centrilobular hepatocyte hypertrophy in the liver, and localized thyroid follicular cell hyperplasia (male)										

* With a statistically significant difference ($P < 0.01$)

5.5 Reproductive and developmental toxicity

A study of fertility and early embryonic development to implantation in rats was conducted (Table 16). The NOAEL for male and female fertility was determined to be 600 mg/kg/day. On Day 12 of repeated administration at this dose, $C_{\max}$ and AUC_{0-24h} of sebetralstat were 133,000 ng/mL and 1,170,000 ng·h/mL, respectively, in males, corresponding to approximately 24- and 60-fold the respective clinical exposures in humans (for male fertility). In females, $C_{\max}$ and AUC_{0-24h} were 129,000 ng/mL and 1,400,000 ng·h/mL, respectively, corresponding to approximately 23- and 72-fold the respective clinical exposures in humans (for female fertility and early embryonic development).¹⁵⁾

Studies of embryo-fetal development in rats and rabbits were conducted (Table 16). The main toxicological finding was external and visceral malformations in rat fetuses. The NOAEL for embryo-fetal development was determined to be 300 mg/kg/day in both rats and rabbits. Following repeated administration at this dose, $C_{\max}$ and AUC_{0-24h} of sebetralstat in rats on gestation day 16 were 43,200 ng/mL and 510,000 ng·h/mL, respectively, corresponding to approximately 7.7- and 26-fold the respective clinical exposures in humans. In rabbits on gestation day 16, $C_{\max}$ and AUC_{0-24h} were 62,300 ng/mL and 359,000 ng·h/mL, respectively, corresponding to approximately 11- and 18-fold the respective clinical exposures in humans.¹⁵⁾

A study of prenatal and postnatal development, including maternal function, in rats was conducted (Table 16). The NOAEL for offspring development was determined to be 450 mg/kg/day. In this toxicity study, blood sebetralstat concentrations were not evaluated, and systemic exposures to sebetralstat at 300 mg/kg/day ($C_{\max}$ and AUC_{0-24h})¹⁶⁾ in the study for embryo-fetal development in rats (CTD 4.2.3.5.2-2) were used as reference data for comparison with the corresponding clinical exposures in humans.¹⁵⁾ The applicant explained that the exposures at 450 mg/kg/day would provide safety margins equivalent to or greater than approximately 7.7- and 26-fold, respectively, relative to the clinical exposures in humans.

¹⁶⁾ $C_{\max}$, 43,200 ng/mL; AUC_{0-24h} , 510,000 ng·h/mL

Table 16. Summary of reproductive and developmental toxicity studies

Type of study	Test system	Route of administration	Duration of administration	Dose (mg/kg/day)	Main findings	NOAEL (mg/kg/day)	Attached document CTD
Fertility and early embryonic development to implantation	Male and female rat (Wistar [Han])	Oral gavage	Male: From 14 days before mating to necropsy (once daily) Female: From 14 days before mating to Gestation Day 6 (once daily)	0, 100, 300, 600	<u>Parent animals</u> None <u>Fertility and early embryonic development</u> None	Parent animals: 600 Fertility and early embryonic development: 600	4.2.3.5.1-1
Embryo-fetal development	Female rat (Wistar [Han])	Oral gavage	From Gestation Day 6 to Gestation Day 17 (once daily)	0, 100, 300, 600	<u>Dam</u> ≥300: Decreased food consumption ^{a)} 600: Reduced body weight gain, increased number of early and late resorptions, increased postimplantation loss percentage, and decreasing trend of the mean number of live fetuses <u>Embryo-fetal development</u> ≥300: Variations (unossification and incomplete ossification) ^{b)} and abnormality (accessory hepatic lobe) ^{b)} 600: Decreased fetal body weight; abnormalities (edema, long bone curvature, cleft palate, incomplete ventricular septum, delayed ossification of overall skeleton, anasarca, unilateral or bilateral anophthalmia, small orbital cavity [unilateral or bilateral], number of vertebrae anterior to sacrum [≤24], severely fused thoracic vertebrae, severely fused ribs, irregular aortic arch valve)	Dam: 300 Embryo-fetal development: 300	4.2.3.5.2-2
	Female rabbit (NZW)	Oral gavage	From Gestation Day 6 to Gestation Day 18 (once daily)	0, 30, 100, 300	<u>Dam</u> 300: Reduced body weight gain and decreased food consumption <u>Embryo-fetal development</u> 30: Abnormalities (severely fused vertebral bodies, severely fused neural arches, severely fused ribs, and incomplete ventricular septum) ^{b)} 100: Abnormalities (subclavian artery from pulmonary arch and diaphragmatic hernia) ^{b)} 300: Decreased fetal body weight ^{a)} and abnormalities (incomplete ossification or unossification of parietal bone, sternum, and metacarpal bone; excessive ossification of neural arch; excessive ossification of vertebral body; absence of hemivertebra; absence of or severely fused neural arch; and absence of or severely fused ribs) ^{b)}	Dam: 100 Embryo-fetal development: 300	4.2.3.5.2-4
	Female rat (Wistar [Han])	Oral gavage	From Gestation Day 6 to Lactating Day 20 (once daily)	0, 100, 200, 450	<u>Dam</u> ≥100: Extended pregnancy period ^{a)} 450: Pyelectasis ^{c)} and red stomach surface ^{c)} <u>F₁ offspring</u> 450: Decreased offspring body weight (both sexes) ^{a)} and reduced body weight gain on Post-natal Day 21 (male) ^{a)}	Dam: 450 Development of offspring: 450	4.2.3.5.3-1

a) Changes observed at doses not exceeding the NOAEL were not considered toxic because the changes were minor.

b) The changes were not considered toxic because they fell within the historical control range.

c) The change was not considered to be an effect of sebetralstat because it occurred in only 2 of 22 animals.

5.6 Toxicity in juvenile animals

A repeated-dose toxicity study in juvenile rats (dose-finding study) was conducted (Table 17). In males at 1,000 mg/kg/day, decreased body weight of up to 19% was observed, but the dose was well-tolerated.

On Day 21 of repeated administration at 1,000 mg/kg/day, AUC_{0-24h} of sebetralstat was 1,895,000 ng·h/mL (mean for both sexes).

Table 17. Summary of repeated-dose toxicity study in juvenile rats

Test system	Route of administration	Duration of administration	Dose (mg/kg/day)	Main findings	Attached document CTD
Male and female rat (SD)	Oral gavage	21 days (once daily) (the first dose at the age of 22 days)	0, 100, 300, 1,000	≥100: Splenic extramedullary hematopoiesis (female) 1,000: Decreased body weight (male)	4.2.3.5.4-1 Reference data

5.7 Other studies

5.7.1 Phototoxicity

Because sebetralstat showed absorption in the wavelength range from 290 to 700 nm (with the maximum absorption at 303 nm) (CTD 4.2.3.7.7-1), *in vitro* photoreactivity study (reactive oxygen species [ROS] study) was conducted (CTD 4.2.3.7.7-2 and 4.2.3.7.7-3). In this test system, photoirradiation caused precipitation in solutions at some sebetralstat concentrations, precluding definitive conclusion on phototoxicity, and thus an *in vitro* phototoxicity study in mouse 3T3 fibroblasts was conducted and ruled out the phototoxicity potential (Table 18).

Table 18. Summary of phototoxicity study

Type of study	Test system	Method	Main findings	Attached document CTD
Phototoxicity	Mouse fibroblast (Balb/c 3T3)	Sebetralstat 0, ^{a)} 0.0316, 0.100, 0.316, 1.00, 3.16, 10.0, 31.6, 100 µg/mL Photoirradiation of UV-A (5 J/cm ²) and UV-B (low light intensity) for 19 minutes	PIF: - ^{b)} No phototoxicity potential	4.2.3.7.7-4

a) Vehicle, DMSO

b) It was not calculated because absence of cytotoxicity precluded IC₅₀ determination of sebetralstat.

5.7.2 Toxicity of impurities

Impurities in the drug substance and drug product, PPP7584 and PPP758 desfluoro, were subjected to Ames and *in vitro* micronucleus assays and were considered negative for mutagenicity and clastogenicity (CTD 4.2.3.7.6-1 to 4.2.3.7.6-4). Sebetralstat containing impurities such as PPP7584 and PPP758 desfluoro was subjected to a repeated-dose toxicity study [see Section 5.2]. No safety concerns were identified for these impurities at the upper limit of their acceptance criteria.

5.R Outline of the review conducted by PMDA

5.R.1 Effects on the liver

PMDA's view on effects of sebetralstat on the liver:

In the repeated oral dose toxicity studies of sebetralstat, adverse changes were mainly observed in the liver, including hypertrophic changes of hepatocytes, degeneration and necrosis of hepatocytes, inflammatory cell infiltration, brown pigmentation, and bile duct hyperplasia in mice, rats, or cynomolgus monkeys. Repeated daily administration (5 weeks) of sebetralstat in cynomolgus monkeys resulted in hepatotoxicity at ≥300 mg/kg/day, and at 500 mg/kg/day, severe hepatotoxicity causing moribundity was observed. However, in animals which received sebetralstat 300 mg/kg/dose twice weekly for 26 weeks, no hepatotoxicity was observed. Hepatotoxicity of sebetralstat is thus considered

related to the dosage regimen and duration of systemic exposure. The dose at which no hepatotoxicity was observed was determined to be 50 mg/kg/day in cynomolgus monkeys receiving sebetralstat daily for 5 weeks and 300 mg/kg/dose in those receiving sebetralstat twice weekly for 26 weeks. Based on AUC_{0-24h} at these doses, safety margins were approximately 0.4- and 2.2-fold, respectively, relative to the clinical exposure in humans¹⁵⁾ [see Section 5.2], and the safety margin on the intermittent dosing regimen is not adequate.

In view of the above, the risk of hepatotoxicity and the safety of sebetralstat for the treatment of HAE attacks in humans should be discussed based on clinical study results [see Section 7.R.3.4].

5.R.2 Carcinogenicity

The applicant's explanation about findings in the carcinogenicity study of sebetralstat in rats, including increased incidences of hepatocellular adenoma (females at 300 mg/kg/day), pituitary adenoma (males at 300 mg/kg/day), and testicular interstitial cell tumor (males at ≥ 100 mg/kg/day) as well as increased incidences of thyroid follicular epithelial cell adenoma (males at 300 mg/kg/day) and ovarian granulosa cell tumor (females at 300 mg/kg/day) that were higher than the historical range without a statistically significant difference:

- Sebetralstat tested negative for genotoxicity in all assays, and the increased incidences of neoplastic lesions observed in rats were considered to involve non-genotoxic mechanisms.
- In the liver, repeated administration of sebetralstat led to increased liver weight and centrilobular hepatocyte hypertrophy, of which the latter was often associated with hepatocellular adenoma and thus deemed as an adaptive change related to enzyme induction. Development of hepatocellular adenoma caused by a non-genotoxic mechanism of development associated with the enzyme induction is deemed unlikely to be extrapolated to humans in general (*Regul Toxicol Pharmacol.* 2018;92:1-7, *Crit Rev Toxicol.* 2021;51:373-94). A study in human hepatocytes has demonstrated that sebetralstat induces CYP3A4 [see Section 4.5.1]. The hepatic enzyme induction is known to enhance metabolism and excretion of thyroid hormones and thereby activate the hypothalamic-pituitary gland-thyroid axis, resulting in a compensatory increase in thyroid-stimulating hormone, which can cause thyroid follicular epithelial cell hypertrophy and hyperplasia followed by development of thyroid follicular epithelial cell adenoma. The development of thyroid follicular epithelial cell adenoma induced by the above mechanism is deemed specific to rodents and unlikely to be extrapolated to humans (*Arch Toxicol.* 2021;95:807-36, *Biochim Biophys Acta.* 1991;1097:19-22). As described above, the development of hepatocellular adenoma and thyroid follicular epithelial cell adenoma observed in rats treated with sebetralstat is considered unlikely to be extrapolated to humans.
- Pituitary adenoma and testicular interstitial cell tumor are spontaneous tumors generally observed in rats. The development of pituitary adenoma is reported to be related to the disturbed hypothalamic-pituitary-gonadal axis, including fluctuations in estrogen concentration in circulating blood (*Environ Pollut.* 2023;318:120843, *Histopathology of Preclinical Toxicity Studies Fourth edition.* Elsevier Academic Press; 2012:725-97). The development of testicular interstitial cell tumor is often induced by exogenous substances that increase luteinizing hormone (LH) in circulating blood, and LH receptors are more abundant in rats than in humans, indicating that sensitivity to LH differs among animal species (*Reprod Toxicol.* 1997;11:107-21, *Crit Rev Toxicol.* 1999;29:169-261). Ovarian

granulosa cell tumor is a spontaneous tumor that occurs in up to 5% of aged Wistar rats (*J Toxicol Pathol.* 2020;33:189-96). Continuous stimulation by increased gonadotropin in circulating blood is reported to lead to cell proliferation, which potentially increases the incidence of tumors (*Toxicol Pathol.* 2001;29:403-10), but in humans, a relationship of increased gonadotropin concentrations in circulating blood with an increased incidence of ovarian tumors is not suggested (*Maturitas.* 1996;23:235-9). Although mechanisms of development of these tumors induced during sebetralstat treatment remain unclear, the increased incidence of the tumors is considered attributable to disturbed hormone regulation by the effect of sebetralstat on hormone homeostasis in the hypothalamic-pituitary-gonadal axis, because the repeated-dose toxicity studies of sebetralstat presented changes in various organs that were suggested to result from effects of hormones [see Section 5.2]. Non-carcinogenic doses for pituitary adenoma (male), testicular interstitial cell tumor (male), and ovarian granulosa cell tumor (female) were determined to be 100, 30, and 100 mg/kg/day, respectively, and AUC_{0-24h} at these non-carcinogenic doses provided safety margins of approximately 14-, 3.8-, and 21-fold, respectively, relative to the clinical exposure in humans.¹⁵⁾

In view of the result of weight-of-evidence evaluation on data from the above genotoxicity, repeated-dose toxicity, and carcinogenicity studies, the applicant considers that on-demand treatment of sebetralstat according to the proposed dosage and administration is unlikely to lead to carcinogenicity in humans.

PMDA's view:

The applicant explained that the increased incidences of hepatocellular adenoma and thyroid follicular epithelial cell adenoma observed in animals treated with sebetralstat would be unlikely to be extrapolated to humans. The above applicant's explanation is acceptable. On the other hand, for pituitary adenoma, testicular interstitial cell tumor, and ovarian granulosa cell tumor, the applicant presented their view that the increased incidences were caused by hormone fluctuations related to sebetralstat. Although the applicant's view is understandable, no specific data on hormones are presented, and whether the mechanism not extrapolated to humans would lead to tumor development remains unclear. However, PMDA considers development of these tumors unlikely in patients who receive sebetralstat according to the proposed dosage and administration in an on-demand manner, because (1) sebetralstat is intended to be used only at the time of HAE attacks and is not intended for continuous repeated administration and (2) the relevant non-clinical exposure provides a certain safety margin over the clinical exposure. However, whether extrapolation of the mechanism of development to humans is applicable remains unclear, and thus, the applicant is required to describe the increased incidences of these tumors in the non-clinical studies in the package insert and provide the information. When continuous regular use of sebetralstat is authorized by the indication expansion, the applicant will be required to explain applicability of the extrapolation to humans and safety based on the safety risk associated with the new dosage regimen and specific findings on hormones.

5.R.3 Effects on embryo-fetal development

The applicant's explanation about effects of sebetralstat on embryo-fetal development:

The study of embryo-fetal development in rats demonstrated embryo-fetal toxicity and major external and visceral malformations, indicating that sebetralstat is considered to be teratogenic. However, C_{max}

and AUC_{0-24h} at the NOAEL in the study of embryo-fetal development in rats provided safety margins of approximately 7.7- and 26-fold relative to the clinical exposures in humans¹⁵⁾ [see Section 5.5]. Although sebetralstat has not been used in pregnant women, the applicant considers it acceptable to use sebetralstat in pregnant women or in women who may be pregnant only if the expected therapeutic benefits outweigh the possible risks associated with treatment. In view of the results of the embryo-fetal development study, women of childbearing potential are recommended to use effective contraception for 24 hours after the administration. The above content will be included in the package insert as a precaution.

PMDA accepted the applicant's explanation.

6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA

6.1 Summary of biopharmaceutic studies and associated analytical methods

The applicant submitted biopharmaceutic data in the form of results from a study investigating the effects of food, etc.

For clinical development of sebetralstat, 4 formulations (capsules [containing 5 or 100 mg of sebetralstat], tablets [containing 100 mg of sebetralstat], white film-coated tablets [containing 100 or 300 mg of sebetralstat], commercial yellow film-coated tablets [containing 300 mg of sebetralstat]) were mainly used.¹⁷⁾ An *in vitro* dissolution study using white film-coated tablets and commercial yellow film-coated tablets¹⁸⁾ demonstrated that dissolution profiles of the two formulations were comparable.

Plasma sebetralstat concentrations were determined by LC-MS/MS (lower limit of quantification, 1, 40, or 100 ng/mL).

6.1.1 Relative bioavailability study (CTD 5.3.1.2-5, Study KVD900-113, January to March 2024)

In this study, non-Japanese healthy adults (n = 36) orally received sebetralstat 600 mg as a single dose in the fasted state or after a high-fat meal,¹⁹⁾ using commercial yellow film-coated tablets or orally disintegrating tablets,²⁰⁾ in a randomized, open-label, 4-treatment, 4-period, crossover design. The study investigated food effects on the bioavailability of commercial yellow film-coated tablets, showing that the administration in the fed state tended to delay absorption and decrease C_{max}, but had no clear effect on AUC (Table 19).

