Report on the Deliberation Results

December 7, 2020

Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau

Ministry of Health, Labour and Welfare

Brand Name	(a) Xarelto Tablets 10 mg
	(b) Xarelto Tablets 15 mg
	(c) Xarelto Fine Granules 10 mg
	(d) Xarelto Fine Granules 15 mg
	(e) Xarelto OD Tablets 10 mg
	(f) Xarelto OD Tablets 15 mg
	(g) Xarelto Dry Syrup for Pediatric 51.7 mg
	(h) Xarelto Dry Syrup for Pediatric 103.4 mg
Non-proprietary Name	Rivaroxaban (JAN*)
Applicant	Bayer Yakuhin, Ltd.
Date of Application	February 14, 2020 for (a), (b), (c), (d), (g), and (h)
	September 11, 2020 for (e) and (f)

Results of Deliberation

In its meeting held on December 2, 2020, the First Committee on New Drugs concluded that the partial change applications for Xarelto Tablets 10 mg, Xarelto Tablets 15 mg, Xarelto Fine Granules 10 mg, Xarelto Fine Granules 15 mg, Xarelto OD Tablets 10 mg, and Xarelto OD Tablets 15 mg, and the marketing applications for Xarelto Dry Syrup for Pediatric 51.7 mg and Xarelto Dry Syrup for Pediatric 103.4 mg may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The products are not classified as biological products or specified biological products. The re-examination period is 4 years. Neither the drug products nor their drug substance are classified as poisonous drugs or powerful drugs.

Approval Condition

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

**Japanese Accepted Name (modified INN)*

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

Review Report

November 16, 2020
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	(a) Xarelto Tablets 10 mg (b) Xarelto Tablets 15 mg (c) Xarelto Fine Granules 10 mg (d) Xarelto Fine Granules 15 mg (e) Xarelto OD Tablets 10 mg (f) Xarelto OD Tablets 15 mg (g) Xarelto Dry Syrup for Pediatric 51.7 mg (h) Xarelto Dry Syrup for Pediatric 103.4 mg
Non-proprietary Name	Rivaroxaban
Applicant	Bayer Yakuhin, Ltd.
Date of Application	February 14, 2020 for (a), (b), (c), (d), (g), and (h) September 11, 2020 for (e) and (f)
Dosage Form/Strength	(a) and (b) Tablets: Each tablet contains 10 mg or 15 mg of rivaroxaban. (c) and (d) Granules: Each sachet contains 10 mg or 15 mg of rivaroxaban. (e) and (f) Orally disintegrating tablets: Each tablet contains 10 mg or 15 mg of rivaroxaban. (g) and (h) Dry syrup: Each bottle contains 51.7 mg or 103.4 mg of rivaroxaban.
Application Classification	(a) to (f) Prescription drugs, (4) Drugs with a new indication, (6) Drugs with a new dosage (g) and (h) Prescription drugs; (4) Drugs with a new indication, (6) Drugs with a new dosage, and (8-2) Drugs in an additional dosage form (not in the re-examination period)

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

Items Warranting Special Mention None
Reviewing Office Office of New Drug II

Results of Review

On the basis of the data submitted, PMDA has concluded that the products have efficacy in the treatment of venous thromboembolism in children, and that the products have acceptable safety in view of their benefits (see Attachment).

As a result of its review, PMDA has concluded that the products may be approved for the indications and dosage and administration shown below, with the following conditions. The incidence of bleeding events, etc. should be further evaluated.

Indications

(a) to (f):

Adults

- Prevention of ischemic stroke and systemic embolism in patients with non-valvular atrial fibrillation
- Treatment of venous thromboembolism (deep vein thrombosis and pulmonary thromboembolism) and prevention of its recurrence

Children

- Treatment of venous thromboembolism and prevention of its recurrence

(Underline denotes additions.)

