Report on the Deliberation Results

March 3, 2021
Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

Brand Name	Volibris Tablets 2.5 mg
Non-proprietary Name	Ambrisentan (JAN*)
Applicant	GlaxoSmithKline K.K.
Date of Application	July 29, 2020

Results of Deliberation

In its meeting held on February 25, 2021, the First Committee on New Drugs concluded that the partial change application for the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The re-examination period is 6 years and 1 day.

Approval Condition

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

*****_Japanese Accepted Name (modified INN)_

Review Report

February 9, 2021
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	Volibris Tablets 2.5 mg
Non-proprietary Name	Ambrisentan
Applicant	GlaxoSmithKline K.K.
Date of Application	July 29, 2020
Dosage Form/Strength	Tablets, each containing 2.5 mg of ambrisentan
Application Classification	Prescription drug, (6) Drug with a new dosage

Items Warranting Special Mention

Orphan drug (Orphan Drug Designation No. 200 of 2007 [*19 yaku*]; PFSB/ELD Notification No. 0516001 dated May 16, 2007, by the Evaluation and Licensing Division, Pharmaceutical and Food 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 in children aged 8 years or older 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.

Indication

Pulmonary arterial hypertension

(No change)

Dosage and Administration

Adults

The usual adult dosage is 5 mg of ambrisentan orally administered once daily. The dose may be increased according to the symptom but should not exceed 10 mg daily.

Children

The usual dosage of ambrisentan for children aged 8 years or older is any of the following orally administered once daily according to body weight:

20 to <35 kg: The usual dosage is 2.5 mg. The dose may be increased according to the symptom but should not exceed 5 mg daily.

35 to <50 kg: The usual dosage is 5 mg. The dose may be increased according to the symptom but should not exceed 7.5 mg daily.

≥50 kg: The usual dosage is 5 mg. The dose may be increased according to the symptom but should not exceed 10 mg daily.

(Underline denotes additions in this submission.)

Approval Condition

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

Attachment

Review Report (1)

December 24, 2020

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	Volibris Tablets 2.5 mg
Non-proprietary Name	Ambrisentan
Applicant	GlaxoSmithKline K.K.
Date of Application	July 29, 2020
Dosage Form/Strength	Tablets, each containing 2.5 mg of ambrisentan

Proposed Indication

Pulmonary arterial hypertension

Proposed Dosage and Administration

Adults

The usual adult dosage is 5 mg of ambrisentan orally administered once daily. The dose may be increased according to the symptom but should not exceed 10 mg daily.

Children

The usual dosage of ambrisentan for children aged 8 years or older is any of the following orally administered once daily according to body weight:

20 to <35 kg: The usual dosage is 2.5 mg. The dose may be increased according to the symptom but should not exceed 5 mg daily.

35 to <50 kg: The usual dosage is 5 mg. The dose may be increased according to the symptom but should not exceed 7.5 mg daily.

≥50 kg: The usual dosage is 5 mg, The dose may be increased according to the symptom but should not exceed 10 mg daily.

(Underline denotes additions.)

Table of Contents

List of Abbreviations

See Appendix.

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

Ambrisentan is a propionic acid derivative endothelin receptor antagonist (ERA) discovered by [redacted] (currently [redacted]) in Germany. The tablet formulation of ambrisentan was approved for the treatment of pulmonary arterial hypertension (PAH) in adults in 2007 in the US, in 2008 in Europe, and in 2010 in Japan.

PAH is a progressive fatal disease. Pediatric PAH is pathologically similar to adult PAH but is known to progress more rapidly and lead to a poorer prognosis than adult's (*Ann Intern Med.* 1991;115:343-9, *Pediatric Cardiology and Cardiac Surgery.* 2000;16:230-7). In Japan, oral drugs for PAH approved for pediatric use are bosentan hydrate, an ERA, and sildenafil citrate, a phosphodiesterase 5 (PDE5) inhibitor. Children with PAH are treated with drugs approved for adult use, including these 2 agents, at an adjusted dose on the basis of efficacy and safety data of adults.

As of July 2020, no countries or regions have approved dosage regimens of ambrisentan for children with PAH outside Japan, while an application for marketing approval has been submitted in Europe targeting pediatric patients with PAH aged ≥8 and <18 years.

In Japan, a clinical development of ambrisentan for pediatric PAH began in 2011. Based mainly on results from a global clinical study in children with PAH, the applicant submitted the partial change application. Ambrisentan was designated as an orphan drug for the intended indication of "pulmonary arterial hypertension" in May 2007 (Orphan Drug Designation No. 200 of 2007 [*19 yaku*]).

2. Data Relating to Quality and Outline of the Review Conducted by PMDA

The present application pertains to the new dosage, no data relating to quality have been submitted.

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

No new study data were submitted. The present application pertains to the new dosage, and non-clinical pharmacological data of ambrisentan have already been reviewed for its initial approval.

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

Because the present application pertains to the new dosage and the non-clinical pharmacokinetics data of ambrisentan have already been reviewed for its initial approval, PMDA considered that additional studies would not be necessary. Meanwhile, the applicant submitted study results on absorption in juvenile rats as toxicokinetic data, which were confirmed to contain information necessary for toxicity evaluation.

5. Toxicity and Outline of the Review Conducted by PMDA

The applicant submitted results from studies in juvenile animals as data relating to the toxicity of ambrisentan.

5.1 Eight-week repeated oral dose toxicity study in juvenile rats

An 8-week repeated-dose study was conducted in 7-day old rats (n = 12/sex/group) (Table 1). On Days 15 and 19 of the study, 1 each of male and female rats died in the 20 mg/kg/day group. Organ weight

measurement revealed low brain weight. In the histopathological examination on the brain, hematoxylin eosin (HE) plus Luxol fast blue-cresyl violet (LFB-CS) staining and an immunostaining for myelin basic protein and glial fibrillary acidic protein showed no histological changes in the brain. The applicant explained that the low brain weight was a change attributable to some effect on respiratory function [see Section "5.R.1 Effects on the brain"]. In the repeated oral dose toxicity study, the AUC and C_{max} values (of males and females combined) at the no-observed-adverse-effect-level (NOAEL) were 8.81 μμg·h/mL and 3.31 μg/mL, which were 1.0- and 3.4-fold, respectively, the exposure at the maximum clinical dose.

Table 1. Eight-week repeated oral dose toxicity study in juvenile rats

Test system	Route of administration	Treatment period	Dose (mg/kg/day)	Major findings	NOAEL (mg/kg/day)
Male and female Rat (SD)	Oral	8 weeks (QD) + 8 weeks for recovery	0,[a] 4, 10, 20	Death: 20 (1 of 12 males[b] and 1 of 12 females[c]), epicarditis ≥4: Respiratory murmur, persistent pupillary membrane,[d] reduced ulnar length ≥10: Turbinate epithelial inflammation 20: Reduced body weight gain; low food consumption; high erythrocyte parameters; atrophy, regeneration, abnormal cell alignment and hyperplasia of the turbinate epithelium; turbinate haemorrhage; high heart weight; and low brain weight Reversible (except for high heart weight and low brain weight)	4

a, 0.66% (w/v) sodium chloride solution
b, The applicant considered that the death was caused by moderate epicarditis.
c, The cause of the death was not identified.
d, No ophthalmological or histopathological effect on the eye structure or no behavioral change was observed. The applicant considered that this finding was not toxicologically meaningful.

5.2 Study for the effect on respiratory function in juvenile rats (1)

To investigate the relationship between low brain weight and the effect on respiratory function observed in Section "5.1 Eight-week repeated oral dose toxicity study in juvenile rats," a study was conducted as per Table 2, in which examinations shown in Table 3 were performed.

Table 2. Study for the effect on respiratory function in juvenile rats (1)

Test system	Route of administration	Treatment period	Dose (mg/kg/day)	Major findings
Male and female Rat (SD)	Oral	14 days 21 days 30 days (QD)	0,[a] 20	20: Reduced body weight gain; abnormal respiratory sound; hypoxemia (low arterial oxygen pressure and arterial oxygen saturation); high carbon dioxide partial pressure (male); erosion, atrophy, regeneration, abnormal cell alignment, and hyperplasia of turbinate epithelium; and low brain weight

a, 0.66% (w/v) sodium chloride solution

Table 3. Results from examinations for the effect on respiratory function (1)

Item	Date of examination	Result
Oxygen saturation	Post-natal Day 19	Male, 2.4% lower than that in the control group Female, 6.5% lower than that in the control group
	Post-natal Day 26	Male, 1.5% lower than that in the control group Female, 1.6% lower than that in the control group
	Post-natal Day 35	Male, 3.8% lower than that in the control group Female, 2.7% lower than that in the control group
End-tidal pause time	Post-natal Day 20	Male, 94% longer than that in the control group Female, 72% longer than that in the control group
	Post-natal Day 27	Male, 723% longer than that in the control group Female, 655% longer than that in the control group
	Post-natal Day 36	Male, 211% longer than that in the control group Female, 233% longer than that in the control group
Arterial oxygen pressure	Post-natal Day 20	Male, 19% lower than that in the control group Female, 44% lower than that in the control group
	Post-natal Day 27	Male, 31% lower than that in the control group Female, 11% lower than that in the control group
	Post-natal Day 36	Male, 39% lower than that in the control group Female, 21% lower than that in the control group
Arterial carbon dioxide partial pressure	Post-natal Day 20	Male, 50% higher than that in the control group Female, 61% higher than that in the control group
	Post-natal Day 27	Male, 43% higher than that in the control group Female, 30% higher than that in the control group
	Post-natal Day 36	Male, 45% higher than that in the control group Female, 33% higher than that in the control group

5.3 Study for the effect on respiratory function in juvenile rats (2)

To investigate the effect on central nervous system associated with low brain weight and hypoxemia observed in Sections "5.1 Eight-week repeated oral dose toxicity study in juvenile rats" and "5.2 Study for the effect on respiratory function in juvenile rats (1)," a study was conducted as per Table 4, in which examinations shown in Table 5 were performed.

Table 4. Study for the effect on respiratory function in juvenile rats[a] (2)

Test system	Route of administration	Treatment period	Dose (mg/kg/day)	Major findings
Male and female Rat (SD)	Oral	20 days (QD)	0,[b] 20	20: Abnormal respiratory sound, hypoxemia, hypercapnia, prolonged end-tidal pause time, and increased peak expiratory flow rate
		20 days (QD) + 2 days for recovery		20: Abnormal respiratory sound, hypoxemia, hypercapnia, prolonged end-tidal pause time, increased peak expiratory flow rate, and low brain weight
		20 days (QD) + 28 days for recovery		20: Abnormal respiratory sound and low brain weight

a, Juvenile rats (n = 24/sex/group) orally received ambrisentan 0[b] and 20 mg/kg/day from Post-natal Days 7 through 26 (Post-natal Day 7 = Day 1 of the study). The animals were divided into subgroups each including 6 each of males and females, and underwent necropsy at the end of treatment, after the short recovery period (2 days), or after the long recovery period (28 days). On Day 10, 1 female in the 20 mg/kg/day group was euthanized because of decreased body weight and dehydration. The cause of the aggravated clinical signs was not identified.

b, 0.66% (w/v) sodium chloride solution

Table 5. Results from examinations for the effect on respiratory function (2)

Item	Date of examination	Result
Neurobehavioral examination	Post-natal Day 25	No ambrisentan-related changes were observed.
	Post-natal Day 53	
Arterial oxygen pressure	Post-natal Day 26	Male, 18% lower than that in the control group Female, 26% lower than that in the control group
	Post-natal Day 28	Male, 18% lower than that in the control group Female, 5% lower than that in the control group
	Post-natal Day 54	Male, no difference was observed between the 20 mg/kg/day and control groups. Female, no difference was observed between the 20 mg/kg/day and control groups.
Arterial carbon dioxide partial pressure	Post-natal Day 26	Male, 44% higher than that in the control group Female, 44% higher than that in the control group
	Post-natal Day 28	Male, 36% higher than that in the control group Female, 31% higher than that in the control group
	Post-natal Day 54	Male, no difference was observed between the 20 mg/kg/day and control groups. Female, no difference was observed between the 20 mg/kg/day and control groups.
Expression of hypoxia-inducible genes in the brain	Post-natal Day 26	No ambrisentan-related changes were observed.
	Post-natal Day 28	
	Post-natal Day 54	
MRI examination[a]	Post-natal Day 26/27	No morphological changes in the soft palate were observed in control and 20 mg/kg/day groups. Interactions with nasopharyngeal tissues (soft palate, epiglottis, and arytenoid cartilage) were not elucidated owing to the limited resolution.
	Post-natal Day 28/29	
	Post-natal Day 53/54	

a, Performed to investigate an association between the dynamical change in nasopharyngeal tissues and abnormal respiration.

5.R Outline of the review conducted by PMDA

On the basis of the data submitted and the following review, PMDA concluded that the non-clinical toxicity evaluation did not raise any problem relevant to the clinical use of ambrisentan.

5.R.1 Effects on the brain

The applicant's explanation about the mechanism of how low brain weight occurs as observed in juvenile rats in the repeated-dose toxicity study and its relevance of to humans:

Based on the following investigation results, low brain weight in juvenile rats was caused by hypoxemia attributable to functional incoordination between the soft palate and epiglottis with breathing, which was associated with morphological abnormalities in the soft palate and surrounding tissues.