¹⁷⁾ Each formulation was used in the following clinical studies:

Capsules, phase I studies (Studies KVD900-101 and 103); tablets, phase I study (Study KVD900-101); white film-coated tablets, phase I studies (Studies KVD900-101, 102, 104, 106, 107, 108, 110, and 112), phase II study (Study KVD900-201), and phase III studies (Studies KVD900-301 and 302); and commercial yellow film-coated tablets, phase I studies (Studies KVD900-109 and 113) and phase III study (Study KVD900-302)

¹⁸⁾ The test was performed using the dissolution medium (1st fluid for dissolution test defined [JP], diluted McIlvaine buffer solution [pH 4], 2nd fluid for dissolution test [JP], and water) at 50 revolutions per minute (also at 100 revolutions per minute for McIlvaine buffer solution [pH 4]) according to the Paddle method. For each test condition, 12 units each of white film-coated tablets and commercial film-coated tablets were used in the test.

¹⁹⁾ A meal of approximately 800 to 1,000 kcal of which approximately 50% is from fat

²⁰⁾ Orally disintegrating tablets containing 300 mg of sebetralstat. Not used in any other clinical studies included in the submitted data for the present application.

Table 19. Pharmacokinetic parameters of sebetralstat after single oral administration of commercial yellow film-coated tablets

Stomach state	n	C _{max} (ng/mL)	AUC _{last} (ng·h/mL)	AUC _{inf} (ng·h/mL)	t _{max} (h)	Geometric least squares mean ratio (fed/fasted) [90% CI]		
						C _{max}	AUC _{last}	AUC _{inf}
Fasted	35	5,308 (58.6)	17,100 (47.1)	17,180 (47.0)	0.76 [0.50, 3.00]			
After high-fat meal	36	4,412 (43.9)	17,780 (39.0)	17,810 (39.0)	2.50 [0.50, 6.00]	0.83 [0.73, 0.95]	1.04 [0.97, 1.11]	1.03 [0.97, 1.11]

Geometric mean (geometric coefficient of variation [CV] %); t_{max}, Median [range]

6.2 Clinical pharmacology

The applicant submitted clinical pharmacology data in the form of results from clinical studies in healthy adults, study participants with hepatic impairment, and patients with HAE as well as a population pharmacokinetic analysis. *In vitro* studies using human biomaterials are reviewed in Sections 4.2, 4.3, and 4.5. Unless otherwise specified, doses are expressed as doses of sebetralstat.

6.2.1 Studies in healthy adults

6.2.1.1 Foreign phase I study (CTD 5.3.3.3-6, Study KVD900-110, November 2021 to April 2022)

Table 20 shows pharmacokinetic parameters in Japanese and non-Japanese healthy adults who orally received sebetralstat 300, 600, or 1,200 mg as a single dose. After single doses of sebetralstat 300 and 1,200 mg, Japanese subjects had the C_{max} higher than that in Caucasian subjects, but individual values greatly varied, and their distributions in these ethnic groups overlapped. AUC values in Japanese and Caucasian subjects were comparable. After a single dose of sebetralstat 600 mg, the C_{max} and AUC were comparable between these ethnic groups. The exposure increased dose-proportionally between doses of 300 and 600 mg but less than dose-proportionally between doses of 600 and 1,200 mg.

Figure 3 shows changes in PKa activity over time in plasma specimens that were collected from study participants after administration of sebetralstat 300 mg and then treated with dextran sulfate for activation of the kallikrein-kinin pathway, and the profiles were comparable between these ethnic groups.

Table 20. Pharmacokinetic parameters of sebetralstat after each administration

Healthy adults	Dose (mg)	n	C _{max} (ng/mL)	AUC _{last} (ng·h/mL)	AUC _{inf} (ng·h/mL)	t _{max} (h)	CL/F (L/h)	V _z /F (L)	t _{1/2} (h)
Caucasian	300	6	2,243 (53.7)	8,162 (22.3)	8,190 (22.2)	1.29 [0.95, 1.60]	37.4 ± 8.46	233 ± 48.3	4.42 ± 0.965
	600	6	5,961 (41.4)	16,200 (28.2)	16,400 (31.8) ^{a)}	1.00 [0.50, 1.25]	38.0 ± 11.4 ^{a)}	304 ± 96.3 ^{a)}	5.65 ± 1.49 ^{a)}
	1,200	6	5,746 (31.6)	23,690 (35.2)	24,450 (35.5)	1.02 [1.00, 1.50]	51.4 ± 16.1	486 ± 261	6.70 ± 2.67
Japanese	300	6	2,832 (90.4)	7,458 (51.2)	7,495 (50.4)	1.26 [0.55, 1.75]	43.9 ± 20.7	274 ± 285	3.75 ± 1.75
	600	6	6,178 (51.8)	16,410 (66.8)	16,600 (64.8)	0.99 [0.50, 1.50]	41.9 ± 25.2	438 ± 493	6.07 ± 3.32
	1,200	6	7,736 (111.8)	23,490 (62.8)	21,800 (39.0) ^{b)}	0.75 [0.50, 4.00]	57.9 ± 20.3 ^{b)}	578 ± 445 ^{b)}	6.67 ± 4.12 ^{b)}
Chinese	300	6	3,173 (20.6)	7,712 (22.7)	7,725 (22.7)	1.00 [0.62, 1.25]	39.7 ± 9.29	200 ± 52.4	3.49 ± 0.37
	600	6	5,197 (92.0)	15,590 (39.3)	16,120 (42.9) ^{a)}	0.64 [0.27, 1.48]	40.2 ± 20.0 ^{a)}	247 ± 180 ^{a)}	4.03 ± 0.97 ^{a)}
	1,200	6	7,645 (78.8)	30,100 (50.1)	30,530 (49.2) ^{b)}	1.16 [0.73, 3.00]	42.9 ± 18.9	440 ± 259	6.91 ± 3.88

C_{max}, AUC_{last}, and AUC_{inf}; Geometric mean (geometric CV %); t_{max}, Median [range]; CL/F, V_z/F, and t_{1/2}, Mean ± SD

a) n = 5; b) n = 4

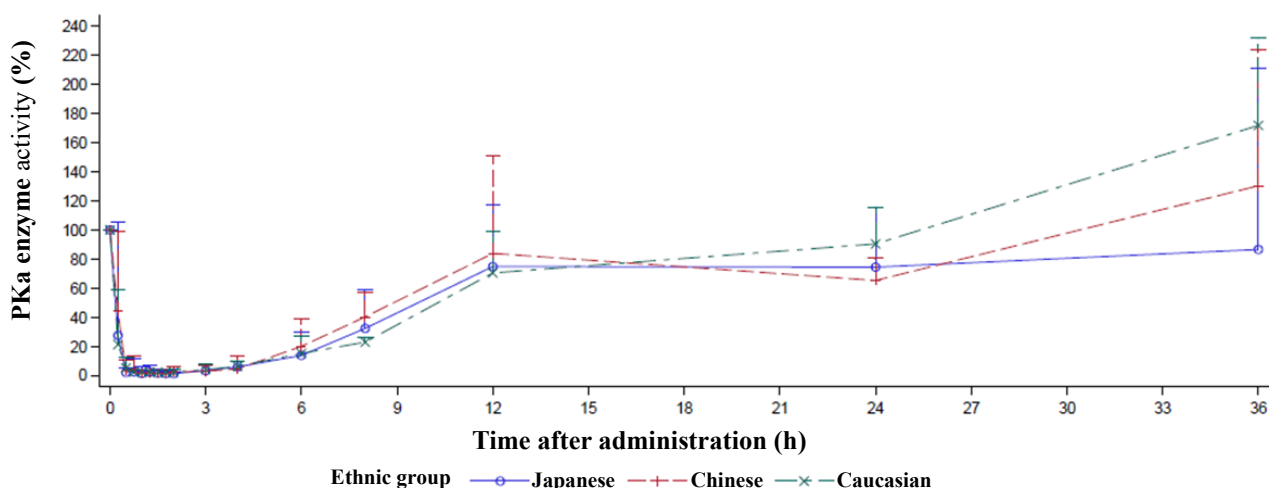


Figure 3. Changes in PKa activity over time after administration of sebetralstat 300 mg (geometric mean + geometric SD)

6.2.1.2 Mass balance study (CTD 5.3.3.1-11, Study KVD900-103, May to June 2020)

When a single dose of ^{14}C -sebetralstat 600 mg was orally administered to 6 non-Japanese healthy adults in the fasted state, the radioactivity and sebetralstat concentrations in plasma peaked at 0.75 [0.50, 3.00] and 0.50 [0.50, 3.00] hours ($t_{\max}$, median [range]) with $t_{1/2}$ (geometric mean [geometric coefficient of variation (CV)%]) of 5.79 [60.6] and 136 [120.9] hours, respectively. The geometric mean ratio of $\text{AUC}_{0-24\text{h}}$ for the total radioactivity in whole blood relative to plasma was 0.65. Of the radioactivity administered, $95.8\% \pm 5.02\%$ (mean $\pm$ SD) was recovered in urine and feces combined until 216 hours post-dose, and $63.4\% \pm 3.59\%$ and $32.4\% \pm 6.57\%$ were excreted in feces and urine, respectively. Table 21 shows profiles of metabolites in plasma, feces, and urine. No metabolites accounted for $>10\%$ of $\text{AUC}_{0-24\text{h}}$ of total radioactivity in plasma.

Table 21. Profiles of metabolites in plasma, feces, and urine

Plasma	Feces	Urine
<u>Up to 24 hours post-dose</u>	<u>Up to 144 hours post-dose</u>	<u>Up to 48 hours post-dose</u>
Unchanged sebetralstat (64.1%), M19 (7.10%), M3 (4.01%), M10 (4.00%), M38/39 (1.79%), M37 (1.34%), M34 (1.06%), M33 (1.01%), M6 (0.765%), M30/M31 (0.391%), etc.	Unchanged sebetralstat (12.5%), M34 (8.32%), M3 (8.16%), M40 (2.88%), M38/M39 (2.68%), M10 (1.84%), M44 (1.48%), M6/M35 (1.38%), M42 (1.24%), etc.	Unchanged sebetralstat (8.66%), M10/M41 (4.88%), M19 (4.21%), M34 (2.95%), M3 (2.55%), M40 (1.24%), M38/M39 (1.21%), etc.

6.2.2 Studies for endogenous factors

6.2.2.1 Study for effects of hepatic impairment on pharmacokinetics of sebetralstat (CTD 5.3.3.3-1, Study KVD900-104, August 2021 to March 2022)

A single dose of sebetralstat 600 mg was orally administered to 16 non-Japanese adults with hepatic impairment (8 with mild impairment [classified as Child-Pugh A] and 8 with moderate impairment [classified as Child-Pugh B]) and 8 non-Japanese adults with normal hepatic function in the fasted state to evaluate pharmacokinetics. Table 22 shows the pharmacokinetic parameters of sebetralstat. Exposure to sebetralstat increased with increasing severity of hepatic impairment.

Table 22. Pharmacokinetic parameters of sebetralstat after administration of sebetralstat 600 mg

Severity of hepatic impairment	n	C _{max} (ng/mL)	AUC _{last} (ng·h/mL)	AUC _{inf} (ng·h/mL)	CL/F (L/h)	t _{1/2} (h)	Geometric least squares mean ratio [90% CI] (hepatic impairment/normal hepatic function)		
							C _{max}	AUC _{last}	AUC _{inf}
Normal	8	4,800 (64.1)	17,700 (60.8)	17,800 (60.7)	37.8 ± 17.2	12.0 ± 4.05			
Mild	8	5,120 (35.1)	20,600 (37.1)	20,700 (37.1)	30.9 ± 12.3	5.77 ± 3.01	1.07 [0.682, 1.67]	1.17 [0.778, 1.75]	1.16 [0.774, 1.74]
Moderate	8	7,800 (40.0)	35,400 (63.4)	35,500 (63.6)	18.4 ± 7.05	6.85 ± 4.12	1.63 [1.04, 2.54]	2.01 [1.34, 3.01]	2.00 [1.33, 3.00]

C_{max}, AUC_{last}, and AUC_{inf}, Geometric mean (geometric CV%); CL/F and t_{1/2}, Mean ± SD

6.2.3 Study for pharmacokinetic interactions (CTD 5.3.2.2-1, Study KVD900-106, October 2021 to May 2022; CTD 5.3.2.2-3, Study KVD900-112, February to May 2023)

In view of results from *in vitro* drug interaction studies and pharmacokinetic profile of sebetralstat, including metabolism and excretion, 2 studies were conducted in non-Japanese healthy adults to investigate interactions between sebetralstat and other drugs. Table 23 shows the results.

Table 23. Effects of concomitant drugs on pharmacokinetic parameters of sebetralstat

Dosage regimen (oral for all regimens)		n	Geometric least squares mean ratio [90% CI] (concomitant/alone)		
Concomitant drug	Sebetralstat		C _{max}	AUC _{last}	AUC _{inf}
Itraconazole 200 mg once daily	600 mg as single dose	17 ^{a)}	2.35 [1.93, 2.87]	5.21 [4.55, 5.96]	5.20 [4.56, 5.94]
Verapamil 240 mg once daily		16	1.76 [1.47, 2.12]	2.04 [1.83, 2.26]	2.02 [1.83, 2.24]
Cimetidine 800 mg single dose		16	0.78 [0.64, 0.96]	0.89 [0.74, 1.06]	0.88 [0.73, 1.05]
Quinidine 300 mg twice daily		16 ^{b)}	1.18 [0.88, 1.57]	1.15 [0.97, 1.35]	1.14 [0.97, 1.34]
Eltrombopag 75 mg once daily		16	1.12 [0.86, 1.45]	1.03 [0.88, 1.21]	1.03 [0.88, 1.19]
Phenytoin 100 mg three times daily		16	0.34 [0.25, 0.46]	0.16 [0.14, 0.20]	0.17 [0.14, 0.21]
Efavirenz 600 mg once daily		16 ^{b)}	0.37 [0.28, 0.48]	0.21 [0.17, 0.26]	0.21 [0.17, 0.26]
Modafinil 200 mg once daily		16 ^{b)}	0.89 [0.64, 1.24]	0.79 [0.65, 0.96]	0.79 [0.65, 0.95]

Itraconazole, CYP3A4 and P-gp inhibitor; verapamil and cimetidine, CYP3A4 inhibitors; quinidine, P-gp inhibitor; eltrombopag, BCRP inhibitor; phenytoin, efavirenz, and modafinil, CYP3A4 inducers

a) n = 16 with concomitant drug; b) n = 15 with concomitant drug

6.2.4 Thorough QT/QTc study (CTD 5.3.3.3-3, Study KVD900-109, March to July 2023)

Placebo or sebetralstat 3,000 mg (900 mg at 0 and 1 hour, and 1,200 mg at 2 hours) was orally administered to 30 non-Japanese healthy adults in a 3-treatment, 3-period, crossover design to investigate the effect on QT interval using moxifloxacin (400 mg oral) as the positive control.

After oral administration of sebetralstat 3,000 mg, the C_{max} (geometric mean [geometric CV%]) was 18,000 (44.4) ng/mL, and the largest least-squares mean difference [90% confidence interval (CI)] in change in QT interval (QT interval corrected using Fridericia's method [QTcF]) from baseline (ΔΔQTcF) between sebetralstat and placebo was 10.4 [5.55, 15.33] ms (at 5 hours post-dose). The largest ΔΔQTcF [90% CI] with moxifloxacin was 13.7 [11.17, 16.16] ms (at 2.5 hours post-dose).

A prespecified linear mixed-effect model was used to investigate a relationship between plasma sebetralstat concentrations and changes in QTcF from baseline, and the upper limit of 90% confidence interval of ΔΔQTcF was estimated to exceed 10 ms at plasma sebetralstat concentrations ≥16,900 ng/mL.

6.2.5 Studies in patients

6.2.5.1 Foreign phase II study (CTD 5.3.5.1-1, Study KVD900-201, July 2019 to December 2020)

Table 24 shows pharmacokinetic parameters in non-Japanese patients with HAE who orally received sebetralstat 600 mg as a single dose.

Table 24. Pharmacokinetic parameters of sebetralstat after administration of sebetralstat 600 mg

n	C _{max} (ng/mL)	AUC _{last} (ng·h/mL)	AUC _{inf} (ng·h/mL)	t _{max} (h)	t _{1/2} (h)	CL/F (L/h)	V _d /F (L)
42	6,080 (40.3)	12,900 (34.5)	17,600 (36.0) ^{a)}	1.00 [0.433, 3.00]	1.56 ± 0.371 ^{a)}	36.6 ± 15.4 ^{a)}	80.6 ± 39.1 ^{a)}

C_{max}, AUC_{last}, and AUC_{inf}, Geometric mean (geometric CV%); t_{max}, Median [range]; t_{1/2}, CL/F, and V_d/F, Mean ± SD

a) n = 30

Figure 4 shows changes in PKa activity over time in plasma specimens treated with dextran sulfate to activate the kallikrein-kinin pathway. At 15 minutes post-dose, 89% of PKa activity was inhibited.

