Report on the Deliberation Results

June 6, 2025
Pharmaceutical Evaluation Division, Pharmaceutical Safety Bureau
Ministry of Health, Labour and Welfare

Brand Name	Airwin for Subcutaneous Injection 45 mg, Airwin for Subcutaneous Injection 60 mg
Non-proprietary Name	Sotatercept (Genetical Recombination) (JAN*)
Applicant	MSD K.K.
Date of Application	November 14, 2024

Results of Deliberation

In its meeting held on June 4, 2025, the First 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 classified as a biological product. The re-examination period is 10 years. The drug product and its drug substance are both classified as powerful drugs.

Approval Condition

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

**Japanese Accepted Name (modified INN)*

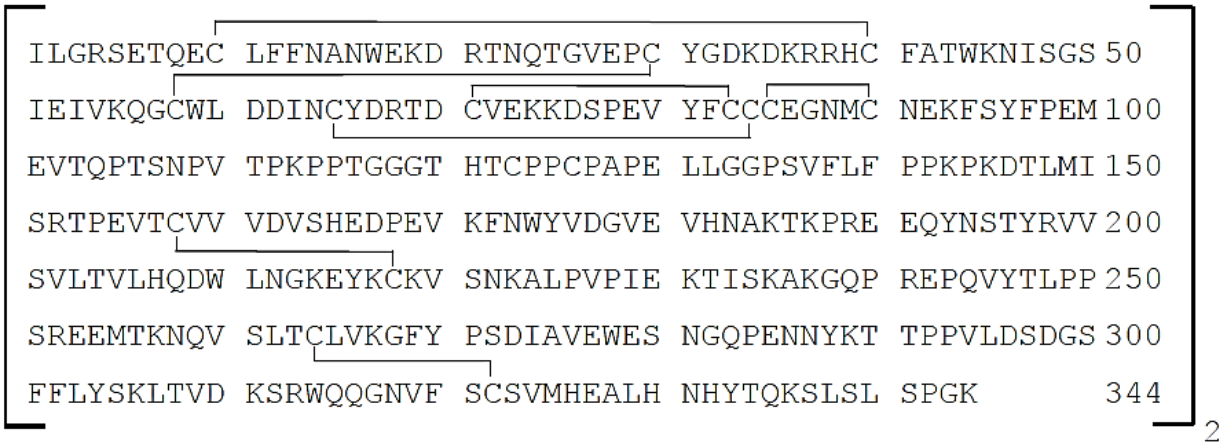
Review Report

May 22, 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	Airwin for Subcutaneous Injection 45 mg, Airwin for Subcutaneous Injection 60 mg
Non-proprietary Name	Sotatercept (Genetical Recombination)
Applicant	MSD K.K.
Date of Application	November 14, 2024
Dosage Form/Strength	Lyophilized injection in vials, each containing 45 or 60 mg of sotatercept (genetical recombination)
Application Classification	Prescription drug, (1) Drugs with a new active ingredient
Definition	Sotatercept is a recombinant fusion protein composed of an extracellular domain of human activin receptor type IIA at positions 1-115, linker at positions 116-119, and modified Fc domain of human IgG1 (A227V) at positions 120-334. Sotatercept is produced in CHO cells. Sotatercept is a glycoprotein (molecular weight: ca. 89,000) composed of 2 subunits consisting of 334 amino acid residues each.

Structure



Intrachain disulfide bond: Solid line in the figure

Partial processing: K344

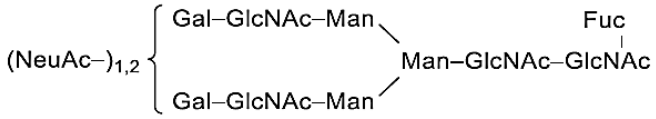
Glycosylation sites: N23, N46, N194

Putative glycosylation sites: T106, S107, T111, T116, T122

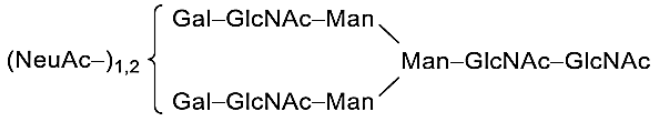
Intersubunit disulfide bonds: C123-C123, C126-C126

Putative structures of major carbohydrate chains

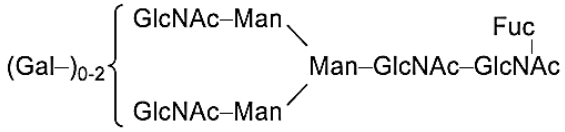
N23



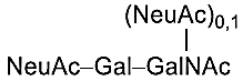
N46



N194



T106, S107, T111, T116, T122



NeuAc, N-acetylneuraminic acid; Gal, galactose; GlcNAc, N-acetylglucosamine; Man, mannose; Fuc, fucose

Molecular formula: $C_{3448}H_{5264}N_{920}O_{1058}S_{42}$ (protein portion, dimer)
Molecular weight: Approx. 89,000

Items Warranting Special Mention

Orphan drug (Orphan Drug Designation No. 599 of 2023 [*R5 yaku*]; PSB/PED Notification No. 0321-1 dated March 21, 2024, by the Pharmaceutical Evaluation Division, Pharmaceutical Safety Bureau, Ministry of Health, Labour and Welfare)

Reviewing Office Office of New Drug II

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has efficacy in the treatment of pulmonary arterial hypertension, 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 classified as a biological product. The drug product and its drug substance are both classified as powerful drugs.

The occurrence of polycythemia, thrombocytopenia, and hemorrhage should be further investigated.

Indication

Pulmonary arterial hypertension

Dosage and Administration

Usually, adult starting dose is 0.3 mg/kg of sotatercept (genetical recombination) followed by escalated doses of 0.7 mg/kg administered subcutaneously once every 3 weeks.

Approval Condition

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

Attachment

Review Report (1)

March 21, 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	Airwin for Subcutaneous Injection 45 mg, Airwin for Subcutaneous Injection 60 mg
Non-proprietary Name	Sotatercept (Genetical Recombination)
Applicant	MSD K.K.
Date of Application	November 14, 2024
Dosage Form/Strength	Lyophilized injection in vials, each containing 45 or 60 mg of sotatercept (genetical recombination).

Proposed Indication

Pulmonary arterial hypertension

Proposed Dosage and Administration

Usually, adult starting dose is 0.3 mg/kg of sotatercept followed by escalated doses of 0.7 mg/kg administered subcutaneously once every 3 weeks.

Table of Contents

List of Abbreviations

See Appendix.

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

Pulmonary arterial hypertension (PAH) is characterized by increased pulmonary vascular resistance (PVR) and elevated pulmonary arterial pressure, primarily owing to pulmonary vascular remodeling associated with excessive pulmonary vasoconstriction and abnormal proliferation of pulmonary arteriolar smooth muscle cells, eventually resulting in right heart failure.

Sotatercept (genetical recombination) (hereinafter referred to as sotatercept), discovered by Acceleron Pharma Inc. in the US (Acceleron), is a recombinant fusion protein composed of an extracellular domain of human activin receptor type IIA (ActRIIA) linked to fragment crystallizable (Fc) region of human immunoglobulin G (IgG)1. Sotatercept is considered to bind to ligands of ActRIIA involved in the proliferation of pulmonary vascular smooth muscle cells and thereby inhibits ActRIIA-mediated pro-proliferative signaling (mothers against decapentaplegic, a group of related intracellular proteins critical for transmitting to the nucleus signals from the TGF-β superfamily at the cell surface [Smad2/3 signaling]). This inhibition against Smad2/3 signaling is expected to suppress pulmonary vascular remodeling associated with abnormal proliferation of pulmonary arteriolar smooth muscle cells.

The clinical development of sotatercept was initiated in 20[redacted] by Acceleron. Sotatercept was first approved for the indication of PAH in the US in March 2024. As of February 2025, sotatercept has been approved in 41 countries and regions including European countries and the US.

In Japan, the applicant initiated clinical development of sotatercept in 20[redacted]. An application for drug marketing approval has recently been filed with the proposed indication of "pulmonary arterial hypertension" based on the results from Japanese and foreign phase III studies. Sotatercept was designated as an orphan drug with the intended indication of "pulmonary arterial hypertension" on March 2024 (Orphan Drug Designation No. 599 of 2023 [*R5 yaku*]; PSB/PED Notification No. 0321-1 dated March 21, 2024).

2. Quality and Outline of the Review Conducted by PMDA

2.1 Drug substance

2.1.1 Generation and control of cell substrate

A gene expression construct of sotatercept was generated using gene sequences that encode the extracellular domain of ActRIIA and the Fc region of modified human IgG1. Of the amino acid sequence of the Fc region, valine at position 108 is substituted for alanine. The concerned gene expression construct was transfected into Chinese hamster ovary (CHO) cells. The clone optimal for manufacture of sotatercept was used as the source material to establish the master cell bank (MCB) and working cell bank (WCB).

Characterization and purity tests were conducted on the MCB, WCB, and limit of *in vitro* cell age (LIVCA) in accordance with Partial revision of the "Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin" (ICH Q5A (R2) guideline), Quality of Biotechnological Products: Analysis of the Expression Construct in Cells Used for Production of r-DNA Derived Protein Products (ICH Q5B guideline), and "Derivation and Characterisation of Cell Substrates Used for Production of Biotechnological/Biological Products" (ICH Q5D guideline). Genetic stability

throughout the manufacturing period was demonstrated, and within the scope of test items performed, neither viral nor non-viral adventitious agents were detected, except endogenous retrovirus-like particles, which are generally found in rodent cell lines.

The MCB and WCB are stored in a vapor phase of liquid nitrogen. MCB [redacted], and WCB [redacted].

2.1.2 Manufacturing process

The manufacturing process for the drug substance consists of expansion culture of inoculum cells, seed culture, production culture, harvest, [redacted] chromatography/[redacted] virus inactivation, [redacted] chromatography, [redacted] chromatography, viral filtration, [redacted], final filtration/bulk filling, and testing/storage.

The critical steps are [redacted], [redacted]/[redacted], [redacted], [redacted] and [redacted].

The manufacturing process for the drug substance has undergone process validation at a commercial scale.

2.1.3 Safety evaluation of adventitious agents

No raw materials of biological origin except CHO cells, host cells, are used in the manufacturing process for the drug substance.

Purity tests were performed on the MCB, WCB, and LIVCA cells [see Section 2.1.1]. The pre-harvest unprocessed bulk obtained at the commercial scale was subjected to a mycoplasma test, a sterility test, an *in vitro* adventitious viral test, a [redacted] test, and transmission electron microscopy. Within the scope of test items performed, neither viral nor non-viral adventitious agents were detected. All the above tests on the pre-harvest unprocessed bulk, except the transmission electron microscopy, are specified as in-process control tests.

The purification process underwent viral clearance studies using model viruses and thereby was demonstrated to have a capacity to remove or inactivate viruses to a certain extent (Table 1).

Table 1. Viral clearance study results

Manufacturing process	Virus reduction factor (log_{10})			
	Xenotropic murine leukemia virus	Minute virus of mice	Reovirus type 3	Pseudorabies virus
[redacted] chromatography	[redacted]	[redacted]	[redacted]	[redacted]
[redacted] virus inactivation	[redacted]	[redacted]	[redacted]	[redacted]
[redacted] chromatography	[redacted]	[redacted][a]	[redacted]	[redacted]
[redacted] chromatography	[redacted][b]	[redacted][b]	[redacted][b]	[redacted][b]
Viral filtration	[redacted]	[redacted]	[redacted]	[redacted]
Overall virus reduction factor	≥19.30	≥6.63	≥12.87	≥17.53

a Not used in calculation of the overall virus reduction factor, because [redacted].

b The result in the [redacted] chromatography was not used in calculation of the overall virus reduction factor, because contributions of [redacted] and [redacted] chromatography processes to virus clearance were not considered relevant.

2.1.4 Manufacturing process development

For changes made to the manufacturing process during development of the drug substance, comparability of the pre- and post-change drug substances has been demonstrated in accordance with the Comparability of Biotechnological/Biological Products Subject to Changes in their Manufacturing Process (ICH Q5E guideline). The drug substance manufactured in the proposed process was used in manufacture of the formulation that was supplied to phase III studies.

2.1.5 Characterization

2.1.5.1 Structure and characterization

Table 2 shows characterization performed.

Table 2. Parameters for characterization

Primary/higher order structures	Amino acid sequence, posttranslational modification ([redacted], [redacted], [redacted], [redacted], [redacted]), disulfide bonds, free thiols, secondary structure, tertiary structure, quaternary structure, thermostability
Physicochemical properties	Molecular weight, extinction coefficient, size variants, charge variants
Carbohydrate structure	N-linked oligosaccharide profile, O-linked oligosaccharide profile, glycosylation sites, [redacted]
Biological properties	Binding affinity to TGF-β superfamily ligands (activin A, activin B, activin C, GDF3, GDF5, GDF7, GDF8, GDF11, BMP2, BMP4, BMP5, BMP6, BMP7, BMP9, BMP10, BMP15, and Inhibin A) [see Section 3.1.1.1]
	Binding activity to FcγRs (FcγRI, FcγRIIa, FcγRIIb/c, FcγRIIIa, and FcγRIIIb), binding activity to C1q, binding activity to FcRn
	Inhibitory activity against TGF-β superfamily ligands (activin A, activin B, GDF8, GDF11, BMP6, BMP9, BMP10) [see Section 3.1.1.2]
	ADCC activity, CDC activity

Main evaluation results on the biological properties are as follows:

- The inhibitory activity against transforming growth factor-β (TGF-β) superfamily ligands (activin A, activin B, growth and differentiation factor [GDF]8, GDF11, bone morphogenetic protein [BMP]6, BMP9, and BMP10) was measured in a reporter assay using cells transfected with the luciferase gene

in which the response element of Smad2/3 or Smad1/5/8 was integrated.[1)] Sotatercept was demonstrated to mainly inhibit Smad2/3 signaling induced by activin A, activin B, and GDF11.

- Antibody-dependent cell-mediated cytotoxicity (ADCC) activity was measured in a reporter assay in which effector cells were [redacted] cells expressing [redacted] and being engineered to express luciferase gene under regulation of [redacted], and target cells were [redacted] cells expressing ActRIIA. The results demonstrated absence of the ADCC activity.
- Complement-dependent cytotoxicity (CDC) activity was measured in a test system in which target cells were [redacted] expressing ActRIIA, and human complement was added. Sotatercept was demonstrated to have no CDC activity.

2.1.5.2 Product-related substances/Product-related impurities

Based on characterization results in Section 2.1.5.1, Related Substances A, B, C, D, E, F, and G were classified as product-related substances. High molecular weight (HMW) and low molecular weight (LMW) substances were classified as product-related impurities. The HMW and LMW substances are controlled by the specifications for the drug substance and drug product.

2.1.5.3 Process-related impurities

Host cell deoxyribonucleic acid (DNA), host cell protein, and Impurity A were classified as process-related impurities. Any of the process-related impurities is demonstrated to be adequately removed in the manufacturing process.

2.1.6 Control of drug substance

The proposed specifications for the drug substance include the content, description, identification (peptide mapping), purity ([redacted], imaged capillary isoelectric focusing [iCIEF], size exclusion chromatography [SEC], capillary electrophoresis with sodium dodecyl sulfate [CE-SDS] [non-reduced and reduced conditions], and [redacted]), pH, bioburden, bacterial endotoxins, relative potency, [redacted], and assay (ultraviolet-visible spectroscopy).

2.1.7 Stability of drug substance

Table 3 shows main stability studies of the drug substance.

Table 3. Main stability studies of the drug substance

	Number of batches[a]	Storage condition	Study period	Storage package
Long-term	3	-80 ± [redacted] °C	72 months	PETG container and HDPE cap
Accelerated	3	-20 ± [redacted] °C	6 months	
	3	5 ± [redacted] °C		
Stress	3	25 ± [redacted] °C/60 ± [redacted] %RH	6 months	
	3	40 ± [redacted] °C/75 ± [redacted] %RH		

a Drug substance manufactured in the proposed process

1) [redacted] cells transfected with the luciferase gene in which the response element of Smad2/3 was integrated were used for GDF8, GDF11, activin A, and activin B; [redacted] cells transfected with the luciferase gene in which the response element of Smad1/5/8 was integrated were used for BMP6, and [redacted] cells transfected with the luciferase gene in which the response element of Smad1/5/8 was integrated were used for BMP9 and BMP10.

Under the long-term storage and accelerated conditions, no clear changes were observed in quality attributes throughout the study period.

Under stress conditions, increased HMW and LMW [redacted], increased [redacted] in [redacted], and decreased [redacted] were observed. These changes were more marked at [redacted]°C ± [redacted]°C[redacted]% ± [redacted]% relative humidity (RH) than at [redacted]°C ± [redacted]°C[redacted]% ± [redacted]%RH.

Based on the above, a shelf life of [redacted] months has been proposed for the drug substance when stored in a polyethylene terephthalate glycol (PETG) container with a high-density polyethylene (HDPE) cap at −80°C ± [redacted]°C.

2.2 Drug product

2.2.1 Description and composition of drug product and formulation development

The drug product is a lyophilized injection containing 55 or 72.5 mg of sotatercept per vial (2 mL). The drug product contains citric acid hydrate, sodium citrate hydrate, polysorbate 80, and sucrose as excipients. The vial contains the drug product in excess of the labeled amount to ensure that 45 or 60 mg of sotatercept can be extracted from the solution prepared by reconstituting with 1.0 or 1.3 mL of water for injection (protein concentration in the reconstituted solution is 50 mg/mL).

2.2.2 Manufacturing process

The manufacturing process of the drug product consists of thawing the drug substance, preparing buffer solutions, formulation/bioburden-reduction filtration, sterile filtration, filling/partial stoppering, lyophilization, crimping, and labeling/packaging/testing/storage.

[redacted] and [redacted] have been defined as critical steps.

The manufacturing process for the drug product has undergone process validation at a commercial scale.

2.2.3 Manufacturing process development

After several changes in the manufacturing process during product development, including a change from [redacted] to the lyophilized formulation, comparability of the pre- and post-change drug products has been demonstrated in accordance with the ICH Q5E guideline. The formulation manufactured in the proposed process was used in phase III studies.

2.2.4 Control of drug product

The proposed specifications for the drug product include the strength, description, identification (peptide mapping), osmolality, pH, purity (appearance of solution, [redacted], iCIEF, SEC, CE-SDS [non-reduced and reduced conditions]), water content, bacterial endotoxins, uniformity of dosage units, foreign insoluble matter, insoluble particulate matter, sterility, relative potency [redacted], and assay (ultraviolet-visible spectroscopy). Osmolality was included during the course of the review.

2.2.5 Stability of drug product

Main stability studies of the drug product are shown in Table 4.

Table 4. Main stability studies of the drug product

	Strength	Number of batches[a]	Storage condition	Study period	Storage package
Long-term	45 mg	2	5 ± 3°C	24 months[b]	Glass vial and [redacted] bromobutyl rubber stopper
		1		36 months[b]	
	60 mg	2		36 months[b]	
		1		[redacted] months	
Accelerated	45 mg	3	25 ± 2°C/ 60 ± 5%RH	6 months	
	60 mg	3			
Stress	45 mg	3	40 ± 2°C/ 75 ± 5%RH	6 months	
	60 mg	3			
Photostability	60 mg	1	Overall illumination of approximately 1.2 million lx·hr, an integrated near ultraviolet energy of approximately 200 W·h/m^2		

a Drug product manufactured using the drug substance manufactured in the proposed process
b For all, the stability study is ongoing for up to [redacted] months.

Under the long-term storage and accelerated conditions, no clear changes were observed in quality attributes throughout the study period.

In the stress study, an increase in [redacted] was observed in [redacted].

The photostability study showed that the drug product is photolabile.

Based on the above stability data, shelf lives of 24 and 36 months have been proposed for the 45 mg and 60 mg drug products, respectively, when stored in a glass vial, the primary container, with a [redacted] bromobutyl rubber stopper, protected from light in a carton box at 2°C to 8°C.

2.3 Quality control strategy

Based on the following investigations, the control method of quality attributes of sotatercept was developed using control in the manufacturing process, characterization, comparability studies, and validation studies as well as release tests and stability studies for the drug substance and drug product in combination [for control of product-related impurities and process-related impurities, see Sections 2.1.5.2 and 2.1.5.3]).

- Identification of CQA

  Based on information and relevant findings obtained through the development of sotatercept, the following critical quality attributes (CQAs) were identified:

  Aggregation, fragmentation, [redacted], [redacted], [redacted], bacterial endotoxins, bioburden, sterility, adventitious agents, pH, protein concentration, [redacted], [redacted], appearance of lyophilizate, appearance of reconstituted solution (color, clarity), identify of the active ingredient, osmolality, foreign insoluble matter, insoluble particulate matter, [redacted], water content, [redacted], uniformity of dosage units, and potency

- Process characterization

  Risk assessment on the manufacturing process parameters and process characterization identified the CQAs and process parameters affecting the process performance and specified acceptable operating ranges for each manufacturing process parameter.

2.R Outline of the review conducted by PMDA

Based on the submitted data, PMDA 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

3.1 Primary pharmacodynamics

3.1.1 *In vitro* studies

3.1.1.1 Binding affinity to TGF-β superfamily ligands (CTD 4.2.1.1.3 [reference data])

Binding affinity[2)] of sotatercept and RAP-011[3)] to human and mouse TGF-β superfamily ligands was determined by a surface plasmon resonance (SPR) method. Table 5 shows the determined equilibrium constant (K_D) values for sotatercept and RAP-011.

Table 5. Binding affinity of sotatercept and RAP-011 to human and mouse TGF-β superfamily ligands

Ligand	Human		Mouse	
	K_D (pmol/L)		K_D (pmol/L)	
	Sotatercept	RAP-011	Sotatercept	RAP-011
Activin A	43	9.06		
Activin B	10.8	11.01	19.1	46.0
Activin C	48900[a]	Transient binding[a]	86100[a]	Transient binding[a]
GDF3	1190	835	12600[a]	Transient binding[a]
GDF5	29600[a]	Transient binding[a]	34400[a]	Transient binding[a]
GDF6	-[b]	-	65100[a]	Transient binding[a]
GDF7	23000[a]	Transient binding[a]	117000[a]	Transient binding[a]
GDF8	390	161		
GDF11	67.8	51.7		
GDF15	-[b]	-	-	-
BMP2	199000[a]	Transient binding[a]		
BMP3	-[b]	Transient binding[a]		
BMP4	31100[a]	Transient binding[a]	70700[a]	Transient binding[a]
BMP5	893	217	423	566
BMP6	1120	255	1490	181
BMP7	466	294	688	390
BMP8a	-[b]	-	-	-
BMP9	7480[a]	Transient binding[a]	77300[a]	67.2
BMP10	77.4	12.81	43.3	34.7
BMP15	230000[a]	Transient binding[a]	31600[a]	Transient binding[a]
TGF-β1	-[b]	-		
TGF-β2	-[b]	-		
TGF-β3	-[b]	-		
InhibinA	15200[a]	Transient binding[a]		
Nodal	-[b]	-		

n = 1; -, Not bound

a The complex formation and dissociation were too fast to calculate the correct K_D value. The K_D value of sotatercept was calculated using a steady-state affinity model.

b The binding affinity was determined at 25°C.

2) Binding affinity to each ligand was determined at 37°C for sotatercept and at 25°C for RAP-011.

3) Recombinant fusion protein composed of the same extracellular domain of ActRIIA, as that used in sotatercept, linked to the Fc region of mouse IgG2a.

3.1.1.2 Inhibitory effect against signaling via TGF-β superfamily ligands (CTD 4.2.1.1.4)

Inhibitory effect of sotatercept against activation of Smad2/3 and Smad1/5/8 signaling via various human TGF-β superfamily ligands was measured by a reporter assay using cells[1)] transfected with the luciferase gene in which the response element of Smad2/3 or Smad1/5/8 was integrated. Table 6 shows the determined half-maximal inhibitory concentration (IC_{50}) values.

Table 6. Inhibitory effect of sotatercept against activation of Smad2/3 and Smad1/5/8 signaling

Smad	Ligand	IC_{50} (pmol/L)
Smad2/3	GDF8	8080
	GDF11	351.1
	Activin A	143.5
	Activin B	56.4
Smad1/5/8	BMP6	>256250
	BMP9	>128120
	BMP10	28640

Mean, n = 2

3.1.2 *In vivo* studies

3.1.2.1 Effect of RAP-011 in MCT-induced pulmonary hypertension rats (CTD 4.2.1.1.1, *Sci Transl Med.* 2020;12:eaaz5660 [reference data], 4.2.1.1.5 [reference data])

One day after a single subcutaneous administration of monocrotaline (MCT) (40 mg/kg), male rats (n = 3-9/group) intraperitoneally received RAP-011 (15 mg/kg) or vehicle (tris-buffered saline [TBS]) twice-weekly, which was continued for 4 weeks. The mean pulmonary arterial pressure (mPAP) (mean ± standard error [SE]) at Week 4 was 19.9 ± 1.2 mmHg in the RAP-011 group and 46.2 ± 2.4 mmHg in the vehicle group. The mPAP was significantly lower in the RAP-011 group than in the vehicle group. The ratio of right ventricular free wall (RV) to left ventricular free wall plus septum (LV+S) (RV/[LV+S]) ratio), indicative of right ventricular hypertrophy, was significantly lower in the RAP-011 group than in the vehicle group. The percentage[4)] of completely muscularized pulmonary vessels was significantly lower in the RAP-011 group than in the vehicle group, suggesting that RAP-011 could reduce pulmonary vascular remodeling.

Male rats (n = 6-8/group) subcutaneously received a single dose of MCT (60 mg/kg) and then, on the same day, subcutaneously received RAP-011 (5 mg/kg) or vehicle (phosphate-buffered saline [PBS]) twice-weekly, which was continued for 4 weeks. The right ventricular systolic pressure (RVSP) at Week 4 was significantly lower in the RAP-011 group than in the vehicle group. The amount of CD11b-positive macrophages in the lung was significantly lower in the RAP-011 group than in the vehicle group, suggesting that RAP-011 could suppress inflammation in the lung.