- In the repeated-dose toxicity study in juvenile rats, as compared to the control group, the animals with low brain weight also presented with abnormal respiratory sound (click) and prolonged end-tidal pause time (apneic time) during a respiratory cycle. A histopathological examination on the respiratory tract showed an inflammatory change in the nasal epithelium but no findings suggestive of airway obstruction. These changes suggested transient mechanical airway obstruction during each respiratory cycle.
- The mechanical airway obstruction observed in juvenile rats presenting with the abnormal respiration (click) is considered due to morphological abnormalities in the soft palate and surrounding tissues, based on the consistency between the treatment period of Post-natal Days 7 to 63 in the repeated-dose toxicity study in juvenile rats and the development period of the soft palate in rats (continued to Post-natal Weeks 6-8) (*J Anat.* 1979;128:97-105). This observation is supported by an article reporting the association between clicks in human children with abnormal movement of the soft palate muscle (*Pediatr Emerg Care.* 2012;28:158-9), and the reported

ambrisentan-induced morphological abnormalities of the cervicofacial part including the soft palate, hard palate, and lower jaw in an embryo-fetal development study in rats that suggested ambrisentan's effect on these tissues (see "Review Report on Volibris Tablets 2.5 mg dated May 26, 2010"). In view of these observations, functional incoordination between the soft palate and epiglottis with breathing, which was associated with morphological abnormalities in the soft palate and surrounding tissues, led to transient mechanical airway obstruction, eventually causing hypoxemia.

- Rodents grown under a hypoxic condition from Post-natal Days 2 to 20, the period that is critical for brain development, presented with low brain weight (*Dev Brain Res.* 1998;111:197-203, *Pediatr Pulmonol.* 2008;43:20-8). In Section "5.2 Study for the effect on respiratory function in juvenile rats (1)," juvenile rats receiving ambrisentan from Post-natal Day 7 presented with hypoxemia at the examinations on Post-natal Days 20 to 36.

These observations do not negate the possibility that the use of ambrisentan in infants (aged 0-3 years) with immature laryngopharyngeal region, because of uncompleted laryngeal descent as observed in juvenile rats, may cause them to have a respiratory disorder and hypoxemia, which may affect brain weight. In contrast, in children aged ≥8 years, the target patient population of the application, the risk of these conditions is considered extremely low because of completed laryngeal descent in children aged ≥8 years (*Dysphagia.* 1993;8:318-25, *Sleep Breath.* 1999;3:17-22); the location of the soft palate not adjacent to the epiglottis; and rapid growth of the human brain after birth by the age of 2 to 3 years, by which brain weight reaches approximately 90% to 95% of that in adults (*Prog in Neurobiol.* 2013;106-7:1-16). The toxicity study results presented in Section "5.1 Eight-week repeated oral dose toxicity study in juvenile rats" are provided in the "Other Precautions" section of the package insert of ambrisentan to raise caution (revised in October 2018).

PMDA's view:
The applicant's explanation about the onset mechanism of low brain weight is acceptable. Ambrisentan is considered unlikely to affect brain weight in children aged ≥8 years, the target patient population of the present application. Therefore, additional cautionary advice needs not be provided in the package insert, etc.

5.R.2 Reduced ulnar length

The applicant's explanation about the mechanism of how reduced ulnar length develops as observed in juvenile rats in all dose groups in the 8-week repeated oral dose toxicity study and the relevance of this change to humans:
Reduced ulnar length was observed transiently in the ambrisentan 4 and 10 mg/kg/day groups and throughout the treatment period in the 20 mg/kg/day group. Animals in the ≥10 mg/kg/day groups showed low body weight or food consumption and reduced body weight gain, which nearly coincided with reduced ulnar length. In this study, clinical signs observed were abnormal respiration in the ≥10 mg/kg/day groups on Day 6 or 7 and thereafter and respiratory murmur in the 4 mg/kg/day group on Day 13 and thereafter, albeit in a small number of animals. These changes nearly coincided with low body weight and reduced body weight gain. Post-weening pellet feeding tended to improve body weight gain. In view of these observations, the reduced ulnar length is a change associated with

growth retardation attributable to decreased milk intake due to abnormal respiration, and is unlikely to occur in children aged ≥8 years, for whom ambrisentan is indicated in the present application.

PMDA considers the applicant's explanation acceptable.

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

Unless otherwise specified, values of pharmacokinetic (PK) parameters are expressed as means.

6.1 Summary of biopharmaceutic studies and associated analytical methods

Plasma concentrations of ambrisentan were determined by liquid chromatography and tandem mass spectrometry (LC-MS/MS). The lower limit of quantification was 5 ng/mL.

In the global phase II study (Study AMB112529) and long-term treatment study (Study AMB114588), children with PAH were treated with 2.5 mg tablets commercialized in Japan and 5 and 10 mg tablets commercialized overseas. Bioequivalence (BE) has been demonstrated between the 2.5 mg commercial tablets in Japan and the 5 and 10 mg commercial tablets overseas (see "Review Report on Volibris Tablets 2.5 mg dated May 26, 2010").

6.2 Clinical pharmacology

6.2.1 *In vitro* studies using human biological samples

6.2.1.1 Inhibition against transporters (CTD 4.2.2.6)

The inhibitory effect of ambrisentan (investigated at up to 100 μmol/L) against the transport of each transporter's substrate was investigated using CHO cells expressing organic anion transporting polypeptide (OATP) 1B1, OATP1B3, or Na+/taurocholate cotransporting polypeptide (NTCP), membrane vesicles prepared from Sf9 cells expressing bile salt export pump (BSEP) or multidrug resistance-associated protein 2 (MRP2), and MDCKII cells expressing breast cancer resistance protein (BCRP) or P-glycoprotein (P-gp). Ambrisentan inhibited OATP1B1 and OATP1B3 with the half-maximal inhibitory concentration (IC_{50}) values of 47 and 45 μmol/L, respectively. Ambrisentan inhibited NTCP by approximately 50% at the highest concentration investigated (100 μmol/L), but hardly inhibited BSEP, MRP2, BCRP, and P-gp.

6.2.2 PPK analysis (CTD 5.3.3.5)

A population pharmacokinetic (PPK) analysis was performed on measured plasma concentrations of ambrisentan covering 211 sampling points in 39 patients in Study AMB112529.

In this analysis, the 2-compartment model with the first-order absorption, first-order elimination, and absorption lag time was used as the basic model according to the PPK model constructed from data in adults. CL/F, Q/F, V_c/F, and V_p/F of ambrisentan were expressed as allometric formulae based on body weight, and allometric factors were determined to be 0.75 for CL/F and Q/F, and 1 for V_c/F and V_p/F.

Selected covariate candidates that might affect the PK parameters of ambrisentan were age, sex, race, bilirubin, alkaline phosphatase (ALP), and creatinine clearance for CL/F, bilirubin, ALP, and creatinine

clearance for V_c/F, and dose group for absorption lag time. The search for covariates revealed that none of these candidates were identified as covariates for CL/F, V_c/F, or absorption lag time of ambrisentan, and the basic model was decided to be used as the final model.

The mean population parameter values in the final model were 1.17 L/h for CL/F, 12.3 L for V_c/F, 0.457 L/h for Q/F, 81.3 L for V_p/F, 2.46 h^{-1} for absorption rate constant, and 0.525 h for absorption lag time, and their relative standard errors were 6.33%, 16.1%, 21.1%, 24.5%, 25.7%, and 14.7%, respectively.

6.R Outline of the review conducted by PMDA

6.R.1 Differences in PK between Japanese and non-Japanese children aged ≥8 years

The applicant's explanation about differences in the PK of ambrisentan between Japanese and non-Japanese children aged ≥8 years:

Table 6 shows AUC_{ss} and $C_{max,ss}$ of ambrisentan estimated from measured plasma concentrations of ambrisentan in Study AMB112529 using the PPK model [see Section "6.2.2 PPK analysis"]. All PK parameters showed similarity between Japanese and non-Japanese patients. As observed in adults (see "Review Report on Volibris Tablets 2.5 mg dated May 26, 2010"), there are no clear differences in the PK of ambrisentan between Japanese and non-Japanese children aged ≥8 years.

Table 6. PK parameters[a] of ambrisentan in pediatric patients with PAH aged ≥8 years

Population	Dose (mg)	Body weight category	Number of subjects	AUC_{ss} (μg·h/mL)	$C_{max,ss}$ (μg/mL)
Japanese	2.5 and 5	-	5	4.22 [3.42, 5.20]	497 [355, 698]
	2.5	≥20 kg and <35 kg	3	3.94 [3.03, 5.11]	442 [217, 898]
	5	≥35 kg and <50 kg	1	5.60	668
	5	≥50 kg	1	3.87	530
Non-Japanese	2.5 and 5	-	15	5.04 [4.13, 6.14]	527 [453, 614]
	2.5	≥20 kg and <35 kg	5	4.09 [3.11, 5.39]	501 [407, 615]
	5	≥35 kg and <50 kg	7	6.56 [5.00, 8.62]	497 [384, 643]
	5	≥50 kg	3	3.84 [1.98, 7.45]	659 [255, 1700]

Geometric mean (95% confidence interval [CI]); a, Estimated using the PPK model

Based on the study results submitted, PMDA considers the applicant's explanation acceptable that there are no clear differences in the PK of ambrisentan between Japanese and non-Japanese children.

6.R.2 Dosage regimen in Study AMB112529

The applicant's explanation about the rationale for the dosage regimen of ambrisentan in Study AMB112529:

In Study AMB112529, the dosage regimens were designed to obtain AUC_{0-24} value of ambrisentan in children with PAH aged ≥8 years comparable to the value at which the efficacy and safety had been demonstrated in adults with PAH. Ambrisentan undergoes glucuronidation, a major metabolic reaction. The glucuronidation metabolic pathway develops rapidly after birth until it is comparable to adults' in approximately 3 to 6 months (*J Antimicrob Chemother.* 1994;34:19-24), and the pediatric dosage regimens of glucuronidation-metabolized drugs are recommended to be specified based on body weight (*Clin Pharmacokinet.* 2006;45:1077-97). Given these, children aged ≥8 years are expected to achieve an AUC_{0-24} level comparable to that in adults when treated with a per-body weight dose of

ambrisentan as practiced in adults. The dosage amounts of ambrisentan for respective body weight categories were to be specified in multiples of the strength of available commercial tablets.

Accordingly, the body weight categories were determined with cut-off values of 20, 35, and 50 kg, for which the dosage amounts were specified as per Table 7. On the assumption that CL/F of ambrisentan in children aged ≥8 years was comparable to that in adults, $AUC_{0\text{-}24}$ of ambrisentan in these children at the per-body weight doses were estimated. The $AUC_{0\text{-}24}$ estimates in children aged ≥8 years receiving high doses (5, 7.5, and 10 mg) were not below the $AUC_{0\text{-}24}$ value in adults weighing 70 kg receiving the maximum dose (10 mg); and the estimates in children aged ≥8 years receiving low doses (2.5 and 5 mg) were not below that in adults weighing 70 kg receiving the usual dose (5 mg). Accordingly, in Study AMB112529, the doses of ambrisentan were specified as per Table 10 [see Section "7.1.1 Study AMB112529"].

Table 7. Dose by body weight category

Population	Body weight category	Low dose	High dose
Children aged ≥8 years	≥50 kg	5 mg	10 mg
	≥35 kg and <50 kg	5 mg	7.5 mg
	≥20 kg and <35 kg	2.5 mg	5 mg

Then, exposure to ambrisentan (AUC_{ss} and $C_{max,ss}$) was estimated using the PPK model from plasma concentrations of ambrisentan obtained in Study AMB112529, which yielded results shown in Table 8 and Figure 1. The results indicate that the dosage regimen specified in Study AMB112529 will be able to obtain an exposure level in children aged ≥8 years comparable to that in adults, irrespective of their body weight.

Table 8. Comparison of ambrisentan PK parameters between children aged ≥8 years[a] and adults[b]

Population	Dose (mg)	Body weight category	Number of subjects	AUC_{ss} (μg·h/mL)	$C_{max,ss}$ (ng/mL)
Low dose					
Adults	5	-	157	4.98 [4.68, 5.29]	469 [447, 493]
Children (overall)	2.5 and 5	-	20	4.82 [4.14, 5.61]	519 [458, 589]
Children (Japanese)	2.5 and 5	-	5	4.22 [3.42, 5.20]	497 [355, 698]
Children	2.5	≥20 kg and <35 kg	8	4.03 [3.48, 4.68]	478 [401, 568]
Children	5	≥35 kg and <50 kg	8	6.42 [5.09, 8.11]	516 [408, 651]
Children	5	≥50 kg	4	3.87 [2.73, 5.48]	624 [369, 1060]
High dose					
Adults	10	-	79	9.12 [8.30, 10.0]	830 [757, 909]
Children (overall)	5, 7.5, and 10	-	19	9.15 [8.41, 9.96]	981 [894, 1080]
Children	5	≥20 kg and <35 kg	9	8.73 [7.75, 9.83]	953 [850, 1070]
Children	7.5	≥35 kg and <50 kg	4	8.70 [7.62, 9.92]	1100 [679, 1790]
Children	10	≥50 kg	6	10.2 [8.04, 12.8]	948 [791, 1140]

Geometric mean [95% CI]
a, Estimates based on the PPK model (Study AMB112529); b, Estimates based on the PPK model (data in subjects treated with ambrisentan 5 or 10 mg in Studies AMB-220, AMB-222, AMB-320, and AMB-321)