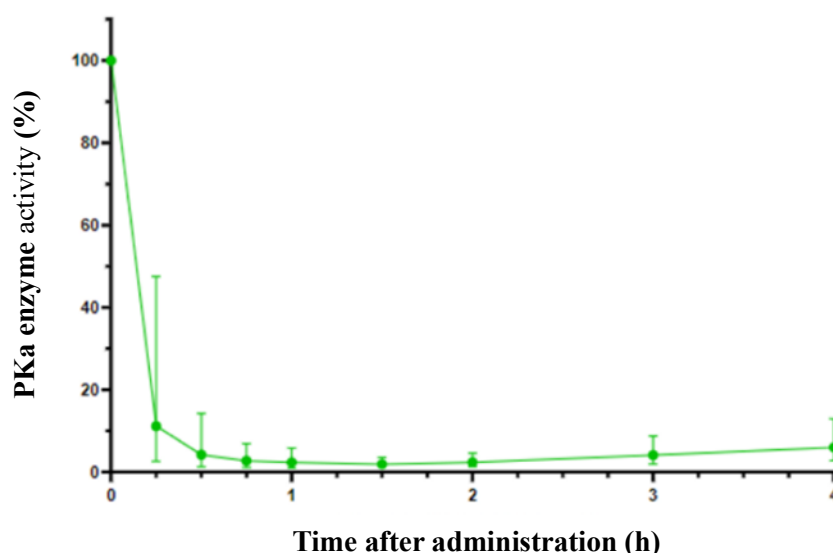


Figure 4. Changes in PKa activity over time after administration of sebetralstat 600 mg (geometric mean ± geometric SD)

6.3 Population pharmacokinetic analysis (CTD 5.3.3.5-2)

A population pharmacokinetic analysis (NONMEM version 7.4.3) was performed on plasma sebetralstat concentration data from 345 participants (at 6,674 sampling points) obtained from 8 clinical studies²¹⁾ in healthy adults and adult patients with HAE.

Pharmacokinetics of sebetralstat were described as a 2-compartment model with the first-order and zero-order absorption with an absorption lag time on the zero-order process, and the base model was established with effects of body weight²²⁾ on CL/F, Q/F, V2/F, and V3/F included. The following covariates were selected in covariate evaluation²³⁾ and then used to establish the final model: Baseline

²¹⁾ Studies KVD900-101, 102, 104, 106, 107, 108, and 110 in healthy adults and Study KVD900-201 in patients with HAE

²²⁾ Allometric scaling on the basis of body weight 70 kg using an exponent of 0.75 for CL/F and Q/F and 1 for V2/F and V3/F

²³⁾ Potential covariates evaluated for the effect on CL/F, V2/F, first-order absorption rate constant (K_a), D2, F1, and lag time of zero-order absorption (ALAG2) included age, sex, race (Caucasian, Asian, or African American), ethnic group (Hispanic or non-Hispanic), baseline creatinine clearance, baseline estimated glomerular filtration rate, baseline serum albumin, baseline ALT, baseline aspartate aminotransferase (AST), baseline total bilirubin, meal (fasted, after high-fat meal, or after a standard meal), dose and formulation (white film-coated tablets, chewed white film-coated tablets, orally disintegrating tablets, capsules, or uncoated tablets).

albumin and race (Asian) for CL/F; meal for duration of zero-order absorption (D2); and formulation²⁴⁾ for D2 and fraction of first order absorption (F1).

Table 25 shows results from evaluation for effects of the covariates in the final model. No clinically meaningful differences were observed in exposure to sebetralstat for any of the covariates.

Table 26 shows estimated pharmacokinetic parameters in adults and children aged 12 years and older after single administration of sebetralstat 300 or 600 mg in the final model.

Table 25. Effects of covariates in the final model^{a)} (after single administration of sebetralstat 600 mg)

Covariate	Category	n	C _{max} (ng/mL)	AUC _{0-24h} (ng·h/mL)
Overall population		439	5,250 [2,160, 10,400]	17,000 [8,820, 31,500]
Baseline albumin (U/L) ^{b)}	≥2.9 and <4.5	98	5,450 [2,070, 11,900]	16,100 [8,600, 31,500]
	≥4.5 and <4.8	134	5,470 [2,620, 10,400]	15,900 [9,450, 29,100]
	≥4.8	124	5,110 [2,140, 9,960]	16,100 [8,590, 26,400]
Race	Non-Asian	400	5,230 [2,300, 10,400]	17,500 [9,240, 31,700]
	Asian	39	5,770 [1,180, 10,600]	14,700 [7,960, 25,500]
Meal	Fasted	415	5,370 [2,170, 10,400]	16,900 [8,810, 31,300]
	After high-fat meal or standard meal	24	4,000 [1,690, 6,070]	21,100 [9,520, 40,900]
Formulation	White film-coated tablets or uncoated tablets	321	5,200 [2,000, 10,300]	17,600 [8,990, 32,400]
	Capsules	56	4,920 [2,960, 9,200]	13,000 [8,220, 27,100]
	Orally disintegrating tablets	36	5,990 [2,900, 10,500]	18,300 [10,100, 29,100]
	Chewed white film-coated tablets	26	7,300 [4,170, 10,900]	22,500 [12,800, 30,900]
Body weight	<69 kg	107	6,390 [2,140, 10,800]	18,000 [8,560, 37,900]
	≥69 kg and <78.5 kg	120	5,810 [2,460, 10,400]	18,400 [10,300, 29,400]
	≥78.5 kg and <87.6 kg	108	5,150 [1,800, 10,700]	15,900 [8,590, 32,200]
	≥87.6 kg	104	4,190 [2,180, 9,090]	15,500 [9,330, 29,300]

Median [5th percentile, 95th percentile]

a) Simulation results of pharmacokinetics after single administration of sebetralstat 600 mg based on post-hoc estimated pharmacokinetic parameters in healthy adults and patients, which were used in the population pharmacokinetic analysis

b) Of the overall population, 83 participants had missing baseline albumin data.

Table 26. Estimated pharmacokinetic parameters after single administration of sebetralstat in the final model

Dose	Population	C _{max} (ng/mL)	AUC _{0-24h} (ng·h/mL)
300 mg	Adults ^{a)}	2,460 (61.1)	7,210 (27.8)
	Children aged ≥12 years ^{b)}	3,520 (51.7)	11,300 (46.2)
600 mg	Adults ^{a)}	5,260 (53.0)	18,000 (39.7)
	Children aged ≥12 years ^{b)}	7,040 (51.7)	22,500 (46.2)

Geometric mean (geometric CV%)

a) Estimates based on study data obtained after single administration of sebetralstat 300 or 600 mg (n = 18 or n = 237, respectively) in the fasted state using white film-coated tablets

b) Values obtained from simulation (n = 600) of pharmacokinetics in the putative patient population (patients aged 12-17.9 years and weighing 31.0-93.3 kg, consisting of males and females in a 1:2 ratio) after single administration of sebetralstat 300 or 600 mg in the fasted state using white film-coated tablets

6.R Outline of the review conducted by PMDA

6.R.1 Differences in pharmacokinetics or pharmacodynamics of sebetralstat between ethnic groups

Based on the submitted data, PMDA concluded that no clinically meaningful differences were observed in the pharmacokinetics or pharmacodynamics of sebetralstat between Japanese and non-Japanese subjects.

²⁴⁾ On the basis of white film-coated tablets, orally disintegrating tablets or capsules for D2 and chewed white film-coated tablets or orally disintegrating tablets for F1 were included as covariates.

6.R.2 Use of sebetralstat in patients with hepatic or renal impairment

The applicant's explanation about the use of sebetralstat in patients with hepatic or renal impairment: The clinical pharmacology study in which the effect of hepatic impairment on the pharmacokinetics of sebetralstat was investigated [see Section 6.2.2.1] showed that exposure to sebetralstat increased with increasing severity of hepatic impairment; however, dose adjustment of sebetralstat is not required for adult patients with mild or moderate hepatic impairment because no safety concerns were identified even in Study KVD900-102²⁵⁾, where higher exposure was observed. Data on the use of sebetralstat in patients with severe hepatic impairment are not available, and the extent of the increase in exposure is unknown. Therefore, sebetralstat will be contraindicated in these patients.

Although no clinical pharmacology studies in patients with renal impairment have been conducted, renal excretion is not the primary excretion route of sebetralstat [see Section 6.2.1.2], and the effect of renal impairment on exposure to sebetralstat is considered to be limited. No dose adjustment of sebetralstat is required for patients with renal impairment.

PMDA accepted the applicant's explanation.

6.R.3 Pharmacokinetic interactions

The applicant's explanation about the potential for drug interactions during clinical use of sebetralstat, based on the results from non-clinical pharmacokinetic studies [see Section 4.5] and clinical studies assessing pharmacokinetic interactions [see Section 6.2.3]:

Concomitant use of phenytoin or efavirenz, a strong or moderate CYP3A4 inducer, decreased the exposure (C_{max}) to sebetralstat to approximately one third of that observed without concomitant drug. The applicant will include precautionary statements in the package insert that use of sebetralstat requires consideration for replacement of any existing strong or moderate CYP3A4 inducer with another drug in the same class that has no or weak CYP3A4 induction.

Concomitant use of itraconazole or verapamil, a strong or moderate CYP3A4 inhibitor, a P-gp inhibitor, or a BCRP inhibitor increased exposure to sebetralstat. The applicant will also include precautionary statements about such concomitant use in the package insert. However, in this study and Study KVD900-102²⁵⁾ where higher exposure was observed, no safety concerns were raised, and no dose adjustment of sebetralstat is required for concomitant use of any of the above drugs.

PMDA accepted the applicant's explanation.

6.R.4 Risk of QTc interval prolongation

The applicant's explanation about the risk of QT interval prolongation during use of sebetralstat: In Study KVD900-109, the maximum $\Delta\Delta QTcF$ [90% CI] after oral administration of sebetralstat 3,000 mg was 10.4 ms [5.55, 15.33] [see Section 6.2.4], and the upper limit of the 90% confidence interval exceeded 10 ms. Thus, the package insert should include precautionary statements that QT interval prolongation may occur.

²⁵⁾ When 3 doses of sebetralstat 600 mg were administered to healthy adults at intervals of 2 hours, C_{max} (geometric mean [geometric CV%]) was 15,627 [32.2] ng/mL and AUC_{inf} (geometric mean [geometric CV%]) was 74,221 [40.6] ng·h/mL.

The plasma sebetralstat concentration of sebetralstat at which the upper limit of the 90% confidence interval for $\Delta\Delta Q_{TcF}$ would exceed 10 ms was estimated to be 16,900 ng/mL [see Section 6.2.4], and effects of concomitant CYP3A4 inhibitors and hepatic impairment, which were shown to increase the exposure to sebetralstat, on QT interval were investigated (Table 27).²⁶⁾ If sebetralstat 600 mg is administered to patients with moderate hepatic impairment receiving a strong CYP3A4 inhibitor, a risk of QT interval prolongation cannot be ruled out. The package insert should include precautionary statements that such patients should avoid a second dose of sebetralstat 300 mg even if the response to the first dose of sebetralstat 300 mg is inadequate.

Table 27. Increases in exposure to sebetralstat in the presence of a concomitant CYP3A4 inhibitor and hepatic impairment

CYP3A4 inhibition by concomitant drug	Severity of hepatic impairment	Increase in exposure	C _{max} after single administration of sebetralstat (ng/mL)	
			300 mg	600 mg
-	Normal/mild	-	2,620 ^{a)}	5,260 ^{a)}
Moderate	Normal/mild	× 1.76 ^{b)}	4,611	9,258
Strong	Normal/mild	× 2.35 ^{b)}	6,157	12,361
-	Moderate	× 1.63 ^{c)}	4,271	8,574
Moderate	Moderate	× 2.87 ^{b),c)}	7,516	15,090
Strong	Moderate	× 3.83 ^{b),c)}	10,036	20,148

a) Geometric mean estimated in the population pharmacokinetic model [see Section 6.3] using study data obtained from single administration of sebetralstat 300 mg (white film-coated tablets or capsules) or 600 mg (white film-coated tablets) in the fasted state

b) Increase in C_{max} in the presence of a concomitant CYP3A4 inhibitor, observed in Study KVD900-106 [see Section 6.2.3]

c) Increase in C_{max} in the presence of moderate hepatic impairment, observed in Study KVD900-104 [see Section 6.2.2.1]

PMDA accepted the applicant's explanation and concluded that the following precautionary statements should be included in the package insert: For use of sebetralstat in patients with moderate hepatic impairment receiving a strong CYP3A4 inhibitor, such concomitant use should be avoided because there is a risk of QT interval prolongation, and replacement of the existing strong CYP3A4 inhibitor with another drug in the same class that has moderate or weaker CYP3A4 inhibitory effect should be considered; and if use of the strong CYP3A4 inhibitor is inevitable, a second dose of sebetralstat should not be administered after the first dose for the treatment of a single attack.

6.R.5 Exposure to sebetralstat in children aged 12 years and older

The applicant's explanation about exposure to sebetralstat in children aged 12 years and older:

The population pharmacokinetic model established using data in healthy adults and adult patients with HAE predicted that exposure to sebetralstat in children aged 12 years and older would be greater than that in adults [see Section 6.3]. This population pharmacokinetic model was then updated using plasma sebetralstat concentrations (at 15 sampling points) from 6 pediatric patients aged 12 years and older with HAE in Study KVD900-302. In the updated model, exposure (geometric mean [geometric CV%]) in adults and children aged 12 years and older after administration of sebetralstat 600 mg in the fasted state was estimated as follows: (1) C_{max} was estimated to be 5,260 [53.1] and 4,540 ng/mL [23.8]; and (2) AUC_{0-24h} was estimated to be 17,900 [39.7] and 20,000 ng·h/mL [31.2], respectively.

²⁶⁾ To avoid underestimation of the extent of the increase in exposure, decreased clearance in patients with hepatic impairment and increased blood sebetralstat concentrations by CYP3A4 inhibition were handled as independent mechanisms.

Clinical studies in which sebetralstat 300 mg or 600 mg was administered to adults and children aged 12 years and older as a single dose or twice have not raised any safety concerns [see Section 7.R.3].

Based on the above, exposure to sebetralstat in children aged 12 years and older is similar to that in adults, and no dose adjustment of sebetralstat is required for pediatric patients with HAE.

PMDA accepted the applicant's explanation.

7. Clinical Efficacy and Safety and Outline of the Review Conducted by PMDA

The applicant submitted efficacy and safety evaluation data in the form of results from 3 studies presented in Table 28.

Table 28. Efficacy and safety evaluation data

Phase	Study code	Region	Study population	No. of subjects	Dosage regimen (oral)	Main endpoints [Primary endpoint]
II	KVD900-201	Foreign	Patients with HAE type 1 or 2 (adults)	68	Part 1 (open-label) Single dose of sebetralstat 600 mg Part 2 (double-blind) Single dose of sebetralstat 600 mg or placebo for treatment of 2 HAE attacks in a crossover design	Part 1 (open-label) Safety, pharmacokinetics, and pharmacodynamics Part 2 (double-blind) Efficacy, safety [Time to use of conventional treatment of HAE attacks within 12 hours after dosing the study drug]
III	KVD900-301	Global	Patients with HAE type 1 or 2 (≥ 12 years)	110	Single dose of sebetralstat 300 or 600 mg or placebo for treatment of 3 HAE attacks in a crossover design ^{a)}	Efficacy, safety [Time to beginning of symptom relief within 12 hours after the first dose of the study drug]
III	KVD900-302	Global	Patients with HAE type 1 or 2 (≥ 12 years)	134	Single oral dose of sebetralstat 600 mg for treatment of HAE attacks ^{a)}	Safety, efficacy

a) A second dose of the study drug ≥ 3 hours after the first dose of the study drug was allowed for each attack.

7.1 Phase II study

7.1.1 Foreign phase II study (CTD 5.3.5.1-1, Study KVD900-201, July 2019 to December 2020)

This study was conducted to evaluate efficacy, safety, and pharmacokinetics of sebetralstat in adult patients with HAE type 1 or 2 (target sample size, 60 subjects²⁷⁾) in 10 countries or regions including the US, the UK, Italy, and Germany.

Table 29 shows key inclusion and exclusion criteria for this study.²⁸⁾

²⁷⁾ On the assumption that the proportion of HAE attacks requiring conventional treatment of HAE attacks within 12 hours after dosing the study drug, the primary endpoint, is 10% during the sebetralstat treatment period and 40% during the placebo treatment period, a sample size of 50 patients was calculated as the size providing 90% power at a 2-sided significance level of 5%. In view of the presence of patients who might not complete all the treatment periods due to a low frequency of attacks or who might discontinue the study early, the target sample size of 60 patients was selected.

²⁸⁾ The patients were confirmed to meet the eligibility criteria at both visits for screening and Part 1.

Table 29. Key inclusion and exclusion criteria

Key inclusion criteria
1. ≥ 18 years of age
2. A confirmed diagnosis of HAE type 1 or 2 with documented clinical history consistent with HAE (subcutaneous or mucosal, nonpruritic swelling episodes not accompanied by urticaria) and meeting either of the following conditions: • C1-INH antigen or functional level $<40\%$ of the normal level • C1-INH antigen or functional level 40% to 50% of the normal level, a C4 level below the normal range, and a family history consistent with HAE type 1 or 2
3. At least 3 documented HAE attacks in the past 93 days, as supported by medical history
4. Access to and ability to use conventional treatment of HAE attacks
Key exclusion criteria
1. Diagnosis of coexisting chronic angioedema in the other types (e.g., acquired C1 inhibitor deficiency, HAE with normal C1-INH [HAE type 3], idiopathic angioedema, angioedema accompanied by urticaria)
2. Use of C1-INH, androgens, lanadelumab, or tranexamic acid for HAE prophylaxis
3. Use of ACE inhibitors or any estrogen-containing medications with systemic absorption (e.g., oral contraceptives, hormonal replacement therapy) within 93 days before the first dose of the study drug
4. Use of androgens or antifibrinolytics within 30 days before the first dose of the study drug
5. Use of lanadelumab within 10 weeks before the first dose of the study drug
6. Use of strong CYP3A4/CYP2C9 inhibitors or inducers to be needed during the study period

This study consisted of 2 parts, Part 1 in which all the patients received sebetralstat in an open-label manner and Part 2 in which patients who completed Part 1 were randomized to receive sebetralstat or placebo in a double-blind manner according to a 2-treatment, 2-period, crossover design.