3.1.2.2 Effect of RAP-011 in SuHx-induced pulmonary hypertension rats (CTD 4.2.1.1.1 [reference data])

Male rats (n = 5-10/group) kept in a hypoxic environment (10%) for 1 day after a single subcutaneous administration of Sugen-5416[5)] (200 mg/kg) intraperitoneally received RAP-011 (10 mg/kg) or vehicle (TBS) twice-weekly, which was continued for 4 weeks. The mPAP (mean ± SE) at Week 4 was 21.1 ±

4) In a lung section immunohistochemically stained using anti-alpha smooth muscle actin (α-SMA) antibody, peripheral arteries (20-30 vessels per section) were classified into non-muscularized, partially muscularized, or completely muscularized vessels, and their proportions to all vessels were calculated.

5) Vascular endothelial growth factor receptor (VEGFR) 1/2 antagonist

1.1 mmHg in the RAP-011 group and 43.3 ± 2.4 mmHg in the vehicle group. The mPAP was significantly lower in the RAP-011 group than in the vehicle group. The RV/(LV+S) ratio, indicative of right ventricular hypertrophy, was significantly lower in the RAP-011 group than in the vehicle group.

3.1.2.3 Effect of RAP-011 in SuHxNx-induced pulmonary hypertension rats (CTD 4.2.1.1.6, 4.2.1.1.7 [reference data])

Male rats (n = 4-14/group) with pulmonary hypertension (PH) induced in a hypoxic environment (10%) after a single subcutaneous administration of Sugen-5416 (20 mg/kg) and then progressed in a normal oxygen environment (21%) subcutaneously received RAP-011 (2.5 mg/kg) or vehicle (PBS) twice-weekly 5 weeks after the administration of Sugen-5416. The twice-weekly administration was continued for 4 weeks. RVSP in the RAP-011 group at Week 4 was significantly lower than not only that in the vehicle group but also the baseline value in the same group. Changes in total pulmonary resistance index (TPRI) as well as RV/(LV+S) ratio and right ventricular wall thickness (RVWT), which are indicative of right ventricular hypertrophy, showed similar trends. Tricuspid annular plane systolic excursion (TAPSE), pulmonary artery acceleration time (PAAT), and right ventricular fractional area change (RVFAC) in the RAP-011 group were significantly higher than those in the vehicle group and significantly increased from the values before administration of RAP-011, suggesting that RAP-011 could improve right ventricular function. For the extent of lumenal occlusion[6)] in the pulmonary artery vessels, the proportion of Grade 0 vessels (no lumenal occlusion) in the RAP-011 group was significantly higher than that in the vehicle group and increased from the value before administration of RAP-011, suggesting that RAP-011 could reduce pulmonary vascular remodeling.

The effects of RAP-011 on RVSP, TPRI, right ventricular hypertrophy, and TAPSE continued until 4 weeks after the end of the RAP-011 treatment.

3.1.2.4 Effect of RAP-011 on *Bmpr2*$^{+/R899X}$ mice (CTD 4.2.1.1.8 [reference data])

Male *Bmpr2*$^{+/R899X}$ mice[7)] with PH induced in a hypoxic environment (10%) (n = 7-12/group) subcutaneously received RAP-011 (10 mg/kg) or vehicle (PBS) twice weekly for 5 weeks. RVSP at Week 5 was significantly lower in the RAP-011 group than in the vehicle group. RV/(LV+S) ratio and RVWT, indicative of right ventricular hypertrophy, were significantly lower in the RAP-011 group than in the vehicle group. Both TAPSE and PAAT were significantly higher in the RAP-011 group than in the vehicle group, suggesting that RAP-011 could prevent reduction in right ventricular function. Macrophage infiltration in the lung[8)] was significantly reduced in the RAP-011 group compared with the vehicle group.

3.2 Secondary pharmacodynamics

3.2.1 Effects of RAP-011 on erythrocyte parameters (CTD 4.2.1.2.1 [reference data])

RAP-011 (10 mg/kg) or vehicle (TBS) was administered to male mice (n = 5/group), and the effects on erythrocyte parameters (red blood cell count, hemoglobin concentrations, and hematocrit level) were

---

6) In a lung section immunohistochemically stained using anti-α-SMA antibody, arteries (approximately 100 vessels per section) were stratified into 3 groups based on the external diameter of the vessel (<50 μm, 50-100 μm, >100 μm). The vessels in each group were classified into one of Grade 0 (no lumenal occlusion), Grade 1 (lumenal occlusion <50%), and Grade 2 (lumenal occlusion ≥50%) based on the extent of the lumenal occlusion. The proportions of vessels at each grade to all the vessels were calculated.

7) Hereditary PAH model mouse with *Bmpr2* haploinsufficiency

8) Evaluated by immunohistochemical staining with anti-F4/80 antibody, which recognizes the mouse macrophage marker.

evaluated. On Day 3,[9)] no significant difference was observed in any erythrocyte parameter between the vehicle and RAP-011 groups, but on Day 4,[10)] all erythrocyte parameters were significantly higher in the RAP-011 group than in the vehicle group. On Day 7,[11)] the red blood cell count and hematocrit level were significantly higher in the RAP-011 group than in the vehicle group, suggesting that RAP-011 could stimulate erythropoiesis.

3.3 Safety pharmacology

Table 7 shows results from safety pharmacology studies.

Table 7. Outline of safety pharmacology studies

Item	Test system	Endpoints, methods, etc.	Dose	Route of administration	Findings	CTD
Central nervous system	Cynomolgus monkeys (n = 4/sex/group)	General behavior, body temperature	0,[a] 1, 2.6, 10 mg/kg[b]	Subcutaneous	No effect	4.2.3.2.7
Cardiovascular system	HEK293 cells stably expressing hERG channel	hERG current	0,[c] 300, 600, 1000 μg/mL	*In vitro*	In the 0, 300, 600 and 1000 μg/mL groups, hERG current was reduced by 2.4%, 7.2%, 28.6%, and 33.8%, respectively.	4.2.1.3.1
	Cynomolgus monkeys (n = 4/sex/group)	Blood pressure, heart rate, electrocardiogram (6-lead)	0,[a] 1, 2.6, 10 mg/kg[b]	Subcutaneous	No effect	4.2.3.2.7
Respiratory system	Cynomolgus monkeys (n = 4/sex/group)	Respiratory rate	0,[a] 1, 2.6, 10 mg/kg[b]	Subcutaneous	No effect	4.2.3.2.7

a PBS
b In the 0, 1, and 2.6 mg/kg groups, the Q4W regimen was used, while in the 10 mg/kg group, the Q2W and Q4W regimens were used. The repeated administration was continued for 9 months.
c 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (HEPES)-buffered physiological saline containing dimethyl sulfoxide (DMSO) at 0.3% (v/v)

3.R Outline of the review conducted by PMDA

3.R.1 Pharmacological effects of sotatercept on PAH

The applicant's explanation about pharmacological effects of sotatercept on PAH:

Growth of pulmonary vascular endothelial cells is regulated by pro-proliferative ActRIIA-mediated signaling (Smad2/3 signaling) and anti-proliferative bone morphogenetic protein receptor 2 (BMPR2)-mediated signaling (Smad1/5/8 signaling). In patients with PAH, a pro-proliferative signaling dominant state is generated from enhanced pro-proliferative signaling by increased expression of ActRIIA ligands such as activin A and GDF11 and reduced anti-proliferative signaling by a loss-of-function mutation in BMPR2 in pulmonary vascular endothelial cells (*Sci Transl Med.* 2020;12:eaaz5660, *Nat Genet.* 2000;26:81-4, etc.), enhancing cell growth and leading to pulmonary vascular remodeling (*N Engl J Med.* 2021;384:1204-15).

Sotatercept is a recombinant fusion protein composed of an extracellular domain of human ActRIIA linked to the Fc region of human IgG1 and was shown to bind to TGF-β superfamily ligands and thereby inhibit Smad2/3 signaling in *in vitro* studies. In *in vivo* studies using PAH model animals, RAP-011[2)] was shown to reduce mPAP and RVSP and prevent right ventricular hypertrophy, suggesting that it could prevent pulmonary vascular remodeling and improve the pulmonary vessel condition. Based on the

9) RAP-011 was administered on Day 0, while TBS was administered on Days 0 and 2.
10) RAP-011 was administered on Day 0, while TBS was administered on Days 1 to 4.
11) RAP-011 was administered on Days 0 and 3, while TBS was administered on Days 0, 2, 3, and 4.

above results, sotatercept is considered to prevent pulmonary vascular remodeling caused by abnormal growth of pulmonary vascular smooth muscle cells and improve the pathological condition of PAH by inhibiting ActRIIA-mediated Smad2/3 signaling and thereby normalizing the balance between pro-proliferative and anti-proliferative signaling.

In view of the applicant's explanation, PMDA considers that sotatercept can be expected to have efficacy in patients with PAH.

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

Serum sotatercept concentrations in rats, rabbits, and monkeys were determined by enzyme-linked immunosorbent assay (ELISA), and the lower limit of quantitation was 0.98 to 40.0, 40.0, and 7.81 ng/mL, respectively. Plasma sotatercept concentrations in rats and monkeys were determined by ELISA, and the lower limit of quantitation was 3.9 and 86 ng/mL, respectively.

Unless otherwise specified, pharmacokinetic (PK) parameters are expressed as the mean.

4.1 Absorption

4.1.1 Single dose studies (CTD 4.2.2.2.1 [reference data], 4.2.2.2.2 [reference data], 4.2.2.2.3 [reference data], 4.2.2.2.5 [reference data], 4.2.2.2.6 [reference data])

Table 8 shows PK parameters of sotatercept in male rats and female monkeys which intravenously or subcutaneously received a single dose of sotatercept.

Table 8. PK parameters of sotatercept after a single intravenous or subcutaneous administration of sotatercept

Animal species	Route of administration	Dose (mg/kg)	Number of animals	C_{max} (μg/mL)	t_{max} (h)	$AUC_{0-\infty}$ (μg·h/mL)	V_{ss} (mL/kg)	CL (mL/kg/h)	$t_{1/2}$ (h)
Rat	Intravenous	1	3	34.9	6	8682	36.4	0.12	196.5
		3	2	69.4, 97.9[a]	4, 72[a]	19378, 25806[a]	41.0, 54.8[a]	0.15, 0.20[a]	186, 217[a]
		10	1	349.0[a]	4[a]	70735[a]	32.0[a]	0.14[a]	154.1[a]
Rat		1	2	44.5, 46.1[a]	4, 4[a]	10789, 11657[a]	-	0.09, 0.09[a]	293, 308[a]
		10	3	366.5	4	74465.2	-	0.13	140.8
		30	3	948.3	4	278907.8	-	0.12	203.9
Monkey		1	2	22.2, 25.5[a]	0.25, 0.50[a]	1881, 4732[a]	59.3, 137[a]	0.21, 0.53[a]	175, 178[a]
		10	2	147, 117[a]	0.25, 96[a]	18440, 19822[a]	134, 139[a]	0.54, 0.50[a]	164, 166[a]
		30	2	214, 390[a]	0.25, 0.25[a]	19580, 51577[a]	152, 273[a]	0.25, 0.25[a]	117, 151[a]
Rat	Subcutaneous	3	12	23	32	6561	124.3	0.5	188
		10	12	80	48	15224	99.3	0.7	105
		30	12	232	48	38516	98.7	0.8	88
Monkey		1	3	9.05	48	2415	99.6	0.41	167
		10	3	57.4	8	14839	176.6	0.67	181
		30	3	133.5	4	35841	260.0	0.84	215

-, Not calculated
a Individual values at n = 1 or n = 2

4.1.2 Repeated-dose studies (CTD 4.2.3.2.2, 4.2.3.2.5, 4.2.3.5.2.3)

Table 9 shows PK parameters of sotatercept in male and female rats and female rabbits which subcutaneously received sotatercept once weekly.

Table 9. PK parameters of sotatercept after once-weekly repeated subcutaneous administration of sotatercept

Animal species	Dose (mg/kg)	Number of animals[a]	Day	C_{max}[b] (μg/mL)		$AUC_{0\text{-}168h}$[b] (μg·h/mL)	
				Male	Female	Male	Female
Rat	0.3	6/6	1	1.63	1.91	214	251
			92	4.39	4.15	654	564
	3	6/6	1	15.5	17.4	2110	2240
			92	20.3	9.32	2960	1220
	30	6/6	1	122	235	16200	24700
			92	188	168	28000	22600
Rabbit	0.5	3	1	5.23		686	
			8	6.89		796	
	1.5	3	1	13.7		1880	
			8	17.6		1630	
	5	3	1	40.7		5150	
			8	61.5		7800	

a males/females
b PK parameters were calculated as the mean of individual values for each dose.

Table 10 shows PK parameters of sotatercept in male and female monkeys which subcutaneously received sotatercept once every 2 weeks (Q2W).

Table 10. PK parameters of sotatercept in monkeys after Q2W subcutaneous administration of sotatercept

Dose (mg/kg)	Number of animals	Day	C_{max}[a] (μg/mL)	$AUC_{0\text{-}336h}$[a] (μg·h/mL)
10	12	1	103	21942
		183	187	29336
30	12	1	283	59828
		183	443	87589
50	12	1	676	104022
		183	1404	165039

a PK parameters were calculated based on changes in mean concentration over time for each dose.

4.2 Distribution

4.2.1 Tissue distribution

Although no studies for tissue distribution of sotatercept have been conducted, in view of the following points, the applicant explained that the tissue distribution of sotatercept would be limited:

- Sotatercept is a fusion protein of large molecular weight (131 kDa).
- The mean V_{ss} of sotatercept in rats and monkeys determined in single intravenous dose studies (32.0-36.7 and 107.7-252.0 mL/kg, respectively) did not greatly differ from the plasma volume in rats (31.2 mL/kg, *Pharm Res.* 1993;10:1093-5) or the sum of the plasma volume and extracellular fluid volume (252.8 mL/kg, *Pharm Res.* 1993;10:1093-5).

4.2.2 Placental transfer (CTD 4.2.3.5.2.2 [reference data])

Sotatercept 5, 15, or 50 mg/kg was administered subcutaneously to pregnant rabbits (n = 9) on Gestation Days 7 and 14. Fetal serum sotatercept concentrations on Gestation Day 29 were 1% to 39% of the maternal serum sotatercept concentrations, showing that sotatercept crosses the placenta.

4.3 Metabolism and excretion (CTD 4.2.3.5.3.1)

No studies for metabolism and excretion of sotatercept have been conducted.

The applicant's explanation about metabolism and excretion of sotatercept:

As with other extrinsic proteins, sotatercept is expected to undergo protein catabolic pathways and thereby be degraded into amino acids. In view of the following observations, sotatercept may be excreted into human milk. Therefore, avoidance of breastfeeding during the sotatercept therapy and 4 months after therapy completion should be advised via the package insert.

- In a study for effects on pre- and post-natal development, including maternal function in rats, sotatercept was administered to lactating maternal rats at a dose leading to the exposure at least twice that at the maximum recommended clinical dose, and decreased body weight and delayed sexual maturation were observed in the offspring [see Section 5.5].
- Sotatercept is a recombinant fusion protein composed of an extracellular domain of human ActRIIA linked to the Fc region of human IgG1, and monoclonal antibody similar to sotatercept in terms of structure and molecular weight is excreted into human milk (*Neurol Neuroimmunol Neuroinflamm.* 2020;7:e769).

4.R Outline of the review conducted by PMDA

Although no non-clinical pharmacokinetic studies of sotatercept for distribution except the placental transfer, metabolism, and excretion except the excretion into milk have been conducted, PMDA concluded based on the submitted data and applicant's explanation that non-clinical pharmacokinetics of sotatercept was appropriately evaluated. In view of potential excretion of sotatercept into milk, the applicant intends to raise caution by including a statement that lactation should be avoided during the sotatercept therapy and for 4 months after the end of the treatment. PMDA concluded that the applicant's action is appropriate.

5. Toxicology and Outline of the Review Conducted by PMDA

Toxicity studies of sotatercept conducted were single-dose toxicity, repeated-dose toxicity, reproductive and developmental toxicity, and other toxicity (using RAP-011, etc.) studies. Unless otherwise specified, PBS was used as vehicle.

5.1 Single-dose toxicity

A single-dose toxicity study in rats was conducted (Table 11). In repeated-dose toxicity studies in rats and cynomolgus monkeys, acute toxicity of sotatercept was evaluated based on the results obtained after the first dose (Table 12).

Table 11. Single-dose toxicity study

Test system	Route of administration	Dose (mg/kg)	Main findings	Approximate lethal dose (mg/kg)	Attached document CTD
Female rat (SD)	Intravenous	0, 10, 30	≥10: Cortical necrosis with mineralization in the adrenal gland on Day 28	>30	4.2.3.1.1[a] (reference data)

a On Days 8 and 28, adrenal gland, liver, kidney, and pancreas were collected, and the adrenal gland was subjected to histopathological examination.

Table 12. Repeated-dose toxicity study (findings after the first dose)

Test system	Route of administration	Dose (mg/kg)	Main findings	Approximate lethal dose (mg/kg)	Attached document CTD
Male and female rats (SD)	Subcutaneous	0, 0.3, 3, 30	Death: None	>30	4.2.3.2.1
Male and female cynomolgus monkeys	Subcutaneous	0, 10, 30, 50	Death: None	>50	4.2.3.2.4

5.2 Repeated-dose toxicity

Repeated-dose toxicity studies in rats (up to 3 months) and in cynomolgus monkeys (up to 9 months) were conducted (Table 13). Main findings included toxicity in the kidney, adrenal gland, and testis. In a 3-month repeated-dose toxicity study in rats, the exposure ($AUC_{0\text{-}504h}$) at the no observed adverse effect level (NOAEL) (3 mg/kg/dose) was 8880 μg·h/mL in males and 3660 μg·h/mL in females. In a 9-month repeated-dose toxicity study in monkeys, the exposure ($AUC_{0\text{-}504h}$) at the NOAEL (1 mg/kg/dose) was 4847 μg·h/mL in males and 4198 μg·h/mL in females. The exposure in male rats and female rats as well as male and female monkeys was 2 and 0.9 times as well as 1 time, respectively, higher than the exposure ($AUC_{0\text{-}504h}$, 4110.24 μg·h/mL) at a steady state in humans who received sotatercept according to the recommended clinical dosage regimen.

The applicant's explanation:

Toxicity studies in rats with the treatment period exceeding 3 months were unlikely to be feasible for the following reasons:

- In the 3-month repeated-dose toxicity study in rats and a study for fertility and early embryonic development to implantation in male rats, anti-drug antibodies (ADA) were found in 58% and 57.3% of animals in the sotatercept groups overall, respectively, at the end of treatment. In studies with a longer treatment period, increased ADA incidences would preclude appropriate toxicity evaluation.
- In the 3-month repeated-dose toxicity study in rats, renal toxicity (membranoproliferative glomerulonephritis) was observed at ≥0.3 mg/kg, and increased renal dysfunction markers were additionally observed at 30 mg/kg. Worsening of chronic progressive nephropathy, which is known to occur spontaneously in rats with aging, would decrease tolerability.

Table 13. Repeated-dose toxicity studies

Test system	Route of administration	Treatment period	Dose (mg/kg/dose)	Main findings	NOAEL (mg/kg/dose)	Attached document CTD
Male and female rats (SD)	Intravenous	4 weeks (QW) + 4 weeks	0, 1, 10, 30	Death[a]: 10 (1 of 15 males), 30 (1 of 15 males) ≥1: Mildly high erythrocyte parameters (RBC, HCT, HGB); mildly high reticulocyte count; mildly low MCH; high AST (female); high adrenal gland weight (female); hypertrophy, discoloration, and necrosis of cortex and medulla in the adrenal gland (female); apoptosis of acinar cells, depletion of zymogen granules, and atrophy of pancreatic acinus in the pancreas; low heart weight 10: Mildly high basophil count (male), mildly high ALT (male) ≥10: Mildly high large unstained cell count; mildly low MCHC and platelet count (male); mildly high ALT and ALP (female); high testis weight; low kidney weight; nodules in the epididymis; spermatic granuloma, testis degeneration (seminiferous tubular dilatation, decreased sperm count in the seminiferous tubule, multinucleated giant cells) 30: Low uterus weight; decreased sperm motility, decreased sperm count in the epididymis, spermatic fragmentation Partially reversible[b]	<1	4.2.3.2.3 (reference data)
Male and female rats (SD)	Subcutaneous	3 months (QW) + 1 month	0, 0.3, 3, 30	0.3: Slightly to moderately decreased spermatogenesis (1 animal) ≥0.3: High food consumption (female); mildly high erythrocyte parameters (RBC, RDW, HGB); low MCV and MCH; low heart weight; mildly localized or diffuse congestion in the adrenal gland cortex; slightly membranous or membranoproliferative glomerulonephritis and slightly to mildly increased basophilic renal tubules in the kidney 3: Mass in the epididymis, slight mononuclear cell infiltration related to small testis/vesicular gland, and azoospermia with multinucleated giant cells (1 animal) ≥3: High reticulocyte count 30: High MPV; high BUN; fluid retention in the vicinity of the kidney; low kidney weight; high adrenal gland weight; slightly to moderately decreased spermatogenesis; mild unilateral and multifocal atrophy of the testis; multifocal mineralization in the adrenal gland cortex; kidney renal tubular dilatation, interstitial fibrogenesis, mild to slightly localized renal tubular degeneration and atrophy with mononuclear inflammatory cell infiltration; high liver weight (female) Partially reversible[c]	3[d]	4.2.3.2.1
Male and female rats (SD)	Subcutaneous	3 months (QW) + 1 month	0,[e] 0.3, 3, 30	Death: 30 (1 of 16 males)[f] ≥0.3: Slightly high mean weight (female); mildly high erythrocyte parameters (RBC, HCT, HGB); high RDW and reticulocyte count; low MCH, MCHC, and MCV; high urine osteopontin, lipocalin-2, and albumin; mild to moderate membranoproliferative glomerulonephritis (female) ≥3: Mild to moderate membranoproliferative glomerulonephritis (male), chronic progressive nephropathy (female) 30: Abdominal distention; low platelet count; slight to mild cystic dilatation attributable to fluid retention in the renicapsule and left kidney hypertrophy with fibrogenesis in the renicapsule; mineralization in the renal interstitium Partially reversible[g]	3[h]	4.2.3.2.2[i]
Male and female cynomolgus monkeys	Intravenous	4 weeks (QW)	0, 1, 10, 30	≥1: Mildly high erythrocyte parameters (HGB, HCT, RBC) and reticulocyte count, high ALP (male) ≥10: Mildly low bone marrow myeloid/erythroblast cell ratio	30[j]	4.2.3.2.8 (reference data)

Test system	Route of administration	Treatment period	Dose (mg/kg/dose)	Main findings	NOAEL (mg/kg/dose)	Attached document CTD
Male and female cynomolgus monkeys	Subcutaneous	3 months (Q2W) + 2 months	0, 10, 30, 50	≥10: Mildly high erythrocyte parameters (HGB, HCT, RBC, RDW) and reticulocyte count; low MCH and MCHC; slightly high blood creatinine and BUN ≥30: Mild to moderate multifocal or diffuse membranoproliferative hypercellularity in the kidney glomerulus 50: Corticomedullary fibrogenesis in the renal tubules, mononuclear cell infiltration, increased basophilic renal tubules, and dilatation of renal tubules Reversible	30[k]	4.2.3.2.4
Male and female cynomolgus monkeys	Subcutaneous	27 weeks (Q2W)[l] + 13 weeks	0, 10, 30, 50	Death: 30 (2 of 6 females) Hunchback position; emaciation; cool to touch; decrease in locomotor activity; abnormal fur; severely decreased food consumption; dehydration; high BUN and creatinine; yellow-brown kidney; moderate to severe renal tubule interstitial nephritis and glomerulonephritis; lymphocyte depletion in the thymus; slightly localized acute myocardial necrosis with mononuclear cell infiltration; multifocal chronic inflammation in the pancreas with localized arteritis; red adrenal gland ≥10: Mildly high erythrocyte parameters (HGB, HCT, RBC) and reticulocyte count; multifocal or fused renal tubule atrophy with interstitial fibrogenesis related to discoloration of the kidney (pale, yellow-brown, patchy), disposition of loose interstitial connective tissue, related glomerulus atrophy, renal tubule interstitial nephritis characterized by sclerosis; lymphocyte depletion in the thymus ≥30: Slight to moderate glomerulus membranoproliferative hypercellularity in the kidney (glomerulonephritis), slight to mild foamy macrophage infiltration in the choroid plexus 50: Mildly high BUN and creatinine (female), high kidney weight, high thymus weight Partially reversible[m]	<10	4.2.3.2.5
Male and female cynomolgus monkeys	Subcutaneous	9 months (Q2W or Q4W) + 3 months	Q4W: 0, 1, 2.6, 10 Q2W: 10	Death[n]: 2.6 (1 of 6 females), 10 (Q4W) (1 of 6 males) 1: Slightly increased substance deposition in the kidney corticomedullary junction (female) ≥1: Fluctuated erythrocyte parameters (high HGB, HCT, RBC, and RDW and low MCV and MCH); high reticulocyte count; mildly high monocyte count; infiltration of mononuclear cells (lymphocytes and plasma cells) and foamy macrophages in the choroid plexus, slightly to mildly localized small aggregates of mononuclear inflammatory cells; slight infiltration of mononuclear cells in the liver; slightly to mildly perivascular or blood vessel basophilic deposits in the heart, aorta, and pancreas ≥2.6: Slightly to mildly high BUN and creatinine; high urine protein; slight interstitial inflammation with fibrogenesis in the kidney (male) and small glomerulus loop; slight to mild perivascular accumulation of foamy macrophages in the choroid plexus; mildly to moderately low size and count of splenic follicle germinal centers (lymphocyte depletion) ≥10 (Q4W): Slightly increased urine occult blood; kidney hypertrophy, discoloration, uneven cortex surface; slight to mild membranoproliferative glomerulopathy in the kidney, slight to mild interstitial inflammation with fibrogenesis (female), and slightly increased substance deposition in the corticomedullary junction; low spleen weight 10 (Q2W): Slightly low bone marrow myeloid/erythroblast cell ratio; slightly low platelet count (male); high kidney weight (male); slight intimal thickening of arterioles in the choroid plexus Reversible	1[o]	4.2.3.2.7

Test system	Route of administration	Treatment period	Dose (mg/kg/dose)	Main findings	NOAEL (mg/kg/dose)	Attached document CTD

a In the 10 mg/kg group, 1 male was found dead on Day 19, and in the 30 mg/kg group, 1 male was euthanized in moribund condition on Day 23. A relationship between the death observed in this study and the test article treatment is considered unclear.
b Except change of the heart weight and findings in the epididymis and adrenal gland in the ≥10 mg/kg groups
c Except testis toxicity in the 30 mg/kg group
d The findings in the ≤3 mg/kg groups are considered of little toxicological significance based on their low incidence and severity.
e [redacted]
f In the 30 mg/kg group, 1 male died on Day 57. A relationship between the death and the test article treatment is considered unclear.
g Changes of body weight and erythrocyte parameters in females in the ≤3 mg/kg groups were found reversible.
h The findings in the kidney in the ≤3 mg/kg groups are considered of little toxicological significance because of their low incidences and absence of remarkable changes in renal dysfunction biomarkers.
i Histopathological examination was performed only on the kidney.
j The findings in the concerned study are slight changes attributable to the pharmacological action of sotatercept and thus considered of little toxicological significance.
k The findings in the ≤30 mg/kg groups are considered of little toxicological significance based on their severity.
l The treatment period of 9 months was initially planned, but because death attributable to renal toxicity including glomerulonephritis occurred in 2 females in the 30 mg/kg group, the treatment period in the study overall was shortened from 9 months to 27 weeks.
m Except histomorphological changes in the kidney
n Euthanized in moribund condition attributable to enteritis on Day 153. A relationship between the concerned finding and the test article treatment is considered unlikely.
o The findings in the 1 mg/kg group are considered of little toxicological significance based on their severity.