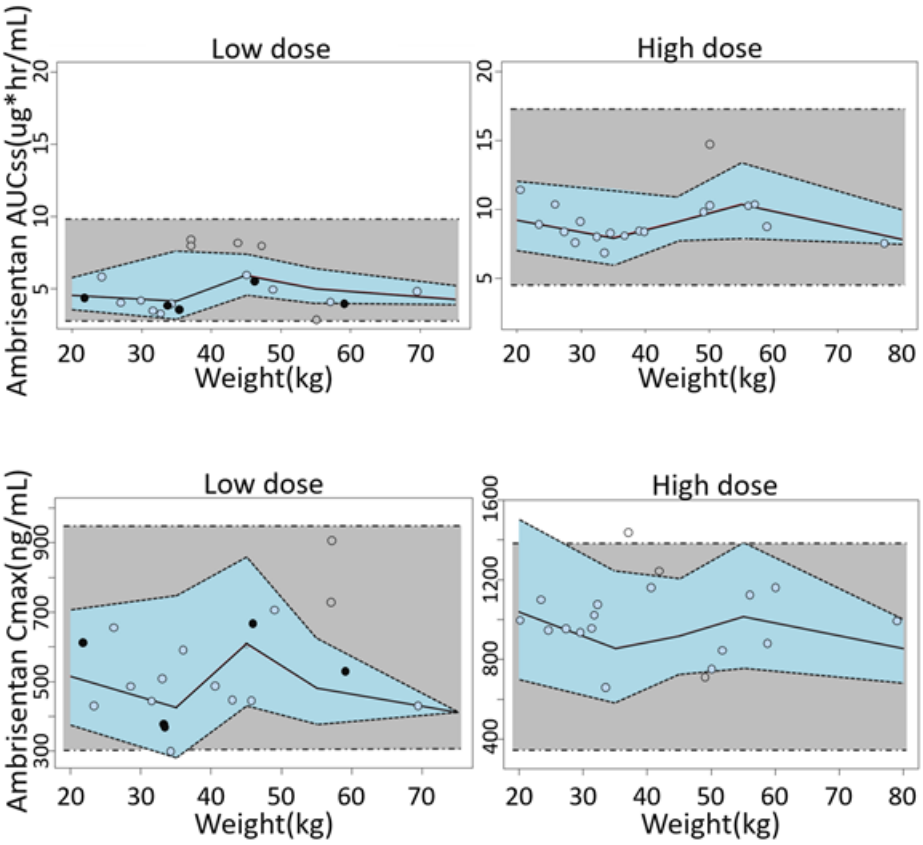

Figure 1. Association between the PK parameters of ambrisentan and body weight following multiple dose treatment according to the dosage regimens in Table 10 (estimates based on the PPK model) (Study AMB112529)

Open circle, AUC_{ss} or $C_{max,ss}$ estimate in non-Japanese children; Closed circle, AUC_{ss} or $C_{max,ss}$ estimate in Japanese children; Solid line, median AUC_{ss} or $C_{max,ss}$ estimate in children; Shaded area enclosed by a broken line, 90% prediction interval of AUC_{ss} or $C_{max,ss}$ estimate; Shaded area enclosed by a dot-dash line, 5 to 95 percentiles of AUC_{ss} or $C_{max,ss}$ estimate in adults at a low (5 mg) or high (10 mg) dose group

PMDA's view:

Based on the study results submitted and the review conducted, the dosage regimen in Study AMB112529 is acceptable from the viewpoint of the exposure level achieved in children aged ≥8 years that is comparable to that in adults. Yet, clinically appropriate dosage regimen of ambrisentan for Japanese children PAH aged ≥8 years is subject to further discussion in view of its efficacy and safety in Study AMB112529 [see Section "7.R.6 Dosage and administration"].

6.R.3 Pharmacokinetic interactions with cyclosporine

The concomitant use of ambrisentan with cyclosporine approximately doubles AUC of ambrisentan. The package insert (draft) of ambrisentan therefore cautions that the dose of ambrisentan used in combination with cyclosporine should be limited to once daily ≤5 mg. While the proposed dosage regimens for children with PAH weighing ≥20 to <35 kg and ≥35 to <50 kg are different from approved dosage regimens for adults with PAH, the maximum dose of ambrisentan used in combination with cyclosporine is proposed to be 5 mg, as in adult regimens. PMDA asked the applicant to explain the rationale for the maximum dose of ambrisentan in the combination therapy.

The applicant's explanation:

No clinical studies have been conducted to investigate the effect of concomitant cyclosporine on the PK of ambrisentan in children. However, the dosage regimens of ambrisentan in children with PAH

aged ≥8 years were determined aiming to obtain an exposure level comparable to adults' on the basis of physiological characteristics of the target age group. In children aged ≥8 years, concomitant cyclosporine is presumed to increase exposure to ambrisentan as in adults, and therefore the maximum dose of ambrisentan for concomitant use with cyclosporine needs to be specified as is adults. Because the exposure of children aged ≥8 years to ambrisentan in concomitant use with cyclosporine should not exceed that in adults at the approved maximum dose, the maximum dose should be 5 mg for children weighing ≥50 kg as with adults and 2.5 mg for children weighing <50 kg. This will be mentioned in modified cautionary statement in the package insert.

PMDA's view:
Based on the rationale for the dosage regimens of ambrisentan in children with PAH aged ≥8 years and an extent of the effect of cyclosporine on the PK of ambrisentan, the modified cautionary statement in the package insert (draft) is acceptable.

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 2 clinical studies shown in Table 9 (for the PK, see Section "6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA").

Table 9. Efficacy and safety evaluation data

Data category	Region	Study	Phase	Population	Number. of patients enrolled	Dosage regimen	Main endpoints
Evaluation	Global	AMB112529	II	Patients with PAH aged ≥8 and <18 years	41	The following respective per-body weight doses were orally administered once daily. Low dose group, ambrisentan 2.5 or 5 mg High dose group, ambrisentan 2.5 or 5 mg for the first 2 weeks followed by 5, 7.5, or 10 mg	Safety Efficacy
	Global	AMB114588	II	Patients continued from Study AMB112529	38	Ambrisentan was orally administered once daily at 2.5, 5, 7.5, or 10 mg, and the dose is increased up to 0.25 mg/kg/day according to the symptom.	Safety Efficacy

7.1 Global phase II study

7.1.1 Study AMB112529 (CTD 5.3.5.1; January 2011 to February 2019)

An open-label, randomized study was conducted to investigate the safety, efficacy, and the PK of ambrisentan in patients with PAH aged ≥8 and <18 years at 23 study sites in Japan and overseas (target sample size, 66 subjects [33 per group]). Subjects were stratified by baseline age (≥8 and ≤11 years or ≥12 and <18 years) and clinical classification of PAH (idiopathic pulmonary arterial hypertension [IPAH]; heritable pulmonary arterial hypertension [HPAH]; or PAH associated with connective tissue disease; persistent PAH after surgical repair of atrial septal defect, ventricular septal defect, atrioventricular septal defect, and patent ductus arteriosus). When 41 subjects had been enrolled in the study, low brain weight was reported from a non-clinical study of ambrisentan in juvenile rats [see

Section “5.1 Eight-week repeated oral dose toxicity study in juvenile rats”]. In response, further enrollment was suspended, and the target evaluable sample size was changed to 40.

Ambrisentan was orally administered once daily at the dose specified according to the body weight category as per Table 10.

Table 10. Doses of ambrisentan specified according to the body weight category

Body weight	Low dose	High dose	
	First dose to Week 24	First dose	Weeks 2 to 24
≥50 kg	5 mg	5 mg	10 mg
≥35 kg and <50 kg	5 mg	5 mg	7.5 mg
≥20 kg and <35 kg	2.5 mg	2.5 mg	5 mg

The major inclusion criteria are as follows:

- Aged ≥8 and <18 years
- Body weight of ≥20 kg
- IPAH, HPAH, PAH associated with a connective tissue disease, or persistent PAH after surgical repair of a congenital heart defect
- World Health Organization (WHO) Functional Class II or III
- Right heart catheterization measurements including the mean pulmonary artery pressure (mPAP) of ≥25 mmHg, pulmonary vascular resistance (PVR) of ≥240 dyne sec/cm^5, and left ventricular end diastolic pressure (LVEDP) or pulmonary capillary wedge pressure (PCWP) of ≤15 mmHg
- Patients who discontinued ERA ≥1 month before screening owing to increased liver function test values which were <3 fold the upper limit of the reference range at the discontinuation

Change of the medication for PAH (prostacyclin [PGI_2] preparation, pulmonary vasodilator, or PDE5 inhibitor) was not allowed throughout the period from ≥1 month before the screening visit to the end of study treatment. Patients who changed or discontinued the PGI_2 preparation or PDE5 inhibitor due to tolerability were to be withdrawn from the study. Concomitant use of any ERA other than ambrisentan or cyclosporine was prohibited throughout the study period.

1) Results from the entire study

All of 41 patients randomized (21 in the low dose group, 20 in the high dose group) were included in the safety analysis population and intent to treat (ITT) population. The ITT population was subjected to the primary efficacy analysis. A total of 4 patients (2 in each group) were withdrawn mainly owing to adverse events (1 patient each).

Table 11 shows changes in 6-minute walk distance (6MWD) from baseline to Week 24.

Table 11. Changes in 6MWD (meters) from baseline to Week 24 (ITT)

	Low dose	High dose	Pooled
Baseline	n = 21 442.23 ± 108.15 453.00	n = 20 407.32 ± 118.42 420.00	n = 41 425.20 ± 113.23 425.50
Week 24	n = 18 509.08 ± 92.56 492.50	n = 18 450.31 ± 122.81 470.00	n = 36 479.69 ± 111.24 474.50
Change from baseline to Week 24	n = 18 55.14 ± 102.18 49.00	n = 18 26.25 ± 62.01 25.50	n = 36 40.69 ± 84.58 32.00

Top, number of patients evaluated; middle, mean ± standard deviation (SD); bottom, median

Adverse events occurred in 81% (17 of 21) of patients in the low dose group and 80% (16 of 20) of patients in the high dose group. Table 12 shows major adverse events.

Table 12. Adverse events reported by ≥10% of patients in either group (safety analysis population)

	Low dose (n = 21)	High dose (n = 20)
Headache	19 (4)	30 (6)
Nausea	19 (4)	15 (3)
Abdominal pain	19 (4)	5 (1)
Abdominal pain upper	14 (3)	10 (2)
Nasopharyngitis	14 (3)	10 (2)
Upper respiratory tract infection	14 (3)	5 (1)
Pneumonia	14 (3)	0 (0)
Nasal congestion	10 (2)	10 (2)
Gastroenteritis	10 (2)	5 (1)
Oedema peripheral	10 (2)	5 (1)
Pain in extremity	10 (2)	5 (1)
Pharyngitis	10 (2)	5 (1)
Pyrexia	10 (2)	5 (1)
Diarrhoea	10 (2)	0 (0)
Vomiting	10 (2)	0 (0)
Back pain	5 (1)	10 (2)
Erythema	5 (1)	10 (2)
Face oedema	5 (1)	10 (2)
Laryngitis	0 (0)	10 (2)

% (number of patients)

Death occurred in 1 patient each in the low dose (pneumonia) and high dose (cardiac failure acute)[1)] groups, but both deaths were assessed as causally unrelated to the study drug. Other serious adverse events occurred in 5 patients (pharyngitis, general physical condition decreased, syncope, device breakage, and pulmonary hypertension) in the low dose group and 1 patient (device related infection and right ventricular failure) in the high dose group. General physical condition decreased in the low dose group was assessed as causally related to the study drug. An adverse event leading to discontinuation of the study drug occurred in 1 patient (pneumonia) in the low dose group.

2) Results in Japanese patients

All of 5 Japanese patients randomized received the study drug (low dose group) and were included in the safety analysis population and ITT population. None of the patients discontinued the treatment.

1) The patient experienced acute cardiac failure during the treatment period and withdrew from the study. The patient proceeded to the long-term extension study (Study AMB114588) and continued the treatment with ambrisentan. Several days later, the patient died from the acute cardiac failure.

Table 13 shows changes in 6MWD from baseline to Week 24.

Table 13. Changes in 6MWD (meters) from baseline to Week 24 (ITT, Japanese population)

	Low dose
Baseline	n = 5 424.18 ± 78.19 453.00
Week 24	n = 5 490.58 ± 35.50 482.00
Change from baseline to Week 24	n = 5 66.40 ± 96.12 29.00

Top, Number of patients evaluated; Middle, Mean ± SD; Bottom, Median

The incidence of adverse events was 100% (5 of 5 patients). The major events were nausea (4 patients), headache, nasopharyngitis, and abdominal pain (2 patients each). No deaths occurred. A serious adverse event occurred in 1 patient (pulmonary hypertension), but the event was assessed as causally unrelated to the study drug. No adverse events leading to discontinuation of the study drug occurred.

7.1.2 Study AMB114588 (CTD 5.3.5.2; ongoing since June 2011; data cut-off on [redacted], 20[redacted])

An open-label study was conducted to investigate the safety and efficacy of ambrisentan in patients with PAH aged ≥8 and <18 years at 22 study sites in Japan and overseas.

This study was a long-term extension treatment study of the preceding study (Study AMB112529), and subjects enrolled in this study continued to receive ambrisentan for ≥6 months. Ambrisentan was orally administered once daily at 2.5, 5, 7.5, or 10 mg, and the dosage amount for each subject was adjusted within 0.25 mg/kg/day. Investigators or sub-investigators determined for each subject whether to continue with the last dosage amount taken in Study AMB112529 or to increase or decrease 2.5 mg per daily dose within the specified range, in a comprehensive manner based on the last dosage amount taken in Study AMB112529, body weight, clinical symptoms, and tolerability.

The major inclusion criteria were patients who participated in Study AMB112529 and complied with the protocol; and those who completed Week 24 visit in Study AMB112529; or those who did not complete Week 24 visit but met any of the following conditions:

(a) Inadequate response to the ongoing treatment or worsened clinical symptoms before Week 24 of Study AMB112529 consequently led to the use of an additional for PAH medication.
(b) The addition of ambrisentan led to dose reduction of a baseline PAH medication.
(c) The (sub-) investigator judged that ambrisentan needed to be continued.

The addition of the other PAH medication (PGI_2 preparation, PDE5 inhibitor, etc.) was allowed at the discretion of the (sub-) investigator. Concomitant use with any ERA other than ambrisentan or cyclosporine was prohibited throughout the study period.