In Part 1, a single dose of sebetralstat 600 mg was orally administered between HAE attacks. In Part 2, a single dose of sebetralstat 600 mg or placebo was orally administered for an attack meeting the criteria.²⁹⁾ A washout period of at least 48 hours was required before the next dose of the study drug.

Use of angiotensin-converting enzyme (ACE) inhibitors, estrogen-containing medications with systemic absorption, androgens, antifibrinolytics, and lanadelumab was prohibited throughout the study period. In Part 2, for use of conventional treatment of HAE attacks,³⁰⁾ the patients were required to notify the investigator (or sub-investigator) of its use in advance and then were permitted to use such medication if (a) at least 4 hours had passed since the last dose of the study drug, (b) the attack was considered by the patient to be severe enough to require treatment, or (c) the attack did not meet the criteria.²⁹⁾

All of the 68 patients who received the study drug in Part 1 were included in the safety analysis population. Subsequently, all of the 68 patients were randomized in Part 2, and among them, 53 patients who received both sebetralstat and placebo were included in the full analysis set (FAS), which was used as the efficacy analysis population.

In Part 2, 15 of 68 patients (22.1%) discontinued the study. The main reason for discontinuation was early discontinuation at the discretion of the sponsor because a sufficient number of attacks had been achieved for efficacy evaluation, which occurred in 13 of 68 patients (19.1%).

²⁹⁾ When an HAE attack occurred, the patient notified the investigator (or sub-investigator) and then took the study drug for the attack that was judged eligible for administration of the study drug, meeting all of the following criteria: (a) The attack affects body parts below the head and neck (not affecting larynx or head); (b) the attack started <1 hour ago; (c) the attack is not assessed as "severe" or severer in severity according to the patient global impression of severity (PGI-S) [for definitions, see Section 10]; and (d) a washout period of ≥ 7 days from the last dose of C1-INH or ≥ 3 days from the last dose of icatibant is confirmed.

³⁰⁾ Plasma-derived C1-INH preparations, recombinant human C1-INH preparations, and icatibant

Table 30 shows the results of “time to use of conventional treatment of HAE attacks within 12 hours after dosing the study drug,” the primary efficacy endpoint in Part 2. A statistically significant difference was observed between the sebetralstat treatment and placebo treatment periods.

Table 30. Time to use of conventional treatment of HAE attacks within 12 hours after dosing the study drug (Part 2, FAS)

	Sebetralstat 600 mg	Placebo
Proportion of patients who used conventional treatment of HAE attacks within 12 hours after dosing the study drug	8/53 (15.1)	16/53 (30.2)
Time to use of conventional treatment of HAE attacks (hours) ^{a)}	NE [9.5, NE]	8.0 [3.8, NE]
<i>P</i> value ^{b)}	0.0010	-

Number of subjects (%)

a) First quartile [95% CI], b) Gehan’s generalized Wilcoxon test at a 2-sided significance level of 5% (*Stat Med.* 1996;15:953-67)

Adverse events occurred in 12 of 68 patients (17.6%) in Part 1, and 14 of 58 patients (24.1%) during the sebetralstat 600 mg treatment period and 7 of 55 patients (12.7%) during the placebo treatment period in Part 2. Table 31 shows main adverse events.

No deaths, serious adverse events, or adverse events leading to study discontinuation occurred.

Adverse drug reactions occurred in 5 of 68 patients (7.4%) in Part 1, and 3 of 58 patients (5.2%) during the sebetralstat 600 mg treatment period and 2 of 55 patients (3.6%) during the placebo treatment period in Part 2.

Table 31. Adverse events reported by ≥2 patients after administration of either study drug (safety analysis population)

Event	Part 1	Part 2	
	Sebetralstat 600 mg (n = 68)	Sebetralstat 600 mg (n = 58)	Placebo (n = 55)
Headache	2 (2.9)	3 (5.2)	3 (5.5)
Back pain	2 (2.9)	1 (1.7)	0
Nasopharyngitis	2 (2.9)	0	2 (3.6)
Urinary tract infection	2 (2.9)	0	0
Nausea	1 (1.5)	2 (3.4)	0
Cystitis	0	2 (3.4)	0

Number of subjects with events (%)

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7.2 Phase III studies

7.2.1 Global phase III study (CTD 5.3.5.1-7, Study KVD900-301, February 2022 to December 2023)

A placebo-controlled, randomized, double-blind, 3-treatment, 3-period, crossover study was conducted to evaluate efficacy and safety of sebetralstat in adult and pediatric patients aged 12 years and older with HAE type 1 or 2 (target sample size, 114³¹⁾) in 20 countries or regions including Japan, the US, and the UK.

³¹⁾ On the assumption that the time to beginning of symptom relief within 12 hours after the first dose of the study drug, the primary endpoint, is 1.6 hours during the sebetralstat treatment period and 9 hours during the placebo treatment period, and proportion of patients lost to follow up is 17% and 49%, respectively, based on the results from Study KVD900-201, a sample size of 66 patients was calculated as the size providing 90% power at a 2-sided significance level of 2.5%. In view of lack of clinical experience with sebetralstat in children aged 12 years and older, the target number of 84 patients completing the study was proposed. Furthermore, on the assumption that the proportion of patients who fail to complete the study or drop out is approximately 30% in view of the presence of patients who might not complete all the treatments due to a low frequency of attacks or who might discontinue the study early, the target sample size of 114 patients was selected.

Table 32 shows key inclusion and exclusion criteria for this study.

Table 32. Key inclusion and exclusion criteria

Key inclusion criteria 1. ≥ 12 years of age 2. A confirmed diagnosis of HAE type 1 or 2 with documented clinical history consistent with HAE (subcutaneous or mucosal, nonpruritic swelling episodes not accompanied by urticaria) and meeting any of the following conditions: • C1-INH antigen or functional level $<40\%$ of the normal level • C1-INH antigen or functional level 40% to 50% of the normal level, C4 level below the normal range • Documented genetic results confirming known mutations for HAE type 1 or 2 3. Access to and ability to use conventional treatment of HAE attacks 4. If a patient is receiving long-term HAE prophylactic treatment allowed in the protocol, the patient must have been on a stable dose and regimen for at least 3 months prior to the screening visit and must be willing to remain on a stable dose and regimen during the study period. 5. Last dose of attenuated androgens administered at least 28 days before randomization 6. ≥ 2 documented HAE attacks within 3 months before randomization Key exclusion criteria 1. Diagnosis of coexisting chronic angioedema in the other types (e.g., acquired C1 inhibitor deficiency, HAE with normal C1-INH [HAE 3], idiopathic angioedema, angioedema accompanied by urticaria) 2. History of poor response to a bradykinin receptor 2 blocker, C1-INH preparation, or a PKa inhibitor for HAE attacks as judged by the investigator (or sub-investigator) 3. Use of ACE inhibitors after the screening visit or within 7 days before randomization 4. Use of estrogen-containing medications with systemic absorption (e.g., oral contraceptives containing ethinyl estradiol, hormonal replacement therapy) within 7 days before the screening visit 5. Prior participation in Study KVD900-201 6. Use of strong CYP3A4 inhibitors or inducers to be needed during the study period
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This study was conducted in a 3-treatment, 3-period, crossover design, and sebetralstat 300 mg, sebetralstat 600 mg, and placebo were administered in 6 different sequences.

A single dose of sebetralstat 300 or 600 mg or placebo was orally administered for an attack meeting the criteria.³²⁾ Patients were allowed to take a second dose at the same dose level as the first dose at least 3 hours after the first dose if considered necessary by the patient.

Use of long-term HAE prophylactic treatment was allowed if patients had been on a stable dose and regimen, and use of short-term HAE prophylactic treatment³³⁾ was allowed as long as a washout period of at least 48 hours was provided before administration of the study drug. Use of conventional treatment of HAE attacks³⁴⁾ was allowed when any of the following criteria was met: (a) 1 hour has passed since the second dose of the study drug, and the patient considers it necessary; (b) progressive airway symptoms are observed; (c) after the first dose of the study drug for a non-severe laryngeal attack, worsening of the symptoms is observed or the patient considers it necessary; or (d) the attack does not meet the criteria.³²⁾

Of 136 patients randomized,³⁵⁾ 110 patients receiving the study drug at least once were included in the safety analysis population. A total of 110 patients receiving the study drug at least once for eligible attacks were included in the FAS, which was used as the efficacy analysis population.

³²⁾ An attack eligible for administration of the study drug must meet all of the following criteria: (a) The attack is not a laryngeal attack that is "severe" or "very severe" in severity according to the PGI-S [for definitions, see Section 10]; (b) the patient can identify time of start of the attack; (c) at least 48 hours have passed since the last dose of conventional treatment of HAE attacks or the study drug; (d) the patient can complete the diary that covers at least 4 hours after administration of the study drug for the attack and is evaluable; and (e) for the second or third attack, the televisit after the previous eligible attack has been completed.

³³⁾ Recombinant human C1-INH preparations, lanadelumab, and berotralstat

³⁴⁾ Plasma-derived C1-INH preparations, recombinant human C1-INH preparations, icatibant, ecallantide, etc.

³⁵⁾ It was stratified by the presence or absence of long-term HAE prophylactic treatment at a stable dose and regimen.

Study discontinuation occurred in 42 of 110 patients (38.2%). The main reasons for discontinuation were early discontinuation at the discretion of the sponsor because a sufficient number of attacks had been achieved for efficacy evaluation (32 of 110 patients [29.1%]) and consent withdrawal (3 of 110 patients [2.7%]).

Of the efficacy and safety analysis populations, the Japanese subgroup consisted of 7 patients, 3 of whom discontinued the study (all due to early discontinuation at the sponsor's discretion).

Table 33 and Figure 5 show the results of time to beginning of symptom relief within 12 hours after the first dose of the study drug [for definitions, see Section 10], the primary efficacy endpoint.³⁶⁾ Both pairwise comparisons between sebetralstat 300 mg and placebo and between sebetralstat 600 mg and placebo showed a statistically significant difference, demonstrating superiority of sebetralstat 300 and 600 mg over placebo. Table 33 shows the results in the Japanese subgroup.

Table 33. Time to beginning of symptom relief within 12 hours after the first dose of the study drug (FAS)

	Overall population			Japanese subgroup		
	Sebetralstat 300 mg	Sebetralstat 600 mg	Placebo	Sebetralstat 300 mg	Sebetralstat 600 mg	Placebo
Proportion of patients in whom symptom relief began within 12 hours	66/87 (75.9)	71/93 (76.3)	41/84 (48.8)	5/6 (83.3)	6/6 (100)	4/5 (80.0)
Time to beginning of symptom relief within 12 hours (hours) ^{a)}	1.61 [1.28, 2.27]	1.79 [1.33, 2.27]	6.72 [2.33, NE]	2.06 [0.34, NE]	1.56 [0.28, NE]	7.22 [0.28, NE]
<i>P</i> value ^{b)}	<0.0001	0.0006	-			

Number of subjects (%)

a) Median [95% CI]

b) Gehan scores [for definitions, see Section 10] were analyzed as the response variable using a linear mixed-effect model, including sequence, period, and treatment effects as fixed effects and patients nested within sequence as a random effect (Gehan score transformation test). For the study overall, the 2-sided significance level of 4.5% (to control the type-I error probability at ≤5% in view of characteristics of the Gehan score transformation test in which the type-I error probability may exceed the nominal significance level [Stat Med. 1996;15:953-67]) was specified. For each pairwise comparison, the 2-sided significance level of 2.25% was initially specified using the Bonferroni multiplicity adjustment.

³⁶⁾ The patients in whom symptom relief did not begin within 12 hours or conventional treatment of HAE attacks was used before beginning of symptom relief were censored at 12 hours. The patients in whom no evaluable results were available because of lack of at least 2 consecutive post-baseline assessments were censored at baseline.

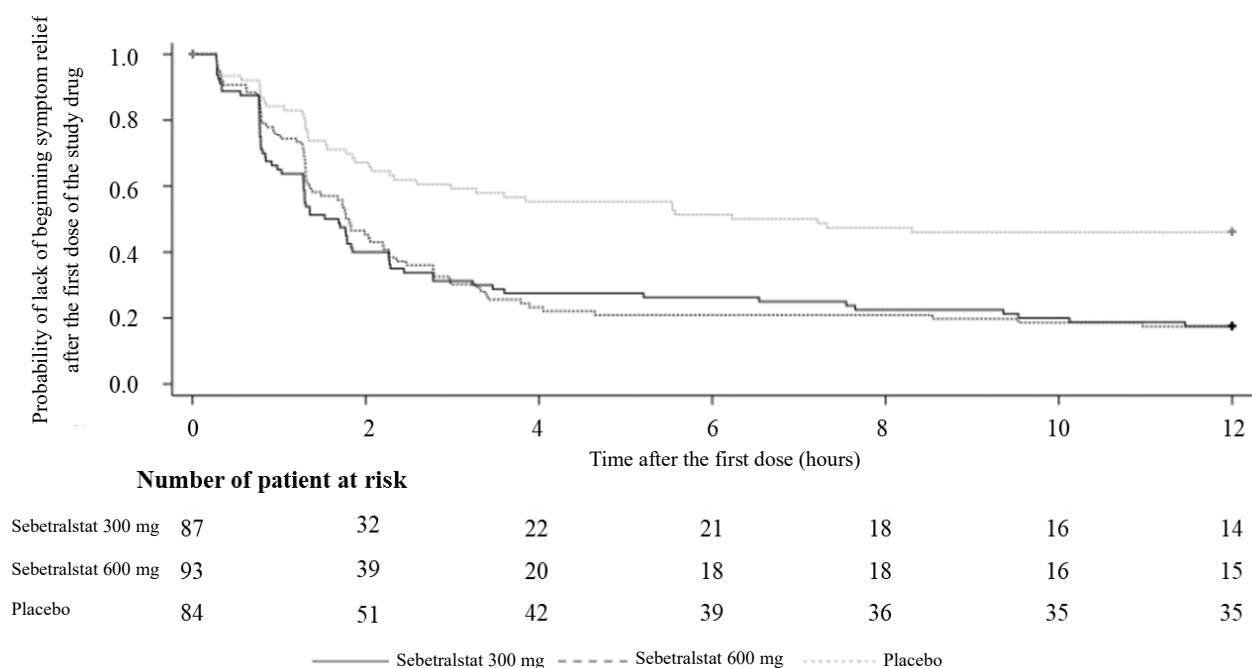


Figure 5. Kaplan-Meier curve of time to beginning of symptom relief after the first dose of the study drug (FAS)

Adverse events occurred in 17 of 86 patients (19.8%) during the sebetralstat 300 mg treatment period, 14 of 93 patients (15.1%) during the sebetralstat 600 mg treatment period, and 17 of 83 patients (20.5%) during the placebo treatment period. Table 34 shows main adverse events.

Neither deaths nor adverse events leading to study discontinuation occurred.

Serious adverse events occurred in 1 of 86 patients (1.2%) during the sebetralstat 300 mg treatment period (intervertebral disc protrusion) and 2 of 93 patients (2.2%) during the sebetralstat 600 mg treatment period (anisocoria and hereditary angioedema in 1 patient each), but a causal relationship to the study drug was ruled out for any of them.

Adverse drug reactions occurred in 2 of 86 patients (2.3%) during the sebetralstat 300 mg treatment period, 3 of 93 patients (3.2%) during the sebetralstat 600 mg treatment period, and 4 of 83 patients (4.8%) during the placebo treatment period.

Table 34. Adverse events reported by ≥ 2 patients after administration of sebetralstat (safety analysis population)

Event	Sebetralstat 300 mg (n = 86)	Sebetralstat 600 mg (n = 93)	Placebo (n = 83)
Headache	1 (1.2)	4 (4.3)	1 (1.2)
Vomiting	1 (1.2)	1 (1.1)	1 (1.2)
Dyspepsia	1 (1.2)	1 (1.1)	0
COVID-19	1 (1.2)	1 (1.1)	0

Number of subjects with events (%)

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In the Japanese subgroup, an adverse event occurred in 1 of 5 patients (20%) during the placebo treatment period.

No deaths, serious adverse events, adverse events leading to study discontinuation, or adverse drug reactions occurred.

7.2.2 Global phase III study (CTD 5.3.5.2-2, Study KVD900-302, ongoing since October 2022, data cut-off in September 2024)

An open-label, uncontrolled study was conducted to evaluate long-term safety and efficacy of sebetralstat in adult and pediatric patients aged 12 years and older with HAE type 1 or 2 (target sample size, 150 subjects) including patients who completed the preceding study (Study KVD900-301) (rollover patients) in 23 countries or regions including Japan, the US, and the UK.

Table 35 shows key inclusion and exclusion criteria for patients other than rollover patients from Study KVD900-301.