5.3 Genotoxicity

Sotatercept is a recombinant fusion protein and considered unlikely to interact with DNA and other chromosomal components. No genotoxicity studies have been conducted.

5.4 Carcinogenicity

Long-term toxicity studies in rodents are unlikely to be feasible [see Section 5.2], and no carcinogenicity studies of sotatercept have been conducted. But for the following reasons, the applicant explained that no definite carcinogenic risk is found for sotatercept:

- For TGF-β superfamily ligands, which are found to have binding affinity to sotatercept, there are no consistent reports on the effect of their inhibition on tumor growth in the published literature (*Front Oncol.* 2019;9:1039, etc.).
- In non-clinical studies of sotatercept, neither neoplastic nor preneoplastic changes were observed. In addition, sotatercept is not expected to have a genotoxicity risk.
- The effects on the testis observed in the repeated-dose toxicity studies of sotatercept, etc. are not attributable to sex hormone variations, and no findings suggestive of secondary hormone variations were obtained in the hormone-sensitive genital organs (prostate, vesicular gland) or Leydig cells.
- In the repeated-dose toxicity studies, no particular effects were observed in female genital organs or female fertility.
- Data from non-clinical and clinical studies of sotatercept as well as foreign post-marketing information do not include any findings or adverse events suggestive of immunosuppressive activity of sotatercept.

5.5 Reproductive and developmental toxicity

The following studies were conducted: A study for fertility and early embryonic development to implantation in rats, studies for embryo-fetal development in rats and rabbits, a study for pre- and post-natal development, including maternal function in rats, and studies in juvenile rats (Tables 14 and 15).

In the study for fertility and early embryonic development to implantation in male rats, toxicity findings in the male genital organs and decreased fertility were observed. The exposure ($AUC_{0\text{-}504h}$) at the

NOAELs for general toxicity (<0.3 mg/kg/dose) and for reproductive potential (3 mg/kg/dose) was <1962 μg·h/mL and 8880 μg·h/mL, which are <0.5 and 2 times higher than $AUC_{0\text{-}504h}$ (4110.24 μg·h/mL) at a steady state in humans who received sotatercept according to the recommended clinical dosage regimen.

In the study for fertility and early embryonic development to implantation in female rats, a high post-implantation loss rate was observed. The exposure ($AUC_{0\text{-}504h}$) at the NOAEL for reproductive potential (5 mg/kg/dose) was 8205 μg·h/mL, which was 2 times higher than $AUC_{0\text{-}504h}$ (4110.24 μg·h/mL) at a steady state in humans who received sotatercept according to the recommended clinical dosage regimen.

In the studies for embryo-fetal development in rats and rabbits, findings suggestive of embryo-fetal development toxicity of sotatercept such as increased post-implantation loss rate and delayed ossification were observed. The exposure ($AUC_{0\text{-}504h}$) at the NOAEL (5 mg/kg/dose and 0.5 mg/kg/dose) for embryo-fetal development in rats and rabbits were 7926 μg·h/mL and 1477 μg·h/mL, which were 2 and 0.4 times higher than $AUC_{0\text{-}504h}$ (4110.24 μg·h/mL) at a steady state in humans who received sotatercept according to the recommended clinical dosage regimen.

In the study for effects on pre- and post-natal development, including maternal function in rats, decreased body weight and delayed sexual maturation of the offspring were observed. The exposure ($AUC_{0\text{-}504h}$) at the NOAEL for offspring (1.5 mg/kg/dose in the concurrent lactation-treatment group) was 2403 μg·h/mL, which was 0.6 times higher than $AUC_{0\text{-}504h}$ (4110.24 μg·h/mL) at a steady state in humans who received sotatercept according to the recommended clinical dosage regimen.

Table 14. Reproductive and developmental toxicity studies

Type of study	Test system	Route of administration	Treatment period	Dose (mg/kg/dose)	Main findings	NOAEL (mg/kg/dose)	Attached document CTD
Fertility and early embryonic development to implantation	Male rat (SD)	Subcutaneous	From 10 weeks before mating to 3 weeks after mating (QW, 13 weeks) + 13 weeks	0,[a] 0.3, 3, 30	≥0.3: Transiently low body weight gain; degeneration and atrophy of the testis or unilateral or bilateral small or abnormally sclerotic testis and epididymis related to decreased sperm density in the ductus epididymis; sperm granuloma with occlusion in the efferent duct, sperm congestion, fibrogenesis, mineralization, and mixed-cell infiltration 30: Decreased conception rate and fertility rate; seminiferous tubule dilatation; rete testis dilatation, sperm congestion, sperm granuloma; decreased cellularity in the epididymis (decreased sperms in the duct), decreased sperm density in the cauda epididymis Partially reversible[b]	General toxicity: <0.3 Reproductive potential: 3	4.2.3.5.1.1
	Female rat (SD)		From 2 weeks before mating to Gestation Day 7 (QW)	0, 5, 15, 50	Death: 50 (2 of 25 animals) Edematous and swollen hindlimb with remarkable movement disorder; hypertrophic and red adrenal gland ≥5: Low mean numbers of implantation sites and live conceptuses; low pregnant uterus weight ≥15: High mean body weight and mean body weight gain related to high food consumption; low pregnancy rate and fertility rate; high pre- and post-implantation loss rates including an increased incidence of complete resorptions; low litter size; hypertrophic and discolored adrenal gland 50: Swollen hindlimb; movement disorder; prolonged estrous cycle with low mean number of cycles; low mating rate	General toxicity: 15[c] Reproductive potential: 5[d]	4.2.3.5.1.2
Embryo-fetal development	Female rat (SD)	Subcutaneous	Gestation Days 6 to 21 (administered on Gestation Days 6 and 13)	0, 5, 15, 50	Maternal animals: 50: Slightly low food consumption, low body weight gain Embryo and fetuses: ≥5: Low fetal body weight ≥15: Delayed ossification of thoracic vertebra, lumbar vertebra, hindlimb metatarsal bone, and hindlimb phalanx 50: High post-implantation loss rate, high mean number of late resorptions, supernumerary ribs with the high numbers of thoracic vertebrae and the low numbers of lumbar vertebrae	Maternal animals (general toxicity): 50[e] Embryo-fetal development: 5[f]	4.2.3.5.2.1

Type of study	Test system	Route of administration	Treatment period	Dose (mg/kg/dose)	Main findings	NOAEL (mg/kg/dose)	Attached document CTD
	Female rabbit (NZW)	Subcutaneous	Gestation Days 6 to 29 (administered on Gestation Days 7 and 14)	0, 5, 15, 50	Death: 50 (2 of 5 animals) Poor clinical condition Maternal animals: 5: Spontaneous abortion with poor clinical condition (1 animal) ≥5: Pericardial effusion ≥15: Red and swollen eyelid, low body weight gain 50: Spontaneous abortion with poor clinical condition (2 animals), red substances in the cage tray Embryo and fetuses: ≥5: Low fetal body weight ≥15: High numbers of early and late resorptions as well as post-implantation loss rate, low mean number of litter and live fetuses, high per-litter conceptus resorption rate 50: Total conceptus resorption (1 animal)		4.2.3.5.2.2 (reference data)
	Female rabbit (NZW)	Subcutaneous	Gestation Days 6 to 29 (administered on Gestation Days 7 and 14)	0,[a] 0.5, 1.5, 5	Maternal animals: No remarkable findings Embryo and fetuses: ≥1.5: Low mean fetal body weight 5: High mean post-implantation loss rate, low mean number of live fetuses, low mean ossification score (metacarpal bone, forelimb phalanx, hindlimb phalanx)	Maternal animals (general toxicity): 5 Embryo-fetal development: 0.5	4.2.3.5.2.3
Effects on pre- and post-natal development, including maternal function	Female rat (SD)	Subcutaneous	Gestation Day 7 to Lactation Day 21[g]	0,[a] 1.5, 5, 10 (concurrent lactation-treatment group only)	Maternal animals: Concurrent lactation-treatment group 10: Low food consumption F1 offspring: Concurrent pregnancy-treatment group ≥1.5: Transiently low offspring body weight Concurrent lactation-treatment group ≥5: Low body weight and body weight gain, delayed sexual maturation, delayed mean age of preputial separation 10: Delayed mean age of vaginal patency	Maternal animals (general toxicity): 5 (concurrent pregnancy-treatment group), 10 (concurrent lactation-treatment group)[h] F1 offspring: 5 (concurrent pregnancy-treatment group), 1.5 (concurrent lactation-treatment group)[i]	4.2.3.5.3.1

a [redacted]

b Except histopathological findings in the efferent duct, testis, and epididymis

c The findings in the adrenal gland in the 15 mg/kg group are considered of little toxicological significance because they occurred infrequently and were deemed as changes potentially caused by premortal hemoperfusion.

d The low mean numbers of implantation sites and live conceptuses in the 5 mg/kg group are considered of little toxicological significance because they were within the historical data at the testing facility.

e The low food consumption and associated low body weight gain in the 50 mg/kg group are considered of little toxicological significance because they were changes secondary to decreased pregnant uterus weight.

f The decreased fetal body weight in the 5 mg/kg group is considered of little toxicological significance because it was mild and within the historical data at the testing facility.

g To rats treated with sotatercept on Gestation Days 6 and 13, physiological saline was administered on Lactation Days 1, 8, and 15 (concurrent pregnancy-treatment group). To rats treated with physiological saline on Gestation Days 6 and 13, sotatercept was administered on Lactation Days 1, 8, and 15 (concurrent lactation-treatment group).

h The low food consumption in the 10 mg/kg group in the concurrent lactation-treatment group is considered of little toxicological significance because neither related clinical symptoms nor effects on body weight were observed.

i The low mean offspring body weight in the ≥1.5 mg/kg groups in the concurrent pregnancy-treatment group is considered of little toxicological significance because it was transient.

Table 15. Studies in juvenile animals

Test system	Route of administration	Treatment period	Dose (mg/kg/dose)	Main findings	NOAEL (mg/kg/dose)	Attached document CTD
Juvenile male and female rats (SD)	Subcutaneous	12 weeks, Postnatal Days 7 to 91 (QW) + 13 weeks	0,[a] 0.3, 3, 30[b]	Death: 3 (6 of 30 males, 2 of 30 females), 30[b] Dehydration; emaciation; decrease in locomotor activity; abnormal fur; low body weight gain; high red cell mass; high ALT and AST; high parameters suggestive of renal damage (BUN, creatinine [male], phosphorus, potassium); red kidney; renal tubule dilatation, atrophy, hypoplasia, and mineralization in the kidney; hemorrhage and congestion in the renal medulla; congestion and vacuolation in the adrenal gland; mineralization in the glandular stomach mucosa; decreased cellularity in the splenic white pulp or marginal zone of the spleen 0.3: High BMC and BMD in the femur overall and the proximal, middle, and distal portions ≥0.3: Restricted functions of limbs; high erythrocyte parameters (RBC, HGB, HCT); sclerosed and small testis; small prostate; discoloration and fluid-filled cysts in the kidney; low heart weight (male); mineralization in the renal tubule, renal tubular dilatation, chronic progressive nephropathy, membranoproliferative glomerulonephritis, hemorrhage, atrophy and hypoplasia of medullary renal tubules, and increased medullary interstitium in the kidney; mineralization in the glandular stomach mucosa (male); degeneration and atrophy of the seminiferous tubules; testicular edema; decreased sperms with increased cell residues in the epididymis; decreased cellularity in the splenic periarteriolar sheath and splenic white pulp marginal zone (female), decreased splenic red pulp extramedullary haematopoiesis (female), increased cellularity in the splenic red pulp (female); decreased myeloblast myeloid cells (female); single cell necrosis in the thymic cortex and medulla (female); cellular hypertrophy in the adrenal gland cortex (female); decreased pregnancy rate in female animals during the recovery period; high CD45-positive lymphocyte count with high counts of total T cells, B cells, CD4-positive T cells, and CD8-positive T cells; low proportions of NK cells and T cells (female) 3: Low mean body weight and body weight gain; low food consumption (male); delayed sexual maturation in males and females; short total moving time of locomotor activity (male); high leukocyte parameters (leukocyte, neutrophil, and monocyte counts) (female); high blood fibrinogen; low platelet count; high blood BUN, creatinine, and phosphorus; low blood albumin; low testis, epididymis, prostate, and spleen (female) weights; high kidney weight; mineralization in the glandular stomach mucosa (female); hyperplasia of Leydig cells in the testis; atrophy of the prostate and vesicular gland; decreased cellularity in the splenic periarteriolar sheath and splenic white pulp marginal zone (male), decreased splenic red pulp extramedullary haematopoiesis (male), increased cellularity in the splenic red pulp (male); hypertrophy of anterior and intermediate pituitary cells (female); decreased pregnancy rate in female animals during the recovery period, high number of female animals with dead embryos; high LH (male); low LH and FSH (female); decreased T-cell dependent anti- KLH IgM production capacity; low NK cell proportion (male); high proportion of B cells with high counts of CD45-positive lymphocytes and B cells (male) Partially reversible[c]	<0.3	4.2.3.5.4.1 (reference data)[d]

Test system	Route of administration	Treatment period	Dose (mg/kg/dose)	Main findings	NOAEL (mg/kg/dose)	Attached document CTD
Juvenile male and female rats (SD)	Subcutaneous	13 weeks, Postnatal Days 7 to 91 (QW) + 18 weeks	0,[a] 1, 3, 10	≥1: Low body weight and food consumption (male); delayed sexual maturation (male); high erythrocyte parameters (RBC·HGB, HCT, reticulocyte count, RDW, HDW); low MCH, MCHC, MCV, and platelet count; low proportion of NK cells (female); high ALP (female); high BUN; low chloride; softened and small testis and epididymis; low heart, epididymis, and prostate weights; high ovary weight; decreased cellularity in the splenic marginal zone lymphoid tissue and increased cellularity in the splenic red pulp; chronic progressive nephropathy in the kidney, membranoproliferative glomerulonephritis, atrophy and hypoplasia of medulla and renal papillary tubule with increased interstitium, renal papillary necrosis, dilatation of renal tubule and renal pelvis, and hemorrhage; mineralization in the glandular stomach mucosa; vacuolation in the periportal hepatocytes; hypertrophy of zona fasciculata in the adrenal cortex; degeneration of seminiferous tubules, decreased sperm count in the duct; cell residues in the ductus epididymis; decreased mean mating rate in male animals and decreased conception rate and fertility during the recovery period; high EPO concentration (male) ≥3: Delayed sexual maturation (female); low hindlimb grip strength (male); high creatinine and phosphorus; low albumin, globulin, and total protein; increased finding of positive urine protein reaction; dilatation and nodes of the renal pelvis in the kidney; low testis weight; cortex necrosis in the adrenal gland; low FSH (female); high lymphocyte count (B cell compartment) (male) 10: Swelling and impairment of the hindlimb, high MPV and fibrinogen, low urine specific gravity, high urine volume, low FSH and estradiol (male), high EPO concentration (female), decreased NK cell count (female) Partially reversible[c]	<1	4.2.3.5.4.2[e]

a [redacted]

b In the 30 mg/kg group, death related to the test article treatment occurred in many animals, and surviving animals were also found in a poor clinical condition. The study was thus discontinued on Postnatal Day 30.

c Except most of the histopathological findings at the end of the treatment

d Parameters: Mortality, clinical observation, food consumption, body weight, sexual maturation, locomotor activity, functional observational battery (FOB) and Morris water maze, estrous cycle, reproductive potential, blood hormone concentrations (follicle stimulating hormone [FSH], luteinizing hormone [LH], testosterone, progesterone, estradiol, and erythropoientin [EPO]), T-cell dependent antibody response [TDAR] and immunophenotyping parameter, urinalysis, bone densitometry (femur), clinicopathological examination, histopathological examination, toxicokinetics (TK), and ADA

e Parameters: Mortality, clinical observation, food consumption, body weight, sexual maturation, locomotor activity, FOB, learning and memory (Biel maze test), estrous cycle, reproductive potential, blood hormone concentrations (FSH, LH, testosterone, progesterone, estradiol, and EPO), TDAR and immunophenotyping parameter, urinalysis, bone densitometry (femur), clinicopathological examination, histopathological examination, TK, and ADA

5.6 Local tolerance

Local tolerance of sotatercept administered subcutaneously was evaluated in the repeated-dose toxicity studies in rats and monkeys, and sotatercept administered subcutaneously was considered unlikely to be locally irritant.

5.7 Other toxicity studies

5.7.1 Toxicity studies using mouse surrogate (RAP-011)

A repeated-dose toxicity study in mice using RAP-011, a mouse analog of sotatercept of which human IgG1 Fc domain was replaced with mouse IgG2 Fc domain, was conducted (Table 16).

Table 16. Toxicity studies of RAP-011

Test system	Route of administration	Treatment period	Dose (mg/kg/dose)	Main findings	Attached document CTD
Male and female mice (CD-1)	Intraperitoneal	3 months (BIW) + 1 month	RAP-011 0, 10, 30, 50[a]	Death: 10 (1 of 20 males, 1 of 20 females), 30 (7 of 20 males, 8 of 20 females), 50 (9 of 20 males, 8 of 20 females) Respiratory distress, abnormal fur ≥10: Slight and transient changes in body weight and body weight change; high erythrocyte parameters (RBC, RDW, HGB, HCT, reticulocyte count); high AST and ALT with high Na and TG; intrathoracic red fluid retention; multifocal mineralization in the choroid plexus; multifocal and bilateral degeneration and necrosis of the renal tubular epithelium in the renal cortex; multifocal alveolar histiocytosis; degeneration and necrosis of the ventricular myocardium; enhanced splenic haematopoiesis; lymphocyte depletion in the lymphoid tissue (spleen, thymus, lymph nodes)	4.2.3.7.7.1 (reference data)
Female rat (SD) 5/6 nephrectomized model and UUL	Subcutaneous	13 weeks (QW)	Sotatercept 0,[b] 1,[c] 10[c] RAP-011 10	5/6 nephrectomized model Sotatercept ≥1: High red cell mass (RBC, HGB, HCT); high albumin, TIM-1, lipocalin-2, and osteopontin; changes in the glomerulus (hyaline deposition, epithelial crescent formation, hyperplasia of Bowman's capsule, dilatation of Bowman's space or atrophy of the glomerulus); increased incidence and severity of lesions in the renal tubule interstitium (dilatation of the renal tubule, basophilic changes, fibroplasia and fibrogenesis of the interstitium, infiltration of mononuclear inflammatory cells); increased immunostained areas of phosphorylated Smad2 (pSmad2) and αSMA in the glomerulus and renal tubule interstitium RAP-011 10: High red cell mass (RBC, HGB, HCT); high albumin, TIM-1, lipocalin-2, and osteopontin; changes in the glomerulus (hyaline deposition, epithelial crescent formation, hyperplasia of Bowman's capsule, dilatation of Bowman's space or atrophy of the glomerulus); increased incidence and severity of lesions in the renal tubule interstitium (dilatation of the renal tubule, basophilic changes, fibroplasia and fibrogenesis of the interstitium, infiltration of mononuclear inflammatory cells); increased immunostained areas of phosphorylated Smad2 (pSmad2) and αSMA in the glomerulus and renal tubule interstitium	4.2.3.7.7.2 (reference data)
				UUL Sotatercept 10: High red cell mass (RBC, HGB, HCT), high lipocalin-2 RAP-011 10: High red cell mass (RBC, HGB, HCT), high lipocalin-2	

a In the 50 mg/kg group, death related to the test article treatment occurred in many animals. The study at the concerned dose was thus terminated on Day 74 for females and on Day 92 for males.
b 10 mM TBS, pH 7.2
c Prepared at [redacted]

5.R Outline of the review conducted by PMDA

5.R.1 Effect on pregnancy and potential teratogenicity

In the reproductive and developmental toxicity studies, increased pre- and post-implantation loss rates and late resorptions were observed.

The applicant's explanation about whether these findings would lead to problems in clinical use:
The above findings are attributable to the pharmacological action of sotatercept based on the following points. Sotatercept may affect conception and maintenance of pregnancy in humans throughout the pregnancy period as well.

- In rodents, activin A, the target molecule of sotatercept, plays an important role in conception and maintenance of pregnancy, being involved in enhancement of growth, differentiation, and infiltration

of trophoblastic cell, a process critical to implantation, as well as regulation of angiogenesis and vasculogenesis in the placenta during the late pregnancy (*Physiol Rev*. 2019;99:739-80, *Endocrinology*. 1997;138:3976-86, etc.)
- In humans, blood activin concentrations increase throughout the pregnancy period from the early pregnancy (gestation week 6) to the delivery (*Hum Reprod*. 1999;14:827-32).

TGF-β superfamily ligand-knockout mice,[12)] which lack the target molecule of sotatercept, are known to have various congenital anomalies including the external, visceral, and skeletal abnormalities (*Nature.* 1995;374:354-6, *Development.* 2004;131:2219-31, etc.), but no findings indicative of teratogenicity were detected in the embryo-fetal development studies of sotatercept. In view of the following points in addition to the results from the concerned studies, sotatercept is considered unlikely to be teratogenic in humans:
- In the dose range investigated in the embryo-fetal development studies of sotatercept in rats and rabbits (leading to exposure up to 15 and 4 times higher than the clinical exposure), none of the findings indicative of anomaly reported in the above knockout mice were observed in the fetuses.
- In embryo-fetal development studies of luspatercept (genetical recombination) that has the extracellular domain of Activin receptor type IIB (ActRIIB) and mainly targets GDF-11 and GDF-8, no findings indicative of teratogenicity were observed.

There are no reports on a risk of critical congenital defects or spontaneous abortions related to sotatercept in pregnant women. Pregnancy reported in Japanese and foreign clinical studies was limited to 1 subject in the sotatercept group (missed abortion, moderate, serious, causally unrelated to the study drug) and 1 subject in the placebo group (spontaneous abortion [induced abortion by oral contraceptive], severe, non-serious, causally unrelated to the study drug) in the foreign phase III study (Study 003).

Based on the above, the applicant will raise caution in the package insert, instructing healthcare professionals to explain women of childbearing potential about necessity of using contraception during sotatercept therapy and for 4 months after the last dose and about appropriate contraception measures as well as to refrain from using sotatercept in pregnant women or women who may possibly be pregnant.

PMDA's view:
PAH commonly occurs in women of childbearing age, but of drugs for treatment of PAH, endothelin receptor antagonists (ERAs) and soluble guanylate cyclase (sGC) agonists are contraindicated for pregnant women or women who may possibly be pregnant because of their teratogenic potential, and thus treatment options for patients who want to be pregnant and maintain the pregnancy are limited. In view of results from the reproductive and developmental toxicity studies of sotatercept, the possibility that use of sotatercept in pregnant women or women who may possibly be pregnant adversely affects conception and maintenance of pregnancy cannot be ruled out. However, no findings indicative of teratogenicity were observed in fetuses in the embryo-fetal development studies of sotatercept, and thus sotatercept can be considered unlikely to be teratogenic in humans; and drugs for treatment available for pregnant women or women who may possibly be pregnant are highly desired at the present time.

12) Activin βA-homozygous knockout mouse, GDF-11-heterozygous and homozygous knockout mice, BMP-10-homozygous knockout mouse, etc.

Considering the above, use of sotatercept in pregnant women or women who may possibly be pregnant is acceptable on the precondition that adequate caution is provided concerning the effects of sotatercept on conception and maintenance of pregnancy. In addition to the statement proposed by the applicant, healthcare professionals and patients should be informed of absence of clinical experience with sotatercept in pregnant women and the effect of sotatercept on pregnancy, and thus to raise caution, the package insert, a guide for healthcare professionals, and a brochure for patients and their families should include appropriate information.