1) Results from the entire study

All 38 patients proceeded from Study AMB112529 were included in the safety analysis population and ITT population. The ITT population was subjected to the primary efficacy analysis. Of these, 18

patients completed the study. A total of 16 patients withdrew mainly owing to the decision of the (sub-) investigator in 7 patients and due to adverse events in 5 patients. Of 34 patients who completed or withdrew from the study, 4 patients received the last ambrisentan dose of 2.5 mg, 16 patients 5 mg, 4 patients 7.5 mg, and 10 patients 10 mg.

Table 14 shows changes in 6MWD from baseline.

Table 14. Changes in 6MWD (meters) from baseline (ITT)

	Ambrisentan
Baseline[a]	n = 38 434.42 ± 110.37 438.00
Change from baseline	
Start of the study	n = 37 41.49 ± 83.54 32.00
Month 6 of the study	n = 34 50.66 ± 83.78 43.70
Month 12 of the study	n = 30 43.72 ± 81.43 49.20

Top, Number of patients evaluated; Middle, Mean ± SD; Bottom, Median
a, Baseline in Study AMB112529

Adverse events occurred in 89% (34 of 38) of patients. Table 15 shows major adverse events.

Table 15. Adverse events reported by ≥10% of patients (safety analysis population)

	Ambrisentan (n = 38)
Upper respiratory tract infection	26 (10)
Nasopharyngitis	24 (9)
Headache	18 (7)
Anaemia	16 (6)
Pharyngitis	16 (6)
Pyrexia	16 (6)
Gastroenteritis	13 (5)
Influenza	13 (5)
Nausea	13 (5)
Oropharyngeal pain	13 (5)
Epistaxis	11 (4)
Pain in jaw	11 (4)
Pulmonary arterial hypertension	11 (4)
Vomiting	11 (4)

% (number of patients)

Deaths occurred in 6 patients (cardiac failure acute and PAH in 2 patients each, and acute right ventricular failure and failure to thrive), but all death were assessed as causally unrelated to the study drug. The other serious adverse events occurred in 15 patients, and events reported by multiple patients were anaemia and pneumonia (2 patients each). All event were assessed as causally unrelated to the study drug. Adverse events leading to discontinuation of the study drug occurred in 2 patients (cardiac failure acute and failure to thrive).

2) Results in Japanese patients

All 5 Japanese patients who participated in Study AMB112529 proceeded to the extension study, received the study drug, and were included in the safety analysis population and ITT population. Of these, 4 patients completed the study, and 1 patient was withdrawn (decision of the [sub]investigator). The last dose of ambrisentan in 5 patients who completed the study or were withdrawn was 5 mg in 3 patients, 7.5 mg in 1 patient, and 10 mg in 1 patient.

Table 16 shows changes in 6MWD from baseline.

Table 16. Changes in 6MWD (meters) from baseline (ITT, Japanese population)

	Ambrisentan
Baseline[a]	n = 5 424.18 ± 78.19 453.00
Change from baseline	
Start of the extension study	n = 5 66.40 ± 96.12 29.00
Month 6 of the extension study	n = 5 54.06 ± 72.46 57.00
Month 12 of the extension study	n = 5 45.62 ± 91.00 26.00

Top, Number of patients evaluated; Middle, Mean ± SD; Bottom, Median
a, Baseline in Study AMB112529

Adverse events occurred in all 5 Japanese patients. The major adverse events were nasopharyngitis (5 patients), nausea (4 patients), pharyngitis, upper respiratory tract infection, epistaxis, oropharyngeal pain, rhinitis allergic, dermatitis contact, and headache (3 patients each). No deaths occurred. Serious adverse events occurred in 4 patients (pneumonia in 2 patients, hyperventilation, non-cardiac chest pain and pulmonary arterial hypertension), but all events were assessed as causally unrelated to the study drug. No adverse events leading to discontinuation of the study drug occurred.

7.R Outline of the review conducted by PMDA

7.R.1 Clinical positioning

The applicant's explanation about clinical positioning of ambrisentan in treatment of PAH in children:
Approved drugs for adult PAH in Japan are ERAs targeting the endothelin-mediated pathway, PDE5 inhibitors and guanylate cyclase agonists targeting the nitric oxide (NO)-mediated pathway, and PGI_2 preparations targeting the prostacyclin-mediated pathway. The treatment guidelines for IPAH/HPAH in adults contained in the Guidelines for Treatment of Pulmonary Hypertension (JCS 2017) in Japan indicate that a treatment strategy is determined by the severity-based prognostic risk classification. Some low-risk patients are treated with a monotherapy with an oral or inhaled PAH medication. Others undergo a combination therapy from the early stage of treatment, in which the higher the risk classification is, the more priority is placed on the use of intravenous or subcutaneous PGI_2 preparations. The addition of a concomitant drug is considered for patients with inadequate clinical response. The combination of the above-mentioned 3 drugs with diverse action mechanisms are more commonly used with progression of PAH symptoms.

The treatment algorithm for pediatric PAH follows the treatment guidelines for adults (Guidelines for Treatment of Pulmonary Hypertension). As with for adults, children receive a monotherapy or combination therapy according to the prognostic risk classification. Ambrisentan, an ERA, can be clinically recognized equally both in adults and children and thus is indicated for both low-risk and high-risk patients. The treatment algorithm in children in the Guidelines for Treatment of Pulmonary Hypertension is generally consistent with that in the guidelines for treatment of pulmonary hypertension in Europe and the US (Pediatric Pulmonary Hypertension: Guidelines From the American Heart Association and American Thoracic Society [AHA/ATS guidelines] [*Circulation.* 2015;132:2037-99] and Guidelines for the diagnosis and treatment of pulmonary hypertension: From the European Society of Cardiology (ESC) and the European Respiratory Society (ERS) [ESC/ERS guidelines] [*Eur Heart J*. 2016;37:67-119]), and in the treatment algorithm in pediatric patients (*Eur Respir J.* 2019;53:1801916) established based on the Sixth World Symposium on Pulmonary Hypertension (WSPH) held in 2018.

In Japan, approved dosage regimens of drugs for pediatric PAH include oral bosentan hydrate (twice daily), an ERA, and oral sildenafil citrate (3 times daily), a PDE5 inhibitor, and epoprostenol sodium, a PGI_2 preparation for intravenous administration. Bosentan hydrate interacts with multiple important concomitant drugs (sildenafil citrate, warfarin, etc.) and has a risk of hepatotoxicity (*Heart.* 2016;102:ii67-85). Sildenafil citrate is also known to interact with multiple important concomitant drugs (bosentan, warfarin, etc.), and its package insert gives a caution against such concomitant use. Epoprostenol sodium is generally used for severe conditions, but it needs to be administered by continuous intravenous infusion, for which central venous catheterization is essential. Many epoprostenol preparations including Flolan for injection, the original drug, have not been approved for the dosage regimen for children. Ambrisentan, in contrast, is orally administered once daily and has shown a favorable safety profile in the liver in the clinical evaluation in adults as compared with bosentan, another ERA. Ambrisentan is thus less likely to interact with drugs.

In view of the above and according to the treatment algorithms in the current Japan and foreign guidelines, ambrisentan is expected to be recognized as an option of ERAs to be used alone for low-risk patients or concomitantly used with intravenous epoprostenol sodium for high-risk patients. Thus, ambrisentan will be available for both low-risk and high-risk patients.

PMDA's view on the treatment algorithm for pediatric PAH:
Pediatric PAH has been treated on the basis of clinical study results in adults with PAH or based on clinical experience of physicians specialized in pediatric PAH. Clinical practice guidelines for pediatric pulmonary hypertension in Europe and the US (AHA/ATS guidelines [*Circulation.* 2015;132:2037-99] and ESC/ERS guidelines [*Eur Heart J.* 2016;37:67-119]) and an expert consensus statement on the diagnosis and treatment of pediatric pulmonary hypertension (*Heart.* 2016;102:ii86-ii100) recommend the use of an ERA or PDE5 inhibitor alone or in combination for both low-risk and high-risk patients who have tested negative for acute vasoreactivity response. The Paediatric Task Force (*Eur Respir J.* 2019;53:1801916) of the Sixth WSPH held in 2018 presented a clear statement that early introduction of combination therapies can be beneficial for low-risk patients

who have tested negative for acute vasoreactivity response, while recommending starting the use of an oral pulmonary vasodilator alone such as an ERA and PDE5 inhibitor.

In Japan, the Guidelines for Treatment of Pulmonary Hypertension presented the modified treatment algorithm for pediatric IPAH/HPAH based on the above guidelines in Europe and the US. The "Guidelines on the Clinical Examinations for Decision Making of Diagnosis and Drug therapy in Pediatric Patients with Congenital Heart Disease and Cardiovascular Disorder (revised version, 2018)" advise that patients who have tested negative for acute vasoreactivity be treated with an ERA or PDE5 inhibitor as practiced overseas. "The Clinical Guidelines for Medical Treatment of Pediatric Heart Failure" (revised version, 2015. *Pediatric Cardiology and Cardiac Surgery*. 2015;31:1-36) state that the treatment of pediatric PAH should basically follow the conventional supportive therapy and 3 types of pulmonary vasodilators, i.e., PGI_2 preparations, PDE5 inhibitors, and ERAs, as recommended for adults in the Guidelines for Treatment of Pulmonary Hypertension (revised version, 2012; FY 2011 Joint Study Group Report).

In view of these relevant guidelines and results from clinical studies conducted for the present application [see Sections "7.R.3 Efficacy" and "7.R.4 Safety"], ambrisentan is expected to be recognized as an ERA that can be used alone or in combination in both low- and high-risk patients with PAH, as with the other approved similar drugs with the dosage regimen for children available in Japan. Ambrisentan offers a new treatment option for children with PAH.

7.R.2 Differences in intrinsic and extrinsic ethnic factors and the appropriateness of Japan's participation in the global study

The applicant's explanation about differences in intrinsic and extrinsic ethnic factors between Japanese patients and non-Japanese patients in the major regions participating in Study AMB112529 as well as the appropriateness of Japan's participation in the study:

In PAH, excessively growth of vascular endothelial cells and smooth muscle cells in the pulmonary artery causes pulmonary artery dysfunction, inflammation, and thrombogenesis, which consequently increase pulmonary vascular resistance and pulmonary arterial pressure. In terms of intrinsic ethnic factors, basic pathophysiology of PAH in pediatric and adolescent patients is considered generally similar in Japan and overseas. The prevalence rate of IPAH is 2.1 to 4.4 per 1 million children, and the annual incidence rate is 0.5 to 1 or 2 per 1 million children (*Pediatr Pulmonol.* 2019;54:1516-26). No large differences are observed in the prevalence or incidence rate among countries including Japan (*Heart.* 2010;96:1401-6, *Pulm Circ*. 2017;7:126-36, etc.). PAH associated with congenital heart disease occurs more frequently than the other types of PAH, with the prevalence rate of 10.1 to 15.6 per 1 million children and the annual incidence rate of 1.9 to 2.2 per 1 million children in Europe (*Pediatr Pulmonol.* 2019;54:1516-26). Because there is no published literature on the prevalence or incidence rate of PAH associated with congenital heart disease in Japan, similarities of these rates between Japan and overseas remain unknown. Of 80 children aged ≥8 years enrolled in the use-results survey of ambrisentan, 20 patients had IPAH, and 38 patients had PAH associated with congenital heart disease, showing a tendency of relatively high prevalence of PAH associated with congenital heart disease in Japan as well. The PK of ambrisentan did not differ markedly between Japanese and non-Japanese adults in healthy adults or adult patients with PAH. The results from Study AMB112529

have demonstrated no clear differences in the PK of ambrisentan between Japanese and non-Japanese children [see Section "6.R.1 Differences in PK between Japanese and non-Japanese children aged ≥8 years"].

The guidelines for pediatric pulmonary hypertension in the US (*Circulation.* 2015;132:2037-99) and the guidelines for the diagnosis and treatment of pulmonary hypertension in Europe (*Eur Respir J.* 2015;46:903-75) recommend that the diagnosis criteria and clinical classification for adult PAH be employed for pediatric PAH diagnosis as well. The Japanese Guidelines for Treatment of Pulmonary Hypertension follow the guidelines in Europe and the US. As for extrinsic ethnic factors, therefore, PAH diagnostic criteria and the definitions of the clinical classification for pediatric PAH in Japan are similar to those overseas. Japanese children are treated according to the algorithm-based guidelines pediatric IPAH/HPAH (Guidelines for Treatment of Pulmonary Hypertension) developed in accordance with the above US guidelines and the guidelines for treatment of pediatric pulmonary hypertension in Europe (*Heart.* 2016;102:ii67-85) with the current situation in Japan also taken into account. The use of pulmonary vasodilators is recommended in Japan and overseas. Bosentan hydrate and sildenafil citrate have been approved for the treatment of PAH in Japan and overseas, and the approved dosage regimens of these drugs are generally the same in Japan and overseas.

As described above, there are no large differences in intrinsic or extrinsic ethnic factors between Japanese and non-Japanese patients with PAH. Moreover, Japan's participation in Study AMB112529 was appropriate for the development of ambrisentan for pediatric PAH in light of difficulties obtaining a sufficient number of participants within Japan alone to evaluate safety and efficacy in a study due to the rareness of the disease. The applicant also considers it acceptable to evaluate the efficacy and safety of ambrisentan in Japanese children with PAH based on results in the overall population in Study AMB112529 by assessing the consistency of results in the Japanese population with those in the overall population.