Table 35. Key inclusion and exclusion criteria (other than rollover patients from Study KVD900-301)

Key inclusion criteria 1. ≥12 years of age 2. A confirmed diagnosis of HAE type 1 or 2 with documented clinical history consistent with HAE (subcutaneous or mucosal, nonpruritic swelling episodes not accompanied by urticaria) and meeting any of the following conditions: • C1-INH antigen or functional level <40% of the normal level • C1-INH antigen or functional level 40% to 50% of the normal level, C4 level below the normal range • Documented genetic results confirming known mutations for HAE type 1 or 2 3. Access to and ability to use conventional treatment of HAE attacks 4. If a patient is receiving long-term HAE prophylactic treatment allowed in the protocol, the patient must have been on a stable dose and regimen for at least 3 months prior to the screening visit and must be willing to remain on a stable dose and regimen during the study period. If a patient in the US is receiving danazol for HAE prophylactic treatment, the patient must have been on a stable dose and regimen for at least 6 months prior to the enrollment visit. 5. ≥2 documented HAE attacks within 3 months before the enrollment visit Key exclusion criteria 1. Diagnosis of coexisting chronic angioedema in the other types (e.g., acquired C1 inhibitor deficiency, HAE with normal C1-INH [HAE 3], idiopathic angioedema, angioedema accompanied by urticaria) 2. History of poor response to a bradykinin receptor 2 blocker, C1-INH preparation, or a PKa inhibitor for HAE attacks as judged by the investigator (or sub-investigator) 3. Use of ACE inhibitors within 7 days before the enrollment visit 4. Use of estrogen-containing medications with systemic absorption (e.g., oral contraceptives containing ethinyl estradiol, hormonal replacement therapy) within 7 days before the screening visit 5. Use of attenuated androgens or antifibrinolytics within 28 days before the enrollment visit
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A single dose of sebetralstat 600 mg was orally administered for each attack. Patients were allowed to take a second dose at the same dose level as the first dose at least 3 hours after the first dose if considered necessary by the patient. No more than 2 doses could be administered in a 24-hour period. Use of sebetralstat for short-term prophylactic treatment before surgical, dental, or medical procedures was also allowed.³⁷⁾

Use of long-term HAE prophylactic treatment³⁸⁾ was allowed as long as the treatment was continued at a stable dose and regimen. In addition, use of short-term HAE prophylactic treatment was allowed. Use

³⁷⁾ The present application aims at approval of the indication of on-demand treatment of HAE attacks, and efficacy and safety of sebetralstat for short-term HAE prophylactic treatment have not been evaluated.

A single dose of sebetralstat 600 mg was orally administered from 1 hour before and until 24 hours after start of the procedure, and administration of up to 3 doses at intervals ≥6 hours was allowed. At the time of onset of an attack, sebetralstat for short-term prophylactic treatment was discontinued. The attack within 24 hours after start of the procedure was subjected to conventional treatment of HAE attacks, and attack >24 hours after that was allowed to be treated with sebetralstat. Sebetralstat was used for short-term prophylactic treatment in 11 patients (including 1 Japanese patient).

³⁸⁾ Recombinant human C1-INH preparations, lanadelumab, and berotralstat

of conventional treatment of HAE attacks³⁹⁾ was allowed in the following cases: (a) The patient considered it necessary; (b) after the first dose for a laryngeal attack, the symptoms worsened; or (c) the patient was receiving CYP3A4 inhibitors or inducers.

A total of 134 patients who received the study drug at least once were included in the safety analysis population.

Study discontinuation occurred in 26 of 134 patients (19.4%). The main reasons for discontinuation were consent withdrawal (17 of 134 patients [12.7%]) and adverse events (5 of 134 patients [3.7%]).

Of the safety analysis population, 12 patients were included in the Japanese subgroup. Study discontinuation occurred in 1 patient (8.3%) because of withdrawal of consent.

Adverse events occurred in 74 of 134 patients (55.2%). Table 36 shows main adverse events.

No deaths occurred.

Serious adverse events occurred in 9 of 134 patients (6.7%) (hereditary angioedema; hiatus hernia and dehydration; inguinal hernia; hyperthermia, headache, and intracranial mass; bronchitis; erysipelas; meningitis viral; Waldenstrom's macroglobulinaemia; and hypotension in 1 patient each), but a causal relationship to the study drug was ruled out for any of the events.

Adverse events leading to study discontinuation occurred in 5 of 134 patients (3.7%).

Adverse drug reactions occurred in 12 of 134 patients (9.0%).

Table 36. Adverse events reported by $\geq 2\%$ of patients after administration of sebetralstat (safety analysis population)

Event	Sebetralstat 600 mg (n = 134)	Event	Sebetralstat 600 mg (n = 134)
Nasopharyngitis	20 (14.9)	Migraine	5 (3.7)
Headache	15 (11.2)	Nausea	4 (3.0)
COVID-19	13 (9.7)	Seasonal allergy	4 (3.0)
Upper respiratory tract infection	13 (9.7)	Gastroesophageal reflux disease	3 (2.2)
Back pain	6 (4.5)	Toothache	3 (2.2)
Rhinitis allergic	6 (4.5)	Bronchitis	3 (2.2)
Urinary tract infection	6 (4.5)	Pharyngitis streptococcal	3 (2.2)
Diarrhoea	5 (3.7)	Myalgia	3 (2.2)
Vomiting	5 (3.7)	Cough	3 (2.2)
Influenza	5 (3.7)	Oropharyngeal pain	3 (2.2)
Viral upper respiratory tract infection	5 (3.7)	Urticaria	3 (2.2)

Number of subjects with events (%)

MedDRA ver.26.0

In the Japanese subgroup, adverse events occurred in 7 of 12 patients (58.3%), and adverse events reported by ≥ 2 patients were nasopharyngitis and rhinitis allergic in 2 patients each.

³⁹⁾ Plasma-derived C1-INH preparations, recombinant human C1-INH preparations, icatibant, ecallantide, etc.

No deaths, serious adverse events, adverse events leading to study discontinuation, or adverse drug reactions occurred.

7.R Outline of the review conducted by PMDA

7.R.1 Development plan

The applicant's explanation about development plan of sebetralstat:

Diagnostic criteria and treatment strategy for HAE do not differ between Japan and foreign countries (*Allergy*. 2022;77:1961-90, Japanese guideline), and because of the hereditary nature of HAE, the pathophysiology does not differ between adults and children aged ≥ 12 years (*Allergy*. 2017;72:300-13). In the phase I study in Japanese and non-Japanese healthy adults (Study KVD900-110), pharmacokinetics and pharmacodynamics of sebetralstat did not clearly differ among ethnic groups [see Section 6.2.1.1].

Based on the above findings, the global phase III study (Study KVD900-301) was conducted in a placebo-controlled, randomized, double-blind, crossover manner to confirm the efficacy and evaluate the safety of sebetralstat in adult and pediatric patients aged 12 years and older with HAE type 1 and 2, the major disease types of HAE. The applicant decided to prepare a clinical data package primarily based on the results from this study and to evaluate the efficacy and safety of sebetralstat in Japanese patients with HAE.

For Study KVD900-301, the efficacy endpoints and dosage regimen were specified as follows.

● Efficacy endpoints

The patient global impression of change [PGI-C] scale [for definitions, see Section 10], by which patients assess general symptoms of HAE attacks on their own, was used as the efficacy measure. To specify the efficacy endpoints of sebetralstat for Study KVD900-301, examinations were performed. Based on the results from phase II study (Study KVD900-201)⁴⁰⁾ and comments from adult patients with HAE and clinical experts, the "A little better" score in the symptom assessment was considered to correspond to a clinically meaningful improvement. The primary endpoint was specified as time to beginning of symptom relief within 12 hours after the first dose of the study drug, and beginning of symptom relief was defined as the case where "A little better" or better score was reported at 2 consecutive timepoints to confirm that the observed improvement of symptoms was sustained.

● Dosage regimen

In the phase II study in non-Japanese patients with HAE (Study KVD900-201), efficacy of sebetralstat 600 mg superior to placebo was demonstrated [see Section 7.1.1]. In Study KVD900-101, an ascending dose study in non-Japanese healthy adults,⁴¹⁾ specimens collected after administration of sebetralstat exhibited $\geq 95\%$ PKa inhibition (geometric mean) for up to 3 hours post-dose at both 300 and 600 mg. Based on the above findings, the dose of sebetralstat in the phase III study was set at 300 or 600 mg.

⁴⁰⁾ In Study KVD900-201, of patients who reported a "A little better" or better score on the PGI-C, 56% of patients achieved complete HAE attack resolution within 24 hours after dosing the study drug, while of those who reported a score lower than the "A little better" score, 3% achieved the resolution; and similarly 16.0% and 65.6%, respectively, used conventional treatment of HAE attacks. Of patients who reported a "A little better" or better score on the PGI-C, 85.2% reported a "Better" or better score within 48 hours after dosing the study drug.

⁴¹⁾ It was a randomized, double-blind, placebo-controlled, phase I study in healthy adults, and sebetralstat was administered according to a single-ascending-dose sequence (5, 10, 20, 40, 80, 160, 300, and 600 mg) to evaluate the safety, pharmacokinetics, and pharmacodynamics.

Considering that a second dose of sebetralstat might be required for HAE attacks with an inadequate response in clinical practice, up to 2 doses of the study drug at least 3 hours apart were allowed for a single HAE attack.

PMDA accepted the applicant's explanation and concluded that clinical study results mainly from Study KVD900-301 would allow evaluation of efficacy and safety of sebetralstat in Japanese patients with HAE.

7.R.2 Efficacy

The applicant's explanation about efficacy of sebetralstat in patients with HAE:

In Study KVD900-301 in patients aged 12 years and older with HAE type 1 and 2, statistically significant differences were observed in the primary endpoint, time to beginning of symptom relief within 12 hours after the first dose of the study drug, between either sebetralstat 300 or 600 mg and placebo, demonstrating superiority of sebetralstat 300 and 600 mg over placebo (Table 33).

Table 37 and Figures 6 and 7 show results on the other main efficacy endpoints [for definitions, see Section 10].⁴²⁾ The results on all endpoints showed an improving trend with sebetralstat 300 and 600 mg over placebo.

Table 33 shows results on the primary endpoint in the Japanese subgroup in Study KVD900-301, and Table 37 shows results on the other main efficacy endpoints, indicating an improving trend with sebetralstat 300 and 600 mg over placebo for all endpoints, consistent with the overall population.

Table 37. Results on the main efficacy endpoints (Study KVD900-301, FAS)

	Overall population			Japanese subgroup		
	Sebetralstat 300 mg	Sebetralstat 600 mg	Placebo	Sebetralstat 300 mg	Sebetralstat 600 mg	Placebo
Proportion of patients who achieved a decrease in severity within 12 hours after the first dose of the study drug	44/87 (50.6)	49/93 (52.7)	26/84 (31.0)	5/6 (83.3)	3/6 (50.0)	1/5 (20.0)
Time to a first decrease in severity within 12 hours after the first dose of the study drug (hours) ^{a)}	9.27 [4.08, NE]	7.75 [3.27, NE]	NE [NE, NE]	4.91 [0.34, NE]	NE [0.28, NE]	NE [1.76, NE]
Proportion of patients who achieved complete HAE attack resolution within 24 hours after the first dose of the study drug	37/87 (42.5)	46/93 (49.5)	23/84 (27.4)	4/6 (66.7)	4/6 (66.7)	2/5 (40.0)
Time to complete HAE attack resolution within 24 hours after the first dose of the study drug (hours) ^{a)}	NE [16.60, NE]	24.00 [10.60, NE]	NE [NE, NE]	8.91 [0.34, NE]	16.57 [0.28, NE]	NE [1.76, NE]

Number of subjects (%)

a) Median [95% CI]

⁴²⁾ The patients in whom conventional treatment of HAE attacks was used before beginning of symptom relief were censored at 12 hours. Of note, in the analysis on time to complete HAE attack resolution within 24 hours after the first dose of the study drug, they were censored at 24 hours. The patients in whom no evaluable results were available because of lack of at least 2 consecutive post-baseline assessments were censored at baseline.

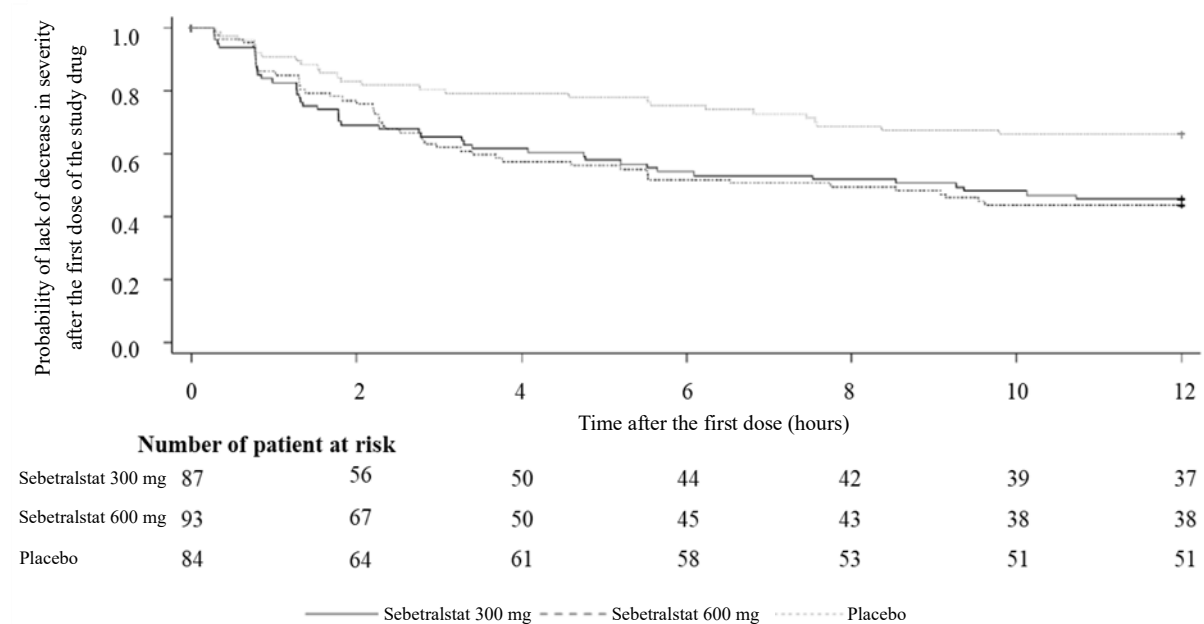


Figure 6. Kaplan-Meier curve of time to a first decrease in severity after the first dose of the study drug (FAS)

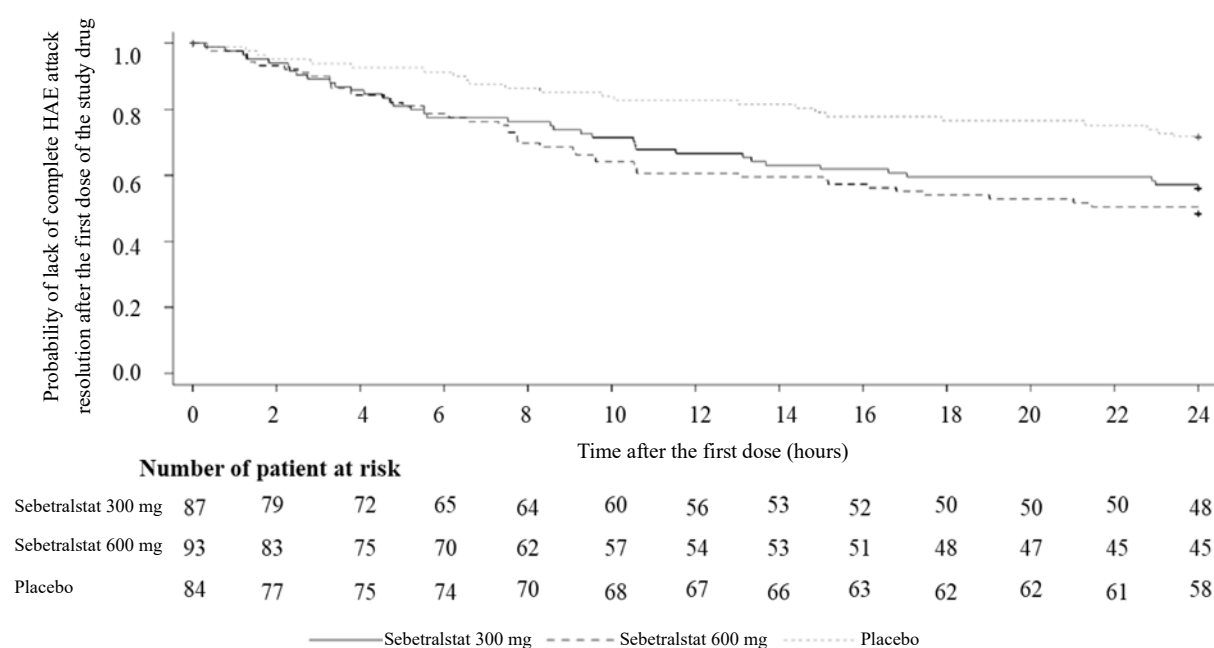


Figure 7. Kaplan-Meier curve of time to complete HAE attack resolution after the first dose of the study drug (FAS)

Table 38 shows results on the primary endpoint (time to beginning of symptom relief within 12 hours after the first dose of the study drug) in subgroups defined by patient characteristics in Study KVD900-301.³⁶⁾ Sebetralstat 300 and 600 mg tended to have efficacy superior to placebo in many subgroups, including subgroups defined by age, although some subgroups had a limited number of patients, requiring careful interpretation of the results.