5.R.2 Effects on testis and male reproductive potential

In toxicity studies of sotatercept in rats, testis toxicity accompanied by an effect on male reproductive potential was observed, and the exposure at NOAEL was only 2 times the clinical exposure at a steady state in humans, falling short of an adequate safety margin. PMDA asked the applicant to explain whether the findings concerned could cause problems in clinical use.

The applicant's explanation:
Activin A is involved in body fluid reabsorption and sperm movement in the epididymis (*Andrology.* 2024;12:964-72, *Biol Reprod.* 2012;87:41). The testis toxicity (degeneration and atrophy of the testis, sperm granuloma in the epididymis, decreased male fertility, etc.) observed in the repeated-dose toxicity study in rats and the study for fertility and early embryonic development to implantation in male rats was deemed to reflect sperm granuloma and outflow tract occlusion as well as secondary pressure atrophy of the testis resulted from altered body fluid dynamics in the epididymis attributable to the pharmacological action of sotatercept.

The possibility that body fluid dynamics in the outflow duct is altered in humans as well cannot be ruled out. However, rat efferent ducts are long and integrated into a single tract entering the epididymis, while human efferent ducts are short and integrated into multiple tracts entering the epididymis (*Toxicol Pathol.* 2012;40:705-14), and thus body fluid outflow tracts are expected to be maintained even if occlusion occurs in some efferent ducts. In view of the above anatomical differences, sotatercept in humans is considered unlikely to have the effects on male genital organs and male fertility as observed in rats. The applicant will raise caution in the package insert, instructing healthcare professionals to explain the potential risk of sotatercept's affecting fertility to patients of reproductive age.

In view of the applicant's explanation, PMDA concluded that the testis toxicity observed in toxicity studies in rats is not shown to cause problems in humans at the present time.

5.R.3 Safety in children

In view of the findings in juvenile animal studies, PMDA asked the applicant to explain the safety of sotatercept in children.

The applicant's explanation:
In juvenile rats, toxicity findings were observed at all doses, and the NOAEL was determined to be <1 mg/kg, which was lower than the NOAEL (3 mg/kg) in a 3-month repeated-dose toxicity study in rats. Organs mainly affected in juvenile rats were kidney and male genital organs, and no toxicity target

organs specific to juvenile animals were identified, but in juvenile rats which appeared to be more sensitive to sotatercept, the adverse effects tended to worsen. The possibility that sotatercept has remarkable toxicity in the above organs at a developmental stage cannot be ruled out, but in view of the timing of organ development in humans, extrapolation of the toxicity findings to children aged ≥1 year is considered unapplicable as done to adults. However, toxicity attributable to the pharmacological action of sotatercept may manifest in children aged <1 year in whom many organs rapidly grow and mature.

PMDA's view:
In juvenile animal studies, more severe toxicity findings were observed in the kidney, adrenal gland, and male genital organs, the main toxicity target organs of sotatercept, than in mature rats [see Sections 5.2 and 5.5]. Concerning the findings in the kidney and male genital organs, no adverse events related to the kidney occurred in clinical studies, and extrapolation of the toxicity findings in rat male genital organs to humans is considered unapplicable [see Section 5.R.2], but the possibility that children with organs being developing including those aged ≥1 year are more markedly affected than adults cannot be ruled out. In addition, concerning the findings in the adrenal gland, in view of the undeniable possibility that sotatercept affected organ development and the developmental course of the adrenal gland in humans, the adrenal gland may be affected in children aged <1 year.

At the present time, sotatercept may be recommended to adult patients with PAH, the population included in Study 003 and Japanese phase III study (Study 020) [see Section 7.R.5]. Whether children are eligible should be finally determined in view of results from a currently ongoing foreign clinical study in children [see Section 7.R.8]. However, the treatment algorithm for PAH in children is applied in accordance with the treatment guidelines in adults, and potential use of sotatercept in children in post-marketing settings cannot be ruled out. The package insert, a guide for healthcare professionals, and other materials should include the information that sotatercept may affect organ development in children (adrenal gland, kidney, and male genital organs).

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

Unless otherwise specified, PK parameters are expressed as the mean ± standard deviation (SD).

6.1 Summary of biopharmaceutic studies and associated analytical methods

During development of sotatercept, changes were made to the manufacturing process and manufacturing site for the drug substance as well as the formulation, manufacturing process, and manufacturing site for the drug product, but comparability of products before and after each change has been demonstrated [see Sections 2.1.4 and 2.2.3]. The to-be-marketed formulation is presented in vials and is the same as that used in a Japanese phase I study (Study 019), a foreign phase III study (Study 003), and a Japanese phase III study (Study 020).

Serum sotatercept concentrations were determined by 2 types of competitive ELISA (first or second generation),[13] and the lower limit of quantitation was 8.0 or 40 ng/mL.

Serum concentrations of ADA against sotatercept were determined by ELISA or electrochemiluminescence (ECL), and detection sensitivity was 100 or 5.0 ng/mL. Serum concentrations of neutralizing antibodies against sotatercept were determined by ELISA or ECL, and detection sensitivity was 207 or 176 ng/mL.

6.2 Clinical pharmacology

6.2.1 Studies in healthy adults

6.2.1.1 Single-dose study in non-Japanese healthy adults (Study 009, CTD 5.3.3.1.1 [reference data], study period ■ 20■ to ■ 20■)

Table 17 shows PK parameters of sotatercept in healthy postmenopausal non-Japanese women who received a single dose of sotatercept 0.01, 0.03, 0.1, 0.3, 1.0, or 3.0 mg/kg intravenously over approximately 60 minutes or a single dose of sotatercept 0.03 or 0.1 mg/kg subcutaneously.

Table 17. PK parameters of sotatercept after single intravenous or subcutaneous administration of sotatercept

Route of administration	Dose (mg/kg)	Number of subjects	C_{max} (μg/mL)	t_{max} (day)	$AUC_{0\text{-last}}$ (μg·day/mL)	$AUC_{0\text{-}\infty}$ (μg·day/mL)	$t_{1/2}$ (day)	CL[b] (mL/h/kg)	V_z[b] (mL/kg)
Intravenous	0.01	3	0.199 ± 0.0205	0.063 [0.06, 0.08]	2.92 ± 1.27	1.98, 5.01[a]	14.1, 76.1[a]	0.083, 0.211[a]	103, 219[a]
	0.03	3	0.496 ± 0.0826	0.063 [0.06, 0.08]	9.89 ± 1.34	9.58, 13.9[a]	34.7, 63.2[a]	0.090, 0.130[a]	157, 197[a]
	0.1	5	2.19 ± 0.447	0.064 [0.06, 0.07]	31.1 ± 4.76	32.4 ± 5.30	24.6 ± 4.1	0.132 ± 0.023	113 ± 31.3
	0.3	5	8.22 ± 0.974	0.063 [0.06, 0.08]	112 ± 20.0	120 ± 23.5	31.8 ± 17.6	0.108 ± 0.023	113 ± 50.3
	1.0	5	26.8 ± 3.32	0.083 [0.06, 0.38]	436 ± 75.2	452 ± 84.9	23.7 ± 5.0	0.095 ± 0.018	75.8 ± 10.5
	3.0	5	82.4 ± 12.3	0.063 [0.06, 0.13]	1270 ± 180	1330 ± 215	25.6 ± 5.0	0.096 ± 0.015	83.7 ± 11.8
Subcutaneous	0.03	5	0.269 ± 0.121	6.96 [1.00, 28.0]	10.9 ± 3.60	11.7 ± 3.89	30.8 ± 10.1	0.117 ± 0.039	126 ± 67.8
	0.1	5	0.747 ± 0.160	3.99 [3.98, 6.99]	30.2 ± 8.00	32.5 ± 9.86	28.6 ± 7.4	0.139 ± 0.043	129 ± 15.9

t_{max} is expressed as the median [minimum, maximum].
a Individual values in 2 subjects
b For subcutaneous, the value was calculated as CL/F or V_z/F.

6.2.1.2 Multiple-dose study in non-Japanese healthy adults (Study 010, CTD 5.3.3.1.2 [reference data], study period ■ to ■ 20■)

Tables 18 and 19 show PK parameters of sotatercept in healthy postmenopausal non-Japanese women who subcutaneously received up to 4 doses[14] of sotatercept 0.1, 0.3 or 1.0 mg/kg Q4W.

[13] The 2 analytical procedures used the same reagents but differed in terms of the range of the calibration curve and minimum dilution factor. In foreign phase I studies (Studies 009 and 010), the first generation analytical procedure was used, and in a Japanese phase I study (Study 019), a foreign phase III study (Study 003), and a Japanese phase III study (Study 020), the second generation analytical procedure was used.

[14] The study was early terminated after the second dose in the 1.0 mg/kg group because of a serious adverse event in 1 subject in the 1.0 mg/kg group. Only in the 0.1 mg/kg group, subjects received 4 doses, and those in 0.3 mg/kg and 1.0 mg/kg groups received 3 and 2 doses, respectively.

Table 18. PK parameters of sotatercept after the first dose of sotatercept following multiple subcutaneous administration Q4W

Dose (mg/kg)	Number of subjects	$AUC_{0\text{-}28d}$ (μg·day/mL)	C_{max} (μg/mL)	t_{max} (day)
0.1	8	15.5 ± 3.91	0.746 ± 0.225	7.00 [2.95, 14]
0.3	8	54.5 ± 13.2	2.46 ± 0.601	6.99 [6.95, 13.98]
1.0	8	148 ± 33.9	7.39 ± 1.18	7.01 [6.96, 26.93]

t_{max} is expressed as the median [minimum, maximum].

Table 19. PK parameters of sotatercept after the last dose of sotatercept following multiple subcutaneous administration Q4W

Dose (mg/kg)	Number of subjects	$AUC_{0\text{-}28d}$ (μg·day/mL)	C_{max} (μg/mL)	t_{max} (day)	$t_{1/2}$ (day)	K_a (/day)	CL/F (mL/day/kg)	V_z/F (mL/kg)
0.1	8	33.0 (22.8)	1.54 (21.63)	6.98 [1.97, 8.02]	23.37 (15.16)	0.45 (63.83)	3.22 (27.73)	97.47 (19.79)
0.3	8	-	-	-	22.79 (19.2)	0.38 (42.32)	3.05 (31.62)	99.09 (20.49)
1.0	8	-	-	-	22.83 (24.48)	0.32 (37.74)	3.90 (44.24)	103.03 (19.41)

Arithmetic mean (coefficient of variation %); t_{max} is expressed as the median [minimum, maximum].
-, Not calculated in the 0.3 mg/kg and 1.0 mg/kg groups because samples for PK were not frequently collected.

6.2.1.3 Single dose study in Japanese healthy adults (Study 019, CTD 5.3.3.3.1, study period [redacted] 20[redacted] to [redacted] 20[redacted])

Table 20 shows PK parameters of sotatercept in Japanese healthy adults who subcutaneously received a single dose of sotatercept 0.3 or 0.7 mg/kg.

Table 20. PK parameters of sotatercept after single subcutaneous administration of sotatercept

Dose (mg/kg)	Number of subjects	$AUC_{0\text{-}\infty}$[a] (μg·day/mL)	$AUC_{0\text{-}28d}$[a] (μg·day/mL)	C_{max}[a] (μg/mL)	t_{max}[b] (day)	$t_{1/2}$[c] (day)	CL/F[c] (mL/day/kg)	V_z/F[c] (mL/kg)
0.3	10[d]	74.1 [62.6, 87.6]	42.6 [36.5, 49.8]	2.15 [1.81, 2.56]	4.00 [2.00, 7.00]	21.5 (21.7)	4.05 (22.0)	126 (32.6)
0.7	10	171 [146, 201]	102 [88.5, 119]	5.15 [4.33, 6.13]	4.00 [2.00, 7.00]	19.2 (19.3)	4.09 (26.1)	113 (18.6)

a Reverse transformed values of the least square mean and 95% confidence interval (CI) calculated from natural-logarithmic transformed values in an analysis of variance model
b Median [minimum, maximum]
c Geometric mean (coefficient of variation %)
d Because 1 subject who received sotatercept 0.3 mg/kg on Day 19 was withdrawn from the study, $AUC_{0\text{-}\infty}$, $AUC_{0\text{-}28d}$, $t_{1/2}$, CL/F, and V_z/F were calculated from the data in 9 subjects.

Two subjects in the sotatercept 0.3 mg/kg group and 5 subjects in the 0.7 mg/kg group were positive for ADA,[15)] but no neutralizing antibody was detected in any subject.

6.2.2 PPK analysis

6.2.2.1 PPK analysis on clinical study data in non-Japanese subjects (CTD 5.3.3.5.1)

A population pharmacokinetic (PPK) analysis was performed on serum sotatercept concentration data at 3906 sampling points from 350 subjects in the foreign phase I studies in healthy postmenopausal women (Studies 009 and 010) and foreign phase II studies (Studies 001 and 002) and a foreign phase III study (Study 003) in patients with PAH (NONMEM Version 7.3.0).

The PK of sotatercept was described in a 2-compartment model with first-order absorption.

15) Subjects who were not positive for ADA before sotatercept therapy but became positive for ADA after that. None of the subjects were positive for ADA on Day 120, day of the last evaluation.

The analysis involved 52 men and 298 women at 50 [18, 81] (median [minimum, maximum]) years of age, with baseline body weight of 67.2 [39.6, 136] kg, and baseline albumin level of 4.5 [2.9, 5.8] g/dL. The population included 290 Caucasians, 25 Asians, 11 African Americans, 4 Native Hawaiians or other Pacific islanders, 1 Native American or Alaska Native, and 19 other-ethnic group subjects. Renal function was normal in 116 subjects, mildly impaired in 183 subjects, and moderately impaired in 51 subjects. A total of 64 subjects were healthy, while 286 were PAH patients. Potential covariates for PK parameters investigated were the disease status (healthy or PAH), race, sex, ADA status, body weight at baseline and over time as well as age, albumin level, estimated glomerular filtration rate (eGFR), background PAH therapy, and baseline World Health Organization (WHO) Functional class (FC). In the final model, statistically significant covariates selected were body weight over time and baseline albumin level for CL, and body weight over time for V_c. However, none of these covariates were considered to have clinically significant effects on the PK parameters of sotatercept, because body weight-based doses were administered.

6.2.2.2 PPK analysis on clinical study data in non-Japanese and Japanese subjects (CTD 5.3.3.5.2)

A PPK analysis was performed on serum sotatercept concentration data at 4392 sampling points from 416 subjects in 5 foreign clinical studies included in Section 6.2.2.1 and a Japanese phase I study in Japanese healthy adults (Study 019) and a Japanese phase III study in Japanese patients with PAH (Study 020). In this analysis, the final model developed in Section 6.2.2.1 was used as the base model. Effects of race (Japanese or non-Japanese) on PK parameters (CL, V_c, V_p, K_a, and F) were investigated, but the race did not have a significant effect on any of the PK parameters.

The population mean (relative standard error) of the PK parameters in the final model was 0.175 L/day (6.06%) for CL, 3.65 L (5.10%) for V_c, 1.53 L (15.2%) for V_p, 0.300 /day (12.0%) for K_a, and 0.644 (6.16%) for F. Table 21 shows estimated PK parameters of sotatercept after a single subcutaneous administration of sotatercept 0.3 mg/kg or after subcutaneous administration every 3 weeks (Q3W) of sotatercept 0.7 mg/kg.

Table 21. PK parameters of sotatercept estimated in the PPK analysis

Dose (mg/kg)	Population	$AUC_{0\text{-}21d}$ (μg·day/mL)	C_{max} (μg/mL)	C_{min} (μg/mL)
0.3	Japanese	30.19 (24.08)	1.82 (21.93)	1.10 (30.99)
	Non-Japanese	33.38 (26.41)	1.98 (24.46)	1.28 (33.39)
0.7	Japanese	154.99 (30.59)	8.94 (25.64)	5.31 (41.36)
	Non-Japanese	171.71 (34.03)	9.74 (29.89)	6.03 (41.26)

Geometric mean (coefficient of variation %)

6.2.3 Investigation of endogenous factors

6.2.3.1 Effects of hepatic impairment and renal impairment on PK of sotatercept

The applicant's explanation:

Although no clinical pharmacological studies in patients with hepatic or renal impairment have been conducted, in view of the following points, decreased hepatic or renal function is unlikely to affect PK of sotatercept:

- Sotatercept is a protein comprised of only natural amino acids, and is expected to be degraded into amino acids and eliminated from the body via catabolic pathways.

- In Section 6.2.2.1, eGFR was not selected as a covariate significantly affecting the exposure to sotatercept.

6.R Outline of the review conducted by PMDA

6.R.1 Difference in PK between Japanese and non-Japanese subjects

The applicant's explanation about difference in PK between Japanese and non-Japanese subjects:
Based on the results from the foreign phase I study (Study 010) and Japanese phase I study (Study 019), C_{max} and $AUC_{0\text{-}28d}$ after a single subcutaneous administration of sotatercept 0.3 mg/kg in Japanese subjects were similar to those in non-Japanese subjects (Tables 18 and 20).

In simulation in the PPK analysis using data from the foreign phase I studies (Studies 009 and 010), foreign phase II studies (Studies 001 and 002), foreign phase III study (Study 003), Japanese phase I study (Study 019), and Japanese phase III study (Study 020), the exposure after a single subcutaneous administration of sotatercept 0.3 mg/kg or subcutaneous administration Q3W of sotatercept 0.7 mg/kg in Japanese subjects were almost similar to that in non-Japanese subjects (Table 21).

The proposed dosing regimen is considered to cause no clear difference in PK between Japanese and non-Japanese subjects.

PMDA accepts the applicant's explanation about no clear difference in PK between Japanese and non-Japanese subjects.

6.R.2 ADA

The applicant's explanation about effects of ADA and neutralizing antibody on PK, efficacy, and safety of sotatercept:
Table 22 shows proportions of ADA-positive and neutralizing antibody-positive subjects in the sotatercept group in Studies 003 and 020.

Table 22. Proportions of ADA-positive and neutralizing antibody-positive subjects in the sotatercept group in Studies 003 and 020

Study	Sotatercept	
	ADA-positive	Neutralizing antibody-positive[a]
Study 003	27.0 (44/163)	27.3 (12/44)
Study 020	39.1 (18/46)	33.3 (6/18)

% (number of subjects)
a The denominator is the number of ADA-positive subjects.

Serum trough sotatercept concentrations (median [minimum, maximum]) in ADA-positive, ADA-negative, and neutralizing antibody-positive subjects in Study 003 were 1.39 [0.609, 7.11], 1.35 [0.00, 4.62], and 1.44 [0.678, 2.32] μg/mL at Week 3 and 5.98 [0.186, 15.6], 5.88 [0.848, 14.1], and 5.68 [0.186, 15.6] μg/mL at Week 24, respectively. Serum trough sotatercept concentrations in ADA-positive, ADA-negative, and neutralizing antibody-positive subjects in Study 020 were 1.34 [0.611, 2.25], 1.15 [0.286, 2.26], and 1.17 [0.784, 1.85] μg/mL at Week 3 and 5.24 [0.0875, 11.1], 5.17 [1.90, 10.9], and 3.55 [0.0875, 5.51] μg/mL at Week 24, respectively. As a result of search for covariates in the PPK analysis, ADA was not selected as a covariate for the PK parameter (CL) of sotatercept [see Section 6.2.2.1].

In Studies 003 and 020, status of ADA or neutralizing antibody did not clearly affect changes in 6-minute walk distance (6MWD) or PVR from baseline. Results from Studies 003 and 020 showed no clear relationship between occurrence of immunogenicity-related events (hypersensitivity, anaphylactic reaction, and administration site reaction) and development of ADA and neutralizing antibody.

Based on the above, ADA or neutralizing antibodies do not affect PK, efficacy, or safety of sotatercept.

PMDA has concluded that the clinical study results were not suggestive of ADA or neutralizing antibodies substantially affecting PK, efficacy, or safety of sotatercept.

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 4 studies listed in Table 23 [for PK, see Section 6].

Table 23. Outline of main clinical studies

Data category	Region	Study identifier	Phase	Study population	Number of subjects enrolled	Dosage regimen	Main endpoints
Evaluation	Japan	019	I	Healthy adults	26	Single subcutaneous administration of placebo or sotatercept 0.3 or 0.7 mg/kg	Safety PK
	Foreign	001	II	Patients with PAH	106	[Main treatment period] Subcutaneous administration Q3W of placebo or sotatercept 0.3 or 0.7 mg/kg for 24 weeks [Extended treatment period] Subcutaneous administration Q3W of sotatercept 0.3 or 0.7 mg/kg for up to 129 weeks	Efficacy Safety
	Foreign	003	III	Patients with PAH	323	[Main treatment period] Subcutaneous administration Q3W of placebo or sotatercept 0.7 mg/kg (starting dose of 0.3 mg/kg)[a] for 24 weeks [Extended treatment period] Subcutaneous administration Q3W of placebo or sotatercept 0.7 mg/kg[a] for up to 72 weeks	Efficacy Safety
	Japan	020	III	Patients with PAH	46	[Main treatment period] Subcutaneous administration Q3W of sotatercept 0.7 mg/kg (starting dose of 0.3 mg/kg)[a] for 24 weeks [Extended treatment period] Subcutaneous administration Q3W of sotatercept 0.7 mg/kg[a]	Efficacy Safety

a The dose was modified according to the dose modification guidelines.

7.1 Japanese phase I study (Study 019, CTD 5.3.3.3.1, study period [redacted] 20[redacted] to [redacted] 20[redacted])

A randomized, double-blind study was conducted at 1 study center in Japan to investigate safety and PK of sotatercept in Japanese healthy adults who subcutaneously received a single dose of sotatercept 0.3 or 0.7 mg/kg (target sample size, 26 subjects [Panel A, 3 in the placebo group and 10 in the sotatercept 0.3 mg/kg group; Panel B, 3 in the placebo group and 10 in the sotatercept 0.7 mg/kg group]).

All of 26 randomized subjects received the study drug and were included in the safety analysis population. One subject in the sotatercept 0.3 mg/kg group discontinued the study because of consent withdrawal.

Table 24 shows incidences of adverse events, and no deaths, serious adverse events, or adverse events leading to discontinuation of the study drug occurred.

Table 24. Incidences of adverse events (safety analysis population)

	Placebo (n = 6)	Sotatercept	
		0.3 mg/kg (n = 10)	0.7 mg/kg (n = 10)
All adverse events	66.7 (4)	40.0 (4)	70.0 (7)
Main events[a]			
Red blood cell count increased	16.7 (1)	20.0 (2)	50.0 (5)
Haemoglobin increased	0 (0)	10.0 (1)	20.0 (2)
Orthostatic hypotension	16.7 (1)	0 (0)	20.0 (2)

% (number of subjects)
a Events reported by ≥2 subjects in either group

7.2 Foreign phase II studies

7.2.1 Study 001 (CTD 5.3.5.1.1, study period June 2018 to March 2022)

A placebo-controlled, randomized, double-blind study was conducted at 43 study centers outside Japan to investigate efficacy and safety of sotatercept in non-Japanese patients with PAH (target sample size, 100 subjects [30 in the placebo group, 30 in the sotatercept 0.3 mg/kg group, 40 in the sotatercept 0.7 mg/kg group][16]).

This study consisted of the screening period of up to 4 weeks, main treatment period of 24 weeks, extended treatment period of up to 129 weeks,[17] and follow-up period of 8 weeks.[18]

Patients with PAH aged ≥18 years who met the following criteria were enrolled.

- Diagnosis of any of the following subtypes classified into WHO PH Group 1: Idiopathic pulmonary arterial hypertension (IPAH), heritable pulmonary arterial hypertension (HPAH), drug/toxin-induced PAH, PAH associated with connective tissue diseases, or PAH associated with simple, congenital systemic-to-pulmonary shunts at least 1 year following repair
- WHO FC II or III
- Screening PVR, ≥400 dyn·sec/cm^5
- Two 6MWD values during the screening period, both ≥150 m and ≤550 m; and the difference between the 2 values, ≤15% of the greater value
- Receiving background PAH therapy at stable doses for ≥90 days before the first dose of the study drug (no dose modification allowed until the completion of the main treatment period)

16) At the time of study planning, the target sample size was 90 subjects, who were planned to be randomized to 1 of 3 groups in a 1:1:1 ratio, but in view that a certain number of patients in the sotatercept 0.7 mg/kg group were supposed to require dose reduction, the target sample size and randomization ratio were changed to 100 subjects and 3:3:4 (placebo: sotatercept 0.3 mg/kg: sotatercept 0.7 mg/kg), respectively, in the protocol version 5 (dated December 5, 2018).
17) It was changed from 18 months to a period of up to 30 months allowed by the investigator in the protocol version 6 (dated April 1, 2020).
18) Baseline values were defined for each evaluation item as follows:
PVR and WHO FC, values at screening; 6MWD, mean of 2 measured values at screening or before administration on day of the first dose of the study drug; echocardiography parameters and quality of life (QOL), values before administration on day of the first dose of the study drug

Patients enrolled were randomized to the placebo group, sotatercept 0.3 mg/kg group, or 0.7 mg/kg group at a 1:1:1 ratio using baseline WHO FC (Class II or III) as a stratification factor. The randomization ratio was changed to 3:3:4 in the protocol version 5 (dated December 5, 2018).

(a) Main treatment period

Placebo or sotatercept 0.3 or 0.7 mg/kg was administered subcutaneously Q3W. Interruption and dose reduction of the study drug were allowed based on the dose modification guidelines [see Table 25] or investigator's assessment up to 3 times and 2 times, respectively, throughout the study period.

Table 25. Dose modification guidelines of the study drug

[Doses of sotatercept after reduction]

Starting dose	Dose after first reduction	Dose after second reduction
0.3 mg/kg	0.1 mg/kg	0.05 mg/kg
0.7 mg/kg	0.3 mg/kg	0.1 mg/kg

- If a dose was reduced because of an adverse event for which a causal relationship to the study drug was ruled out, dose escalation of the study drug was allowed after resolution of the event.
- If a dose was reduced because of increased hemoglobin level or decreased platelet count, dose escalation was allowed after the hemoglobin level or platelet count was confirmed to be stabilized in consecutive 2 cycles.