PMDA's view:
With respect to intrinsic ethnic factors, the pathology and incidence rate of pediatric PAH are considered similar in Japan and overseas as with adult PAH. Further, the PK of ambrisentan presumably does not clearly differ between Japanese and non-Japanese [see Section "6.R.1 Differences in PK between Japanese and non-Japanese children aged ≥8 years"]. In terms of extrinsic ethnic factors, Japan and other countries employ the same diagnostic criteria and the classifications of disease and severity, and the Japanese guidelines for treatment of PAH have been developed in accordance with the current European and US guidelines. Both in and outside Japan, pediatric PAH are treated based on the guidelines recommended for adults. Given these, there are no differences in medical environments between Japan and overseas that can influence the efficacy and safety of ambrisentan in children with PAH. In terms of concomitant drugs, approved drugs for PAH differ among countries. For instance, the US has not approved sildenafil citrate for pediatric use. How such differences can affect the study results remains unknown. However, in Study AMB112529, all possible measures seemed to have been taken to minimize the impact of concomitant drugs on the efficacy and safety evaluation of ambrisentan, such as the restriction of changing concomitant drugs throughout a period from ≥1 month before the screening visit to the end of study treatment in Study AMB112529

[see Section "7.1.1 Study AMB112529"]. Thus the differences in concomitant drugs did not significantly affect the interpretation of results from Study AMB112529.

Accordingly, Japan's participation in Study AMB112529 is appropriate, and it is acceptable that the efficacy of ambrisentan in Japanese children with PAH be explored based on results in the overall population in Study AMB112529 via the verification of consistency in study results between the Japanese population and the overall population. Considering the extremely small Japanese population in Study AMB112529, this review primarily focuses on the results in the overall population in Study AMB112529, while paying as much attention to data of individual cases in the Japanese population as well, and discusses the efficacy and safety of ambrisentan in Japanese patients.

7.R.3 Efficacy

7.R.3.1 Development plan targeting children with PAH

The applicant's explanation:

The applicant submitted [redacted] ([redacted]) in patients with PAH aged ≥1 and <18 years to the European Medicines Agency (EMA) in [redacted] 20[redacted]. After consultation with EMA, the applicant agreed with EMA to [redacted] and [redacted], prioritize the development for target patients with PAH aged ≥8 and <18 years, and to [redacted] and [redacted]. To design Study AMB112529 in patients with PAH aged ≥8 and <18 years, the dosage regimen of ambrisentan was determined with reference to body weight and PK parameters in adults [see Section "6.R.2 Dosage regimen in Study AMB112529"]. For the following reasons, Study AMB112529 was conducted in an open-label uncontrolled manner with the main objective being the safety evaluation:

- PAH is a rare, fatal disease with poor prognosis, and only limited number of subjects can be enrolled in the study. It would be difficult to demonstrate the clinically significant efficacy in a relatively small population in a study, even where it was feasible.
- When the study planning was underway, approved adult PAH medications including ambrisentan were commonly used off-label to treat children in Japan and overseas, because of which a placebo-control study was considered infeasible.
- When the study planning was underway, there were no sufficient treatment data utilizable for pediatric PAH, or there was no agreed-upon standard treatment. It was considered inappropriate to conduct a comparative study with ambrisentan and the standard treatment.

After Study AMB112529 started, the non-clinical toxicity study in juvenile rats reported low brain weight that was attributable to a hypoxic condition relating to apnoeic attack [see Section "5.1 Eight-week repeated oral dose toxicity study in juvenile rats"], and subject enrollment was temporally suspended in [redacted] 20[redacted]. After a discussion with EMA about this toxicological finding, the applicant conducted evaluation in the additional toxicity studies [see Sections "5.2 Study for the effect on respiratory function in juvenile rats (1)" and "5.3 Study for the effect on respiratory function in juvenile rats (2)"]. Given the similarity seen in the developing process of the laryngopharyngeal area in early human neonates to that in juvenile rats, i.e., the descent of the larynx to the final position with age, low brain weight is a potential risk only in infants due to the immaturity of laryngopharyngeal

area (aged 0-3 years). The independent data-monitoring committee on ambrisentan closely investigated the non-clinical study data, consulted with the applicant's advisory and governance committee, and reached the prediction that this potential risk was low in patients with PAH aged ≥8 and <18 years. A total of 41 subjects had been enrolled before the enrollment suspension in Study AMB112529 and had completed or been withdrawn from the study by the time when the additional non-clinical study data became available. To evaluate clinical results in patients with PAH aged ≥8 and <18 years, an ad hoc interim analysis was performed in [redacted] 20[redacted] using all data available as of [redacted] 20[redacted]. Factors potentially influential to data interpretation included the time passed since the enrollment suspension, environmental change in the treatment of PAH during the suspension, issues likely to emerge with resumed enrollment, and the presence of a population participating in different time period post-resumption. Given these, the interim analysis from 41 subjects was considered to have yielded valid data to be submitted to EMA. As a result of consultation with EMA, Study AMB112529 was officially terminated on February 11, 2019 without resuming the subject enrollment, with modified target sample size to 40 (evaluable subjects), which was initially planned as 66 (60 evaluable subjects).

PMDA asked the applicant to justify the use of 6MWD as the primary efficacy endpoint in Study AMB112529, on the presumption that basic physical strength and exercise tolerance in children vary by age.

The applicant's explanation:
Unlike in adults, children's exercise tolerance is expected to increase as they grow. However, 6MWD has been widely accepted as an indicator of the response to PAH treatment in children aged ≥6 years as well since before the study planning time until now (*J Pediatr.* 2007;150:395-9, *J Am Heart Assoc.* 2019;8:e011306, etc.). The applicant therefore considers that the use of 6MWD as an indicator of the efficacy of ambrisentan is acceptable in Study AMB112529. In the study, to reduce the influence of the age range in the subject population on the efficacy evaluation, subjects were stratified by age (aged ≥8 and ≤11 years or ≥12 and <18 years) at randomization.

PMDA's view:
The applicant has pointed out the rareness and seriousness of PAH and explained that, since the approval of ambrisentan for adult PAH, the drug has been commonly used off-label to treat pediatric PAH, posing difficulty implementing placebo-controlled studies or dose-ranging studies in Japan and overseas. Given this situation, it would be inevitable for the applicant to plan Study AMB112529, a global study in children with PAH, as an open-label uncontrolled study in the development of ambrisentan for pediatric PAH. In addition, there was a drastic environmental change in the treatment of PAH during the suspension of Study AMB112529, including an additional approval of a conventional drug for PAH with a dosage regimen for children and early introduction of multi-drug combination therapies with multiple pulmonary vasodilators in the treatment. Thus, the applicant came to the conclusion that it would be difficult to enroll additional subjects even the enrollment was resumed, with concerns about evaluating subjects who had enrolled before the suspension and those who would enroll after the resumption as one population. The applicant's conclusion is reasonable at a certain extent, and the termination of Study AMB112529 after the submission of the interim analysis

results of 41 subjects to EMA, which were then regarded as the final analysis results of this study, is considered also inevitable.

The true efficacy endpoint in treatment of PAH is improvement of vital prognosis. The discussion at the Fifth WSPH, however, pointed out that the endpoint in a phase III study of a drug for PAH needs to be a morbidity/mortality event (*J Am Coll Cardiol.* 2013;62:D82-91). Designs and endpoints of clinical studies on pediatric PAH were discussed at the Paediatric Task Force (*Eur Respir J.* 2019;53:1801916) of the Sixth WSPH. The conclusion reached was that age-appropriate growth and development would be a highly useful endpoint in children but difficult to follow up as endpoint. Body weight, echocardiography, serum biomarkers (desirably, N-terminal pro brain natriuretic peptide [NT-proBNP]), magnetic resonance imaging (MRI), and exercise tolerance test were suggested as alternative endpoints, which have yet to be justified as primary endpoints at present. The Task Force indicated that 6MWD, a conventional endpoint in clinical studies in adults with PAH, would be a feasible test for children aged ≥6 years and a potentially useful endpoint, but not obviously applicable to infants. Thus, currently there are no established efficacy endpoints that can be employed in clinical studies in children with PAH. Nevertheless, 6MWD was used as the primary endpoint of clinical studies in adults at the time of planning Study AMB112529, based on a report that corelates 6MWD with the severity of PAH and vital prognosis (*Am J Respir Crit Care Med.* 2000;161:487-92). Other reports point out 6MWD as a useful indicator of therapeutic effect in children aged >6 years, who are capable of undergoing the 6MWD test (*Int J Cardiol.* 2017;227:393-8, *Int J Cardiol.* 2016;202:34-9). With all these taken into account, 6MWD, the primary efficacy endpoint chosen by the applicant for Study AMB112529 in children with PAH aged ≥8 years, was appropriate. Furthermore, with the approaches explained by the applicant, e.g., age-based stratification, specifications for concomitant drugs, and the monitoring of pulmonary hemodynamic parameters in some patients (Japanese patients) as objective indicators, a certain level of efficacy evaluation is possible in Study AMB112529.

7.R.3.2 Efficacy of ambrisentan

The applicant's explanation:

The overall population in Study AMB112529 showed improved change in 6MWD from baseline to Week 24 (Table 11). The improvement was observed from Week 4 and continued throughout the remaining 24-week treatment period. Study AMB114588, the extension study of Study AMB112529, also showed an improvement comparable to that in Study AMB112529 throughout the study period including Month 12 and the final evaluation point.

To investigate the efficacy in Japanese children with PAH, 5 subjects were enrolled in Study AMB112529. Being allocated to the low dose group, all Japanese subjects completed the 24-week study and proceeded to Study AMB114588, the long-term extension study. In Study AMB114588, 1 subject had been withdrawn at the discretion of the (sub-) investigator at the time of data cut-off, while the remaining 4 subjects completed the study, continuing ambrisentan until the age of 18 years (>5 years, at the longest). Demographic characteristics and baseline disease condition of the Japanese population were generally comparable to those in the overall population. In the Japanese population, change in 6MWD from baseline to Week 24 also indicated an improvement, of which degree is comparable to that in the overall population (Table 13). Of cardiopulmonary hemodynamic parameters

monitored only in the Japanese subjects after receiving ambrisentan, mPAP, cardiac index (CI), PVR, and post hoc analyzed pulmonary vascular resistance index (PVRI) indicated numerical improvement (Table 17).

Table 17. Individual results in the Japanese population (Study AMB112529, ITT)

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Mean ± SD
mPAP (mmHg)						
Baseline	49	32	70	61	25	47.4 ± 18.96
Change from baseline to Week 24	-12	4	1	-1	-3	-2.2 ± 6.06
CI (calculated value, L/min/m^2)						
Baseline	4	3.5	3.7	2.7	3.2	3.42 ± 0.50
Change from baseline to Week 24	0.7	2	1.1	0.3	0.6	0.94 ± 0.66
PVR (mmHg/L/min)						
Baseline	6.8	4.5	18.5	23	6.6	11.88 ± 8.30
Change from baseline to Week 24	-2.8	-0.9	-5.2	-5.5	-2.9	-3.46 ± 1.90
PVRI (mmHg/L/min/m^2) (post hoc analysis)						
Baseline	4.46	3.26	20.99	19.22	6.06	10.799 ± 8.58
Change from baseline to Week 24	-1.97	-0.70	-6.89	-5.68	-2.70	-3.589 ± 2.60

Although the limited sample size allowed for only limited interpretation of the results, ambrisentan was indicated to show promising efficacy in treatment of PAH in the Japanese population as with in the overall population.

In light of the following review results, ambrisentan is also effective in children with PAH aged ≥8 and <18 years, as was the case in adults:

- The exposure levels in children, irrespective of their body weight or age, treated with the dosage regimen of ambrisentan in Study AMB112529 were comparable to those in adult patients [see Section "6.R.2 Dosage regimen in Study AMB112529"].
- The pathology of PAH in children is similar to that in adults, and there is no difference in the action mechanism of ambrisentan between children and adults.
- A Bayesian analysis performed post hoc using 6MWD data in Study AMB112565 in adults with PAH (n = 108) also suggested that changes in 6MWD in children with PAH after receiving ambrisentan would be comparable to those observed in adults with PAH [see Section "7.R.6 Dosage and administration"].
- As observed in Japanese adults with PAH, ambrisentan tended to decrease PVRI in Japanese children with PAH in Study AMB112529.

PMDA's view:

Because Study AMB112529 is the open-label uncontrolled study not primarily intended for efficacy evaluation, 6MWD can vary largely and can be readily influenced by pre-existing information, etc. the evaluator or the subject has, posing limitations in the efficacy evaluation of ambrisentan based on the results from this study alone. Nevertheless, according to the applicant's claim about the similarities in the pathology of PAH and PK of ambrisentan at the recommended clinical dose between children and adults and comprehensive discussion on the following observations, ambrisentan is suggested to be effective in children with PAH aged ≥8 years as in adults, and to have promising efficacy in Japanese children with PAH as well. In Study AMB112529, however, the efficacy of the high dose was not greater than that in the low dose. The effect of increased dose of ambrisentan is further discussed in Section "7.R.6 Dosage and administration."

- Change in 6MWD from baseline to Week 24 in the overall population (the low and high dose groups combined) in Study AMB112529 indicate an improving trend, which is considered similar to that in a clinical study of ambrisentan in adults with PAH (Study AMB-320).
- The Japanese population in Study AMB112529 showed an improving trend similar to that in the overall population not only in change in 6MWD but also in change in PVRI from baseline, a pulmonary hemodynamic parameters that are more objective than 6MWD. Individual results of 6MWD and PVRI also support the efficacy of ambrisentan.