**Table 38. Results on the primary endpoint in subgroups defined by patient characteristics
(Study KVD900-301, FAS)**

	Proportion of patients in whom symptom relief began within 12 hours			Time to beginning of symptom relief within 12 hours (hours) ^{a)}		
	Sebetralstat 300 mg	Sebetralstat 600 mg	Placebo	Sebetralstat 300 mg	Sebetralstat 600 mg	Placebo
Overall population	66/87 (75.9)	71/93 (76.3)	41/84 (48.8)	1.61 [1.28, 2.27]	1.79 [1.33, 2.27]	6.72 [2.33, NE]
Age						
≥12 years and <18 years	8/10 (80.0)	8/11 (72.7)	5/9 (55.6)	2.27 [0.28, 9.36]	2.16 [0.33, 9.53]	5.54 [0.56, NE]
≥18 years	58/77 (75.3)	63/82 (76.8)	36/75 (48.0)	1.35 [1.03, 1.85]	1.77 [1.31, 2.27]	7.22 [2.33, NE]
≥18 years and <30 years	14/19 (73.7)	12/17 (70.6)	9/18 (50.0)	1.28 [0.77, 7.65]	2.41 [0.79, 10.97]	2.33 [0.78, NE]
≥30 years and <40 years	13/16 (81.3)	17/19 (89.5)	7/16 (43.8)	1.56 [0.78, 2.28]	1.38 [1.28, 1.81]	NE [2.59, NE]
≥40 years and <50 years	17/22 (77.3)	17/25 (68.0)	8/22 (36.4)	1.57 [0.79, 6.54]	1.73 [1.27, 3.39]	NE [0.79, NE]
≥50 years and <60 years	11/15 (73.3)	13/15 (86.7)	7/13 (53.8)	1.73 [0.78, 3.24]	1.49 [0.78, 2.97]	7.22 [0.82, NE]
≥60 years	3/5 (60.0)	4/6 (66.7)	5/6 (83.3)	1.05 [0.79, NE]	1.83 [0.80, NE]	2.51 [1.06, NE]
Sex						
Male	29/33 (87.9)	25/37 (67.6)	12/29 (41.4)	1.28 [0.78, 1.83]	1.83 [1.31, 3.28]	NE [1.34, NE]
Female	37/54 (68.5)	46/56 (82.1)	29/55 (52.7)	1.78 [1.29, 2.78]	1.77 [1.30, 2.46]	5.57 [2.28, NE]
Body weight						
<73.3 kg ^{b)}	34/44 (77.3)	38/49 (77.6)	20/42 (47.6)	1.78 [1.28, 2.78]	1.76 [1.29, 2.46]	5.54 [1.78, NE]
≥73.3 kg ^{b)}	32/43 (74.4)	33/44 (75.0)	21/42 (50.0)	1.33 [0.79, 1.85]	1.99 [1.33, 2.78]	7.22 [2.28, NE]
Disease type of HAE						
Type 1	61/79 (77.2)	67/87 (77.0)	40/79 (50.6)	1.70 [1.28, 2.27]	1.77 [1.31, 2.27]	5.90 [2.28, NE]
Type 2	5/8 (62.5)	4/6 (66.7)	1/5 (20.0)	1.28 [0.34, NE]	2.80 [0.31, NE]	NE [2.99, NE]
Family history of HAE						
Yes	53/72 (73.6)	58/78 (74.4)	35/71 (49.3)	1.70 [1.28, 2.28]	1.93 [1.35, 2.78]	5.54 [2.07, NE]
No	13/15 (86.7)	13/15 (86.7)	6/13 (46.2)	0.78 [0.34, 2.27]	1.52 [0.93, 1.99]	NE [0.56, NE]
Past history of laryngeal attacks						
Yes	3/6 (50.0)	2/4 (50.0)	2/5 (40.0)	1.77 [0.77, NE]	1.30 [0.75, NE]	NE [1.54, NE]
No	63/81 (77.8)	69/89 (77.5)	39/79 (49.4)	1.53 [1.28, 2.27]	1.81 [1.35, 2.27]	6.23 [2.28, NE]
HAE prophylactic treatment						
No	51/68 (75.0)	54/72 (75.0)	28/66 (42.4)	1.35 [0.98, 1.83]	1.77 [1.31, 2.27]	NE [2.04, NE]
Yes	15/19 (78.9)	17/21 (81.0)	13/18 (72.2)	1.85 [0.79, 3.47]	2.03 [0.78, 3.41]	4.71 [2.28, 8.30]
Berotrastat	8/10 (80.0)	7/9 (77.8)	7/10 (70.0)	2.52 [0.34, 10.12]	1.88 [0.28, 2.97]	6.39 [0.28, NE]
Lanadelumab	2/4 (50.0)	6/7 (85.7)	4/4 (100)	NE [0.78, NE]	1.55 [0.29, NE]	3.22 [1.27, NE]
Others	5/5 (100)	4/5 (80.0)	2/4 (50.0)	1.29 [0.79, NE]	3.41 [0.62, NE]	NE [1.29, NE]
Baseline severity of attacks (PGI-S)^{c)}						
No or mild	29/36 (80.6)	34/41 (82.9)	20/38 (52.6)	1.70 [0.84, 2.28]	1.82 [1.30, 2.78]	7.22 [2.59, NE]
Moderate	26/35 (74.3)	22/34 (64.7)	17/33 (51.5)	1.56 [0.85, 3.60]	2.11 [1.31, 2.79]	2.07 [1.32, NE]
Severe or very severe	11/14 (78.6)	15/18 (83.3)	4/13 (30.8)	1.41 [0.78, 2.78]	1.51 [0.79, 2.27]	NE [0.77, NE]
Baseline primary attack location^{d)}						
Neck and head	5/11 (45.5)	10/12 (83.3)	7/13 (53.8)	2.78 [0.34, NE]	1.51 [0.28, 2.03]	3.67 [0.33, NE]
Abdomen only	23/32 (71.9)	30/39 (76.9)	17/34 (50.0)	1.29 [0.78, 5.21]	1.41 [0.79, 2.27]	8.30 [1.85, NE]
Others	38/42 (90.5)	31/42 (73.8)	17/37 (45.9)	1.53 [1.28, 1.85]	2.28 [1.76, 3.33]	7.22 [2.28, NE]
Number of doses of the study drug for single attack						
1	42/53 (79.2)	48/56 (85.7)	23/37 (62.2)	1.30 [0.81, 1.77]	1.38 [1.02, 1.81]	2.30 [1.30, 6.23]
2	24/34 (70.6)	23/37 (62.2)	18/47 (38.3)	2.36 [1.29, 7.55]	2.97 [1.83, 9.53]	NE [3.60, NE]
Time from onset of attack to the first dose of the study drug^{e)}						
<30 minutes	27/40 (67.5)	32/41 (78.0)	16/35 (45.7)	1.77 [0.79, 5.21]	2.46 [1.73, 3.39]	3.85 [2.04, NE]
≥30 minutes and <60 minutes	10/13 (76.9)	7/9 (77.8)	5/9 (55.6)	1.31 [0.81, 3.24]	1.16 [0.28, 1.81]	3.80 [0.28, NE]
≥60 minutes	29/33 (87.9)	32/43 (74.4)	20/40 (50.0)	1.32 [0.79, 2.27]	1.49 [1.29, 2.21]	8.30 [1.85, NE]

Number of subjects (%)

a) Median [95% CI]

b) Median body weight in patients enrolled in Study KVD900-301

c) Of the overall population, 2 patients had missing records on baseline severity of attacks (patient global impression of severity [PGI-S]) during the sebetralstat 300 mg treatment period.

d) Of the overall population, 2 patients had missing records on baseline primary attack location during the sebetralstat 300 mg treatment period.

e) Of the overall population, 1 patient had a missing record on time from onset of attack to the first dose of the study drug during the sebetralstat 300 mg treatment period.

The applicant's explanation about efficacy of sebetralstat in patients on HAE prophylactic treatment with PKa inhibitors as well as subgroups and clinical situations for which data were limited in Study KVD900-301:

● Efficacy in patients on HAE prophylactic treatment with PKa inhibitors

To investigate the efficacy of sebetralstat in patients on HAE prophylactic treatment with PKa inhibitors (berotrastat and lanadelumab), which share a mechanism of action with sebetralstat, a subgroup analysis

was performed on results on the primary endpoint in Study KVD900-301 by status of the prophylactic treatment, as shown in Table 38.³⁶⁾ The subgroup analysis showed a trend toward improvement compared with placebo in the subgroups without HAE prophylactic treatment and on HAE prophylactic treatment with berotralstat, but did not indicate any trend toward superiority of sebetralstat over placebo in the subgroup on HAE prophylactic treatment with lanadelumab, although the number of patients in each subgroup was limited, requiring careful interpretation of the results. Table 39 shows results on the primary endpoint by status of HAE prophylactic treatment in the open-label extension study (Study KVD900-302) where more attacks were evaluated. Efficacy of sebetralstat was suggested even in patients on HAE prophylactic treatment with PKa inhibitors, and the above inconsistent finding in Study KVD900-301 is considered attributable to variability. Sebetralstat, berotralstat, and lanadelumab all bind to the catalytic site of PKa and thereby commonly inhibit PKa (*J Med Chem.* 2021;64:12453-68, *J Biol Chem.* 2014;289:23596-608, etc.), but during an HAE attack, the kallikrein-kinin pathway needs to be further inhibited. Therefore, the applicant considers that sebetralstat should be used for the treatment of HAE attacks irrespective of the use of HAE prophylactic treatment.

Table 39. Results on the primary endpoint in subgroups defined by status of HAE prophylactic treatment (Study KVD900-302, FAS)

	Status of HAE prophylactic treatment		
	No	Berotralstat	Lanadelumab
Number of patients in whom attacks were treated with the study drug and assessed	99	16	13
Attacks reaching beginning of symptom relief within 12 hours ^{a)}	876/1,324 (66.2)	139/178 (78.1)	61/80 (76.3)
Time to beginning of symptom relief within 12 hours ^{b)}	2.52 [2.16, 2.58]	1.46 [1.26, 1.79]	1.47 [1.26, 2.18]

a) Number of attacks (%). The denominator is the number of attacks that were treated with the study drug and assessed.

b) Median [95% CI]

● Efficacy in the treatment of severe or very severe laryngeal attacks

In Study KVD900-301, severe or very severe laryngeal attacks were not eligible for the study drug. However, in the open-label extension study (Study KVD900-302), treatment data were available at the data cut-off for 32 laryngeal attacks, including severe or very severe attacks, treated with sebetralstat 600 mg (Table 40).³⁶⁾ The study results suggested the efficacy of sebetralstat in the treatment of severe or very severe laryngeal attacks.

Table 40. Results on the primary endpoint in treatment of laryngeal attacks (Study KVD900-302, FAS)

	All laryngeal attacks	Severe or very severe laryngeal attacks
Attacks reaching beginning of symptom relief within 12 hours ^{a)}	21/32 (65.6)	6/9 (66.7)
Time to beginning of symptom relief within 12 hours ^{b)}	1.72 [1.04, 3.18]	1.76 [0.27, 5.31]

a) Number of attacks (%). The denominator is the number of attacks that were treated with the study drug and assessed.

b) Median [95% CI]

● Efficacy in Japanese pediatric patients aged 12 years and older or Japanese patients with HAE type 2
No clinical study results in Japanese pediatric patients aged 12 years and older or Japanese patients with HAE type 2 who received sebetralstat were available. However, the applicant considers that efficacy of sebetralstat can be expected in Japanese pediatric patients aged 12 years and older and Japanese patients with HAE type 2 as well, because (1) the pathophysiology of HAE is not considered to differ between adults and children aged 12 years and older or between Japanese and non-Japanese patients; and (2) similar efficacy is observed irrespective of age or HAE type (1 or 2) in Study KVD900-301 (Table 38).

- Efficacy of sebetrastat in patients with HAE type 3

Patients with HAE type 3 were not included in clinical studies of sebetrastat (Study KVD900-301, etc.), and thus results on efficacy of sebetrastat in this patient population are not available. However, other drugs for the treatment of HAE attacks and for HAE prophylactic treatment which inhibit kallikrein-kinin pathway are reported to have efficacy in patients with HAE type 3 (*Clin Rev Allergy Immunol.* 2025;68:24, *Clin Exp Allergy.* 2022;52:1048-58). In view of the above reports, the applicant considers that sebetrastat can be expected to have efficacy in patients with HAE type 3 as well. Information regarding efficacy of sebetrastat in patients with HAE type 3 will be collected through post-marketing surveillance, etc.

The applicant's explanation about issues in statistical analyses identified in the planning and results of Study KVD900-301 and their limited impact on the efficacy evaluation of sebetrastat:

- Treatment effect across the periods

Study KVD900-301 was conducted using a crossover design, and the primary analysis on the primary endpoint yielded a *P* value of 0.0485 for the period effect. Results on time to beginning of symptom relief within 12 hours after the first dose of the study drug (median [95% CI]), the primary endpoint, for sebetrastat 300 and 600 mg and placebo were 1.32 [0.79, 2.28], 1.32 [0.93, 2.78], and 1.96 [1.30, 6.23] for Period 1, compared with 1.77 [1.03, 2.44], 1.76 [1.30, 2.35], and not evaluable [NE] [5.57, NE] for Period 2 and 1.42 [0.81, 9.54], 2.27 [1.73, 3.79], and NE [0.85, NE], respectively, for Period 3. For time to beginning of symptom relief within 12 hours after the first dose of the study drug and the corresponding Gehan score⁴³⁾ [for definitions, see Section 10] as well as Kaplan-Meier curve, the results were not considered generally comparable across the 3 periods, and especially the results for Period 1 tended to be different from those across the periods and for each of the other periods. In view of the half-life of sebetrastat [see Section 6.2], which is shorter than the interval between attacks,⁴⁴⁾ a possibility of the carry-over effect of sebetrastat can be ruled out, and for any period, the Gehan score with sebetrastat was more favorable than that with placebo.⁴³⁾ In the model with the interaction term between the period effect and treatment effect additionally integrated as an explanatory variable, *P* values for the period effect and the interaction term between the period effect and treatment effect were 0.0659 and 0.4151, respectively, failing to support the interpretation that the treatment effect clearly differed among periods. Furthermore, for any period, the Gehan score with sebetrastat was more favorable than that with placebo.⁴⁵⁾ In conclusion, the results for each of the periods and across the periods in Study KVD900-301 consistently demonstrated the efficacy of sebetrastat.

- Handling of missing data

In Study KVD900-301, the patients in whom no evaluable results were available because of lack of at least 2 consecutive post-baseline assessments were censored at baseline.⁴⁶⁾ This procedure may have

⁴³⁾ Least-squares mean Gehan scores (SD) with sebetrastat 300 and 600 mg and placebo were -33.97 (23.30), -28.43 (20.34), and 2.33 (21.97) for Period 1, compared with -30.79 (21.21), -15.08 (22.85), and 98.66 (20.20) for Period 2 and -24.77 (26.79), 2.50 (26.79), and 55.56 (34.15), respectively, for Period 3.

⁴⁴⁾ Median period between attacks [first quartile, third quartile] was 771.37 hours [322.98, 1655.20] for the period between the first and second attacks, and 592.57 hours [309.79, 1061.60] for that between the second and third attacks.

⁴⁵⁾ Least-squares mean Gehan scores (SD) with sebetrastat 300 and 600 mg and placebo in the model with interaction between the period effect and sequence effect integrated were -38.78 (26.91), -16.23 (24.77), and -5.01 (25.57) for Period 1, compared with -21.56 (26.92), -27.50 (28.70), and 101.19 (25.84) for Period 2, and -24.42 (27.83), 2.04 (27.55), and 57.89 (33.66), respectively, for Period 3.

⁴⁶⁾ This procedure was applied to 7 of 87 patients (8.0%) during the sebetrastat 300 mg treatment period, 7 of 93 patients (7.5%) during the sebetrastat 600 mg treatment period, and 8 of 84 patients (9.5%) during the placebo treatment period.

caused underestimation of the time to beginning of symptom relief within 12 hours after the first dose of the study drug, the primary endpoint, for each period. However, an analysis in which patients without evaluable results were right-censored at 12 hours, the final assessment timepoint, also provided results⁴⁷⁾ consistent with the primary analysis, demonstrating superiority of sebetralstat 300 mg and 600 mg over placebo.

PMDA accepted the applicant's explanation.

PMDA's view:

In Study KVD900-301, a statistically significant difference was observed in the primary endpoint, time to beginning of symptom relief within 12 hours after the first dose of the study drug, for both sebetralstat 300 and sebetralstat 600 mg compared with placebo, and the other efficacy endpoints also showed a trend toward greater improvement with sebetralstat 300 and 600 mg than with placebo. For severe or very severe laryngeal attacks, which were not eligible for the study drug in Study KVD900-301, a certain degree of efficacy was suggested in Study KVD900-302. In addition, similar trends were observed in the Japanese subgroup to those observed in the overall population .

Based on the above, PMDA has concluded that the efficacy of sebetralstat has been demonstrated in adult and pediatric patients aged 12 years and older with HAE. PMDA considers that sebetralstat may be effective in patients with HAE type 3 when used according to the same dosage regimen as in patients with HAE type 1 or 2 in view of information about drugs in the same class, although there is no clinical experience with sebetralstat in this patient population.

The above conclusion of PMDA will be discussed at the Expert Discussion.

7.R.3 Safety

7.R.3.1 Summary of safety

The applicant's explanation about safety of sebetralstat in patients with HAE based on the results of analyses using pooled data from Part 2 (double-blind period) in Study KVD900-201 and Study KVD900-301 (double-blind safety analysis population) as well as analysis results from Study KVD900-302, the open-label extension study (Medical Dictionary for Regulatory Activities [MedDRA] ver. 26.0): In view of the half-life of sebetralstat, which is approximately 3 to 6 hours, adverse events occurring within 3 days after administration of the study drug are presented in the summary of safety of sebetralstat.

Table 41 shows the summary of safety of sebetralstat in the double-blind safety analysis population, and Table 42 shows main adverse events in this population. Most of the adverse events occurred within 2 days post-dose. Incidences of adverse events and adverse drug reactions during the sebetralstat 300 mg or 600 mg treatment period were similar to those during the placebo treatment period. In the Japanese subgroup, no adverse events occurred.

⁴⁷⁾ In the analysis in which the patients without evaluable results were right-censored at 12 hours, the final assessment timepoint, the median time to beginning of symptom relief within 12 hours after the first dose of the study drug (hours) [95% CI] during the sebetralstat 300 mg treatment, sebetralstat 600 mg treatment, and placebo treatment period was 1.77 [1.29, 2.44], 1.99 [1.49, 2.78], and NE [3.60, NE], respectively, and pairwise comparisons between either sebetralstat 300 or 600 mg and placebo yielded *P* values of <0.0001 and 0.0004, respectively.