[Interruption and resumption after interruption]

Hemoglobin level	• Interrupt treatment if the hemoglobin level increases by >2.0 g/dL from the pre-dose value at the previous visit and exceeds the sex-specific upper limit of normal (ULN). If the increase from baseline is >4.0 g/dL, consider treatment discontinuation in consultation with the sponsor. • If the increase in hemoglobin after the interruption reaches ≤2.0 g/dL, resume treatment at the pre-interruption dose level.
Platelet count	• Interrupt treatment if the platelet count is <50,000 /mm^3. The third interruption is regarded as treatment discontinuation. • If the platelet count after the interruption reaches ≥50,000 /mm^3, resume treatment at the pre-interruption dose level.

All of 106 randomized subjects (32 in the placebo group, 32 in the sotatercept 0.3 mg/kg group, 42 in the sotatercept 0.7 mg/kg group) received the study drug and were also included in the safety analysis population and full-analysis set (FAS). Of the FAS, 91 subjects (30 subjects, 30 subjects, 31 subjects) who received the study drug at the same dose ≥6 times during the main treatment period and provided PVR data at baseline and during the main treatment period or at the end of the study treatment were included in the evaluable population, which served as the primary efficacy analysis population. A total of 9 subjects (2 subjects, 1 subject, 6 subjects) discontinued the study mainly because of adverse events (1 subject, 1 subject, 4 subjects) and consent withdrawal (1 subject, 0 subjects, 1 subject).

Table 26 shows results on the change in PVR from baseline to Week 24, the primary efficacy endpoint.

Table 26. Change in PVR from baseline to Week 24 (dyn·sec/cm^5) (evaluable population)

	Placebo	Sotatercept 0.1 mg/kg dosed population[d]	Sotatercept 0.3 mg/kg dosed population[d]	Sotatercept 0.7 mg/kg dosed population[d]
Baseline[a]	802.0 ± 331.05 (n = 30)	853.3 ± 340.09 (n = 4)	772.0 ± 285.62 (n = 27)	715.5 ± 267.11 (n = 30)
Week 24[a]	774.4 ± 355.00 (n = 30)	677.1 ± 201.75 (n = 4)	603.6 ± 156.61 (n = 27)	456.6 ± 176.52 (n = 30)
Change from baseline[b, c]	-16.1 ± 34.24	-138.2 ± 93.37	-167.2 ± 35.88	-285.5 ± 34.27
Difference from placebo [2-sided 80% CI][c]	-	-122.0 [-250.28, 6.21]	-151.1 [-215.09, -87.14]	-269.4 [-332.03, -206.80]

a Mean ± SD
b Least squares mean ± SE
c Analysis of covariance (ANCOVA) using the dose group as a fixed effect and WHO FC and PVR at baseline as covariates
d Subjects who had received the study drug at a reduced dose were included in a dosed population based on the dose given ≥6 times but not the initially randomized dose.

Table 27 shows results on a change in 6MWD from baseline to Week 24, the secondary endpoint.

Table 27. Change in 6MWD from baseline to Week 24 (m) (evaluable population)

	Placebo	Sotatercept 0.1 mg/kg dosed population	Sotatercept 0.3 mg/kg dosed population	Sotatercept 0.7 mg/kg dosed population
Baseline[a]	409.2 ± 65.94 (n = 30)	391.6 ± 68.59 (n = 4)	392.0 ± 92.52 (n = 27)	392.9 ± 94.28 (n = 30)
Week 24[a]	444.1 ± 82.27 (n = 29)	461.8 ± 66.21 (n = 4)	449.1 ± 113.17 (n = 27)	461.5 ± 82.74 (n = 27)
Change from baseline[b]	31.4 ± 9.69	69.4 ± 26.14	56.0 ± 10.07	53.6 ± 9.84
Difference from placebo [2-sided 80% CI][c]	-	38.0 [2.25, 73.72]	24.6 [6.64, 42.48]	22.3 [4.55, 39.96]

a Mean ± SD
b Least squares mean ± SE
c ANCOVA using the dose group as a fixed effect and WHO FC and 6MWD at baseline as covariates

Table 28 shows incidences of adverse events during the main treatment period.

Table 28. Incidences of adverse events during the main treatment period (safety analysis population)

	Placebo (n = 32)	Sotatercept 0.3 mg/kg (n = 32)	Sotatercept 0.7 mg/kg (n = 42)
All adverse events	90.6 (29)	90.6 (29)	83.3 (35)
Main adverse events[a]			
Haemoglobin increased	0 (0)	3.1 (1)	16.7 (7)
Headache	18.8 (6)	25.0 (8)	14.3 (6)
Diarrhoea	15.6 (5)	21.9 (7)	14.3 (6)
Epistaxis	3.1 (1)	12.5 (4)	11.9 (5)
Nausea	15.6 (5)	9.4 (3)	11.9 (5)
Oedema peripheral	15.6 (5)	9.4 (3)	11.9 (5)
Hypokalaemia	12.5 (4)	9.4 (3)	11.9 (5)
Pain in extremity	6.3 (2)	9.4 (3)	11.9 (5)
Thrombocytopenia	0 (0)	6.3 (2)	11.9 (5)
Dizziness	9.4 (3)	15.6 (5)	9.5 (4)
Fatigue	18.8 (6)	6.3 (2)	9.5 (4)
Vomiting	12.5 (4)	9.4 (3)	7.1 (3)
Upper respiratory tract infection	9.4 (3)	12.5 (4)	4.8 (2)
Arthralgia	15.6 (5)	6.3 (2)	2.4 (1)

% (number of subjects)
a Events reported by ≥10% of subjects in any group

An adverse event leading to death occurred in 1 subject in the sotatercept 0.7 mg/kg group (cardiac arrest), but the causal relationship to the study drug was ruled out. Serious adverse events occurred in 9.4% (3 of 32) of subjects in the placebo group (cardiac arrest; right ventricular failure and migraine; and gastroenteritis in 1 subject each), in 6.3% (2 of 32) of subjects in the sotatercept 0.3 mg/kg group

(right ventricular failure and epistaxis in 1 subject each), in 23.8% (10 of 42) of subjects in the sotatercept 0.7 mg/kg group (red blood cell count increased; femur fracture; syncope and cardiac arrest; chorioretinopathy and device breakage; influenza and tachycardia; oedema peripheral and hypotension; respiratory tract infection, leukopenia, and neutropenia; pyrexia; pericardial effusion; and bronchitis in 1 subject each). Migraine in the placebo group and red blood cell count increased and pyrexia in the sotatercept 0.7 mg/kg group were assessed as causally related to the study drug. Adverse events leading to discontinuation of the study drug occurred in 3.1% (1 of 32) of subjects in the placebo group (dyspnoea), in 3.1% (1 of 32) of subjects in the sotatercept 0.3 mg/kg group (polycythaemia), and in 11.9% (5 of 42) of subjects in the sotatercept 0.7 mg/kg group (red blood cell count increased; cardiac arrest; thrombocytopenia; leukopenia and neutropenia; haemoglobin increased in 1 subject each). Dyspnoea in the placebo group and red blood cell count increased and haemoglobin increased in the sotatercept 0.7 mg/kg group were assessed as causally related to the study drug.

(b) Extended treatment period

The subjects who had completed the main treatment period and undergone PVR assessment at Week 24 were allowed to enter the extended treatment period in which sotatercept was administered subcutaneously Q3W (Table 29). The same dose modification guidelines as those in the main treatment period (Table 25) were applied.

Table 29. Doses of sotatercept in the extended treatment period

	Dose group in the main treatment period /dose group in the extended treatment period	Dose	
		Before unblinding[a]	After unblinding[a]
Group A	Placebo/sotatercept 0.3 mg/kg	0.3 mg/kg	The dose may be escalated to 0.7 mg/kg based on the investigator's decision.
Group B	Placebo/sotatercept 0.7 mg/kg	0.7 mg/kg	
Group C	Sotatercept 0.3 mg/kg/sotatercept	The dose at Week 24 (0.1, 0.3, or 0.7 mg/kg) should be continued.	
Group D	Sotatercept 0.7 mg/kg/sotatercept		

a Unblinded after PVR assessment by the third session of right heart catheterization (RHC)

A total of 97 subjects entered the extended treatment period, and all subjects received the study drug (15 subjects in Group A, 15 subjects in Group B, 31 subjects in Group C, 36 subjects in Group D). During the extended treatment period, 10 subjects (2 subjects, 0 subjects, 3 subjects, 5 subjects) discontinued the study mainly because of death in 4 subjects (1 subject, 0 subjects, 1 subject, 2 subjects), adverse events in 2 subjects (0 subjects, 0 subjects, 1 subject, 1 subject), and consent withdrawal in 3 subjects (1 subject, 0 subjects, 1 subject, 1 subject). A total of 104 subjects who received sotatercept during the study period of Study 001 (main treatment period and/or extended treatment period) were included in the safety analysis population. The period[19)] of exposure to sotatercept in this population (median [range]) was 903 (41-1071) days.

Table 30 shows incidences of adverse events after the first dose of sotatercept in the study period of Study 001 (main treatment period and/or extended treatment period).

19) Including the period of exposure in the main treatment period

Table 30. Incidences of adverse events after the first dose of sotatercept in the main treatment period and/or extended treatment period (safety analysis population)

	Sotatercept 0.3 mg/kg pooled group[b] (n = 47)	Sotatercept 0.7 mg/kg pooled group[c] (n = 57)	Overall (n = 104)
All adverse events	97.9 (46)	100 (57)	99.0 (103)
Main adverse events[a]			
Headache	36.2 (17)	33.3 (19)	34.6 (36)
Diarrhoea	38.3 (18)	28.1 (16)	32.7 (34)
Oedema peripheral	36.2 (17)	28.1 (16)	31.7 (33)
Fatigue	29.8 (14)	21.1 (12)	25.0 (26)
Nasopharyngitis	31.9 (15)	19.3 (11)	25.0 (26)
Nausea	27.7 (13)	21.1 (12)	24.0 (25)
Epistaxis	23.4 (11)	21.1 (12)	22.1 (23)
Arthralgia	25.5 (12)	19.3 (11)	22.1 (23)
Dizziness	25.5 (12)	17.5 (10)	21.2 (22)
Telangiectasia	19.1 (9)	21.1 (12)	20.2 (21)

% (number of subjects)

a Events reported by ≥20% of subjects in the overall population

b Pool of 1 subject in the sotatercept 0.3 mg/kg group who discontinued the study during the main treatment period as well as Groups A and C during the extended treatment period

c Pool of 6 subjects in the sotatercept 0.7 mg/kg group who discontinued the study during the main treatment period as well as Groups B and D during the extended treatment period

During the extended treatment period, adverse events leading to death occurred in 2 subjects in the sotatercept 0.3 mg/kg pooled group[20] (pulmonary hypertension, pneumonia) and 2 subjects in the sotatercept 0.7 mg/kg pooled group[21] (cardiac arrest, brain abscess). Pulmonary hypertension in the sotatercept 0.3 mg/kg pooled group was assessed as causally related to the study drug. Serious adverse events occurred in 16 subjects in the sotatercept 0.3 mg/kg pooled group and 16 subjects in the sotatercept 0.7 mg/kg pooled group. The events reported by ≥3 subjects in the sotatercept group overall were pneumonia (5 subjects) and device malfunction (4 subjects), a causal relationship to the study drug was ruled out for all these events. Adverse events leading to discontinuation of the study drug occurred in 2 subjects in the sotatercept 0.3 mg/kg pooled group (pleural effusion, pulmonary hypertension) and 3 subjects in the sotatercept 0.7 mg/kg pooled group (brain abscess; sepsis, pleural effusion, and respiratory failure; respiratory failure). Events in 2 subjects in the sotatercept 0.3 mg/kg pooled group (pleural effusion, pulmonary hypertension) and respiratory failure in 1 subject in the sotatercept 0.7 mg/kg pooled group were assessed as causally related to the study drug.

7.3 Phase III studies

7.3.1 Foreign phase III study (Study 003, 5.3.5.1.2, 5.3.5.1.3, study period January 2021 to February 2022)

A placebo-controlled, randomized, double-blind study was conducted at 91 study centers outside Japan to investigate efficacy and safety of sotatercept in non-Japanese patients with PAH (target sample size, 284 subjects [142 per group][22]).

---

[20] Pool of 1 subject in the sotatercept 0.3 mg/kg group who discontinued the study during the main treatment period as well as Groups A and C during the extended treatment period

[21] Pool of 6 subjects in the sotatercept 0.7 mg/kg group who discontinued the study during the main treatment period as well as Groups B and D during the extended treatment period

[22] Based on the results from the foreign phase II study (Study 001), a difference in change in 6MWD from baseline to Week 24, the primary endpoint, between the sotatercept group and placebo group was assumed to be 25 m with a common standard deviation for both groups of 50 m. Assuming a significance level of 5% (2-sided) and the sample size of 242 (121 subjects per group), the statistical power for group-comparison under the Wilcoxon rank sum test was approximately 96%. Assuming a 15% dropout rate, the target sample size of 284 (142 per group) was selected. Recruitment was controlled to ensure that at least 50% of enrolled patients were PAH in WHO FC Class III.

This study consisted of the screening period of up to 28 days, main treatment period of 24 weeks, extended treatment period of up to 72 weeks,[23] and follow-up period of 8 weeks. Subjects who had completed the main treatment period were allowed to enter the extended treatment period, during which the study drug assigned for the main treatment period was continued under the double-blind condition.

Patients with PAH aged ≥18 years who met the following criteria were included in this study:

- Diagnosis of any of the following subtypes classified into WHO PH Group 1: IPAH, HPAH, drug/toxin-induced PAH, PAH associated with connective tissue diseases, or PAH associated with simple, congenital systemic-to-pulmonary shunts at least 1 year following repair
- WHO FC II or III
- Screening PVR, ≥400 dyn·sec/cm^5
- Two 6MWD values during the screening period, both ≥150 m and ≤500 m; and the difference between the 2 values, ≤15% of the greater value
- Receiving background PAH therapy at stable doses for ≥90 days before screening (no dose modification was allowed throughout the study period)
- Screening platelet count, ≥50,000/mm^3
- Screening hemoglobin level, equal to or below the upper limit of normal (ULN)

Patients enrolled were randomized to the placebo group or sotatercept group at a 1:1 ratio using WHO FC (Class II or III) at baseline and background PAH therapy (mono/double or triple therapy) as stratification factors.

In this study, placebo or sotatercept was administered subcutaneously Q3W. Sotatercept was started at 0.3 mg/kg and then escalated to 0.7 mg/kg, the target dose, according to the dose modification guidelines in Table 31. During the study, the dose was modified based on the dose modification guidelines or investigator's assessment.

[23] The extended treatment period was continued until the last randomized subject completed the main treatment period.

Table 31. Dose modification guidelines for study drug

[Dose modification due to increased hemoglobin]
(a): Increase in hemoglobin >2.0 g/dL from last dosing visit which is above the sex-specific ULN

When the dose is 0.3 mg/kg:	• If (a) is not applicable, escalate the dose to 0.7 mg/kg. • If (a) is applicable, interrupt treatment. If an increase from baseline is >4.0 g/dL, consider treatment discontinuation in consultation with the sponsor. If (a) is applicable at consecutive 4 visits, consider discontinuation of the study drug in consultation with the sponsor. • If (a) becomes no longer applicable after interruption, resumed treatment at the pre-interruption dose level. • If (a) is not applicable even after resumption of dosing, escalate the dose to 0.7 mg/kg.
When the dose is 0.7 mg/kg:	• If (a) is applicable, interrupt treatment. If an increase from baseline is >4.0 g/dL, consider treatment discontinuation in consultation with the sponsor. If (a) is applicable at consecutive 4 visits, reduce the dose to 0.3 mg/kg. • If (a) becomes no longer applicable after interruption, resume treatment at the pre-interruption dose level. • If hemoglobin level remains stably below the sex-specific ULN at 2 consecutive visits after dose reduction to 0.3 mg/kg, the dose may be escalated to 0.7 mg/kg again.

[Dose modification due to low platelet count]
(b): Platelet count <50,000 /mm^3

- If (b) is applicable, interrupt treatment. If (b) is applicable at consecutive 4 visits, discontinue treatment.
- If (b) becomes no longer applicable after interruption, resume treatment at the reduced dose of 0.3 mg/kg. If the pre-interruption dose level is already 0.3 mg/kg, resume treatment at 0.3 mg/kg.
- If platelet count remains stably >50,000/mm^3 at 2 consecutive visits after reduction to 0.3 mg/kg without bleeding-associated adverse events that are related to platelet count, the dose may be escalated to 0.7 mg/kg again.

[Dose modification in response to telangiectasia]
(c): New onset of moderate to severe telangiectasia or telangiectasia worsening from mild to moderate.

When the dose is 0.3 mg/kg:	• If (c) is applicable, interrupt at consecutive 3 visits. • If telangiectasia is not worsened during interruption, resume treatment at the pre-interruption dose level. • If telangiectasia is worsened during interruption, consider discontinuation of the study drug in consultation with the sponsor.
When the dose is 0.7 mg/kg:	• If (c) is applicable, interrupted at 1 visit. • If telangiectasia is not worsened during interruption, resume treatment at 0.3 mg/kg. • If telangiectasia is worsened during interruption, consider discontinuation of the study drug in consultation with the sponsor. • Only if the event has completely resolved after interruption, the dose may be escalated to 0.7 mg/kg.

[Dose modification in response to adverse events unrelated to the study drug]
- If the dose was reduced to 0.3 mg/kg due to an adverse event unrelated to the study drug, it may be escalated to 0.7 mg/kg again after the adverse event has resolved.

(a) Main treatment period

Of 324 randomized subjects,[24] 323 subjects (160 in the placebo group, 163 in the sotatercept group) received the study drug and were also included in the safety analysis population and FAS, which served as the primary efficacy analysis population. A total of 16 subjects (12 subjects, 4 subjects) discontinued the study mainly because of death in 5 subjects (5 subjects, 0 subjects), adverse events in 4 subjects (2 subjects, 2 subjects), clinical worsening in 2 subjects (2 subjects, 0), and consent withdrawal in 2 subjects (1 subject, 1 subject).

When clinically classified by PAH subtype, the FAS consisted of 189 patients with IPAH (106 subjects, 83 subjects), 59 patients with HPAH (24 subjects, 35 subjects), 11 patients with drug/toxin-induced PAH (4 subjects, 7 subjects), 48 patients with PAH associated with connective tissue disease (19 subjects, 29 subjects), and 16 patients with PAH associated with simple, congenital systemic-to-pulmonary shunts at least 1 year following repair (7 subjects, 9 subjects). When classified by WHO FC at baseline, the FAS consisted of 157 patients with PAH in Class II (78 subjects, 79 subjects) and 166 patients with PAH in

[24] One subject who failed at screening was randomized by mistake but did not receive the study drug and was excluded from all analyses.

Class III (82 subjects, 84 subjects). When classified by status of background PAH therapy, the FAS consisted of 13 patients on mono therapy (4 subjects, 9 subjects), 112 patients on double therapy (56 subjects, 56 subjects), and 198 patients on triple therapy (100 subjects, 98 subjects), and 129 patients received prostaglandin I_2 (PGI_2) injections (64 subjects, 65 subjects).

Table 32 shows change in 6MWD from baseline to Week 24, the primary efficacy endpoint, demonstrating superiority of sotatercept over placebo.

Table 32. Change in 6MWD from baseline to Week 24 (m) (FAS)

	Placebo	Sotatercept
Baseline[a]	404.7 ± 80.59 427.1 [151.5, 514.5] (n = 160)	397.6 ± 84.28 417.0 [160.5, 497.5] (n = 163)
Week 24[a]	408.4 ± 101.92 425.0 [63.0, 647.0] (n = 147)	439.7 ± 97.42 451.0 [42.0, 691.0] (n = 157)
Change from baseline[b]	1.0 [-1.0, 5.0]	34.4 [32.5, 35.5]
Difference between groups [2-sided 95% CI][c]	-	40.8 [27.53, 54.14]
P value[d]	-	<0.001

a Top, Mean ± SD; Middle, Median [minimum, maximum]; Bottom, Number of subjects
b For subjects who died, missing data were imputed with −2000 m to place them at the worst rank, and for those who experienced a clinical worsening event, missing data were imputed with −1000 m to place them at the second worst rank. The other missing data were imputed by the multiple imputation method based on the data in the same strata (WHO FC at baseline and background PAH therapy) on missing at random (MAR) assumption. A total of 100 imputed datasets were generated, and of the medians for each dataset (100 in total), the mean [minimum, maximum] was calculated.
c Estimated by the Hodges-Lehmann method
d Aligned rank stratified Wilcoxon test with the randomization stratification factors (WHO FC at baseline and background PAH therapy) as strata (*Ann Math Stat.* 1962;33:482-97), significant level of 5% (2-sided)

Table 33 shows change in PVR from baseline to Week 24, the secondary endpoint.

Table 33. Change in PVR from baseline to Week 24 (dyn·sec/cm^5) (FAS)

	Placebo	Sotatercept
Baseline[a]	745.8 ± 313.53 684.0 [400.0, 2624.0] (n = 160)	781.3 ± 398.47 624.0 [400.0, 2688.0] (n = 163)
Week 24[a]	779.9 ± 334.70 744.0 [272.0, 2448.0] (n = 141)	545.8 ± 265.15 488.0 [144.0, 1864.0] (n = 154)
Change from baseline[b]	32.8 [24.0, 40.0]	-165.1 [-184.0, -152.0]
Difference between groups [2-sided 95% CI][c]	-	-234.6 [-288.37, -180.75]

a Top, Mean ± SD; Middle, Median [minimum, maximum]; Bottom, Number of subjects
b For subjects who died, missing data were imputed with 20000 dynes·sec/cm^5 to place them at the worst rank, and for those who experienced a clinical worsening event, missing data were imputed with 15000 dynes·sec/cm^5 to place them at the second worst rank. The other missing data were imputed by the multiple imputation method based on the data in the same strata (WHO FC at baseline and background PAH therapy) on MAR assumption. A total of 100 imputed datasets were generated, and of the medians for each dataset (100 in total), the mean [minimum, maximum] was calculated.
c Estimated by the Hodges-Lehmann method

Table 34 shows incidences of adverse events during the main treatment period.

Table 34. Incidences of adverse events during the main treatment period (safety analysis population)

	Placebo (n = 160)	Sotatercept (n = 163)
All adverse events	87.5 (140)	84.7 (138)
Main adverse events[a]		
Headache	15.0 (24)	20.2 (33)
COVID-19	13.1 (21)	14.7 (24)
Diarrhoea	7.5 (12)	12.3 (20)
Epistaxis	1.9 (3)	12.3 (20)
Fatigue	7.5 (12)	10.4 (17)
Telangiectasia	3.1 (5)	10.4 (17)
Dizziness	1.9 (3)	10.4 (17)
Nausea	11.3 (18)	9.8 (16)
Injection site pain	6.3 (10)	6.7 (11)
Hypokalaemia	3.1 (5)	5.5 (9)
Rash	2.5 (4)	5.5 (9)
Flushing	1.9 (3)	5.5 (9)
Oedema peripheral	6.3 (10)	4.9 (8)
Nasopharyngitis	5.6 (9)	4.3 (7)
Dyspnoea	8.8 (14)	2.5 (4)

% (number of subjects)
a Events reported by ≥5% of subjects in either group

Adverse events leading to death occurred in 6 subjects in the placebo group (cardiac arrest in 2 subjects, cardiogenic shock, right ventricular failure, sepsis, and pulmonary arterial hypertension in 1 subject each), and a causal relationship to the study drug was ruled out for all of them. Serious adverse events occurred in 22.5% (36 of 160) of subjects in the placebo group and 14.1% (23 of 163) of subjects in the sotatercept group. Events reported by ≥2 subjects in either group were atrial flutter (0 subjects, 2 subjects), fall (0 subjects, 2 subjects), haemoptysis (0 subjects, 2 subjects), pulmonary arterial hypertension (4 subjects, 1 subject), dyspnoea (2 subjects, 1 subject), cardiac arrest (2 subjects, 0 subjects), right ventricular failure (2 subjects, 0 subjects), and coronavirus disease 2019 (COVID-19) (2 subjects, 0 subjects). Fall and haemoptysis in the sotatercept group were assessed as causally related to the study drug. Adverse events leading to discontinuation of the study drug occurred in 10 subjects in the placebo group (pulmonary arterial hypertension in 3 subjects, cardiac arrest in 2 subjects, right ventricular failure, sepsis, malnutrition, abortion, and respiratory failure in 1 subject each) and 3 subjects in the sotatercept group (haemoptysis, arthralgia, and epistaxis and telangiectasia). Haemoptysis, epistaxis, and telangiectasia in the sotatercept group were assessed as causally related to the study drug.

(b) Extended treatment period

During the extended treatment period, 300 subjects (142 in the placebo group, 158 in the sotatercept group) received the study drug. During the extended treatment period, 30 subjects (24 subjects, 6 subjects) discontinued the study mainly because of clinical worsening in 9 subjects (8 subjects, 1 subject), death in 3 subjects (1 subject, 2 subjects), consent withdrawal in 3 subjects (3 subjects, 0 subjects), and adverse events in 2 subjects (0 subjects, 2 subjects). The period of exposure to the study drug[25)] (median [range]) was 313 (61-561) days.

Table 35 shows changes in 6MWD from baseline over time.