7.R.4 Safety

The applicant's explanation about differences in safety profiles between adults and children:

The safety profile in adults with PAH has been shown not to differ largely between Japanese and non-Japanese patients (see "Review Report on Volibris Tablets 2.5 mg dated May 26, 2010"); and the small Japanese population in Study AMB112529 precludes precise comparison. Therefore, to discuss differences in safety profile between adults and children, the safety profile in the overall population in Study AMB112529 in children with PAH was mainly compared with that in a foreign phase III study in adults with PAH (Study AMB-320/321-C[2)]). Table 18 shows the incidences of adverse events in Studies AMB112529 and AMB-320/321-C. The incidences of adverse events in the pediatric low and high dose groups were comparable to those in the adult ambrisentan 5 mg and 10 mg groups, respectively. Events that commonly occurred in children (≥4 subjects in the overall population) are headache, nausea, abdominal pain, abdominal pain upper, nasopharyngitis, upper respiratory tract infection, and nasal congestion, all of which were reported in adults as well. Nausea occurred more frequently in children than in adults even with the difference in treatment period taken into account, but the event was mild in all the affected subjects except for 1 subject (moderate) in the adult ambrisentan 10 mg group. All affected subjects recovered from nausea except for 1 child in the high dose group, and 3 adults in the ambrisentan 5 mg group and 1 adult in the 10 mg group. The results did not indicate any additional concern about nausea. The incidences of liver disorder, fluid retention, and anaemia, adverse events characteristic of ambrisentan, did not differ between adults and children.

2) Pooled results from Studies AMB-320 and AMB-321

Table 18. Adverse events in clinical studies in adult and pediatric patients with PAH (safety population)

	Adults		Children	
	Study AMB-320/321-C (treatment period, 12 weeks)		Study AMB112529 (treatment period, 24 weeks)	
	5 mg (n = 130)	10 mg (n = 67)	Low dose[a] (n = 21)	High dose[b] (n = 20)
All adverse events	78.5 (102)	79.1 (53)	81 (17)	80 (16)
Major events[c]				
Headache	15.4 (20)	19.4 (13)	19 (4)	30 (6)
Nausea	3.8 (5)	4.5 (3)	19 (4)	15 (3)
Abdominal pain	3.1 (4)	3 (2)	19 (4)	5 (1)
Abdominal pain upper	1.5 (2)	3 (2)	14 (3)	10 (2)
Nasopharyngitis	5.4 (7)	3 (2)	14 (3)	10 (2)
Upper respiratory tract infection	4.6 (6)	7.5 (5)	14 (3)	5 (1)
Nasal congestion	5.4 (7)	10.4 (7)	10 (2)	10 (2)
Pneumonia	2.3 (3)	1.5 (1)	14 (3)	0 (0)
Gastroenteritis	0.8 (1)	0 (0)	10 (2)	5 (1)
Oedema peripheral	18.5 (24)	28.4 (19)	10 (2)	5 (1)
Pain in extremity	2.3 (3)	4.5 (3)	10 (2)	5 (1)
Pharyngitis	0.8 (1)	0 (0)	10 (2)	5 (1)
Pyrexia	2.3 (3)	4.5 (3)	10 (2)	5 (1)
Back pain	0.8 (1)	1.5 (1)	5 (1)	10 (2)
Erythema	0 (0)	1.5 (1)	5 (1)	10 (2)
Face oedema	0.8 (1)	0 (0)	5 (1)	10 (2)
Vomiting	0.8 (1)	3 (2)	10 (2)	0 (0)
Diarrhoea	2.3 (3)	4.5 (3)	10 (2)	0 (0)
Laryngitis	0 (0)	0 (0)	0 (0)	10 (2)

% (number of patients)
a, Ambrisentan 2.5 mg (body weight ≥20 kg and <35 kg) or 5 mg (body weight ≥35 kg)
b, Ambrisentan 5 mg (body weight ≥20 kg and <35 kg), 7.5 mg (body weight ≥35 kg and <50 kg), or 10 mg (body weight ≥50 kg)
c, Adverse events reported from multiple subjects in either group in the overall population of Study AMB112529

The comparison of adverse events between the long-term extension study in children with PAH and that in adults with PAH revealed no clinically relevant differences in the safety profiles.

The post-marketing safety information from Japanese patients has not raised any additional concerns with ambrisentan in children [see Section "7.R.8 Post-marketing investigations"].

As described above, the clinical studies of ambrisentan conducted did not raise additional safety concerns characteristic of pediatric PAH as compared with the safety profile in adults with PAH. The applicant therefore considers that the safety profile in children with PAH aged ≥8 years is comparable to that in adults with PAH.

PMDA's view:
In view of the occurrence of adverse events in the clinical studies of ambrisentan in adults and children as well as the adverse events in children receiving ambrisentan that have been reported through the post-marketing surveillance in Japan, the use of ambrisentan in children with PAH indicates no trend toward greater safety concerns than in adults at present. However, the number of patients included in the clinical studies is extremely small; presumably, children with PAH will undergo ambrisentan treatment for a longer period than adults; and a decision on concomitant use of ambrisentan with the other drug or dose increase of ambrisentan requires due consideration. Given these, ambrisentan should be prescribed by physicians with adequate knowledge and experience in the

treatment of pediatric PAH. The descriptions of cautionary advice in the package insert will be finalized taking account of comments from the Expert Discussion.

7.R.5 Indication

7.R.5.1 WHO Functional Classification

The applicant's explanation about the justification for the indication of "pulmonary arterial hypertension," defined without specific WHO Functional Classes mentioned:

Study AMB112529 was conducted in subjects in WHO Class II or III. Table 19 shows results from a subgroup analysis on 6MWD by WHO Functional Class. The change in 6MWD from baseline to Week 24 in WHO Class II patients indicated an improvement. In Class III patients, 6MWD was slightly decreased from baseline to Week 24, but the change (mean ± standard deviation [SD]) from baseline in the high dose group was 3.42 ± 37.91 meters, which meant that 6MWD was almost maintained at a certain level. At Week 24, patients in WHO Class I were re-classified to WHO Class I (9 patients), Class II (21 patients), Class III (1 patient), and unknown or undocumented Class (1 patient). In the same manner, those in Class III were re-classified to Class II (1 patient), Class III (5 patients), and unknown or undocumented class (3 patients) at Week 24. In summary, WHO Class II patients achieved marked improvements in 6MWD as compared with those in WHO Class III, who did not show noticeable change in 6MWD or WHO Class throughout the study period, despite slight improvements in both parameters.

Table 19. Mean changes in 6MWD (meters) from baseline by WHO Functional Class (Study AMB112529, ITT)

	Class II	Class III
Baseline	n = 32[a]	n = 9[a]
Mean ± SD	442.05 ± 112.42	365.28 ± 99.78
Median (range)	451.50 (160.0, 600.0)	370.00 (219.2, 540.0)
Change from baseline to Week 24	n = 30[a]	n = 6[a]
Mean ± SD	51.93 ± 85.34	-15.48 ± 57.39
Median (range)	40.00 (-92.0, 258.0)	-13.40 (-110.0, 65.9)

a, The numbers in the low and high dose groups combined

The incidences of adverse events in patients in WHO Classes II and III were 81% (26 of 32 patients) and 78% (7 of 9 patients), respectively. Major events were headache (9 patients), nausea (7 patients), abdominal pain, abdominal pain upper, nasopharyngitis (5 patients each), upper respiratory tract infection, gastroenteritis, face oedema, and pyrexia (3 patients each) in patients in WHO Class II; and nasal congestion and oedema peripheral (2 patients each) in patients in WHO Class III. The incidences of serious events in WHO Classes II and III were 19% (6 of 32 patients) and 22% (2 of 9 patients), respectively. Patients in WHO Class II accounted for a large portion of the enrolled population. It was difficult to compare the incidences of individual adverse events among WHO Functional Class subgroups, but System Organ Class (SOC) -based incidences of adverse events were similar among all WHO Classes, indicating no increasing trend in adverse event incidences in WHO Class III patients who have severer conditions.

Of 80 patients aged ≥8 and <15 years covered in the use-results survey of ambrisentan, 54 patients provided their baseline WHO Class (12 in I, 25 in II, 16 in III, and 1 in IV). The efficacy and safety of ambrisentan in patients in WHO Class I or IV, the population not targeted in the clinical studies, are

summarized as follows: The efficacy analysis included 11 patients in Class I and 1 patient in Class IV, who were assessed for overall improvement by an investigator on a scale of 3 grades, i.e., "Improved, No change, and Deteriorated." Of patients in Class I, 5 patients were assessed as "Improved" and 6 patients "No change," while none were assessed as "Deteriorated." One patient in Class IV was assessed as "Improved." As a result of the WHO Functional Classification post-ambrisentan treatment, 2 patients in Class I were downgraded to Class II and III, respectively, while 9 patients remained in the same class, and 1 patient in Class IV improved to Class II. The safety analysis included 12 patients in Class I and 1 patient in Class IV. Adverse events were reported from 5 patients in Class I, and none in Class IV. The major events were pharyngitis, vomiting, and upper respiratory tract inflammation (2 patients each). Serious adverse events were hyperthyroidism, pneumonia, and cerebral microhaemorrhage (1 patient each) in 3 patients (at a daily dose up to 3, 5, or 10 mg), respectively, but a causal relationship to ambrisentan was ruled out for all events.

The use-results survey reveals that ambrisentan has been commonly used in children in WHO Classes I to IV, with safety and efficacy results indicating a favorable risk-benefit profile of ambrisentan in patients in Classes I to IV. Ambrisentan is therefore considered to benefit the treatment of pediatric PAH.

Accordingly, the applicant considers that the use of ambrisentan in children with PAH needs not to be restricted by WHO Functional Class; ambrisentan is a potentially important treatment option for children with PAH in any WHO Class; and thus the indication of ambrisentan, "pulmonary arterial hypertension" is appropriate. Furthermore, because of limited information about children in WHO Class IV, the efficacy and safety of ambrisentan have not been established in this population, and this caution will be provided in the "Precautions Concerning Indication" section as practiced for adult patients.

PMDA's view:
The endpoint, 6MWD, can vary in results, and the number of patients in Study AMB112529 was limited. These factors precluded the precise interpretation of the subgroup analysis results. However, the results in the WHO Class II subgroup support the efficacy of ambrisentan, and its safety is considered acceptable in view of the expected efficacy. Although 6MWD did not improve in the WHO Class III patients, the Week 24 WHO Class of all subjects except for those in the unknown or undocumented Class remained unchanged or improved, suggesting that the disease was prevented from worsening or obvious exacerbation. In view of results from clinical studies of ambrisentan in adult patients, which indicate similar improvements in WHO Class II or III patients (see "Review Report on Volibris Tablets 2.5 mg dated May 26, 2010"), a certain level of efficacy is expected with acceptable safety [see Section "7.R.4 Safety"].

The submitted clinical study results do not suffice for the efficacy and safety evaluation of ambrisentan in WHO Class I or IV patients. However, because of the fatal, progressive nature of PAH, adult patients are encouraged to start the treatment from an early stage; and combination therapies using multiple drugs with different action mechanisms are proposed for severe cases or inadequate responders. These approaches are expected to be used for pediatric patients as well; and the WHO

Class can change with changes in the treatment and pathological condition. Given these, it is of significance to leave open the possibility of ambrisentan as a treatment option for children with PAH in WHO Class I, which is diagnosed at its early stage with only mild symptoms, and those in WHO Class IV, who are in severer conditions.

Based on the above, it is acceptable to indicate ambrisentan for all children with PAH aged ≥8 years without specifying WHO Functional Classes as practiced for adult patients, and the provision of cautionary advice for pediatric patients in WHO Class IV, which will be similar to that for adults, is also acceptable. The indication of ambrisentan and information to be contained in the package insert will be finalized taking account of comments from the Expert Discussion.

7.R.5.2 Underlying diseases

The applicant's explanation about the justification for the indication "pulmonary arterial hypertension," irrespective of underlying diseases, inclusive of conditions not studied in Study AMB112529:
The breakdown of the participants in Study AMB112529 by underlying disease was IPAH or HPAH in 29 subjects, PAH after surgical repair of congenital heart disease in 8 subjects, and PAH associated with connective tissue disease in 4 subjects.

The efficacy analysis revealed change (mean ± SD) in 6MWD from baseline to Week 24 in patients with IPAH or HPAH of 39.78 ± 87.81 meters, which was comparable to that in the overall population of this study. Change (mean ± SD) in 6MWD from baseline to Week 24 in patients with PAH after surgical repair of congenital heart disease and patients with PAH associated with connective tissue disease were 3.86 ± 49.29 and 110.88 ± 84.71 meters, respectively. The results suggested improvement in 6MWD albeit limited evaluation in a small number of subjects.

The safety analysis revealed the incidences of adverse events in patients with IPAH or HPAH, patients with PAH after surgical repair, and patients with PAH associated with connective tissue disease, i.e., 76% (22 of 29 patients), 100% (8 of 8 patients), and 75% (3 of 4 patients), respectively, showing no large differences between the underlying disease subgroups. Serious adverse events occurred in 21% (6 of 29) of patients with IPAH or HPAH and 25% (2 of 8) of patients with PAH associated with congenital heart disease but did not occur in patients with PAH associated with connective tissue disease. Patients with IPAH or HPAH accounted for a large portion of the enrolled patients, and thus it was difficult to compare the incidences of individual adverse events by underlying disease. The SOC-based incidences of adverse events however showed similarity among underlying disease subgroups. Other underlying diseases, namely, portal hypertension, HIV infection, drug or poison-induced diseases, and schistosomiasis were not listed in the inclusion criteria for Study AMB112529, and patients with these underlying diseases were not enrolled in the study. Full pathophysiology of PAH associated with portal hypertension and HIV infection remains unelucidated. Pulmonary artery lesions in patients with PAH associated with advanced portal hypertension are pathologically similar to those in patients with the other types of PAH including IPAH. Glycoprotein 120 that acts to allow HIV to enter into macrophages or $CD4^+$ lymphocytes is known to enhance the secretion of endothelin, which induces pulmonary vasospasm by targeting human pulmonary endothelial cells. The Japanese Guidelines for Treatment of Pulmonary Hypertension recommend the

conventional PAH treatment for PAH associated with portal hypertension and HIV infection. For drug- or poison-induced PAH, the use of pulmonary vasodilators is recommended when the discontinuation of the causative drug does not lead to improvement in the pathological condition of PAH. PAH associated with schistosomiasis is cited to be similar to IPAH in terms of the clinical manifestation and pathology, but no particular treatment guidelines are mentioned partly because of its extremely rare cases reported in Japan (Guidelines for Treatment of Pulmonary Hypertension). The use of pulmonary vasodilators including ERAs in patients with PAH associated with schistosomiasis improved WHO Class, 6MWD, and cardiopulmonary hemodynamic parameters without causing any hepatic function abnormality (*Chest.* 2012;141:923-8).