(g) and (h):

Treatment of venous thromboembolism and prevention of its recurrence

Dosage and Administration

(a) to (f):

- Prevention of ischemic stroke and systemic embolism in patients with non-valvular atrial fibrillation

  The usual adult dosage is 15 mg of rivaroxaban administered orally, once daily with food. In patients with renal impairment, the dosage should be reduced to 10 mg once daily, depending on the degree of renal impairment.
- Treatment of venous thromboembolism, ~~deep vein thrombosis and pulmonary thromboembolism,~~ and prevention of its recurrence

  Adults

  The usual adult dosage is 15 mg of rivaroxaban administered orally twice daily with food for the first 3 weeks after the onset of deep vein thrombosis or pulmonary thromboembolism, followed by 15 mg of rivaroxaban administered orally once daily with food.

  Children

  The usual dosage in children weighing ≥30 kg is 15 mg of rivaroxaban administered orally once daily with food.

(Underline denotes additions. Strikethrough denotes deletions.)

(g) and (h):

The usual dosage in children is determined based on body weight (see the table below). For children weighing ≥2.6 kg to <12 kg, the body weight-based dose of rivaroxaban is administered orally three times daily. The dosage in children weighing ≥12 kg to <30 kg is 5 mg of rivaroxaban administered orally twice daily, and the dosage in children weighing ≥30 kg is 15 mg of rivaroxaban administered orally once daily. Xarelto should be administered in the non-fasted state, with a once-daily dosing schedule of approximately 24 hours apart, a twice-daily dosing schedule of approximately 12 hours apart, or a three-times-daily dosing schedule of approximately 8 hours apart.

Recommended dosage of rivaroxaban for treatment of venous thromboembolism and prevention of its recurrence

Body weight	Dose (1 mg of rivaroxaban corresponds to 1 mL of the suspension)			Total daily dose
	Once daily	Twice daily	Three times daily	
≥2.6 kg to <3 kg			0.8 mg	2.4 mg
≥3 kg to <4 kg			0.9 mg	2.7 mg
≥4 kg to <5 kg			1.4 mg	4.2 mg
≥5 kg to <7 kg			1.6 mg	4.8 mg
≥7 kg to <8 kg			1.8 mg	5.4 mg
≥8 kg to <9 kg			2.4 mg	7.2 mg
≥9 kg to <10 kg			2.8 mg	8.4 mg
≥10 kg to <12 kg			3.0 mg	9.0 mg
≥12 kg to <30 kg		5 mg		10 mg
≥30 kg	15 mg			15 mg

Approval Condition

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

Attachment

Review Report (1)

September 18, 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.

Product Submitted for Approval

Brand Name	(a) Xarelto Tablets 10 mg (b) Xarelto Tablets 15 mg (c) Xarelto Fine Granules 10 mg, (d) Xarelto Fine Granules 15 mg (e) Xarelto OD Tablets 10 mg (f) Xarelto OD Tablets 15 mg (g) Xarelto Dry Syrup for Pediatric 51.7 mg (h) Xarelto Dry Syrup for Pediatric 103.4 mg
Non-proprietary Name	Rivaroxaban
Applicant	Bayer Yakuhin, Ltd.
Date of Application	February 14, 2020 for (a), (b), (c), (d), (g), and (h) September 11, 2020 for (e) and (f)
Dosage Form/Strength	(a) and (b) Tablets: Each tablet contains 10 mg or 15 mg of rivaroxaban. (c) and (d) Granules: Each sachet contains 10 mg or 15 mg of rivaroxaban. (e) and (f) Orally disintegrating tablets: Each tablet contains 10 mg or 15 mg of rivaroxaban. (g) and (h) Dry syrup: Each bottle contains 51.7 mg or 103.4 mg of rivaroxaban.

Proposed Indications

(a) to (f):

- Prevention of ischemic stroke and systemic embolism in patients with non-valvular atrial fibrillation
- Treatment of deep vein thrombosis and pulmonary thromboembolism, and prevention of its recurrence
- <u>Treatment of pediatric venous thromboembolism and prevention of its recurrence</u>

(Underline denotes additions for the present application.)