[25)] Including the period of exposure in the main treatment period

Table 35. Changes in 6MWD from baseline over time (m) (FAS)

	Placebo	Sotatercept
Baseline[a]	404.7 ± 80.59 427.1 [151.5, 514.5] (n = 160)	397.6 ± 84.28 417.0 [160.5, 497.5] (n = 163)
Week 24[a]	409.2 ± 100.54 425.0 [63.0, 647.0] (n = 147)	439.9 ± 97.16 454.0 [42.0, 691.0] (n = 158)
Change from baseline	6.0 [-291.5, 238.5]	35.0 [-245.0, 279.0]
Week 36[a]	411.9 ± 102.74 423.0 [144.9, 656.0] (n = 122)	443.8 ± 95.11 459.0 [120.0, 616.0] (n = 147)
Change from baseline	9.7 [-175.5, 205.0]	38.0 [-139.6, 285.0]
Week 48[a]	422.5 ± 89.98 444.0 [188.0, 645.0] (n = 53)	452.8 ± 98.09 465.0 [85.0, 645.0] (n = 83)
Change from baseline	5.0 [-152.0, 194.0]	38.0 [-347.5, 195.0]
Week 60[a]	398.9 ± 105.14 435.0 [196.0, 570.0] (n = 24)	454.5 ± 88.22 459.0 [250.0, 637.0] (n = 41)
Change from baseline	4.3 [-147.5, 184.5]	47.4 [-61.0, 159.0]
Week 72[a]	381.4 ± 111.07 447.1 [208.0, 488.0] (n = 7)	427.8 ± 141.09 457.0 [195.0, 595.0] (n = 13)
Change from baseline	14.5 [-15.5, 50.5]	45.5 [-106.0, 121.0]
Week 84[a]	328.0 328.0 (n = 1)	367.3 ± 34.44 367.3 [342.9, 391.6] (n = 2)
Change from baseline	-161.5	41.6 [19.1, 64.1]

a Top, Mean ± SD; Middle, Median [minimum, maximum]; Bottom, Number of subjects

Table 36 shows incidences of adverse events during the main treatment period and extended treatment period.

Table 36. Incidences of adverse events during main treatment period and extended treatment period (safety analysis population)

	Placebo (n = 160)	Sotatercept (n = 163)
All adverse events	93.1 (149)	92.6 (151)
Main adverse events[a]		
COVID-19	26.3 (42)	29.4 (48)
Headache	17.5 (28)	24.5 (40)
Epistaxis	1.9 (3)	22.1 (36)
Telangiectasia	4.4 (7)	16.6 (27)
Diarrhoea	10.0 (16)	15.3 (25)
Dizziness	6.3 (10)	14.7 (24)
Nausea	11.9 (19)	14.1 (23)
Fatigue	10.0 (16)	14.1 (23)
Thrombocytopenia	1.9 (3)	9.8 (16)
Oedema peripheral	7.5 (12)	8.6 (14)
Hypokalaemia	3.8 (6)	8.6 (14)
Rash	3.8 (6)	8.0 (13)
Nasopharyngitis	8.1 (13)	6.7 (11)
Injection site pain	6.9 (11)	6.7 (11)
Iron deficiency	5.6 (9)	6.7 (11)
Urinary tract infection	3.8 (6)	6.7 (11)
Flushing	2.5 (4)	6.1 (10)
Haemoglobin increased	0.0 (0)	6.1 (10)
Nasal congestion	0.0 (0)	6.1 (10)
Upper respiratory tract infection	6.9 (11)	5.5 (9)
Arthralgia	3.1 (5)	5.5 (9)
Pain in extremity	3.1 (5)	5.5 (9)
Vomiting	5.0 (8)	4.9 (8)
Vertigo	5.0 (8)	3.7 (6)
Dyspnoea	10.6 (17)	3.1 (5)

% (number of subjects)
a Events reported by ≥5% of subjects in either group

During the extended treatment period, adverse events leading to death occurred in 1 subject in the placebo group (COVID-19 pneumonia) and 2 subjects in the sotatercept group (acute myocardial infarction, haemorrhage intracranial), and a causal relationship to the study drug was ruled out for all the events. Serious adverse events occurred in 9.9% (14 of 142) of subjects in the placebo group and 16.5% (26 of 158) of subjects in the sotatercept group. The events reported by ≥2 subjects in the sotatercept group were pneumonia, gastrointestinal haemorrhage, vascular device occlusion, COVID-19, and catheter site infection (2 subjects each), and a causal relationship to the study drug was ruled out for all the events. Adverse events leading to discontinuation of the study drug occurred in 1 subject in the placebo group (COVID-19 pneumonia) and 3 subjects in the sotatercept group (acute myocardial infarction, haemorrhage intracranial, sarcoidosis). Sarcoidosis in the sotatercept group was assessed as causally related to the study drug.

7.3.2 Japanese phase III study (Study 020, 5.3.5.2.3, 5.3.5.2.4, study period ongoing since May 2023, data cut off in October 2024)

An open-label, uncontrolled study was conducted at 17 study centers in Japan to investigate efficacy and safety of sotatercept in Japanese patients with PAH (target sample size, ≥35 patients with PAH in WHO FC Class II or III[26)]).

[26)] The target sample size was established based on the feasibility. In the event where 35 patients completed the first dose of the study drug within 1 year after the first dose of the study drug in the first enrolled patient, enrollment was continued until either of (a) or (b) was met: (a) 1 year passed after the first dose of the study drug in the first enrolled patient; and (b) 40 patients completed the first dose of the study drug. Recruitment was controlled to ensure that patients using PGI_2 injections as background PAH therapy would not account for more than approximately 50% of patients with PAH in WHO FC Class II or III.

This study was comprised of the screening period of up to 4 weeks, main treatment period of 24 weeks, extended treatment period (until approval of Airwin), and follow-up period of 8 weeks.

Patients with PAH aged ≥18 years who met the following criteria were included in this study:

- Diagnosis of any of the following subtypes classified into WHO PH Group 1: IPAH, HPAH, drug/toxin-induced PAH, PAH associated with connective tissue diseases, or PAH associated with simple, congenital systemic-to-pulmonary shunts at least 1 year following repair
- WHO FC Class I to IV
- Screening PVR, ≥400 dyn·sec/cm^5
- Two 6MWD values during the screening period, both ≥150 m and ≤500 m; the difference between the 2 values, ≤15% of the greater value
- Receiving background PAH therapy at stable doses for ≥90 days before screening (no dose modification was allowed throughout the study period[27])
- Screening platelet count, ≥50,000/mm^3
- Screening hemoglobin level, equal to or below the ULN

The dosage regimen and dose modification guidelines were the same as those in Study 003.[28]

(a) Main treatment period

A total of 46 subjects who received the study drug were included in the safety analysis population and FAS, which served as the efficacy analysis population. All the analyses were performed according to the WHO FC at baseline (Class II and III/Class I/Class IV), and patients with PAH in WHO FC Class II and III were included in the primary analysis population. None of the subjects discontinued the study.

When clinically classified by PAH subtype, the FAS consisted of 25 patients with IPAH, 10 patients with HPAH, 5 patients with PAH associated with connective tissue disease, and 6 patients with PAH associated with simple, congenital systemic-to-pulmonary shunts at least 1 year following repair. When classified by WHO FC at baseline, the FAS consisted of 29 patients with PAH in Class II and 17 patients with PAH in Class III, and none of the patients with PAH in Class I or IV were enrolled. When classified by status of background PAH therapy, the FAS consisted of 3 patients on double therapy and 43 patients on triple therapy, and 21 patients received PGI_2 injections.

Table 37 shows results on the change in PVR from baseline to Week 24, the primary efficacy endpoint.

---

[27] For PGI_2 injections, the dose modification within the optimal dose ± 10% was allowed.

[28] In addition to the dose modification criteria in Study 003, the following criteria for serious hemorrhagic adverse events were set:
If an active serious hemorrhagic adverse event occurs, interrupt the study drug until resolution. If the second or subsequent interruption is required because of serious hemorrhagic events, the use of the study drug for the affected subject is to be consulted with the sponsor.

Table 37. Change in PVR from baseline to Week 24 (dyn·sec/cm^5) (FAS)

	Measured value[a]	Change from baseline[b] [2-sided 95% CI]
Baseline (n = 46)	536.0 [405.6, 1337.6]	-99.2 [-129.6, -68.4]
Week 24 (n = 46)[c]	417.2 [235.2, 812.8]	

a Median [minimum, maximum]
b Estimated by the Hodges-Lehmann method
c Imputation was not allowed on missing data owing to death or a clinical worsening event or for other reasons. In the study, no missing data occurred.

Table 38 shows results on a change in 6MWD from baseline to Week 24, the secondary endpoint.

Table 38. Change in 6MWD from baseline to Week 24 (m) (FAS)

	Measured value[a]	Change from baseline[b] [2-sided 95% CI]
Baseline (n = 46)	407.5 [253.5, 496.0]	41.8 [27.8, 55.5]
Week 24 (n = 46)[c]	462.0 [305.0, 560.0]	

a Median [minimum, maximum]
b Estimated by the Hodges-Lehmann method
c Imputation was not allowed on missing data owing to death or a clinical worsening event or for other reasons. In the study, no missing data occurred.

Table 39 shows incidences of adverse events during the main treatment period.

Table 39. Incidences of adverse events during the main treatment period (safety analysis population)

	Overall (n = 46)
All adverse events	93.5 (43)
Main adverse events[a]	
Nasopharyngitis	30.4 (14)
Headache	21.7 (10)
Haemoglobin increased	17.4 (8)
Epistaxis	17.4 (8)

% (number of subjects)
a Events reported by ≥10% of subjects

No death occurred. Serious adverse events occurred in 13.0% (6 of 46) of subjects (large intestine polyp, bacteraemia, catheter site infection, hypocalcaemia, loss of consciousness, device physical property issue), and a causal relationship to the study drug was ruled out for all of them. No adverse events leading to discontinuation of the study drug occurred.

(b) Extended treatment period

Of 46 subjects who completed the main treatment period, 45 subjects entered the extended treatment period and received the study drug. During the extended treatment period, 3 subjects discontinued the study all because of consent withdrawal. The period of exposure to the study drug[29)] (median [range]) was 421.5 (171-523) days.

Table 40 shows changes in 6MWD from baseline over time.

29) Including the period of exposure in the main treatment period

Table 40. Changes in 6MWD from baseline over time (m) (FAS)

	Measured value	Change from baseline
Baseline (n = 46)		
Mean ± SD	408.3 ± 57.7	-
Median [minimum, maximum]	407.5 [253.5, 496.0]	-
Week 24 (n = 46)		
Mean ± SD	451.7 ± 63.2	43.4 ± 48.0
Median [minimum, maximum]	462.0 [305.0, 560.0]	39.5 [-47.0, 180.5]
Week 54 (n = 43)		
Mean ± SD	462.9 ± 63.0	52.4 ± 51.7
Median [minimum, maximum]	473.0 [330.0, 580.0]	43.5 [-32.5, 205.5]
Week 66 (n = 6)		
Mean ± SD	444.3 ± 48.6	20.4 ± 47.4
Median [minimum, maximum]	444.0 [375.0, 510.0]	16.0 [-33.5, 98.5]

Table 41 shows incidences of adverse events during the main treatment period and extended treatment period.

Table 41. Incidences of adverse events during main treatment period and extended treatment period (safety analysis population)

	Overall (n = 46)
All adverse events	97.8 (45)
Main adverse events[a]	
Nasopharyngitis	47.8 (22)
Epistaxis	32.6 (15)
Haemoglobin increased	28.3 (13)
Headache	23.9 (11)
COVID-19	21.7 (10)
Diarrhoea	10.9 (5)
Rash	10.9 (5)

% (number of subjects)
a Events reported by ≥10% of subjects

No death occurred during the extended treatment period. Of note, an adverse event leading to death assessed as causally related to the study drug occurred in 1 subject (gastrointestinal haemorrhage) outside the reporting period for adverse events[30)] (82 days after the last dose of the study drug). Serious adverse events occurred in 19.6% (9 of 46) of subjects (supraventricular tachycardia, large intestine polyp, post procedural haemorrhage, and hepatic cyst infection; cataract; large intestine polyp; bacteraemia; COVID-19; device occlusion; pulmonary alveolar haemorrhage; pulmonary arterial hypertension; nasopharyngitis), and a causal relationship to the study drug was ruled out for all of them. No adverse events leading to discontinuation of the study drug occurred.

7.R Outline of the review conducted by PMDA

7.R.1 Development strategy of sotatercept

The applicant's explanation about development strategy for sotatercept in Japan:

The development of sotatercept preceded outside Japan. At the time it was being planned in Japan, The participation of Japan in the foreign phase III study (Study 003) was difficult. The applicant thus decided to conduct a Japanese phase III study (Study 020) separately, to evaluate the efficacy and safety of sotatercept in Japanese patients with PAH based on results from Study 003 after confirming the similarity between the results from these studies. The applicant considers that investigations in (a) and (b) below justifies this approach that verified the similarity between the results of the 2 studies.

30) From the first dose of the study drug to 8 weeks (56 days) after the last dose

(a) Endogenous and exogenous ethnic factors

In terms of endogenous ethnic factors related to pathology or cause of PAH, no clear differences between Japan and other countries have been reported. Although body weight and albumin level were identified as endogenous factors affecting PK parameters of sotatercept, baseline albumin levels in Studies 003 and 020 (4.60 g/dL in Study 003 [median], 4.50 g/dL in Study 020) showed no difference. Although baseline body weight was lower in Study 020 (50.4 kg) than in Study 003 (67.4 kg), the dose of sotatercept is determined on the basis of body weight, and thus the difference in body weight between Japanese and non-Japanese patients is not considered to affect efficacy and safety evaluation of sotatercept largely.

The Japanese treatment guidelines for PAH (Guidelines for Treatment of Pulmonary Hypertension [revised version in 2017] [The Japanese Circulation Society]) were developed based on the European Society of Cardiology/the European Respiratory Society guidelines (ESC/ERS guidelines) (*Eur Heart J.* 2016;37:67-119). From the aspect of exogenous ethnic factors, the diagnosis and treatment algorithm for PAH in Japan do not clearly differ from those in other countries even when compared to the latest version of ESC/ERS guidelines (*Eur Heart J.* 2022;43:3618-731). (Statements of the Japanese Pulmonary Circulation and Pulmonary Hypertension Society, http://jpcphs.org/pdf/index/deviation_20231106.pdf, last accessed on March 21, 2025). Approved therapeutic drugs for PAH in Japan are generally similar to those approved in the US and European countries. In Japan, upfront combination therapy with pulmonary vasodilators is more actively practiced than in the US and European countries. Studies 003 and 020 were both designed with the background therapy at stable doses of pulmonary vasodilators from ≥90 days before screening to minimize the effect of the background therapy on efficacy evaluation.

(b) Design of Study 020

In view of the infeasibility of a confirmatory study in patients with PAH in Japan alone due to the rareness of the disease, the applicant planned to conduct Study 020 as an open-label, uncontrolled study in which a change in PVR from baseline to Week 24 was the primary endpoint as objective efficacy measure, and 6MWD was the important secondary endpoint as a measure to verify the similarity of the results between Studies 020 and 003. PVR, a hemodynamic parameter, was reported to be related to long-term prognosis of patients with PAH (*Pulm Circ.* 2013;3:523-32) and has been commonly used to check therapeutic effects of drugs against PAH in clinical studies and routine practice. Thus, PVR is an appropriate measure for efficacy evaluation. There are no large differences in study designs between Studies 020 and 003 potentially affecting the similarity verification of study results.

PMDA's view:

In Japan, upfront combination therapy with pulmonary vasodilators has been actively practiced compared to other countries. However, subjects were required not to change types or doses of concomitant pulmonary vasodilators for a certain period before starting the study drug, and thus the endogenous and exogenous ethnic factors are unlikely to affect efficacy and safety evaluation of sotatercept clearly. Based on the applicant's explanation, the different designs of Studies 003 and 020 are not considered to affect the comparison of the results between these studies largely.

PVR, the primary endpoint in Study 020, correlates to outcomes in patients with PAH and is an objective measure. The efficacy of sotatercept in Japanese patients can be evaluated to a certain extent based on changes from baseline in PVR. It is also possible to verify the similarity in the efficacy of sotatercept between Japanese patients and non-Japanese patients by comparing changes from baseline in PVR and 6MWD between Studies 003 and 020.

Accordingly, PMDA has concluded that the efficacy and safety of sotatercept in Japanese patients with PAH are evaluable using results from Study 003 based on the similarity verified between the results from Study 020 and Study 003.

7.R.2 Efficacy

7.R.2.1 Efficacy endpoints in Study 003

The applicant's explanation about the rationale for the primary endpoint in Study 003:

In confirmatory clinical studies of approved therapeutic drugs for treatment of PAH, time to clinical worsening (TTCW) event and morbidity/mortality event were set as the primary endpoint. However, the necessity of evaluation items that accurately reflect patients' quality of life (QOL) and functional improvement was discussed in the sixth World Symposium on Pulmonary Hypertension (2018). In response to this and in view of the earliest possible provision of sotatercept to patients who need it, 6MWD was set as the primary endpoint as it enables short-term evaluation compared to TTCW event. TTCW event was chosen as the secondary endpoint.

PMDA's view:

The true endpoint in treatment of PAH is improvement of prognosis. Since the fourth World Symposium on Pulmonary Hypertension, composite endpoints (TTCW, etc.) comprised of mortality and clinical worsening have been the recommended primary endpoints of clinical studies of PAH (*J Am Coll Cardiol.* 2009;54:S97-107). On the other hand, 6MWD is a measure of exercise tolerance, with some issues including ceiling effect and unclear association with mortality change. Nevertheless, 6MWD has been employed as the primary endpoint of clinical studies on pulmonary vasodilators already approved, and is a component of events such as TTCW (*Eur Respir. J* 2024;64:2401205). Thus, it is acceptable to evaluate efficacy in Study 003 based on the primary endpoint of 6MWD and the secondary endpoint of "time to death or the first clinical worsening event."

7.R.2.2 Efficacy of sotatercept

The applicant's explanation about the efficacy of sotatercept in patients with PAH on background therapy with pulmonary vasodilators, who were included in Studies 003 and 020:

Table 32 shows results of the primary endpoint in Study 003. The difference between the sotatercept and placebo groups in change in Week 24 6MWD (40.8 m) is considered clinically meaningful in view of the following reports:

- A total of 405 patients with PAH underwent 6MWD measurement, and the minimal important difference (MID) was estimated by both distributional and anchor-based methods. The estimated MID ranged from 25.1 to 38.5 m with the estimated consensus MID of 33 m (*Am J Respir Crit Care Med.* 2012;186:428-33).

- In a meta-analysis including 8 randomized studies in patients with PAH (*Am J Respir Crit Care Med.* 2023;207:1070-9), the MID was estimated to be 33 m and was not affected by endogenous factors such as age, sex, body mass index (BMI), cause of PAH, and WHO FC.

PVR, the secondary endpoint of Study 003, improved in the sotatercept group compared to the placebo group (Table 33). Time to death or the first clinical worsening event,[31)] based on the stratified Cox proportional hazards model using baseline WHO FC and background PAH therapy as stratification factors, the hazard ratio [2-sided 95% confidence interval (CI)] of sotatercept to placebo was 0.163 [0.076, 0.347].

Based on the above results, the applicant considers that Study 003 demonstrated the efficacy of sotatercept in non-Japanese patients with PAH on background therapy with pulmonary vasodilators.

In Study 020, the primary endpoint of decrease from baseline in PVR improved with sotatercept, although at a smaller degree than in the sotatercept group of Study 003 (Table 42). The difference in change from baseline in PVR between the studies was considered attributable to the difference in baseline PVR. That is, the baseline PVR in Study 020 was lower than in Study 003 because of the greater proportion of WHO FC Class II patients in Study 020 than in Study 003, and most patients in Study 020 were receiving 3 pulmonary vasodilators in combination as background therapy. However, changes in PVR and pulmonary vascular resistance index (PVRI) did not clearly differ between the sotatercept group of Study 003 and Study 020 (Table 42).

Table 42. Changes in PVR (dynes·sec/cm^5) and PVRI (dynes·sec/cm^5·m^2) from baseline to Week 24 in Study 003 (FAS) and Study 020 (FAS) as well as their percent change (%)

	Study 003		Study 020
	Placebo	Sotatercept	
PVR			
Baseline[a]	684.0 [400.0, 2624.0] (n = 160)	624.0 [400.0, 2688.0] (n = 163)	536.0 [405.6, 1337.6] (n = 46)
Week 24[a]	744.0 [272.0, 2448.0] (n = 141)	488.0 [144.0, 1864.0] (n = 154)	417.2 [235.2, 812.8] (n = 46)
Change from baseline[b]	32.8 [24.0, 40.0]	-165.1 [-184.0, -152.0]	-99.2 [-129.6, -68.4]
Percent change from baseline[c]	3.2 [-1.8, 8.5]	-29.9 [-34.0, -25.5]	-21.3 [-26.7, -15.5]
PVRI			
Baseline[a]	1221.5 [673.6, 4194.8] (n = 160)	1197.5 [641.2, 4238.1] (n = 163)	818.4 [591.9, 1809.4] (n = 46)
Week 24[a]	1361.5 [454.5, 3128.2] (n = 141)	897.6 [306.7, 2771.0] (n = 154)	634.7 [422.6, 1210.9] (n = 46)
Change from baseline[b]	53.8 [-6.7, 112.7]	-343.7 [-416.3, -274.8]	-145.4 [-204.0, -100.5]
Percent change from baseline[c]	3.3 [-1.8, 8.7]	-29.6 [-33.7, -25.2]	-20.8 [-26.1, -15.0]

a Median [minimum, maximum]
b The change in PVR in Study 003 is expressed as the value estimated with missing data imputed by the multiple imputation method [minimum, maximum] [see footnote b in Table 33]; and the change in PVRI in Study 003 and the changes in both parameters in Study 020 are expressed as the values estimated by the Hodges-Lehmann method [2-sided 95% CI].
c Geometric mean [2-sided 95% CI]

Sotatercept also improved 6MWD. Change in 6MWD from baseline (41.8 m, estimated by the Hodges-Lehmann method) was similar to that in the sotatercept group (34.4 m [median]) in Study 003 (Table

31) (a) Worsening-related listing for lung and/or heart transplant; (b) need to initiate rescue therapy with an approved drug for treatment of PAH or the need to increase the dose of PGI_2 injection by ≥10%; (c) need for atrial septostomy; (d) hospitalization for worsening of PAH (≥24 hours); and (e) deterioration of PAH defined by "worsened WHO FC and a decrease in 6MWD by ≥15% (confirmed by 2 tests at least 4 hours apart, but no more than 1 week).

38). The applicant considers that sotatercept is expected to have the efficacy also in Japanese patients with PAH on background therapy with pulmonary vasodilators as in non-Japanese patients.

PMDA's view:
Results on the change in 6MWD from baseline to Week 24, the primary endpoint in Study 003, demonstrated superiority of sotatercept over placebo, and those on PVR and "Time to death or the first clinical worsening event," the secondary endpoints, also supported the therapeutic effect of sotatercept. Sotatercept was demonstrated to have the efficacy in patients with PAH on background therapy with pulmonary vasodilators.

In Study 020, sotatercept improved the primary endpoint of PVR, although the decrease in PVR from baseline to Week 24 was smaller than that in the sotatercept group in Study 003. Because, in Japan, upfront combination therapy with pulmonary vasodilators is more prevalent compared to other countries, the participants in Study 020 had possibly responded to the therapy to a certain extent, which might have led to the difference in the results between the studies. Percent changes in PVR did not differ between the sotatercept group in Study 003 and Study 020, and the change in 6MWD from baseline to Week 24 was similar. PMDA has concluded that sotatercept is expected to have the efficacy in Japanese patients with PAH on background therapy with pulmonary vasodilators as in the patient population in Study 003.

7.R.3 Safety

PMDA has concluded that sotatercept has acceptable safety in patients with PAH based on incidences of adverse events in the clinical studies, foreign post-marketing safety information, and the following review, in view of the efficacy shown in Section 7.R.2. This section reviews the safety of sotatercept based on a pooled safety analysis (Pool B) comprising results in the main treatment period and extended treatment period in Studies 003 and 020 as well as data from the safety analysis population in the foreign phase II studies (Studies 001 and 002[32)]) and foreign phase III studies (Studies 003 and 004[33)]) that were accumulated from the start of sotatercept treatment until 48 weeks/11 months after data cutoff at the end of Study 003 (November 8, 2023).

7.R.3.1 Decrease in platelet count and bleeding-related events

The applicant's explanation about concerns over decrease in platelet count and bleeding-related events in patients treated with sotatercept:
(a) Decrease in platelet count
In view of decreased platelet count in subjects treated with sotatercept in preceding clinical studies,[34)] Studies 003 and 020 excluded patients with the platelet count <50,000 /mm^3, and the dose of sotatercept was modified based on the platelet count with the intention to secure the safety of study participants [see Table 31].

32) An open-label study in which patients with PAH in WHO FC Class III on background PAH therapy using ≥2 drugs subcutaneously received sotatercept 0.7 mg/kg (0.3 mg/kg only for the first dose) Q3W.
33) An open-label study in which eligible subjects with completion of Study 001, 002, or 003 subcutaneously received sotatercept 0.7 mg/kg (0.3 mg/kg only for the first dose in subjects from Study 003) Q3W.
34) A placebo-controlled, randomized, double-blind study in non-Japanese patients with osteolytic lesions of multiple myeloma (Study 011), a placebo-controlled, randomized, double-blind study in non-Japanese patients with chemotherapy-induced anemia associated with metastatic breast cancer (Study 012), and a randomized, open-label, dose-finding study in non-Japanese patients with chemotherapy-induced anemia associated with advanced or metastatic solid tumor (Study 015)

Table 43 shows incidences of thrombocytopenia[35] during the main treatment period in Studies 003 and 020 as well as Pool B. The incidences in Japanese patients were similar to those in non-Japanese patients. Of the serious events in Pool B, thrombocytopenia (Medical dictionary for regulatory activities [MedDRA] Preferred term [PT]) in 3 subjects was assessed as causally related to the study drug, but the events resolved or were resolving later. An analysis on incidence rates (the number of events per unit person-years) adjusted by the total person-years observed to occurrence in Pool B did not indicate that the incidences of these events tend to increase with time. Thrombocytopenia additionally occurred in 1 subject during the extended treatment period in Study 020, but it was mild and non-serious.