Data of a total of 80 patients with PAH aged ≥8 and <15 years available through the use-results survey of ambrisentan showed their underlying diseases including IPAH, HPAH, or PAH associated with congenital heart disease, etc. Patients with underlying diseases which had not been studied in the clinical studies were excluded from this use-result survey population. However, the overall population of the use-results survey included 7 patients with drug-induced PAH and 50 patients with PAH associated with portal hypertension (including 1 patient with PAH that was drug-induced and portal hypertension-associated). The efficacy analysis included 7 patients with drug-induced PAH and 41 patients with portal hypertension-associated PAH, and were assessed for overall improvement and WHO Functional Class by an investigator on a scale of 3 grades, "Improved, No change, or Deteriorated." All patients with drug-induced PAH were assessed as "Improved" or "No change" for both overall improvement and WHO Functional Class, and none were assessed as "Deteriorated." Of patients with portal hypertension-associated PAH, in 11 patients of overall improvement was assessed as "Improved," 24 patients as "No change," and 6 patients as "Deteriorated," while WHO Functional Classes of 3 patients were assessed as "Improved," 19 patients as "No change," and 4 patients as "Deteriorated," except 4 patients unassessed after treatment or at the final evaluation. Of 11 patients unassessed for the WHO Functional Class after treatment, 1 patient was assessed as deteriorated at the final evaluation as compared to baseline. The safety analysis included 7 patients with drug-induced PAH and 50 patients with portal hypertension-associated PAH, of whom 4 patients and 44 patients, respectively, experienced adverse events. In patients with drug-induced PAH, 3 patients experienced serious adverse events, but all these events were reported by 1 patient each and assessed as unrelated to ambrisentan by attending physicians. Major serious adverse events that occurred in patients with portal hypertension-associated PAH were anaemia (7 patients), cardiac failure (4 patients), fluid retention, renal dysfunction, gastrointestinal haemorrhage (3 patients each), blood loss anaemia, hepatic function abnormal, hepatic encephalopathy, ascites, right ventricular failure, pneumonia, and interstitial lung disease (2 patients each). The major serious adverse events assessed as related to ambrisentan were interstitial lung disease in 2 patients, both of whom recovered.

No published literature was available either in Japan or overseas about the efficacy and safety of ambrisentan in children with PAH associated with HIV infection or schistosomiasis.

Based on the above, ambrisentan will have promising efficacy in children with IPAH, HPAH, PAH associated with congenital heart disease, connective tissue disease, or portal hypertension, or drug-induced PAH without safety concerns. Although there are no efficacy and safety data of

ambrisentan in children with PAH associated with other underlying diseases (clinical classification), namely, HIV infection or schistosomiasis, the Japanese guidelines recommend the use of standard treatment for PAH associated with HIV infection, and schistosomiasis-associated PAH is reported to have similar clinical manifestation and pathology to IPAH. Given the recommended use of the same diagnosis criteria and clinical classification (by underlying disease) for adults and the drug therapies for PAH that do not largely differ by underlying disease, the indication of ambrisentan for children with PAH should be defined as "pulmonary arterial hypertension" irrespective of underlying diseases, as is the case for adult patients.

PMDA's view:
Despite the difference between children and adults in the composition of patient population with PAH by underlying disease, the same diagnosis guidelines are referred to for both children and adults at present. In terms of the rareness of PAH, the number of pediatric patients is even smaller than that of adults, and it would be unavoidable to exclude children with PAH other than IPAH or HPAH, PAH after surgical repair of congenital heart disease, and connective tissue disease-associated PAH from the clinical studies intended for the present application. The clinical study data submitted and post-marketing information of ambrisentan suggest that underlying disease-based efficacy and safety of ambrisentan in children are similar among the subgroups of all primary PAH types, i.e., IPAH or HPAH, PAH after surgical repair of congenital heart disease, and connective tissue disease-associated PAH. Japanese and foreign guidelines providing the latest treatment algorithm for adults recommend the common treatment methods for all the primary PAH types, which is assumed to be based on the idea that the treatment methods will have effects on PAH irrespective of underlying diseases. Furthermore, pediatric PAH is treated by methods selected based on clinical study results in adults, and the treatment algorithm for pediatric PAH does not differ by underlying diseases. Accordingly, it is considered acceptable to define the indication of ambrisentan as "pulmonary arterial hypertension" irrespective of underlying diseases, which includes PAH secondary to underlying diseases that were not studied in the clinical study. Yet, the indication and information to be provided in the package insert will be finalized taking account of comments from the Expert Discussion.

7.R.6 Dosage and administration

The applicant's explanation about the dosage regimen of ambrisentan for children with PAH aged ≥8 years:
In Study AMB112529, the mean change in 6MWD from baseline to Week 24, the primary efficacy endpoint, was greater in the low dose group than in the high dose group (Table 11). Ad hoc analyses in subgroups by age bracket and body weight category were performed. Change in 6MWD from baseline in patients aged "≥12 and ≤14 years" and "≥15 and <18 years" were numerically greater in the high dose group than in the low dose group at many sampling points. The change in patients weighing "≥50 kg" was numerically greater in the high dose group than in the low dose group at all sampling points. Potential causative factors for inferior efficacy of the high dose to the low dose shown by 6MWD in Study AMB112529 are the limited number of subjects and disproportionate baseline patient characteristics (6MWD, WHO Class, etc.) between the low and high dose groups. That is, the baseline mean 6MWD was greater in the low dose group than in the high dose group while the number of subjects in WHO Class III was smaller in the low dose group than in the high dose group, indicating

that the low dose group might have a larger proportion of patients who could achieve numerical improvement in 6MWD more easily, in terms of improvement in exercise performance achieved by treatment intervention, than the high dose group. The limited number of subjects preclude the elucidation of a dose-response relationship, and the same is true in adults. In a foreign phase III study in adults with PAH (Study AMB-320/321-C[2)]), results of change in 6MWD demonstrated a dose-response relationship, but in a foreign phase II study (Study AMB-220) with a smaller sample size than that in the phase III study, a dose-response relationship was not clearly shown (see "Review Report on Volibris Tablets 2.5 mg dated May 26, 2010"). Results of the other efficacy endpoints in Study AMB112529 (time to first clinical worsening of PAH, WHO Class, changes in NT-proBNP concentration, etc.) did not show clear differences between these dose groups. The safety analysis showed comparable incidences of adverse events between the low dose group and the high dose group with similar event terms.

In Study AMB114588, a long-term extension study, the (sub-) investigators were allowed to decide whether to continue with the dose of ambrisentan used at the end of Study AMB112529 or to change the dose. Of 38 patients proceeded to Study AMB114588, 10 patients received the last dose higher than the first dose and had no safety or efficacy problems.

The limited number of patients enrolled in Study AMB112529 allowed only limited evaluation, but subgroup analyses in Study AMB112529 suggested the increased effect of ambrisentan with increased doses. Therefore, an increased effect of ambrisentan will be expected in children with PAH at increased doses as is the case with adult patients.

Because Study AMB112529 allowed limited efficacy evaluation of ambrisentan in children with PAH, a Bayesian analysis was performed post hoc using 6MWD data in Study AMB112565 to evaluate whether change in 6MWD in children with PAH in response to ambrisentan were comparable to that in adults with PAH. The efficacy data in the pediatric population were suggested to be consistent with the efficacy observed in the larger adult population. In addition, the PPK analysis performed using the PK data in Study AMB112529 revealed that the PK of ambrisentan in children was similar to that in adults with the difference in body weight taken into account. The exposure to ambrisentan in children treated at a dose according to the body weight category was considered to be comparable to that in adults.

Based on the above, the recommended dosage regimen for children with PAH aged ≥8 years should be specified according to body weight so that the exposure level will be comparable to that in adults, as shown by the doses used in Studies AMB112529 and AMB114588. Furthermore, pediatric patients should also be allowed to receive increased doses depending on their clinical response and tolerability as in the case of adult patients. These approaches will lead to promising therapeutic effect of ambrisentan in children comparable to that in adult patients.

PMDA's view:
As discussed in Section "6.R.2 Dosage regimen in Study AMB112529," the dosage regimen by body weight category in Study AMB112529 in patients with PAH aged ≥8 and <18 years is appropriate

from a viewpoint of the comparable exposure level in children to that in adults. In Study AMB112529, the initial dose was specified for each body weight category both in the low and high dose groups. In the high dose group, the dose was increased at Week 2 according to the patient's body weight for the safety and efficacy evaluation of ambrisentan in children with PAH. The evaluation of the combined results from the low and high dose groups showed acceptable safety and efficacy, and results in both overall and Japanese populations were consistent with study results in adults with PAH [see Sections "7.R.3 Efficacy" and "7.R.4 Safety"]. Therefore, the dosage regimen was generally justified. The efficacy evaluation by comparison between the dose groups revealed that change in 6MWD from baseline were greater in the low dose group than in the high dose group, leaving the dose-response relationship of ambrisentan unclear. While the results from Study AMB112529 hardly demonstrated the increased effect of ambrisentan at the increased dose in children with PAH aged ≥8 years, the design of Study AMB112529 did not allow for adequate efficacy evaluation based on a dose-response relationship; and as the applicant mentioned, disproportional patient characteristics between the dose groups potentially could have affected the comparison between the doses. Therefore it is not appropriate to conclude that dose increase with ambrisentan will not increase its effect in children with PAH aged ≥8 years based on the results of Study AMB112529 alone. The following points indicate the possibility in Japanese children with PAH aged ≥8 years to have an option of dose increase as practiced in adult patients, in which the dosage regimen of ambrisentan investigated in Study AMB112529 should be used:

- The pathology and treatment approach for pediatric PAH are similar to those in adults, and children with PAH both in Japan and overseas are treated based on the guidelines for adults.
- No large differences were observed in the results between the foreign phase III study (Study AMB-320/321-C[2)]) in adults with PAH and Study AMB112529 in patients with PAH aged ≥8 and <18 years. The exposure level at the recommended clinical dose in children aged ≥8 years is comparable to that in adults.

The justification on the above PMDA's judgment about the dosage regimen will be finalized, taking account of comments from the Expert Discussion.

7.R.7 Development of a drug targeting children aged <8 years and a formulation that can be easily taken by young children

The applicant's explanation about the development of ambrisentan for treatment of PAH in children aged <8 years:

A discussion is underway with EMA about product development targeting children aged ≥4 and <8 years, excluding those aged <4 years, in light of the reported low brain weight from non-clinical toxicity studies in juvenile rats. The discussion also covers the designs of clinical studies and doses of ambrisentan to be used in the studies targeting the relevant age bracket, as well as the necessity to develop a formulation for pediatric use. The discussion with EMA is projected to reach agreement in [redacted] 20[redacted], and a clinical study will be initiated by [redacted] 20[redacted].

PMDA's view:

Given the presence of a certain number of children with PAH secondary to IPAH or HPAH, or PAH after surgical repair of congenital heart disease and the refractoriness of PAH, an additional treatment

option is highly demanded for this population in clinical settings. The 5-year survival in adult with PAH is 57%, and 65% in adults with IPAH or HPAH alone (*Chest.* 2012;142:448-56). While the 5-year survival is 74% in children with any type of PAH, 75% in children with IPAH or HPAH alone, and 71% in children with congenital heart disease-associated PAH, indicating children's better prognosis than adults' (*Circulation.* 2012;125:113-22). Diagnostic pulmonary hemodynamic parameter of pediatric patients were comparable or slightly poorer than those in adult patients, indicating that children with PAH will respond to pulmonary vasodilators more favorably than adults (*Pediatric Cardiology and Cardiac Surgery.* 2017;33:297-311). In addition, the prognosis of untreated IPAH in children is considered to be poorer than that in adults, but treated children better respond to the treatment than adults (*J Am Coll Cardiol.* 2009;53:1573-619, *Circulation.* 2009;119:2250-94). Furthermore, given that increased successful cases of surgeries, advanced medical environment, etc. in recent years have lowered the age of patients with congenital heart disease requiring a radical operation, there should be a substantial number of children aged <8 years, neonates, and infants with PAH, the patient population not included in Study AMB112529. Children may have difficulty complaining of symptoms such as shortness of breath and fatigability, thus they can be overlooked. In Japan, approximately 30% of patients with IPAH/HPAH are identified through abnormal electrocardiogram at school heart screening (*Ped Cardiol Card Surg.* 2000;16:230-7) and thus earlier start of treatment is possible. The target age should be carefully determined with the toxicological findings in non-clinical toxicity studies of ambrisentan in juvenile rats taken into consideration. PAH treatment is lifelong, and pediatric patients will undergo the treatment for a longer period than adults. Therefore, clinical studies targeting younger children should be appropriately, promptly planned and implemented, and an easy-to-take dosage form for this patient population should also be developed.