(g) and (h):

Treatment of pediatric venous thromboembolism and prevention of its recurrence

Proposed Dosage and Administration

(a) to (f):

- Prevention of ischemic stroke and systemic embolism in patients with non-valvular atrial fibrillation

  The usual adult dosage is 15 mg of rivaroxaban administered orally once daily with food. In patients with renal impairment, the dosage should be reduced to 10 mg once daily, depending on the degree of renal impairment.
- Treatment of deep vein thrombosis and pulmonary thromboembolism, and prevention of its recurrence

  The usual adult dosage is 15 mg of rivaroxaban administered orally twice daily with food for the first 3 weeks after the onset of deep vein thrombosis or pulmonary thromboembolism, followed by 15 mg of rivaroxaban administered orally once daily with food.
- Treatment of pediatric venous thromboembolism and prevention of its recurrence

  The usual dosage in children weighing ≥30 kg is 15 mg of rivaroxaban administered orally once daily with food.

(Underline denotes additions for the present application.)

(g) and (h):

The usual dosage in children is determined based on body weight (see the table below). For children weighing ≥2.6 kg to <12 kg is the body weight-based dose of rivaroxaban administered orally three times daily with food. The dosage in children weighing ≥12 kg to <30 kg is 5 mg of rivaroxaban administered orally twice daily with food, and the dosage in children weighing ≥30 kg is 15 mg of rivaroxaban administered orally once daily with food.

Recommended dosage of rivaroxaban for treatment of pediatric venous thromboembolism and prevention of its recurrence

Body weight	Dose (1 mg of rivaroxaban corresponds to 1 mL of the suspension)			Total daily dose
	Once daily	Twice daily	Three times daily	
≥2.6 kg to <3 kg			0.8 mg	2.4 mg
≥3 kg to <4 kg			0.9 mg	2.7 mg
≥4 kg to <5 kg			1.4 mg	4.2 mg
≥5 kg to <7 kg			1.6 mg	4.8 mg
≥7 kg to <8 kg			1.8 mg	5.4 mg
≥8 kg to <9 kg			2.4 mg	7.2 mg
≥9 kg to <10 kg			2.8 mg	8.4 mg
≥10 kg to <12 kg			3.0 mg	9.0 mg
≥12 kg to <30 kg		5 mg		10 mg
≥30 kg	15 mg			15 mg

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List of Abbreviations

See Appendix.

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

Rivaroxaban, an oral factor Xa (FXa) inhibitor discovered by Bayer HealthCare (presently known as Bayer), selectively inhibits FXa, thereby inhibiting the blood coagulation system and reducing thrombus formation.

In Japan, rivaroxaban, as a tablet formulation, was approved for the "prevention of ischemic stroke and systemic embolism in patients with non-valvular atrial fibrillation" in January 2012, and for the "treatment of deep vein thrombosis and pulmonary thromboembolism, and prevention of its recurrence" in September 2015. Rivaroxaban received additional approvals for the above indications as a fine granules (sachets) formulation in September and December 2015, and as an orally disintegrating (OD) tablet formulation in August 2020.

Outside of Japan, rivaroxaban has been approved since 2008 for various indications, including "reduction in the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation," "prophylaxis of venous thromboembolism (VTE) in patients undergoing knee or hip replacement surgery," "treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and reduction in the risk of recurrence of DVT or PE," "prevention of atherothrombotic events in patients after an acute coronary syndrome," and "prevention of atherothrombotic events in patients with coronary artery disease or peripheral artery disease." As of September 2020, rivaroxaban is approved in ≥130 countries/regions, including the European Union (EU) and the United State (US). An application for the treatment of VTE in pediatric patients was filed in November 2019 in the EU, and is under review as of September 2020.

On the basis of the results from a global phase III study in pediatric patients with VTE serving as pivotal data, the applicant has recently filed partial change applications to extend the indications and dosage regimen of rivaroxaban to include "treatment of pediatric venous thromboembolism and prevention of its recurrence," and a marketing application to add a new dosage form, a dry syrup formulation for children.