Table 43 shows the summary of safety of sebetralstat in Study KVD900-302, and Table 44 shows the main adverse events observed in this study. Serious adverse events occurred in 3 patients (erysipelas, inguinal hernia, and hereditary angioedema in 1 patient each), but a causal relationship to the study drug was ruled out for any event. In the Japanese subgroup, an adverse event of nasopharyngitis occurred in 1 patient.

Table 41. Summary of safety of sebetralstat (double-blind safety analysis population)

Time to onset	Within 2 days post-dose ^{a)}			>2 days and ≤3 days post-dose ^{a)}			Within 3 days post-dose ^{a)}		
Period	Sebetralstat 300 mg	Sebetralstat 600 mg	Placebo	Sebetralstat 300 mg	Sebetralstat 600 mg	Placebo	Sebetralstat 300 mg	Sebetralstat 600 mg	Placebo
No. of subjects	86	151	138	86	151	138	86	151	138
All adverse events	5 (5.8)	14 (9.3)	13 (9.4)	0	0	3 (2.2)	5 (5.8)	14 (9.3)	16 (11.6)
Serious adverse events	0	0	0	0	0	0	0	0	0
Deaths	0	0	0	0	0	0	0	0	0
Adverse events leading to study discontinuation	0	0	0	0	0	0	0	0	0
Adverse drug reactions	2 (2.3)	5 (3.3)	5 (3.6)	0	0	1 (0.7)	2 (2.3)	5 (3.3)	6 (4.3)

Number of subjects with events (%)

a) Day 2/Day 3 or use of the study drug for a next HAE attack, whichever came first.

Table 42. Adverse events reported by ≥2 patients during any period (double-blind safety analysis population)

Time to onset	Within 2 days post-dose ^{a)}			>2 days and ≤3 days post-dose ^{a)}			Within 3 days post-dose ^{a)}		
Period	Sebetralstat 300 mg	Sebetralstat 600 mg	Placebo	Sebetralstat 300 mg	Sebetralstat 600 mg	Placebo	Sebetralstat 300 mg	Sebetralstat 600 mg	Placebo
No. of subjects	86	151	138	86	151	138	86	151	138
Vomiting	1 (1.2)	2 (1.3)	2 (1.4)	0	0	0	1 (1.2)	2 (1.3)	2 (1.4)
Headache	0	6 (4.0)	2 (1.4)	0	0	1 (0.7)	0	6 (4.0)	3 (2.2)
Nausea	0	3 (2.0)	1 (0.7)	0	0	0	0	3 (2.0)	1 (0.7)
Nasopharyngitis	0	0	2 (1.4)	0	0	0	0	0	2 (1.4)

Number of subjects with events (%)

a) Day 2/Day 3 or use of the study drug for a next HAE attack, whichever came first.

Table 43. Summary of safety of sebetralstat (Study KVD900-302)

Population	Sebetralstat 600 mg					
	Overall population			Japanese subgroup		
Time to onset	Within 2 days post-dose ^{a)}	>2 days and ≤3 days post-dose ^{a)}	Within 3 days post-dose ^{a)}	Within 2 days post-dose ^{a)}	>2 days and ≤3 days post-dose ^{a)}	Within 3 days post-dose ^{a)}
No. of subjects	134	134	134	12	12	12
All adverse events	39 (29.1)	12 (9.0)	41 (30.6)	1 (8.3)	0	1 (8.3)
Serious adverse events	3 (2.2)	0	3 (2.2)	0	0	0
Deaths	0	0	0	0	0	0
Adverse events leading to study discontinuation	3 (2.2)	0	3 (2.2)	0	0	0
Adverse drug reactions	11 (8.2)	0	11 (8.2)	0	0	0

Number of subjects with events (%)

a) Day 2/Day 3 or use of the study drug for a next HAE attack, whichever came first.

Table 44. Adverse events reported by ≥2 patients (Study KVD900-302)

Population	Sebetralstat 600 mg					
	Overall population			Japanese subgroup		
Time to onset	Within 2 days post-dose ^{a)}	>2 days and ≤3 days post-dose ^{a)}	Within 3 days post-dose ^{a)}	Within 2 days post-dose ^{a)}	>2 days and ≤3 days post-dose ^{a)}	Within 3 days post-dose ^{a)}
No. of subjects	134	134	134	12	12	12
Headache	11 (8.2)	0	11 (8.2)	0	0	0
Nasopharyngitis	6 (4.5)	2 (1.5)	8 (6.0)	1 (8.3)	0	1 (8.3)
Vomiting	4 (3.0)	1 (0.7)	4 (3.0)	0	0	0
Upper respiratory tract infection	4 (3.0)	0	4 (3.0)	0	0	0
Nausea	3 (2.2)	0	3 (2.2)	0	0	0
Abdominal pain	2 (1.5)	0	2 (1.5)	0	0	0
Gastroenteritis	2 (1.5)	0	2 (1.5)	0	0	0
Urticaria	2 (1.5)	0	2 (1.5)	0	0	0
Bronchitis	2 (1.5)	0	2 (1.5)	0	0	0
COVID-19	1 (0.7)	1 (0.7)	2 (1.5)	0	0	0
Influenza	1 (0.7)	1 (0.7)	2 (1.5)	0	0	0

Number of subjects with events (%)

a) Day 2/Day 3 or use of the study drug for a next HAE attack, whichever came first.

For safety in children aged 12 years and older, adverse events occurred in 1 of 11 pediatric patients (9.1%) during the sebetralstat 600 mg treatment period (vomiting) and 1 of 9 pediatric patients (11.1%) during the placebo treatment period (influenza) in the double-blind safety analysis population. No deaths, serious adverse events, adverse events leading to study discontinuation, or adverse drug reactions occurred.

In Study KVD900-302, adverse events occurred in 7 of 23 pediatric patients (30.4%) (nasopharyngitis, headache, and osteochondrosis; bronchitis; gastroenteritis; hereditary angioedema and lymphadenopathy; urticaria; tremor and upper respiratory tract infection; and rhinitis allergic and cellulitis in 1 patient each). An adverse drug reaction occurred in 1 of 23 pediatric patients (4.3%) (tremor). A serious adverse event occurred in 1 of 23 pediatric patients (4.3%) (hereditary angioedema), but a causal relationship to the study drug was ruled out for the event. Neither deaths nor adverse events leading to study discontinuation occurred.

Based on the above, the applicant considers that no particular safety concerns have been identified in pediatric patients aged 12 years and older.

Safety profiles by number of doses of sebetralstat were investigated using results from Studies KVD900-201, KVD900-301, and KVD900-302 (Table 45). Incidences of adverse events by number of doses did not show any clear trend.

Table 45. Summary of safety of sebetralstat (Studies KVD900-201, KVD900-301, and KVD900-302)

Number of doses of sebetralstat for attacks ^{a)}	1	2	3	4	5	6-10	≥10	Overall
No. of subjects	249	213	121	105	100	94	57	249
All adverse events	47 (18.9) 0.297	45 (21.1) 0.300	17 (14.0) 0.215	18 (17.1) 0.286	8 (8.0) 0.210	39 (41.5) 0.199	28 (49.1) 0.142	113 (45.4) 0.203
Adverse drug reactions	12 (4.8) 0.060	5 (2.3) 0.028	1 (0.8) 0.017	2 (1.9) 0.019	3 (3.0) 0.040	5 (5.3) 0.021	4 (7.0) 0.013	22 (8.8) 0.023
Serious adverse events	4 (1.6) 0.016	1 (0.5) 0.005	1 (0.8) 0.008	1 (1.0) 0.010	0	2 (2.1) 0.013	4 (7.0) 0.009	13 (5.2) 0.125
Adverse events leading to study discontinuation	1 (0.4) 0.004	0	1 (0.8) 0.017	0	0	2 (2.1) 0.005	1 (1.8) 0.001	5 (2.0) 0.003

Top, Number of subjects with events (%); Bottom, Mean number of events per attack treated with the study drug

a) The following data were used to obtain results by number of doses: Data after administration of sebetralstat 300 or 600 mg in Studies KVD900-201, KVD900-301, and KVD900-302 for 1-dose results; data after administration of sebetralstat 300 or 600 mg in Studies KVD900-301 and KVD900-302 for 2-dose results; and data after administration of sebetralstat 600 mg in Study KVD900-302 for ≥3-dose results.

In view of incidences of adverse events in the clinical studies of sebetralstat, PMDA performed a review with the focus on the following events.

7.R.3.2 Headache

The applicant's explanation about occurrence of headache after administration of sebetralstat:

In the double-blind safety analysis population and Study KVD900-302, the event most commonly occurring within 3 days post-dose was headache, and the incidence of headache is as shown in Tables 46 and 47. The incidence during the sebetralstat 600 mg treatment period tended to be higher than that during the placebo treatment period (Table 46), suggesting dose-dependence. However, all the events were mild or moderate and did not lead to study discontinuation. A serious event occurred in 1 patient 15 days after the last dose of sebetralstat 600 mg, but a causal relationship to the study drug was ruled out for the event.⁴⁸⁾ In the Japanese subgroup, none experienced headache.

The incidence of headache by number of doses of sebetralstat was analyzed but no clear trend was observed, suggesting that the incidence of headache is unlikely to increase with long-term use of sebetralstat.

Table 46. Incidence of headache (double-blind safety analysis population, overall population)

Time to onset	Within 2 days post-dose ^{a)}			>2 days and ≤3 days post-dose ^{a)}			Within 3 days post-dose ^{a)}		
	Sebetralstat 300 mg	Sebetralstat 600 mg	Placebo	Sebetralstat 300 mg	Sebetralstat 600 mg	Placebo	Sebetralstat 300 mg	Sebetralstat 600 mg	Placebo
No. of subjects	86	151	138	86	151	138	86	151	138
Adverse events	0	6 (4.0)	2 (1.4)	0	0	1 (0.7)	0	6 (4.0)	3 (2.2)
Adverse drug reactions	0	2 (1.3)	2 (1.4)	0	0	0	0	2 (1.3)	2 (1.4)
Serious adverse events	0	0	0	0	0	0	0	0	0

Number of subjects with events (%)

a) Day 2/Day 3 or use of the study drug for a next HAE attack, whichever came first.

⁴⁸⁾ In this patient, hyperthermia, vomiting, and intracranial mass occurred in addition to headache, but a causal relationship to the study drug was ruled out for all events by the investigator (or sub-investigator).

Table 47. Incidence of headache (Study KVD900-302, overall population)

Time to onset	Within 2 days post-dose ^{a)}	>2 days and ≤3 days post-dose ^{a)}	Within 3 days post-dose ^{a)}
No. of subjects	134	134	134
Adverse events	11 (8.2)	0	11 (8.2)
Adverse drug reactions	5 (3.7)	0	5 (3.7)
Serious adverse events	0	0	0

Number of subjects with events (%)

a) Day 2/Day 3 or use of the study drug for a next HAE attack, whichever came first.

PMDA's view:

Because the incidence during the sebetralstat treatment period was higher than that during the placebo treatment period, and dose-dependence was suggested, the applicant is required to include precautionary advice about the occurrence of this event in the "Other Adverse Reactions" section in the package insert.

7.R.3.3 Gastrointestinal symptoms

The applicant's explanation about occurrence of gastrointestinal symptoms⁴⁹⁾ after administration of sebetralstat:

Tables 48 and 49 show the incidence of gastrointestinal symptoms within 3 days post-dose in the double-blind safety analysis population and Study KVD900-302. In the double-blind safety analysis population, the incidences of dyspepsia and nausea tended to be higher during the sebetralstat treatment period than during the placebo treatment period, but no clear dose-dependence was suggested. In the double-blind safety analysis population and Study KVD900-302, no gastrointestinal symptoms occurred in the Japanese subgroup.

Gastrointestinal symptoms observed in the double-blind safety analysis population and Study KVD900-302 were all mild or moderate in severity. Adverse events leading to study discontinuation observed were nausea in 2 patients and vomiting in 1 patient in Study KVD900-302, and these events were assessed as causally related to the study drug. No serious adverse events occurred.

Gastrointestinal symptoms are considered likely to be events associated with gastrointestinal mucosal disorder caused by an HAE attack but not sebetralstat for the following reasons: (1) Abdominal HAE attacks are known to be accompanied by gastrointestinal symptoms such as abdominal pain, vomiting, and diarrhoea (*Am J Gastroenterol.* 2006;101:619-27, *BMC Gastroenterol.* 2014;14:71); and (2) many of the gastrointestinal symptoms were reported by patients experiencing an abdominal HAE attack.

⁴⁹⁾ Events coded to "Gastrointestinal signs and symptoms" (High level group terms [HLGT]) were defined as gastrointestinal symptoms.

**Table 48. Incidence of adverse events related to gastrointestinal symptoms
(double-blind safety analysis population, overall population)**

Time to onset	Within 2 days post-dose ^{a)}			>2 days and ≤3 days post-dose ^{a)}			Within 3 days post-dose ^{a)}		
Treatment period	Sebetralstat 300 mg	Sebetralstat 600 mg	Placebo	Sebetralstat 300 mg	Sebetralstat 600 mg	Placebo	Sebetralstat 300 mg	Sebetralstat 600 mg	Placebo
No. of subjects	86	151	138	86	151	138	86	151	138
Adverse events	2 (2.3)	5 (3.3)	5 (3.6)	0	0	0	2 (2.3)	5 (3.3)	5 (3.6)
Adverse drug reactions	1 (1.2)	2 (1.3)	2 (1.4)	0	0	0	1 (1.2)	2 (1.3)	2 (1.4)
Serious adverse events	0	0	0	0	0	0	0	0	0
Individual adverse events									
Vomiting	1 (1.2)	2 (1.3)	2 (1.4)	0	0	0	1 (1.2)	2 (1.3)	2 (1.4)
Dyspepsia	1 (1.2)	0	0	0	0	0	1 (1.2)	0	0
Nausea	0	3 (2.0)	1 (0.7)	0	0	0	0	3 (2.0)	1 (0.7)
Abdominal pain upper	0	1 (0.7)	1 (0.7)	0	0	0	0	1 (0.7)	1 (0.7)
Abdominal pain	0	0	1 (0.7)	0	0	0	0	0	1 (0.7)
Anal incontinence	0	0	1 (0.7)	0	0	0	0	0	1 (0.7)

Number of subjects with events (%)

a) Day 2/Day 3 or use of the study drug for a next HAE attack, whichever came first.

**Table 49. Incidence of adverse events related to gastrointestinal symptoms
(Study KVD900-302, overall population)**

Time to onset	Within 2 days post-dose ^{a)}	>2 days and ≤3 days post-dose ^{a)}	Within 3 days post-dose ^{a)}
No. of subjects	134	134	134
Adverse events	8 (6.0)	1 (0.7)	8 (6.0)
Adverse drug reactions	3 (2.2)	0	3 (2.2)
Serious adverse events	0	0	0
Individual adverse events			
Vomiting	4 (3.0)	1 (0.7)	4 (3.0)
Nausea	3 (2.2)	0	3 (2.2)
Abdominal pain	2 (1.5)	0	2 (1.5)

Number of subjects with events (%)

a) Day 2/Day 3 or use of the study drug for a next HAE attack, whichever came first.

PMDA's view:

For gastrointestinal symptoms occurring after administration of sebetralstat, the possibility of symptoms associated with an HAE attack cannot be ruled out, but a drug in the same class has shown a tendency toward a higher incidence of gastrointestinal symptoms (Review Report on “Orladeyo Capsules 150 mg” dated October 21, 2020). In view of the above, the applicant is required to include precautionary advice about the occurrence of these events in the “Other Adverse Reactions” section in the package insert.

7.R.3.4 Hepatic dysfunction

The applicant's explanation about occurrence of hepatic dysfunction⁵⁰⁾ after administration of sebetralstat:

In the double-blind safety analysis population and Study KVD900-302, no adverse events related to hepatic dysfunction occurred within 3 days post-dose. Neither serious adverse events nor adverse drug reactions occurred more than 3 days post-dose. As an adverse event leading to study discontinuation, moderate alanine aminotransferase (ALT) increased was reported in 1 patient in Study KVD900-302, but this event occurred after occurrence of meningitis viral (a serious adverse event, for which a causal relationship to the study drug was ruled out), and thus a causal relationship to the study drug was ruled out. Based on the above, the applicant considers that a risk of hepatic dysfunction associated with sebetralstat has not been demonstrated.

⁵⁰⁾ Events coded to “Hepatic disorders” (narrow and broad, Standardised MedDRA queries [SMQ]) were defined as hepatic dysfunction.

PMDA's view:

In non-clinical repeated-dose studies of sebetralstat, hepatotoxicity was observed [see Section 5.R.1], but in clinical studies where sebetralstat was used for on-demand treatment of HAE attacks, a risk of hepatic dysfunction attributable to sebetralstat has not been clearly suggested. The applicant is required to continue paying close attention to occurrence of hepatic dysfunction in post-marketing settings and provide obtained information to healthcare professionals as appropriate.

PMDA's view on safety of sebetralstat based on the review in Sections 7.R.3.1 to 7.R.3.4:

The submitted clinical study results on use of sebetralstat do not suggest any critical safety concerns or events unique to Japanese patients with HAE, and the adverse events observed can be managed by appropriate safety measures such as inclusion of precautionary advice in the package insert. The applicant, however, is required to provide information to healthcare professionals appropriately if new information becomes available in post-marketing settings.

The above conclusion of PMDA will be discussed at the Expert Discussion.