7.R.8 Post-marketing investigations

The applicant's explanation about the post-marketing investigations of ambrisentan:

The marketing approval of ambrisentan for adult PAH was granted with a condition requiring the implementation of a use-results survey covering all patients. The use-results survey was conducted from September 2010 through December 2018 with 3,392 patients registered at 769 medical institutions. A total of 695 children were registered at 113 medical institutions, including 148 children aged ≥8 years, the target population of the present application. Of 1,705 patients included in the safety analysis in the use-results survey, 259 patients were children, of which 80 children were aged ≥8 years. The incidence of adverse events in children aged ≥8 years was 41.3% (33 of 80 patients). The major events were cardiac failure (5 patients), headache, bronchitis, gastroenteritis, anaemia, upper respiratory tract inflammation, and liver disorder (4 patients each). The incidence of serious adverse events was 18.8% (15 of 80 patients). The major serious events were cardiac failure (5 patients), pneumonia, hyperthyroidism, haemoptysis, and ascites (2 patients each). The incidence of adverse drug reactions was 20.0% (16 of 80 patients). The major adverse drug reactions were headache (3 patients), nasal congestion, ascites, nausea, and hepatic function abnormal (2 patients each). The serious adverse drug reaction was ascites (2 patients). The types of adverse events and adverse drug reactions in children aged ≥8 years collected in the use-results survey were similar to those reported in Studies AMB112529 and AMB114588. The types and incidences of adverse drug reactions in these children were similar to those in adult patients registered in the same survey, and no children-specific events were observed.

Table 20 shows the distribution of the mean daily dose of ambrisentan in children aged ≥8 years registered in the use-results survey. The mean daily dose tended to be lower than that in the proposed dosage regimen, and the initial dose in many patients was lower than the proposed dosage regimen as well, but the maximum daily dose of most patients fell in the range specified in the proposed dosage regimen. In actual clinical settings, ambrisentan was used in children aged ≥8 years generally as per the proposed dosage regimen.

Table 20. Mean daily dose by body weight in use-results survey (safety analysis population, pediatric patients aged ≥8 years)

		Mean daily dose				Total
		<2.5 mg	≥2.5 mg and <5 mg	≥5 mg and <7.5 mg	≥7.5 mg and <10 mg	
Body weight	<20 kg	n = 3	n = 5	n = 1	n = 0	n = 9
	≥20 kg and <35 kg	n = 12	n = 34	n = 2	n = 2	n = 50
	≥35 kg and <50 kg	n = 2	n = 7	n = 4	n = 2	n = 15
	≥50 kg	n = 0	n = 2	n = 2	n = 2	n = 6
Total		n = 17	n = 48	n = 9	n = 6	n = 80

The underlined number includes patients treated with ambrisentan within the range in the proposed dosage and administration.

Furthermore, even after addition of the dosage regimen for children aged ≥8 years, approximately 95% of the pediatric patients are expected to be treated with ambrisentan at medical institutions as highly specialized as those participated in the use-results survey.

As described above, only 5 Japanese children were enrolled in Studies AMB112529 and AMB114588. However, substantial safety information of ambrisentan in children with PAH aged ≥8 years in Japan has already accumulated; and ambrisentan was confirmed to have been used generally as per the proposed dosage regimen in clinical settings. Ambrisentan will be prescribed at highly specialized medical institutions. Given these, the addition of the dosage regimen for children aged ≥8 years, will not raise any new safety concerns post-approval, cause a significant change in the use of ambrisentan, or markedly alter on hand safety information collected from pediatric patients and evaluated through the use-results survey. At present, it is thus unnecessary to conduct an additional post-marketing survey for the present application and that the ordinary pharmacovigilance activities will suffice.

PMDA's view:
Japanese and foreign guidelines for pulmonary hypertension recommend pulmonary vasodilators including ambrisentan for children with PAH, and information from a certain number of children with PAH aged ≥8 years treated with ambrisentan has accumulated through the use-results survey. Studies AMB112529 and AMB114588 did not show any increasing trend of a risk of adverse events specific to children aged ≥8 years. In light of this situation and the applicant's explanation that the approval of the current application is unlikely to change in the use of ambrisentan largely in clinical settings, the applicant needs not to conduct additional pharmacovigilance activities or additional risk minimization activities at present. However, in response to the addition of the dosage regimen of ambrisentan for children aged ≥8 years, the applicant is required to conduct the relevant pharmacovigilance activities such as the collection of spontaneous reports and literature search and, on the basis of information obtained from the concerned activities, consider the need of post-marketing surveillance, etc.

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

At present, the inspection is ongoing, and the results and PMDA's conclusion will be reported in the Review Report (2).

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

At present, the inspection is ongoing, and the results and PMDA's conclusion 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 ambrisentan has efficacy in the treatment of PAH in children aged ≥8 years and that ambrisentan has acceptable safety in view of its benefits. Ambrisentan is clinically meaningful because it offers a new treatment option for children with PAH aged ≥8 years. PMDA also considered that the target population, indication, dosage and administration, and cautionary statements in the package insert should be further discussed.

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

Review Report (2)

February 5, 2021

Product Submitted for Approval

Brand Name	Volibris Tablets 2.5 mg
Non-proprietary Name	Ambrisentan
Applicant	GlaxoSmithKline K.K.
Date of Application	July 29, 2020

List of Abbreviations
See Appendix.

1. Content of the Review

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

1.1 Safety

PMDA's conclusions, i.e., clinical study results etc. indicated no trend toward greater safety concerns in children with PAH than in adults, and ambrisentan should be prescribed by physicians with adequate knowledge and experience in the treatment of pediatric PAH. The expert advisor made a remark, in view of various types of adverse events observed in pediatric participants in the clinical studies of ambrisentan as in adults, that adverse events need to be managed with appropriate measures such as dose adjustment of ambrisentan or use of a replacement drug. Thus, ambrisentan should be used based on the premise that clinical study results of ambrisentan and other information are properly provided.

Accordingly, PMDA has concluded that cautionary advice should be provided in the "Precautions Concerning Indication" section of the package insert that ambrisentan be used for patients identified as eligible and under the supervision of physicians with adequate knowledge and experience in the treatment of pulmonary arterial hypertension [see Section "1.2 Indication"]. PMDA requested the applicant to provide healthcare professionals with appropriate information including clinical study results of ambrisentan. The applicant agreed.

1.2 Indication

PMDA has accepted the applicant's views that ambrisentan may be indicated for all children with PAH aged ≥8 years irrespective of the WHO Functional Class and underlying disease and that a caution will

be given against the use of ambrisentan in children in WHO Functional Class IV as practiced for adults. The PMDA's conclusion was supported by the expert advisors.

In view of the discussions in the above and Section 1.1, PMDA has concluded that the indication of ambrisentan and the "Precautions Concerning Indication" section of the package insert should be specified as follows.

Indication
Pulmonary arterial hypertension

Precautions Concerning Indication
- The efficacy and safety have not been established in WHO Class IV patients.
- Whether to use ambrisentan should be considered based on the current treatment guidelines.
- The use of ambrisentan should be considered for patients who are identified as eligible for the treatment under the supervision of physicians with adequate knowledge and experience in the treatment of pulmonary arterial hypertension.
- The efficacy and safety of ambrisentan have not been established in children with pulmonary arterial hypertension other than idiopathic or hereditary pulmonary arterial hypertension, pulmonary arterial hypertension after surgical repair of congenital heart disease, and pulmonary arterial hypertension associated with connective tissue disease.

1.3 Dosage and administration

The expert advisors supported all conclusions PMDA had reached, i.e., Study AMB112529 demonstrated the acceptable safety and efficacy of ambrisentan with the body weight category-based dosage regimen, Japanese children with PAH aged ≥8 years have options to be treated with ambrisentan at increased doses as with adult patients, and patients should be treated with ambrisentan according to the dosage regimen used in Study AMB112529. Meanwhile, some expert advisors made remarks about product development, i.e., it is advisable to promote the development targeting children aged <8 years in a prompt manner; and in order to accommodate many PAH children with a low weigh for age, studies on body weight-based doses and the development of dosage forms appropriate for use in children are also needed.

In view of the above discussion and the target population of the clinical studies, children aged ≥8 years who weigh ≥20 kg, PMDA has concluded that the dosage and administration of ambrisentan and the cautionary statements for use in children, etc. should be described in the package insert as follows.

Dosage and Administration
Adults
The usual adult dosage is 5 mg of ambrisentan orally administered once daily. The dose may be increased according to the symptom but should not exceed 10 mg daily.
Children
The usual dosage of ambrisentan for children aged 8 years or older is any of the following orally administered once daily according to body weight:

20 to <35 kg: The usual dosage is 2.5 mg. The dose may be increased according to the symptom but should not exceed 5 mg daily.
35 to <50 kg: The usual dosage is 5 mg. The dose may be increased according to the symptom but should not exceed 7.5 mg daily.
≥50 kg: The usual dosage is 5 mg. The dose may be increased according to the symptom but should not exceed 10 mg daily.

Use in children, etc.
No clinical studies have been conducted in low-birth-weight infants, neonates, infants, toddler, children aged <8 years, or children weighing <20 kg.

1.4 Risk management plan (draft)
In view of the review in Section "7.R.8 Post-marketing investigations" in the Review Report (1) and comments from the expert advisors at the Expert Discussion, PMDA has concluded that the risk management plan (draft) for ambrisentan should include the safety specifications presented in Table 21. On the basis of these specifications, safety signals should be first detected through the regular pharmacovigilance activities without conducting additional pharmacovigilance activities and risk minimization activities.

Table 21. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Teratogenicity • Hemoglobin/ decreased hematocrit, anemia • Liver disorder • Fluid retention and fluid retention-related cardiac failure • Progression of idiopathic pulmonary fibrosis or death in patients complicated by this disease • Interstitial pneumonia	Testicular disorder/ male infertility	None
Efficacy specification		
None		

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 compliance 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 5.3.5.1, CTD 5.3.5.2) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. As a result, PMDA concluded that the clinical studies as a whole were conducted in compliance with the GCP. On the basis of the inspection,

PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted. The inspection however revealed the following flaw at the sponsor. Although it did not significantly affect the overall evaluation of the study, the matter was communicated to the sponsor to seek corrective actions.

Finding requiring corrective action

Sponsor

- Some information about serious and unexpected adverse drug reactions was not communicated to the investigator or the heads of study sites.

3. Overall Evaluation

As a result of the above review, PMDA concludes that the product may be approved for the indication and the dosage and administration as shown below, with the following condition. The product is classified as an orphan drug. PMDA has concluded that no 10-year use results survey is required because the present application is pertinent to the addition of new dosages for pediatric patients; and the product has already been used for approximately 10 years in Japan since its approval in July 2010 for the pulmonary arterial hypertension in adult patients. The re-examination period is 6 years and 1 day, which falls within the "range from >6 to <10 years" in accordance with the provision of Article 14-4, Paragraph 1, Item 1 (1) of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices.

Indication

Pulmonary arterial hypertension

Dosage and Administration

Adults

The usual adult dosage is 5 mg of ambrisentan orally administered once daily. The dose may be increased according to the symptom but should not exceed 10 mg daily.

Children

The usual dosage of ambrisentan for children aged 8 years or older is any of the following orally administered once daily according to weight:

20 to <35 kg: The usual dosage is 2.5 mg. The dose may be increased according to the symptom but should not exceed 5 mg daily.

35 to <50 kg: The usual dosage is 5 mg. The dose may be increased according to the symptom but should not exceed 7.5 mg daily.

≥50 kg: The usual dosage is 5 mg. The dose may be increased according to the symptom but should not exceed 10 mg daily.

Approval Condition

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

Appendix

List of Abbreviations

AHA/ATS guidelines	Pediatric Pulmonary Hypertension: Guidelines From the American Heart Association and American Thoracic Society
ALP	Alkaline phosphatase
Ambrisentan	Ambrisentan
AUC	Area under the serum concentration-time curve
$AUC_{0\text{-}24}$	AUC from Week 0 to week 24
AUC_{ss}	Area under the plasma concentration-time curve at steady state
BCRP	Breast cancer resistance protein
BE	Bioequivalence
BSEP	Bile salt export pump
CI	Cardiac index
CL/F	Apparent total body clearance
$C_{max,ss}$	Maximum serum concentration at steady state
CS	Cresyl Violet
EMA	European Medicines Agency
ERA	Endothelin receptor antagonist
ESC/ERS guidelines	Guidelines for the diagnosis and treatment of pulmonary hypertension: From the European Society of Cardiology (ESC) and the European Respiratory Society (ERS)
Guidelines for Treatment of Pulmonary Hypertension	Guidelines for Treatment of Pulmonary Hypertension (revised version, 2017) (Japanese Circulation Society)
HE	Hematoxylin Eosin
HPAH	Heritable pulmonary arterial hypertension
IC_{50}	Half-maximal inhibitory concentration
IPAH	Idiopathic pulmonary arterial hypertension
ITT	Intent to treat
LC-MS/MS	Liquid chromatography and tandem mass spectrometry
LFB	Luxol fast blue
LVEDP	Left ventricular end diastolic pressure
mPAP	Mean pulmonary artery pressure
MRI	Magnetic resonance imaging
MRP2	Multidrug resistance-associated protein 2
NO	Nitric oxide
NTCP	Na^+/taurocholate cotransporting polypeptide
NT-proBNP	N-terminal pro brain natriuretic peptide
OATP	Organic anion transporting polypeptide
PAH	Pulmonary arterial hypertension
PCWP	Pulmonary capillary wedge pressure
PDE5	Phosphodiesterase 5
PGI_2	Prostacyclin
P-gp	P-glycoprotein
[redacted]	[redacted]
PK	Pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency
PPK	Population pharmacokinetics
PVR	Pulmonary vascular resistance
PVRI	Pulmonary vascular resistance index
Q/F	Apparent intercompartmental clearance
SD	Sprague-Dawley
SOC	System organ class

V_c/F	Apparent central volume
Volibris	Volibris Tablets 2.5 mg
V_p/F	Apparent peripheral volume
WHO	World Health Organization
WSPH	World Symposia on Pulmonary Hypertension
6MWD	6-minute walk distance