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

Since the present partial change applications for Xarelto Tablets 10 mg, Xarelto Tablets 15 mg, Xarelto Fine Granules 10 mg, Xarelto Fine Granules 15 mg, Xarelto OD Tablets 10 mg, and Xarelto OD Tablets 15 mg are intended for a new indication and a new dosage, no additional data relating to the quality of rivaroxaban have been submitted. The marketing applications for Xarelto Dry Syrup for Pediatric 51.7 mg and Xarelto Dry Syrup for Pediatric 103.4 mg are also intended for a new dosage form, and data regarding the quality and bioequivalence of rivaroxaban have been submitted. While this section addresses only information relating to novel excipients, PMDA has reviewed the data submitted in support of the application for a drug in an additional dosage form. The review identified no major problems.

2.R Outline of the review conducted by PMDA

2.R.1 Novel excipients

[redacted] contained in Xarelto Dry Syrup for Pediatric 51.7 mg and Xarelto Dry Syrup for Pediatric 103.4 mg is a novel excipient that has not been used in any existing pharmaceuticals. In addition, microcrystalline cellulose and carmellose sodium contained in the dry syrup formulation, as well

as [redacted], a component of [redacted], are considered to be novel excipients because they have different specifications from those for existing pharmaceuticals.

2.R.1.1 Specifications and stability

Based on the submitted data, PMDA has concluded that [redacted], microcrystalline cellulose and carmellose sodium, and [redacted] have no particular problems in terms of their specifications or stability.

2.R.1.2 Safety

Based on the submitted data, PMDA has concluded that [redacted], microcrystalline cellulose and carmellose sodium, and [redacted] have no particular problems in terms of their safety.

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

Although the present applications are intended for a new indication and a new dosage, no new data on non-clinical pharmacology have been submitted. The non-clinical pharmacology of rivaroxaban was evaluated during the review of the previous application.

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

Although the present applications are intended for a new indication and a new dosage, no new data on non-clinical pharmacokinetics have been submitted. The non-clinical pharmacokinetics of rivaroxaban were evaluated during the review of the previous application.

5. Toxicity and Outline of the Review Conducted by PMDA

Because the present applications are intended for a new indication and a new dosage, no toxicity data on rivaroxaban have been submitted.

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

6.1 Biopharmaceutic studies and associated analytical methods

Table 1 presents the rivaroxaban formulations used in main clinical studies.

Table 1. Rivaroxaban formulations used in main clinical studies

Study identifier	Formulation
Bioequivalence study (Studies 19365 and 20152)	Tablets (the Japanese commercial formulation; 10 or 15 mg), dry syrup (the to-be-marketed formulation)
Foreign phase I study (Study 12892)	Tablets (5, 7.5, 10, 15, or 20 mg), suspension
Foreign phase I study (Study 17992)	Dry syrup (the to-be-marketed formulation)
Foreign phase I/II study (Study 17618)	Suspension, dry syrup (the to-be-marketed formulation)
Foreign phase II study (Study 14373)	Tablets (7.5, 10, 15, or 20 mg), suspension
Global phase II study (Study 14374)	Suspension
Global phase III study (Study 14372)	Tablets (5[a)], 10, 15, or 20 mg), dry syrup (the to-be-marketed formulation)

a) The 5-mg tablet formulation has been demonstrated to be bioequivalent to the 10-mg tablet formulation.

Plasma rivaroxaban concentrations were measured by liquid chromatography and tandem mass spectrometry (LC-MS/MS), with a lower limit of quantification of 0.5 μg/mL.

6.1.1 Bioequivalence study (a) (Study 19365, CTD 5.3.1.2.5, [redacted] to [redacted] [redacted])

A 2-group, 2-period cross-over study (with a washout period of ≥7 days) was conducted to evaluate the bioequivalence between the dry syrup formulation and the tablet formulation of rivaroxaban in 30 non-Japanese healthy adult men. A single oral dose of 10 mg rivaroxaban was administered as dry syrup or tablets to the subjects in the fasted state.