7.R.4 Clinical positioning and indication

The applicant's explanation about clinical positioning of sebetralstat in HAE treatment:

Based on the results on efficacy and safety of sebetralstat obtained in Study KVD900-301, etc. and the treatment system in Japan [see Section 1], sebetralstat offers a new treatment option that can be orally used for the treatment of HAE attacks irrespective of location and severity of the HAE attack and status of HAE prophylactic treatment. In view of information about other drugs for the treatment of HAE attacks and prophylactic treatment, sebetralstat may be used irrespective of disease type of HAE, although sebetralstat has not been used in patients with HAE type 3.

PMDA's view:

In view of the efficacy [see Section 7.R.2] and safety [see Section 7.R.3] of sebetralstat based on the submitted clinical study results, sebetralstat can offer a treatment option for HAE attacks as with the drugs approved for the treatment of HAE attacks. Importantly, sebetralstat must be used by physicians with adequate knowledge and experience in diagnosis and treatment of HAE, and patients and their guardians must be informed of symptoms requiring use of sebetralstat and actions on attacks inadequately responding to sebetralstat.

Genetic characteristics and pathophysiology of HAE type 3 are currently being elucidated. In addition, even in patients with HAE type 3 in whom causative genes are identified, the detailed mechanism of disease development remains unclear. The appropriateness of the use of sebetralstat in patients with HAE type 3, therefore, must be carefully considered in view of the mechanism of action of sebetralstat and the latest findings on HAE type 3, and patients treated with sebetralstat, if any, should be closely monitored. The applicant is required to continue collecting information helpful in determining the appropriateness of the use of sebetralstat and provide information to healthcare professionals as appropriate when new findings become available.

Based on the above review, PMDA has concluded that the indication of sebetralstat may be “Acute attacks of hereditary angioedema” as proposed.

The above conclusion of PMDA will be discussed at the Expert Discussion.

7.R.5 Dosage and administration

The applicant’s explanation about the dosage regimen of sebetralstat:

In Study KVD900-301, the time to beginning of symptom relief was shorter during both sebetralstat 300 and 600 mg treatment periods than during the placebo treatment period with a statistical significance. Because no clear differences are observed in efficacy or safety profile between sebetralstat 300 and 600 mg [see Sections 7.R.2 and 7.R.3], 300 mg of sebetralstat per dose for a single attack was considered appropriate from the viewpoint of minimizing the exposure. In Study KVD900-301, a second dose for a single HAE attack was administered in 34 of 87 patients (39.1%) during the sebetralstat 300 mg treatment period, 37 of 93 patients (39.8%) during the sebetralstat 600 mg treatment period, and 47 of 84 patients (56.0%) during the placebo treatment period. Table 38 shows results on the primary efficacy endpoint and Table 50 shows the incidence of adverse events by number of doses. Irrespective of the number of doses, the time to beginning of symptom relief was shorter during the sebetralstat treatment period than during the placebo treatment period, and no safety concerns were raised.

Table 50. Incidence of adverse events (Study KVD900-301)

Number of doses	1			2		
Period	Sebetralstat 300 mg	Sebetralstat 600 mg	Placebo	Sebetralstat 300 mg	Sebetralstat 600 mg	Placebo
No. of subjects	58	60	44	28	34	39
Adverse events	10 (17.2)	7 (11.7)	5 (11.4)	7 (25.0)	7 (20.6)	12 (30.8)
Adverse drug reactions	2 (3.4)	1 (1.7)	3 (6.8)	0	2 (5.9)	1 (2.6)
Serious adverse events	0	2 (3.3)	0	0	0	0
Adverse events leading to study discontinuation	0	0	0	0	0	0

Number of subjects with events (%)

The number of subjects for each period was counted based on the study drug actually administered. Without the record on time of the second dose of the study drug, the patient was deemed to have received only 1 dose.

In Studies KVD900-301 and KVD900-302, patients were allowed to take a second dose at the same dose level as the first dose at least 3 hours after the first dose, but the dosing interval was specified to confirm the efficacy and safety of sebetralstat administered as a single dose. Based on the following findings, the applicant considers that patients should be allowed to take a second dose at least 2 hours after the first dose when they have an inadequate response to the single dose or if symptoms recur and they judge it necessary: (1) HAE attacks differ in location, severity, and extent of progression from attack to attack; and (2) in Study KVD900-301, approximately half of the patients (55.2%) achieved the primary endpoint within 2 hours after administration of sebetralstat (Figure 5).

In view of the above, the applicant considers it appropriate to amend the proposed dosage and administration of sebetralstat as follows: “The usual dosage for adults and children aged 12 years and older is one dose of 300 mg of sebetralstat administered orally at the earliest recognition of an attack. A second dose may be administered as appropriate if response is inadequate or if symptoms recur. However, the second dose should be administered at least 2 hours after the first dose, and no more than 2 doses should be administered in a 24-hour period.” (Underline denotes additions.)

PMDA's view:

A dose of 300 mg of sebetralstat for an HAE attack is acceptable. In addition, although no clinical study results are available in which a second dose was administered 2 hours after the first dose, a second dose may be administered with a dosing interval of at least 2 hours, based on the applicant's explanation and the fact that no particular safety concerns were identified in patients treated with sebetralstat 600 mg, which is expected to result in exposure exceeding that after administration of 2 doses of sebetralstat 300 mg at an interval of 2 hours.

Based on the above, the dosage regimen of sebetralstat for HAE attacks should be specified as presented below by modifying the above applicant's draft. To ensure that patients can judge the necessity of a second dose appropriately on their own, healthcare professionals should be informed of situations requiring a second dose.

The usual dosage for adults and children aged 12 years and older is one dose of 300 mg of sebetralstat administered orally ~~at the earliest recognition of an attack~~. A second dose of 300 mg may be administered at least 2 hours after the first dose ~~as appropriate~~ if response is inadequate or if symptoms recur. However, no more than 2 doses should be administered in a 24-hour period.

(The underlined words are added to and the strikethrough words are deleted from the proposed text.)

The above conclusion of PMDA will be discussed at the Expert Discussion.

7.R.6 Post-marketing investigations

The applicant plans a use-results survey to collect information on safety and efficacy of sebetralstat in patients with HAE including HAE 3 in post-marketing clinical use.

PMDA's view:

As reviewed in Section 7.R.3, the submitted clinical study results show that sebetralstat has acceptable safety. However, QT interval prolongation was observed in Study KVD900-109 [see Sections 6.2.4 and 6.R.4], although the dose leading to such finding (3,000 mg) exceeded the therapeutic dose. In view of this finding, the applicant should conduct post-marketing surveillance to collect information about the safety of sebetralstat in clinical use, including adverse events potentially related to QT interval prolongation and provide the obtained information to healthcare professionals promptly.

In addition, the applicant is required to take the following measures to enable healthcare professionals to determine the appropriateness of sebetralstat use in patients with HAE type 3 and encourage proper use of sebetralstat: (1) To provide information, including the latest findings on the pathophysiology of HAE type 3 appropriately; (2) to continue collecting information useful for proper use of sebetralstat in post-marketing settings; and (3) to provide information to healthcare professionals when new findings become available as appropriate.

The above conclusion of PMDA will be discussed at the Expert Discussion.

8. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

8.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The new drug application data were subjected to a document-based inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

8.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The new drug application data (CTD 5.3.5.1-7 and CTD 5.3.5.2-2) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

9. Overall Evaluation during Preparation of the Review Report (1)

On the basis of the data submitted, PMDA has concluded that sebetralstat has efficacy in the treatment of acute attacks of HAE, and that sebetralstat has acceptable safety in view of its benefits. The drug substance is classified as a powerful drug. The drug product is not classified as a poisonous drug or a powerful drug. Sebetralstat is clinically meaningful because it offers a new treatment option for acute attacks of HAE.

PMDA has concluded that sebetralstat may be approved if sebetralstat is not considered to have any particular problems based on comments from the Expert Discussion.

10. Others

Efficacy endpoints in clinical studies are defined as follows:

Item	Definition
PGI-C	A 7-point scale used by patients themselves to assess changes in overall symptoms of HAE attacks ("Much better," "Better," "A little better," "No change," "A little worse," "Worse," and "Much worse")
PGI-S	A 5-point scale used by patients to assess the severity of overall symptoms of HAE attacks ("None," "Mild," "Moderate," "Severe," and "Very severe")
Beginning of symptom relief	When "A little better" or better on the PGI-C is documented at 2 consecutive timepoints. Timepoints of assessment were as follows: Study KVD900-301: Assessment was performed at 0, 0.5, 1, 1.5, 2.0, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 16, 18, 20, 22, 24, 36, and 48 hours after the first dose of the study drug. Patients were instructed to perform assessments at all timepoints for at least 4 hours after the first dose of the study drug without fail and then at all timepoints except during sleep. The prescribed assessments were completed before a second dose of the study drug or conventional treatment of HAE attacks where applicable. Study KVD900-302: Assessment was performed at 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 18, and 24 hours after the first dose of sebetralstat. The prescribed assessments were completed before a second dose of sebetralstat or conventional treatment of HAE attacks where applicable.
Decrease in severity	A decrease in severity by ≥ 1 level on the PGI-S is documented.
Complete HAE attack resolution	"None" is reported on the PGI-S.

In Study KVD900-301, time-to-event data for each period in all patients were transformed into Gehan scores (*Biometrika*. 1965;52:203-23) according to the following definitions, and the Gehan scores were used in statistical analyses.

- For uncensored observations, the Gehan score for the i -th observation is the number of uncensored observations with values strictly smaller than that of the i -th observation, minus the number of uncensored observations with values strictly greater than that of the i -th observation, minus the number of right-censored observations with values equal to or greater than that of the i -th observation in the entire data set.
- For right-censored observations, the Gehan score for the i -th observation is the number of uncensored observations with values smaller than or equal to that of the i -th observation in the entire data set.

Review Report (2)

November 11, 2025

Product Submitted for Approval

Brand Name	Ekterly Tablets 300 mg
Non-proprietary Name	Sebetralstat
Applicant	KalVista Pharmaceuticals Ltd.
Date of Application	January 15, 2025

List of Abbreviations

See Appendix.

1. Content of the Review

Comments made during the Expert Discussion and the subsequent review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below. The expert advisors present during the Expert Discussion were nominated based on their declarations, etc. concerning the product submitted for marketing approval, in accordance with the provisions of the Rules for Convening Expert Discussions, etc. by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

1.1 Efficacy, safety, clinical positioning and indication, dosage and administration, post-marketing investigations, and risk management plan (draft)

At the Expert Discussion, the expert advisors supported the conclusions of PMDA on efficacy, safety, clinical positioning and indication, dosage and administration, and post-marketing investigations of sebetralstat presented in the Review Report (1). They also commented that the applicant must continue collecting information about the efficacy and safety of sebetralstat in patients with HAE type 3 and provide the information to healthcare professionals.

In view of the discussions presented in Section “7.R.6 Post-marketing investigations” in the Review Report (1) and comments from the expert advisors at the Expert Discussion, PMDA instructed the applicant to take measures on the following points. The applicant responded that they will take appropriate measures.

- The applicant should conduct post-marketing surveillance to collect information about the safety of sebetralstat in clinical use, including adverse events potentially related to QT interval prolongation and provide the obtained information to healthcare professionals promptly.
- The applicant should take the following measures to enable healthcare professionals to determine the appropriateness of sebetralstat use in patients with HAE type 3: (1) To provide information, including the latest findings on pathophysiology of HAE type 3 appropriately; (2) to continue collecting information useful for proper use of sebetralstat in post-marketing settings; and (3) to provide information to healthcare professionals when new findings become available as appropriate.

PMDA has concluded that the risk management plan (draft) for sebetralstat should include the safety specification presented in Table 51, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Table 52. PMDA requested the applicant to present the outline of general use-results survey (draft).

Table 51. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
None	• QT interval prolongation	None
Efficacy specification		
None		

Table 52. Summary of additional pharmacovigilance activities, efficacy survey and studies, and additional risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Efficacy survey and studies	Additional risk minimization activities
• Early post-marketing phase vigilance • General use-results survey	None	• Disseminate data gathered during early post-marketing phase vigilance

The applicant explained that they will implement a general use-results survey in patients with HAE as presented in Table 53 to evaluate the safety and efficacy of sebetralstat in clinical use.

Table 53. Outline of general use-results survey (draft)

Objective	To evaluate the safety and efficacy of sebetralstat in clinical use
Survey method	Central registry system
Population	Patients with HAE
Observation period	Up to 1 year after the first prescription of sebetralstat
Planned sample size	80 (to be included in a safety analysis)
Main survey items	• Safety specification: QT interval prolongation • Patient characteristics (sex, date of birth or age, disease type of HAE, medical history, comorbidity, etc.) • Status of HAE attacks • Status of use of sebetralstat • Concomitant drug • Concomitant therapy • Adverse events • Efficacy

PMDA accepted the presented outline (draft) and considers that the applicant should provide the collected information to healthcare professionals in an appropriate and prompt manner.

2. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved after modifying the proposed dosage and administration and for the indication shown below, with the following condition. The product is designated as an orphan drug, and the re-examination period is 10 years.

Indication

Acute attacks of hereditary angioedema

(No change)

Dosage and Administration

The usual dosage for adults and children aged 12 years and older is one dose of 300 mg of sebetralstat administered orally ~~at the earliest recognition of an attack~~. A second dose of 300 mg may be administered at least 2 hours after the first dose~~as appropriate~~ if response is inadequate or if symptoms recur. However, no more than 2 doses should be administered in a 24-hour period.

(The underlined words are added to and the strikethrough words are deleted from the proposed text.)

Approval Condition

The applicant is required to develop and appropriately implement a risk management plan.

List of Abbreviations

ACE	Angiotensin-converting enzyme
ALAG2	Lag time of zero-order absorption
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the concentration versus time curve
AUC _{0-24h}	AUC from the time of dosing to 24 hours
AUC _{inf}	AUC extrapolated to infinity
AUC _{last}	AUC from 0 to last measurable concentration
BCRP	Breast cancer resistance protein
Berotrastat	Berotrastat hydrochloride
BSEP	Bile salt export pump
C1-INH	Complement 1 esterase inhibitor
Caco-2	Human colorectal adenocarcinoma
cHK	Cleaved high molecular weight kininogen
CI	Confidence interval
CL	Clearance
CL/F	Apparent clearance
C _{max}	Maximum concentration
CQA	Critical quality attribute
CV	Coefficient of variation
CYP	Cytochrome P450
D2	Duration of zero-order absorption
DMSO	Dimethyl sulfoxide
DSC	Differential scanning calorimetry
Ekterly	Ekterly Tablets 300 mg
F	Bioavailability
F1	Fraction of first order absorption
FAS	Full analysis set
FVIIa	Activated blood coagulation factor VII
FXa	Activated blood coagulation factor X
FXIa	Activated blood coagulation factor XI
FXII	Blood coagulation factor XII
FXIIa	Activated blood coagulation factor XII
GC	Gas chromatography
GLDH	Glutamate dehydrogenase
γ-GT	Gamma glutamyl transferase
HAE	Hereditary angioedema
HAE-C1-INH	HAE with C1-INH deficiency
HAEnCI	HAE with normal C1-INH
HEK293 cells	Human embryonic kidney 293 cell
hERG	Human ether-à-go-go-related gene
HK	High molecular weight kininogen
HLGT	High level group terms
HPLC	High performance liquid chromatography
HPMC	Hydroxypropyl methylcellulose
IC ₅₀	Half-maximal inhibitory concentration
Icatibant	Icatibant acetate
ICP-MS	Inductively coupled plasma-mass spectrometry
IR	Infrared absorption spectroscopy

Japanese guideline	Guideline for hereditary angioedema (HAE) by the Japanese Association for Complement Research: The 2023 revision and update (<i>Journal of Japanese Association for Complement Research</i> . 2023;60:103-31)
K _a	First-order absorption rate constant
K _i	Inhibitory constant
LC-MS/MS	Liquid chromatography with tandem mass spectrometry
LH	Luteinizing hormone
MATE	Multidrug and toxin extrusion protein
MDCK cells	Madin-Darby canine kidney cell
MedDRA	Medical Dictionary for Regulatory Activities
mRNA	Messenger ribonucleic acid
NE	Not evaluable
NMR	Nuclear magnetic resonance spectroscopy
NZW	New Zealand white
OAT	Organic anion transporter
OATP	Organic anion transporting polypeptide
OCT	Organic cation transporter
P _{app A→B}	Apical-to-basolateral apparent permeability coefficient
P _{app B→A}	Basolateral-to-apical apparent permeability coefficient
PGI-C	Patient global impression of change
PGI-S	Patient global impression of severity
P-gp	P-glycoprotein
PIF	Photo irritation factor
PK _a	Plasma kallikrein
PMDA	Pharmaceuticals and Medical Devices Agency
Q/F	Apparent intercompartmental clearance
QTcF	QT interval corrected using Fridericia's method
RH	Relative humidity
ROS	Reactive oxygen species
SD	Sprague Dawley
Sebetralstat	Sebetralstat
SMQ	Standardised MedDRA queries
t _{1/2}	Elimination half-life
t _{max}	Time to maximum concentration
TPGS	D-α-tocopherol polyethylene glycol 1,000 succinate
UGT	Uridine diphosphate-glucuronosyltransferase
UV	Ultraviolet
UV/VIS	Ultraviolet-visible spectroscopy
V _{2/F}	Apparent central volume of distribution
V _{3/F}	Apparent peripheral volume of distribution
V _{ss}	Steady state volume of distribution
V _{z/F}	Apparent volume of distribution of the drug
XRPD	X-ray powder diffraction

* Non-proprietary names of biological products are described by omitting “(Genetical Recombination).”