Table 43. Incidences of thrombocytopenia during the main treatment period in Studies 003 and 020 as well as Pool B (safety analysis population)

	Foreign		Japan	Foreign
	Study 003 (main treatment period)[c]		Study 020 (main treatment period)[c]	Pool B[c]
	Placebo (n = 160)	Sotatercept (n = 163)	Sotatercept (n = 46)	Sotatercept (n = 431)
Thrombocytopenia	2.5 (4)	6.1 (10)	8.7 (4)	12.8 (55)
Thrombocytopenia[a]	1.9 (3)	4.9 (8)	4.3 (2)	11.8 (51)
Platelet count decreased[a]	0.6 (1)	1.2 (2)	4.3 (2)	1.2 (5)
Serious events	0 (0)	0.6 (1)	0 (0)	1.2 (5)
Events leading to treatment discontinuation	0 (0)	0 (0)	0 (0)	0.2 (1)
Events leading to interruption	0 (0)	1.2 (2)	4.3 (2)	4.9 (21)
Events leading to dose reduction	0.6 (1)	0 (0)	0 (0)	1.9 (8)
Events assessed as causally related to the study drug	1.9 (3)	3.1 (5)	4.3 (2)	9.7 (42)
Subjects with the worst platelet count rated as CTCAE-Grade 3[b] during the evaluation period	0 (0)	1.2 (2)	4.3 (2)	3.9 (17)

% (number of subjects)
a MedDRA PT
b Platelet count ≥25,000 /mm^3 and <50,000 /mm^3
c The median period of exposure to sotatercept (days) (range) was 168 (61-193) in Study 003, 168 (145-174) in Study 020, and 657 (21-1973) in Pool B.

The mean platelet count (SD) at Week 24 in the sotatercept group in Study 003 was 192,300 (77,500)/mm^3, which was lower than baseline (206,200 [71,330]/mm^3) but above the lower limit of normal (130,000-182,000/mm^3[36]). The change was not clinically meaningful. Mean changes in platelet count from baseline to Weeks 12, 24, and 60 in the sotatercept group were −14,100, −15,900, and −18,600/mm^3, showing that the platelet count was generally stable after Week 12.

During the study period in Studies 003 and 020 (main treatment period and/or extended treatment period), 5 of 163 subjects (3.1%) and 3 of 46 subjects (6.5%) had the platelet count <50,000 /mm^3 after the first dose of sotatercept, and of them, 1 subject experienced a serious bleeding-related event. In these subjects, dosing was resumed after interruption according to the dose modification guidelines. As of data cutoff,[37] 4 subjects in Study 003 and 3 in Study 020 remained in the study.

(b) Bleeding-related events

Table 44 shows incidences of bleeding-related events[38] during the main treatment period in Studies 003 and 020 as well as Pool B. An analysis on incidence rates (the number of events per unit person-years)

[35] MedDRA Standardised MedDRA queries (SMQ) “Haematopoietic cytopenias”
[36] Institutional value
[37] For 4 subjects in Study 003, as of data cutoff in Pool B
[38] MedDRA SMQ “Haemorrhages (excl laboratory terms)” and PT “Anaemia”

adjusted by the total person-years observed to occurrence in Pool B did not indicate that the incidences of the bleeding-related events tend to increase with time.

Table 44. Incidences of bleeding-related events during the main treatment period in Studies 003 and 020 as well as Pool B (safety analysis population)

	Foreign		Japan	Foreign
	Study 003 (main treatment period)[d]		Study 020 (main treatment period)[d]	Pool B[d]
	Placebo (n = 160)	Sotatercept (n = 163)	Sotatercept (n = 46)	Sotatercept (n = 431)
Bleeding-related events	12.5 (20)	21.5 (35)	28.3 (13)	49.9 (215)
Main bleeding-related events[a]				
Epistaxis[b]	1.9 (3)	12.3 (20)	17.4 (8)	32.3 (139)
Gingival bleeding[b]	0.6 (1)	3.1 (5)	2.2 (1)	4.4 (19)
Anaemia[b]	3.1 (5)	1.2 (2)	2.2 (1)	7.0 (30)
Contusion[b]	0.6 (1)	0.6 (1)	2.2 (1)	3.9 (17)
Haemoptysis[b]	1.3 (2)	1.8 (3)	0 (0)	3.5 (15)
Haematoma[b]	0.6 (1)	1.2 (2)	0 (0)	2.6 (11)
Gastrointestinal haemorrhage[b]	0 (0)	0.6 (1)	0 (0)[c]	2.3 (10)
Serious events	1.3 (2)	2.5 (4)	0 (0)	7.0 (30)
Events leading to treatment discontinuation	0 (0)	1.2 (2)	0 (0)	1.2 (5)
Events leading to interruption	0 (0)	0.6 (1)	0 (0)	NA
Events leading to dose reduction	0 (0)	0.6 (1)	0 (0)	2.3 (10)

% (number of subjects)
a Event reported by ≥10 subjects in Pool B
b MedDRA PT
c Reported by 1 subject outside the reporting period for adverse events
d The median period of exposure to sotatercept (days) (range) was 168 (61-193) in Study 003, 168 (145-174) in Study 020, and 657 (21-1973) in Pool B.

The most prevalent bleeding-related event in subjects treated with sotatercept in clinical studies was epistaxis, most of which, however, were non-serious and not requiring treatment. Serious bleeding-related events were less prevalent, and many of the subjects with serious bleeding-related events had bleeding risk factors. Of 30 subjects with serious bleeding-related events in Pool B, 25 subjects were receiving PGI_2 formulations in the background PAH therapy when the first dose of sotatercept was administered; 14 subjects concomitantly received an anticoagulant following a serious bleeding-related event; 12 subjects had a low platelet count (<150,000/mm^3) when the serious bleeding-related event occurred; and 9 subjects were aged ≥65 years.

During the extended treatment period in Study 003, 1 subject in the sotatercept group died of haemorrhage intracranial. The subject was concomitantly receiving treprostinil, also acting as a platelet aggregation inhibitor, anticoagulants, and antiplatelet drugs and had platelet counts during the study period that all fell within the normal range. The event was assessed as causally unrelated to the study drug. In Study 020, 1 subject died of gastrointestinal haemorrhage, which occurred outside the reporting period for adverse events.[30)] The event occurred 82 days after the last dose of sotatercept, but the subject was confirmed to have no gastrointestinal hemorrhage at baseline. Upper gastrointestinal endoscopy performed 6 days before the death identified microvascular bleeding owing to gastric telangiectasia. The event was assessed as causally related to the study drug.

In view of the occurrence of thrombocytopenia and bleeding-related events in the clinical studies as well as the above review, the package insert will advise caution about thrombocytopenia and hemorrhage as clinically significant adverse reactions, with the following notes in the Precautions Concerning Dosage

and Administration section: Sotatercept therapy should not be started when the platelet count is <50,000/mm^3; platelet count should be checked before every dosing for the first 5 doses and until stabilization, and periodical monitoring should be continued for subsequent doses; and the dose should be modified based on the platelet count according to the guidelines specified in the clinical studies. Careful use of sotatercept will be advised for patients with hemorrhagic diathesis, those receiving PGI_2 injections as therapeutic drug for PAH, patients on concomitant antithrombotic drugs, and those with low platelet count.

PMDA's view:
In view of the occurrence of thrombocytopenia and bleeding-related events in Studies 003 and 020, and in Pool B, thrombocytopenia and bleeding-related events warrant attention during the use of sotatercept.

In Studies 003 and 020, from which patients with platelet count <50,000/mm^3 were excluded and the dose was modified based on platelet count, decreased platelet count and bleeding-related events were manageable to a certain extent. As practiced in these studies, platelet count monitoring and dose modification ensure safety in patients with platelet count ≥50,000/mm^3. Platelet count <50,000/mm^3 generally tends to represent hemorrhagic diathesis. In view of the following points, sotatercept should be contraindicated for patients with at baseline platelet count <50,000/mm^3:

- Patients with PAH are expected to receive PGI_2 formulations, which act as platelet aggregation inhibitors, or anticoagulants. Concomitant sotatercept may worsen bleeding-related events.
- Bleeding-related events causally related to sotatercept and resulted in death occurred although their causal relationship to decreased platelet count remains unclear.

7.R.3.2 Increase in hemoglobin

The applicant's explanation about increase in hemoglobin:
Sotatercept stimulates erythropoiesis, and this may increase hemoglobin [see Section 3.2.1]. Patients with a hemoglobin level above the ULN (approximately 16 g/dL for females and approximately 17.5 g/dL for males) were excluded from Studies 003 and 020, and the dose of sotatercept was modified based on the hemoglobin level [see Table 31].

During the main treatment period in Study 003, increased hemoglobin[39)] was observed in 0% (0 of 160) of subjects in the placebo group and 5.5% (9 of 163) of subjects in the sotatercept group, and the events led to treatment interruption in 4 subjects in the sotatercept group. During the extended treatment period, additional 1 subject in the placebo group and 5 subjects in the sotatercept group experienced increased hemoglobin, and the event led to treatment interruption in 1 subject in the placebo group and 2 subjects in the sotatercept group. There were no serious events or events leading to treatment discontinuation or dose reduction in either period. In the sotatercept group, change from baseline (mean) in hemoglobin was 0.9 g/dL at Week 3 (just before the second dose of the study drug), 1.2 g/dL at Week 9, and were generally stable after that (1.3 g/dL at Week 24, 1.3 g/dL at Week 60).

[39)] MedDRA PTs "Haemoglobin increased," "Red blood cell count increased," "Full blood count increased," "Haematocrit increased," "Polycythaemia," "Stress polycythaemia"

During the main treatment period of Study 020, hemoglobin increased in 17.4% (8 of 46) of subjects. All these events were assessed as causally related to the study drug but were mild and did not lead to treatment discontinuation. Events led to dose reduction or interruption in 1 subject each. During the extended treatment period, additional 5 subjects experienced increased hemoglobin. The events were all assessed as causally related to the study drug but mild and non-serious. A total of 4 subjects had dose interruption, and none experienced treatment discontinuation or dose reduction. Over-time changes from baseline in hemoglobin level were similar to those in Study 003.

In Pool B, clinically significant abnormal hemoglobin levels (increased >2.0 g/dL from baseline, and >17.5 g/dL in males and >16 g/dL in females) were observed in 58.2% (251 of 431) of subjects, and 21.3% (92 of 431) of subjects experienced increased hemoglobin reported as adverse events.

During the main treatment period of Study 003, thrombotic events[40)] occurred in 1.3% (2 of 160) of subjects in the placebo group and 1.2% (2 of 163) of subjects in the sotatercept group. A serious thrombotic event occurred only in 1 subject in the placebo group. No events leading to treatment discontinuation, interruption, or dose reduction occurred. During the extended treatment period, thrombotic events occurred in 4 subjects in the placebo group and 7 subjects in the sotatercept group. Serious events occurred in 5 subjects in the sotatercept group (acute myocardial infarction, vascular device occlusion, acute coronary syndrome, device occlusion, and vascular device occlusion and embolism venous in 1 subject each), but a causal relationship to sotatercept was ruled out for all of these serious events. In Study 020, no thrombotic events occurred during the main treatment period. A serious event occurred in 1 subject (device occlusion) during the extended treatment period, but a causal relationship to sotatercept was ruled out for the event. In Study 004 that enrolled subjects who had completed Study 003, the dose was modified as per Studies 003 and 020. However, due to the absence of exclusion criteria based on hemoglobin levels, many enrolled patients were found to have a hemoglobin level 2 g/dL higher than the ULN. These patients, however, showed no trend of evident increase in the risk of thrombotic events.

Increase in hemoglobin is detectable by simple red blood cell count monitoring before the manifestation of symptoms related to hyperviscosity or thrombotic events. In view of the investigation results available, sotatercept may be administered to patients with the hemoglobin level above the ULN, i.e., the population excluded from Studies 003 and 020, at the dose modified according to the dose modification guidelines specified in the clinical studies.

Increase in hemoglobin is mainly attributable to the mechanism of action of sotatercept, and severe polycythemia may increase a risk of thrombotic events or hyperviscosity syndrome. The package insert will raise caution about an increase in hemoglobin as a serious adverse drug reaction with the following advice: Hemoglobin level should be measured before every dosing for the first 5 doses and subsequent doses until stabilization, and periodical monitoring should be continued even after that; and the dose should be modified based on the hemoglobin level according to the guidelines specified in the clinical studies. Furthermore, healthcare professionals will be advised to use sotatercept carefully for patients with severe polycythemia, who are at an increased risk of thromboembolism or hyperviscosity syndrome.

40) MedDRA SMQ “Embolic and thrombotic events”

PMDA's view:
Studies 003 and 020 reported neither severe hemoglobin increased nor thrombotic events for which a causal relationship to sotatercept could not be ruled out. However, it is appropriate to advise caution about increased hemoglobin as a clinically significant adverse drug reaction, in view of erythropoiesis promoted by sotatercept and an increased risk of thrombotic events by severe polycythemia, etc.

Based on the dose modification guidelines and occurrence of thrombotic events in Studies 003 and 020 as well as Study 004 which enrolled subjects with the hemoglobin level that was 2 g/dL higher than the ULN, sotatercept may be used irrespective of baseline hemoglobin level. Hemoglobin level monitoring and dose modification as per Studies 003 and 020 can ensure safety.

7.R.4 Clinical positioning

The applicant's explanation about clinical positioning of sotatercept in PAH treatment:
Currently, upfront combination therapies provided in accordance with the Japanese and foreign guidelines include multiple pulmonary vasodilators with different action mechanisms for patients with PAH who have not adequately responded to monotherapy with an oral/inhaled pulmonary vasodilator, and PGI_2 injections preferentially used for intermediate-risk severe cases or high-risk cases. These therapies have improved outcomes of PAH. However, there are cases of patients who have not adequately responded to the conventional therapies or are ineligible for the intensive treatment because of adverse drug reactions. Continuous infusion of intravenous or subcutaneous PGI_2 injections can pose a risk of infections and puts burden on patients. Due to such unmet medical needs, expectations are high for a new drug with a novel action mechanism that acts on the pathogenic mechanism of PAH.

Sotatercept was developed as a non-pulmonary vasodilator that targets TGF-β superfamily ligands. Japanese and foreign clinical studies in adult patients with PAH on stable background therapy with 1 to 3 pulmonary vasodilators demonstrated the efficacy and safety of sotatercept irrespective of type or number of drugs used in the background therapy. At the seventh World Symposium on Pulmonary Hypertension held after the approval of sotatercept in the US, sotatercept was recommended as an add-on drug to pulmonary vasodilators for the population including intermediate-risk patients with mild disease and high-risk patients classified according to the ESC/ERS risk assessment tool[41] (*Eur Respir J.* 2024;64:2401325). The treatment algorithm for PAH in Japan is basically similar to that in other countries, and Japanese and foreign studies demonstrated similar efficacy and safety of sotatercept. Thus, in Japan, sotatercept as PAH treatment will be similarly positioned as in other countries.

PMDA's view:
In PAH treatment in Japan, upfront combination therapies with drugs selected from PGI_2 formulations, ERAs and phosphodiesterase (PDE)-5 inhibitors, or sGC agonists with different action mechanisms are commonly used. Established multidrug therapies with pulmonary vasodilators have improved survival of patients with PAH, but pulmonary vasodilators are the only drugs for treatment of PAH currently

[41] Patients were classified as low-risk patients, intermediate-risk patients with mild disease, intermediate-risk patients with severe disease, and high-risk patients based on the 1-year mortality risk, which was assessed using WHO FC, 6MWD, and brain natriuretic peptide (BNP) or N-terminal pro-B-type natriuretic peptide (NT-proBNP) value.

accessible. Treatments with multiple concomitant drugs have not led to adequate prognostic improvement in some patients. Sotatercept acts through a new mechanism different from that of pulmonary vasodilators and is expected to have a therapeutic effect in patients poorly responding to the conventional therapies. In view of its clinical usefulness demonstrated in patients on background therapy with pulmonary vasodilators in Studies 003 and 020 [see Section 7.R.2], it is meaningful to make sotatercept available in Japanese clinical settings as a new treatment option for PAH.

Sotatercept is expected to be used as an add-on drug for patients poorly responding to 2 or 3 types of oral/inhaled pulmonary vasodilators with different action mechanisms or as additional therapy for patients with relatively severe disease who have been on continuous infusion of intravenous or subcutaneous PGI_2 injections.

7.R.5 Indication and intended population

The applicant has proposed "pulmonary arterial hypertension" as the intended population and indication of sotatercept.

The applicant's justification for the proposal:

(a) Underlying diseases of PAH

Table 45 shows efficacy results by underlying disease of PAH in Studies 003 and 020. Sotatercept tended to improve PVR irrespective of underlying disease. In Studies 003 and 020, incidences of adverse events did not largely differ by underlying disease.

Table 45. Change in PVR from baseline to Week 24 (dyn·sec/cm^5) by underlying disease of PAH in Studies 003 and 020 (FAS)

		Study 003		Study 020
		Placebo (n = 160)	Sotatercept (n = 163)	Sotatercept (n = 46)
IPAH	Baseline[a]	696.0 [400.0, 2624.0] (n = 106)	624.0 [400.0, 2200.0] (n = 83)	536.0 [405.6, 1337.6] (n = 25)
	Week 24[a]	760.0 [272.0, 2448.0] (n = 93)	464.0 [192.0, 1368.0] (n = 77)	411.2 [235.2, 812.8] (n = 25)
	Change from baseline[b]	32.0 [-8.0, 72.0]	-192.0 [-252.0, -144.0]	-127.2 [-196.0, -80.8]
	Difference between groups[c]	-	-258.0 [-331.89, -184.20]	
HPAH	Baseline[a]	680.0 [408.0, 1184.0] (n = 24)	712.0 [416.0, 1648.0] (n = 35)	540.8 [413.6, 636.8] (n = 10)
	Week 24[a]	600.0 [336.0, 1240.0] (n = 22)	552.0 [144.0, 944.0] (n = 33)	471.6 [371.2, 580.0] (n = 10)
	Change from baseline[b]	16.0 [-68.0, 84.0]	-176.0 [-248.0, -116.0]	-68.0 [-138.8, -26.0]
	Difference between groups[c]	-	-207.9 [-317.12, -98.61]	
Drug/ toxin-induced PAH	Baseline[a]	556.0 [440.0, 1144.0] (n = 4)	520.0 [448.0, 728.0] (n = 7)	-[e]
	Week 24[a]	568.0 [352.0, 1080.0] (n = 4)	368.0 [296.0, 728.0] (n = 7)	-[e]
	Change from baseline[b]	-32.0 [-88.0, -[d]]	-134.0 [-184.0, -36.0]	-[e]
	Difference between groups[c]	-	-82.0 [-182.00, 102.00]	
PAH associated with connective tissue disease	Baseline[a]	616.0 [408.0, 1224.0] (n = 19)	584.0 [408.0, 1752.0] (n = 29)	440.8 [405.6, 588.8] (n = 5)
	Week 24[a]	644.0 [320.0, 1368.0] (n = 16)	480.0 [216.0, 1864.0] (n = 28)	399.2 [301.6, 454.4] (n = 5)
	Change from baseline[b]	4.0 [-108.0, 192.0]	-168.0 [-284.0, 64.0]	-76.4 [-166.4, 13.6]
	Difference between groups[c]	-	-156.2 [-332.11, 19.73]	
PAH associated with congenital heart disease	Baseline[a]	720.0 [584.0, 1112.0] (n = 7)	1432.0 [520.0, 2688.0] (n = 9)	574.0 [424.8, 712.8] (n = 6)
	Week 24[a]	824.0 [704.0, 1320.0] (n = 6)	840.0 [216.0, 1464.0] (n = 9)	496.0 [361.6, 775.2] (n = 6)
	Change from baseline[b]	160.0 [-76.0, 236.0]	-420.0 [-984.0, -80.0]	-63.2 [-136.8, 46.0]
	Difference between groups[c]	-	-344.4 [-886.00, 197.16]	

a Median [minimum, maximum]
b Estimated by the Hodges-Lehmann method [2-sided 95% CI]
c Estimate calculated as done in the analysis on the overall population [see a footnote in Table 33] [2-sided 95% CI]
d Not calculated
e No patients with drug/toxin-induced PAH were enrolled.

In addition, the analysis revealed similarities among the underlying diseases of PAH in pathophysiological characteristics relevant to sotatercept's action mechanism. Thus, it is reasonable that sotatercept is indicated for PAH irrespective of underlying disease.

(b) WHO FC

Study 003 targeted patients in WHO FC Class II or III. Study 020 allowed inclusion of patients in Class I or IV in addition to those in Class II or III, but only Class II or III patients were actually enrolled in the study. Table 46 shows efficacy results by WHO FC Class in Studies 003 and 020. Sotatercept tended to improve PVR both in Class II and Class III. Table 47 shows safety results by WHO FC Class. The occurrence of adverse events was generally similar between Class II and Class III. Although incidences of serious adverse events tended to be high with Class III in Study 020, a causal relationship to the study drug was ruled out for all these events.

Table 46. Change in PVR from baseline to Week 24 (dyn·sec/cm^5) by WHO FC Class in Studies 003 and 020 (FAS)

		Study 003		Study 020
		Placebo (n = 160)	Sotatercept (n = 163)	Sotatercept (n = 46)
Class II	Baseline[a]	676.0 [408.0, 744.0] (n = 78)	608.0 [400.0, 2120.0] (n = 79)	536.0 [405.6, 854.4] (n = 29)
	Week 24[a]	672.0 [328.0, 1416.0] (n = 71)	484.0 [144.0, 1368.0] (n = 78)	425.6 [235.2, 777.6] (n = 29)
	Change from baseline[b]	0.0 [-36.0, 44.0]	-176.0 [-224.0, -132.0]	-93.2 [-132.8, -57.2]
	Difference between groups[c]	-	-191.9 [-255.96, -127.89]	
Class III	Baseline[a]	688.0 [400.0, 2624.0] (n = 82)	664.0 [400.0, 2688.0] (n = 84)	519.2 [405.6, 1337.6] (n = 17)
	Week 24[a]	840.0 [272.0, 2448.0] (n = 70)	492.0 [192.0, 1864.0] (n = 76)	411.2 [289.6, 812.8] (n = 17)
	Change from baseline[b]	56.0 [8.0, 108.0]	-208.0 [-276.0, -148.0]	-100.8 [-211.6, -60.4]
	Difference between groups[c]	-	-282.2 [-374.23, -190.10]	

a Median [minimum, maximum]
b Estimated by the Hodges-Lehmann method [2-sided 95% CI]
c Estimate calculated as done in the analysis on the overall population [see a footnote in Table 33] [2-sided 95% CI]

Table 47. Incidences of adverse events during the main treatment period and extended treatment period in Studies 003 and 020 by WHO FC Class (safety analysis population)

		Study 003		Study 020
		Placebo (n = 160)	Sotatercept (n = 163)	Sotatercept (n = 46)
Class II	Number of subjects	78	79	29
	All adverse events[a]	94.9 (74)	92.4 (73)	96.6 (28)
	Adverse events assessed as causally related[a]	34.6 (27)	45.6 (36)	72.4 (21)
	Adverse events leading to death[a]	2.6 (2)	1.3 (1)	0 (0)
	Serious adverse events[a]	21.8 (17)	20.3 (16)	13.8 (4)
	Adverse events leading to treatment discontinuation[a]	7.7 (6)	5.1 (4)	0 (0)
Class III	Number of subjects	82	84	17
	All adverse events[a]	91.5 (75)	92.9 (78)	100 (17)
	Adverse events assessed as causally related[a]	22.0 (18)	56.0 (47)	64.7 (11)
	Adverse events leading to death[a]	6.1 (5)	1.2 (1)	0 (0)
	Serious adverse events[a]	36.6 (30)	28.6 (24)	47.1 (8)
	Adverse events leading to treatment discontinuation[a]	6.1 (5)	2.4 (2)	0 (0)

a % (number of subjects)

In view of the following points, the applicant considers that patients in Class I or IV may be eligible for sotatercept, although results in these patients are not available:

- The Japanese and foreign guideline (Guidelines for Treatment of Pulmonary Hypertension [revised version in 2017] [The Japanese Circulation Society] and ESC/ERS guidelines [*Eur Heart J.* 2022;43:3618-731]) recommend that the treatment strategy should be determined based on not only WHO FC but also multiple prognosis factors including right heart failure, syncope, 6MWD, brain natriuretic peptide (BNP)/N-terminal pro-B-type natriuretic peptide (NT-proBNP), and echocardiography findings.
- According to recommendations in the seventh World Symposium on Pulmonary Hypertension (*Eur Respir J.* 2024;64:2401325) and consensus in the expert group in the US (*Am J Respir Crit Care Med.* 2024;210:581-92), patients eligible for sotatercept may include patients in WHO FC Class IV.
- The interim analysis in a foreign phase III study in patients with PAH in WHO FC Class III or IV (Study 006) showed that sotatercept in combination with pulmonary vasodilators tended to reduce a risk of morbidity/mortality events similarly in both Class III and IV patient populations.

- Sotatercept regulates the balance between pro-proliferative signaling and anti-proliferative signaling in vascular endothelial cells and thereby prevents pulmonary vascular remodeling involved in pathological progression of PAH. Thus, sotatercept has promising therapeutic effect in early stage patients, i.e., those in WHO FC Class I.

In view of the results in (a) and (b) above, the applicant specified the intended indication as "Pulmonary arterial hypertension."

PMDA's view:
Although investigation based on the results from an exploratory subgroup analysis has limitations, sotatercept tended to improve PVR in any subgroup by underlying disease, and safety did not clearly differ among subgroups by underlying disease. PAH is caused by a wide range of underlying diseases, some of which were not covered by Study 020 or 003 (*Eur Respir J.* 2024;64:2401324). However, Japanese and foreign guidelines for treatment of PAH recommend the same treatment for patients with PAH irrespective of underlying disease. PMDA considers it possible to specify all patients with PAH irrespective of underlying disease as the intended population of sotatercept.

Study 020 was eventually conducted without enrolling patients in WHO FC Class I or IV despite their eligibility, and the efficacy and safety of sotatercept in these patients thus remain unclear. In light of similar treatment algorithm for PAH practiced in and outside Japan and the recommendation at the seventh World Symposium on Pulmonary Hypertension, for use of sotatercept as an add-on drug to pulmonary vasodilators for intermediate-risk patients with mild disease and high-risk patients based on the ESC/ERS risk assessment tool,[41)] sotatercept will not be used actively in clinical practice for low-risk patients including WHO FC Class I patients. However, the interim analysis result of Study 006 have so far suggested no major concerns about the efficacy or safety of sotatercept. Limited treatment options for patients with severe PAH poorly responding to the conventional treatment and the recommendation at the above-mentioned world symposium will be taken into consideration in the clinical use of sotatercept.

Taken together, and in view of the recommendations in the Japanese and foreign treatment guidelines that the treatment strategy be determined based on multiple prognostic factors rather than WHO FC alone, it is possible to specify the indication as "pulmonary arterial hypertension" as proposed, along with cautionary notes, i.e., the necessity of sotatercept therapy should be examined beforehand by referring to the latest treatment guidelines; and the efficacy and safety have not been established in patients in WHO FC Class I and IV.

Indication
Pulmonary arterial hypertension

Precautions Concerning Indication
- The necessity of sotatercept therapy should be examined beforehand by referring to the latest treatment guidelines.
- Efficacy and safety have not been established in patients in WHO FC Class I and IV.

7.R.6 Dosage and administration

The applicant's explanation about justification for the dosage regimen of sotatercept and dose modification criteria:

(a) Dosage and administration

In Study 003, the starting dose of subcutaneously sotatercept was 0.3 mg/kg, which was followed by 0.7 mg/kg of subsequent doses Q3W unless dose modification was needed. This dosage regimen was intended to maximize the effect of sotatercept while minimizing an increase in hemoglobin level above the ULN, with the following outcomes taken into account. The dose was modified mainly based on hemoglobin level and platelet count.

- In Study 001, results of PVR, the primary endpoint, were more favorable in the sotatercept 0.7 mg/kg dosed population than in the sotatercept 0.3 mg/kg dosed population [see Section 7.2.1].
- Simulations in the PK/pharmacodynamic (PD) analysis showed that the proportion of patients in whom the hemoglobin level reached ≥18 g/dL and increased from baseline by ≥2 g/dL during a 21-day period after the first dose of sotatercept was greater in the 0.7 mg/kg group than in the 0.3 mg/kg group.

In Study 020, PK after a single subcutaneous administration of sotatercept did not clearly differ between Japanese and non-Japanese patients, and the same dosage regimen and dose modification guidelines as those in Study 003 were applied.

Studies 003 and 020 demonstrated the efficacy of sotatercept in patients with PAH with acceptable safety. In both studies, most of the patients received an escalated dose of 0.7 mg/kg and continued the treatment at 0.7 mg/kg (Table 48).

Table 48. Dose escalation, dose reduction, and interruption of the study drug in Studies 003 and 020 (safety analysis population)

	Study 003				Study 020	
	Main treatment period		Main treatment period and extended treatment period		Main treatment period	Main treatment period and extended treatment period
	Placebo (n = 160)	Sotatercept (n = 163)	Placebo (n = 160)	Sotatercept (n = 163)	Sotatercept (n = 46)	Sotatercept (n = 46)
Escalated to 0.7 mg/kg	0 (0)	99.4 (162)	0 (0)	99.4 (162)	100 (46)	100 (46)
No dose reduction	98.1 (157)	93.9 (153)	97.5 (156)	85.9 (140)	95.7 (44)	87.0 (40)
No interruption	96.9 (155)	92.6 (151)	93.1 (149)	85.3 (139)	91.3 (42)	73.9 (34)

% (number of subjects)

Based on the above, the applicant considers that the same dosage regimen as those in Studies 003 and 020 may be proposed. To maximize benefits of sotatercept, the package insert will provide a cautionary note that the maintenance dose of 0.7 mg/kg should be continued unless the dose modification is needed. The treatment should be resumed at the pre-interruption dose level, but if the treatment is resumed after interruption of >9 weeks, it should be resumed at 0.3 mg/kg, the starting dose, because in such case, the serum sotatercept concentration would be decreased to ≤12.5% of the trough concentration at the steady state without interruption. The above instruction about the resuming dose will be included in the package insert to raise caution.

(b) Dose modification criteria

In Studies 003 and 020, the dose was modified mainly based on increased hemoglobin and decreased platelet count, risks associated with sotatercept therapy.

After starting sotatercept treatment in Studies 003 and 020, increased hemoglobin led to dose interruption or reduction in 12.0% (20 of 163) of patients and 13.0% (6 of 46) of patients, respectively, and decreased platelet count led to dose interruption or reduction in 3.1% (5 of 163) of patients and 6.5% (3 of 46) of patients, respectively. None of these cases led to treatment discontinuation according to the criteria. The risks of increase in hemoglobin and decrease in platelet count in patients receiving sotatercept will be manageable with the dose modification criteria based on hemoglobin level and platelet count as practiced in Studies 003 and 020.

In Studies 003 and 020, hemoglobin levels and platelet counts were stabilized by Week 12 at the latest. Hemoglobin level and platelet count should be checked before every dosing for the first 5 doses of sotatercept, or even for the subsequent doses if they remain unstable. Even after stabilization, the both should be monitored periodically.

In Studies 003 and 020, the criteria required that the fourth interruption owing to decreased platelet count be superseded by treatment discontinuation. The study results, however, have shown that safety can be ensured in the clinical settings by dose modification, after overall evaluation of the patient's clinical condition including laboratory values, and the criterion of uniform treatment discontinuation needs not be specified in the package insert. Also, in Studies 003 and 020, sotatercept was to be resumed at 0.3 mg/kg without exception after interruption owing to decreased platelet count. However, sotatercept should preferably be continued at 0.7 mg/kg unless dose modification is needed. Thus, the applicant decided not to include this criterion in the package insert.

PMDA's view:

In Studies 003 and 020, nearly all subjects were able to receive the maintenance dose of 0.7 mg/kg. During the main treatment period, approximately 90% of the subjects continued sotatercept without dose reduction or interruption. Even among those who underwent dose modification, no subjects discontinued the treatment due to increased hemoglobin or decreased platelet count. Accordingly, the dosage and administration may be specified as proposed, with cautionary notes requesting hemoglobin level/platelet count monitoring and appropriate dose modification based on these laboratory values.

In Studies 003 and 020, patients were required to resume the treatment at 0.3 mg/kg across the board after interruption due to decreased platelet count. Given unclear safety in resumption at 0.7 mg/kg after interruption at 0.7 mg/kg, the treatment should be resumed at 0.3 mg/kg even within 9 weeks after the previous dose.

In conclusion, the Dosage and Administration and Precautions Concerning Dosage and Administration for sotatercept should be specified as follows.

Dosage and Administration

Usually, adult starting dose is 0.3 mg/kg of sotatercept (genetical recombination) followed by escalated doses of 0.7 mg/kg administered subcutaneously once every 3 weeks.

Precautions Concerning Dosage and Administration

- Hemoglobin level and platelet count should be measured at the start of and throughout the sotatercept therapy, before every dosing at least for the first 5 doses, and for subsequent doses until stabilization of the values. Both should be measured periodically throughout the sotatercept therapy.
- During use of sotatercept, the dose should be escalated, maintained, or delayed by referring to the instructions below. The maintenance dose (0.7 mg/kg) should be continued unless the dose modification is necessary.
- Use of sotatercept should be delayed for 3 weeks in the following conditions:
  - Increase in hemoglobin level from the previous dose by >2.0 g/dL, exceeding the upper limit of normal
  - Increase in hemoglobin level from baseline by >4.0 g/dL
  - Increase in hemoglobin level to >2.0 g/dL above the upper limit of normal
  - Decrease in platelet count to <50,000 /mm^3
- After a decrease in platelet count to <50,000 /mm^3 or after a >9-week interval from the previous dose, sotatercept should be resumed at the starting dose (0.3 mg/kg).

7.R.7 Pediatric use

The development of sotatercept is underway outside Japan for pediatric patients aged ≥1 year, and it is also currently being discussed in Japan.

In view of the prevalence of PAH in children and the current treatment for pediatric PAH that is based on the treatment algorithm for adults, Considering that there is a need for the development of sotatercept aiming at the inclusion of children with PAH in the eligible population, PMDA reviewed the development plan of sotatercept for pediatric PAH based on the “Planning of the Pediatric Drug Development Program during Development of Drugs for Adults” (PSB/PED Notification No. 0112-3, dated January 12, 2024).

7.R.8 Post-marketing investigations

The applicant’s explanation about post-marketing investigations for sotatercept:

The applicant will implement a specified drug use-results survey using a central registry system (observation period, 54 weeks after the first dose or 11 weeks after treatment discontinuation; target sample size, 300 patients) to investigate the long-term safety including the occurrence of polycythemia and severe thrombocytopenia in clinical use of sotatercept. Among polycythemia-related events in Study 020, increased hematocrit and thrombocytopenia of any severity respectively showed the lowest incidence of 2.2%. Thus, the sample size of 300 will allow to accrue data including detailed patient characteristics to analyze each safety item to a certain extent. Occurrence tendency and causes of these events will be comprehensively evaluated based on safety information obtained from the specified drug use-results survey as well as that collected globally through routine pharmacovigilance activities.

PMDA's view:

Decreased platelet count and increased hemoglobin were observed in the use of sotatercept, but the risk of serious bleeding-related events, thrombotic events, etc. remains unclear at present. In view of the novelty of sotatercept's action mechanism and short experience in post-marketing use outside Japan, the occurrence of these events should be further monitored even after the market launch. In the post-marketing settings, the applicant plans to conduct the specified drug use-results survey in addition to the routine pharmacovigilance activities to investigate product safety including the occurrence of polycythemia and severe thrombocytopenia in clinical use, and this approach is reasonable. In light of the embryo-fetal toxicity of sotatercept [see Section 5.R.1], the survey should also obtain data on the effects of sotatercept on pregnancy, maternal body, and fetal growth.

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 inspection and assessment are currently ongoing. Results and the conclusion of PMDA will be reported in the Review Report (2).

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

The inspection is currently ongoing. Results and the conclusion of PMDA will be reported in the Review Report (2).

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

On the basis of the data submitted, PMDA has concluded that sotatercept has efficacy in the treatment of PAH, and that sotatercept has acceptable safety in view of its benefits. The drug product and its drug substance are both classified as powerful drugs. Sotatercept is clinically meaningful because it offers a new treatment option for patients with PAH. Clinical positioning, indication and intended populations, descriptions of the cautionary notes in the package insert, post-marketing investigations, etc. are subject to further discussion.

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

Review Report (2)

May 21, 2025

Product Submitted for Approval

Brand Name	Airwin for Subcutaneous Injection 45 mg, Airwin for Subcutaneous Injection 60 mg
Non-proprietary Name	Sotatercept (Genetical Recombination)
Applicant	MSD K.K.
Date of Application	November 14, 2024

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).

At the Expert Discussion, the expert advisors supported PMDA's the conclusions on the efficacy, dosage and administration, and pediatric use described in the Review Report (1).

1.1 Safety

(a) Decrease in platelet count and increase in hemoglobin

At the Expert Discussion, the expert advisors supported PMDA's conclusion in Section 7.R.3 of the Review Report (1), i.e., safety will be ensured by platelet count/hemoglobin level monitoring and dose modification as practiced in the phase III studies.

(b) Impact on pregnant women

In Section 5.R.1 of the Review Report (1), PMDA concluded that the use of sotatercept in pregnant women or women who may possibly be pregnant is acceptable only if the following advice is offered in the package insert and healthcare professionals and patients are informed, via written materials, of the lack of clinical experience with sotatercept in pregnant women and the impact of sotatercept on pregnancy.

- Sotatercept should preferably not be administered to pregnant women or those who may possibly be pregnant.

- Before administration, patients of reproductive age should be explained of possible impact of sotatercept on conception and maintenance of pregnancy.

At the Expert Discussion, the above conclusion of PMDA was supported and the following comments were made:

- There have been recent cases of PAH patients who were found to be capable of withstanding pregnancy and delivery after careful severity assessment. Also, teratogenicity of the existing ERAs and sGC agonists was reported. There is a high medical need for therapeutic drugs against PAH that can be continued during pregnancy.
- Because of the low risk of teratogenicity, sotatercept should remain as a treatment option for pregnant women or women who may possibly be pregnant.
- It is important that sotatercept be administered to pregnant women after careful decision made by physicians and by the shared decision-making approach between patients and healthcare professionals. Patients should be adequately informed of the impact of sotatercept on conception and maintenance of pregnancy and the lack of clinical experience with sotatercept in pregnant women.

In view of the discussion at the Expert Discussion, PMDA instructed the applicant to caution about the impact, etc. of sotatercept on pregnancy with relevant information via the package insert, written materials for healthcare professionals, and patient leaflets. The applicant responded appropriately.

(c) Hypoxia due to intrapulmonary right-to-left shunt

After the preparation of Review Report (1), the applicant reported additional 2 cases of hypoxia[42)] in the ongoing foreign phase III study (Study 004[33)]). The event occurred despite improved PAH, including pulmonary hemodynamics shown by right cardiac catheterization. The following describes the clinical course of each patient:

- Patient 1 (HPAH): At Month 14, hypoxia (non-serious, mild, causally unrelated to sotatercept) occurred. At Month 31, contrast echocardiography detected intrapulmonary right-to-left shunt (non-serious, moderate, causally related to sotatercept). At Month 37, cyanosis (non-serious, mild, causally unrelated to sotatercept) occurred, and oxygen therapy started. After the interruption of sotatercept that occurred 3 times over a period of Months 41 to 42, the resumption at the reduced dose of 0.3 mg/kg was decided. None of the reported events have resolved.
- Patient 2 (PAH associated with congenital heart disease): At Month 25, dyspnoea (non-serious, moderate, causally unrelated to sotatercept) occurred, and contrast echocardiography (unknown date) detected intrapulmonary right-to-left shunt.[43)] At Month 28, sotatercept was interrupted and oxygen therapy started. At Month 29, hypoxia (serious, severe, causally related to sotatercept[44)]) occurred. None of the reported events have resolved.

Furthermore, foreign post-marketing reports revealed intrapulmonary right-to-left shunt in 2 cases of hypoxia following sotatercept therapy. The ongoing Japanese phase III study (Study 020) has reported

42) MedDRA PT "hypoxia"
43) Not reported as an adverse event
44) Initially, it was reported as "causally unrelated to sotatercept," but later it was changed to "causally related to sotatercept" by the investigator.

no serious hypoxia. In foreign clinical studies, 3 of 22 cases of hypoxia reported in the pooled safety analysis (Pool B) [see Section 7.R.3 of the Review Report (1)] were serious, for which however a causal relationship to sotatercept was ruled out.

PMDA's view:
Progressive hypoxia observed in Study 004 could have been attributable to intrapulmonary right-to-left shunt. So far, only 1 case of serious hypoxia has been confirmed to be causally related to sotatercept, and there is not much information about its outcome. Thus, whether sotatercept has a risk of intrapulmonary right-to-left shunt remains inconclusive. Yet intrapulmonary right-to-left shunt can lead to serious hypoxia. The package insert should provide information about the occurrence of hypoxia accompanied by intrapulmonary right-to-left shunt in Study 004 and foreign post-marketing settings, and advise appropriate actions against hypoxia of unknown cause or worsening of hypoxia with no evidently compromised pulmonary hemodynamics, such as cause investigation in view of the possibility of intrapulmonary right-to-left shunt.

Also in the post-marketing settings, the collection of information about hypoxia accompanied by intrapulmonary right-to-left shunt or pulmonary capillary dilatation needs to be continued through the specified drug use-results survey, etc. If obtained information is suggestive of a risk of intrapulmonary right-to-left shunt due to sotatercept therapy, additional cautionary advice, modification to the specified drug use-results survey plan, and implementation of a new survey should be discussed.

The above conclusion of PMDA was supported at the Expert Discussion.

Based on the discussion at the Expert Discussion, PMDA instructed the applicant to offer the following advice in the Important Precautions section of the package insert. The applicant responded appropriately.

Important Precautions (excerpt of the description relevant to this section)
- In response to hypoxia of unknown cause or worsening of hypoxia with no evidently compromised pulmonary hemodynamics, cause investigation by contrast echocardiography, or any other appropriate actions, should be taken in view of the possibility of intrapulmonary right-to-left shunt.

1.2 Clinical positioning, indication, and intended population

Based on the review in Section 7.R.5 of the Review Report (1), PMDA has concluded that the indication of sotatercept should be specified as "pulmonary arterial hypertension" with the following cautionary notes:
- Before starting, the necessity of treatment with sotatercept should be examined by referring to the latest treatment guidelines.
- The efficacy and safety have not been established in patients in WHO FC Class I and IV.

The conclusion of PMDA was generally supported at the Expert Discussion. Meanwhile, the following comment was made.
- Clinical usefulness of sotatercept was demonstrated in Studies 003 and 020 in patients on background therapy with pulmonary vasodilators. The use of sotatercept should be considered for patients on

pulmonary vasodilator therapy, and this advice should be communicated via the package insert and written materials for healthcare professionals. The package insert, etc. should also communicate the usage status of concomitant pulmonary vasodilators in the clinical studies.

Based on the comment from the expert advisor, PMDA instructed the applicant to specify the Indication and Precautions Concerning Indication as shown below. The applicant responded appropriately.

Indication

Pulmonary arterial hypertension

Precautions Concerning Indication

- Use of sotatercept should be considered for patients on pulmonary vasodilator therapy.
- The necessity of sotatercept therapy should be examined by referring to the latest treatment guidelines beforehand, with a full understanding of information in the "17. Clinical Studies" section and characteristics (prior treatment, concomitant drugs, etc.) of patients enrolled in the clinical studies.
- Sotatercept should be used only for patients with eligibility confirmed by physicians with adequate knowledge and experience in treatment of pulmonary arterial hypertension.
- Efficacy and safety have not been established in patients in WHO FC Class I and IV.

1.3 Risk management plan (draft)

Based on the reviews in Section 7.R.8 of the Review Report (1) and Section 1.1 of the Review Report (2), PMDA has concluded that the risk management plan (draft) for sotatercept should include the safety specification presented in Table 49, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Table 50, as well as the specified drug use-results survey presented in Table 51.

Table 49. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Hemorrhage • Thrombocytopenia • Polycythemia	• Embryo-fetal toxicity • Hypoxia accompanied by intrapulmonary right-to-left shunt or pulmonary capillary dilatation	• Long-term safety
Efficacy specification		
Not applicable		

Table 50. Summary of additional pharmacovigilance activities and additional risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimization activities
• Early post-marketing phase vigilance • Specified drug use-results survey	• Disseminate data obtained during early post-marketing phase vigilance • Organize and disseminate written materials for healthcare professionals • Organize and disseminate patient leaflets

Table 51. Outline of specified drug use-results survey (draft)

Objective	To confirm safety in clinical use
Survey method	Central registry system
Population	Adult patients with PAH who have received sotatercept
Observation period	54 weeks after the first dose of sotatercept or 11 weeks after treatment discontinuation[a]
Planned sample size	300 patients
Main survey items	Incidence of hemorrhage, thrombocytopenia, polycythemia, and hypoxia accompanied by intrapulmonary right-to-left shunt or pulmonary capillary dilatation, long-term safety, etc.

a Follow-up for pregnant or breastfeeding women should be continued as long as possible in cooperation with patients and physicians responsible for the survey.

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

2.1 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.

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

The new drug application data (CTD 5.3.5.2.3) 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.

3. Overall Evaluation

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

Indication

Pulmonary arterial hypertension

Dosage and Administration

Usually, adult starting dose is 0.3 mg/kg of sotatercept (genetical recombination) followed by escalated doses of 0.7 mg/kg administered subcutaneously once every 3 weeks.

Approval Condition

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

List of Abbreviations

6MWD	6-Minute Walk Distance
α-SMA	Alpha smooth muscle actin
ActRIIA	Activin receptor type IIA
ActRIIB	Activin receptor type IIB
ADA	Anti-drug antibodies
ADCC	Antibody dependent cell-mediated cytotoxicity
Airwin	Airwin for Subcutaneous Injection
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
$AUC_{0\text{-last}}$	AUC from time zero to time of the last quantifiable concentration
$AUC_{0\text{-x}}$	AUC from time zero to fixed time x
$AUC_{0\text{-}\infty}$	AUC from time zero extrapolated to infinity
BMC	Bone mineral content
BMD	Bone mineral density
BMI	Body mass index
BMP	Bone morphogenetic protein
BMPR2	Bone morphogenetic protein receptor 2
BNP	Brain natriuretic peptide
BUN	Blood urea nitrogen
C1q	Complement component 1, q subcomponent
CDC	Complement dependent cytotoxicity
CE-SDS	Capillary electrophoresis with sodium dodecyl sulfate
CHO cells	Chinese hamster ovary cells
CI	Confidence interval
CL	Clearance
CL/F	Apparent total body clearance
C_{max}	Maximum concentration
C_{min}	Minimum concentration
COVID-19	Coronavirus Disease 2019
CQA	Critical quality attributes
CTCAE	Common Terminology Criteria for Adverse Events
CTD	Common technical document
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
ECL	Electrochemiluminescence
eGFR	Estimated glomerular filtration rate
ELISA	Enzyme-linked immunosorbent assay
EPO	Erythropoientin
ERA	Endothelin receptor antagonist
ERS	European Respiratory Society
ESC	European Society of Cardiology
F	Bioavailability
FAS	Full analysis set
Fc	Fragment crystallizable
FC	Functional class
FcγR	Fc gamma receptor
FcRn	Neonatal Fc receptor
FOB	Functional observational battery
FSH	Follicle stimulating hormone

GDF	Growth and differentiation factor
HCT	Hematocrit
HDPE	High-density polyethylene
HDW	Hemoglobin distribution width
HEPES	4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid
hERG	Human ether-à go-go related gene
HGB	Hemoglobin
[redacted]	[redacted]
HMW	High molecular weight
HPAH	Heritable pulmonary arterial hypertension
IC_{50}	Half-maximal inhibitory concentration
ICH Q5A (R2) guideline	Partial revision of the "Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin" (PSB/PED Notification No. 0109-3, dated January 19, 2025)
ICH Q5B guideline	Analysis of the Expression Construct in Cells Used for Production of r-DNA Derived Protein Products (PMSB/ELD Notification No. 3, dated January 6, 1998)
ICH Q5D guideline	Derivation and Characterisation of Cell Substrates Used for Production of Biotechnological/Biological Products (PMSB/ELD Notification No. 873, dated July 14, 2000)
ICH Q5E guideline	Comparability of Biotechnological/Biological Products Subject to Changes in their Manufacturing Process (PFSB/ELD Notification No. 0426001, dated April 26, 2005)
iCIEF	Imaged capillary isoelectric focusing
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IPAH	Idiopathic pulmonary arterial hypertension
K_a	First-order absorption rate constant
K_D	Equilibrium constant
KLH	Keyhole limpet hemocyanin
LH	Luteinizing hormone
LIVCA	Limit of *in vitro* cell age
LMW	Low molecular weight
LV+S	Left ventricular free wall plus septum
MAR	Missing at random
MCB	Master cell bank
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCT	Monocrotaline
MCV	Mean corpuscular volume
MedDRA	Medical dictionary for regulatory activities
MID	Minimal important difference
mPAP	Mean pulmonary arterial pressure
MPV	Mean platelet volume
NA	Not applicable
[redacted]	[redacted]
NK	Natural killer
NT-proBNP	N-terminal pro-B-type natriuretic peptide
NZW	New Zealand White
PAAT	Pulmonary artery acceleration time
PAH	Pulmonary arterial hypertension
PBS	Phosphate-buffered saline
PD	Pharmacodynamics
PDE	Phosphodiesterase

PETG	Polyethylene terephthalate glycol
PGI_2	Prostaglandin I_2
PH	Pulmonary hypertension
PK	Pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency
PPK	Population pharmacokinetics
PT	Preferred term
PVR	Pulmonary vascular resistance
PVRI	Pulmonary vascular resistance index
Q2W	Every 2 weeks
Q4W	Every 4 weeks
QOL	Quality of life
RBC	Red blood cell count
RDW	Red cell distribution width
RH	Relative humidity
RHC	Right heart catheterization
RV	Right ventricular free wall
RVFAC	Right Ventricular fractional area change
RVSP	Right Ventricular Systolic Pressure
RVWT	Right ventricular wall thickness
sGC	Soluble guanylate cyclase
SD	Sprague-Dawley
SEC	Size exclusion chromatography
Smad	Mothers against decapentaplegic, a group of related intracellular proteins critical for transmitting to the nucleus signals from the TGF-β superfamily at the cell surface
SMQ	Standardised MedDRA queries
Sotatercept	Sotatercept (Genetical Recombination)
SPR	Surface plasmon resonance
$t_{1/2}$	Terminal half-life
TAPSE	Tricuspid annular plane systolic excursion
TBS	Tris-buffered saline
TDAR	T-cell dependent antibody response
TG	Triglycerides
TGF-β	Transforming growth factor-β
TIM-1	T cell Ig mucin
TK	Toxicokinetics
t_{max}	Time to maximum concentration
TPRI	Total pulmonary resistance index
TTCW	Time to clinical worsening
[redacted]	[redacted]
ULN	Upper limit of normal
UUL	Unilateral ureteral ligation
V_c	Central volume of distribution
V_p	Volume of distribution for the peripheral compartment
V_{ss}	Volume of distribution at steady state
V_z	Volume of distribution during the terminal phase
V_z/F	Apparent volume of distribution during the terminal phase
WCB	Working cell bank
WHO	World Health Organization