The geometric mean ratios (90% confidence intervals [90% CIs]) of C_{max} and $AUC_{0\text{-last}}$ of rivaroxaban administered as dry syrup, to those administered as tablets were 1.13 [1.04, 1.22] and 1.03 [0.98, 1.07], respectively.

6.1.2 Bioequivalence study (b) (Study 20152, CTD 5.3.1.2.7, [redacted] to [redacted] [redacted])

A 2-group, 2-period cross-over study (with a washout period of ≥5 days) was conducted to evaluate the bioequivalence between the dry syrup formulation and the tablet formulation of rivaroxaban in 44 Japanese healthy adult men. Each formulation A single oral dose of 15 mg rivaroxaban was administered as dry syrup or tablets formulation to the subjects in the fasted state.

The geometric mean ratios [90%CIs] of C_{max} and $AUC_{0\text{-last}}$ of rivaroxaban administered as dry syrup, to those administered as tablets were 1.15 [1.07, 1.24] and 1.07 [1.02, 1.12], respectively.

6.2 Clinical pharmacology

6.2.1 Foreign phase I study (Study 12892, CTD 5.3.3.2.1, November 2010 to July 2015)

This study was conducted to evaluate the pharmacokinetics of rivaroxaban following the administration of a single dose of rivaroxaban (as tablets or suspension) to 59 non-Japanese pediatric patients aged ≥6 months to <18 years who were considered to be at a risk for recurrent VTE after the completion of initial anticoagulant treatment for VTE. Rivaroxaban was administered within 2 hours after meal intake. The dose of rivaroxaban was body weight-adjusted for each pediatric patient to achieve an exposure similar to that observed in non-Japanese healthy adults receiving rivaroxaban 10 mg (low dose) or 20 mg (high dose) (Table 2). Table 3 shows

the pharmacokinetic parameters of rivaroxaban, calculated from a population pharmacokinetics (PPK) model[1)] based on the plasma rivaroxaban concentration data from the study. At the early stage of Study 12892, the undiluted suspension of rivaroxaban was administered with water; however, the dosing method was subsequently changed to allow for the administration of prediluted suspension with water in order to improve the absorption of rivaroxaban. Consequently, of the 42 patients receiving oral suspension formulation, 20 (10 in the low dose group and 10 in the high dose group) received undiluted suspension and 22 (18 in the low dose group and 4 in the high dose group) received prediluted suspension.

Table 2. Dosage regimens for rivaroxaban in Study 12892

Dosage form	Age	Body weight	Dose (mg)	
			High dose[a)]	Low dose[b)]
Tablets	≥6 years to <18 years	≥14 kg to <20 kg	5.0	2.5
		≥20 kg to <30 kg	7.5	3.75
		≥30 kg to <40 kg	10	5
		≥40 kg to <50 kg	15	7.5
		≥50 kg	20	10
Suspension	≥6 month to <6 years	≥2 kg to <3 kg	0.8	0.4
		≥3 kg to <4 kg	1.2	0.6
		≥4 kg to <5 kg	1.8	0.8
		≥5 kg to <6 kg	2.2	1.2
		≥6 kg to <7 kg	2.8	1.4
		≥7 kg to <8 kg	3.2	1.6
		≥8 kg to <9 kg	3.8	1.8
		≥9 kg to <10 kg	4.2	2.2
		≥10 kg to <12 kg	4.8	2.4
		≥12 kg to <14 kg	5.0	2.5
	≥6 years to <18 years	≥14 kg to <20 kg	5.0	2.5
		≥20 kg to <30 kg	7.5	3.75
		≥30 kg to <40 kg	10	5

a) Equivalent to 20 mg of rivaroxaban in non-Japanese healthy adults
b) Equivalent to 10 mg of rivaroxaban in non-Japanese healthy adults

Table 3. Pharmacokinetic parameters[a)] of rivaroxaban

Age group	≥12 years to <18 years		≥6 years to <12 years				≥2 years to <6 years		≥6 months to <2 years	
Dosage form	Tablets		Tablets	Suspension	Tablets	Suspension	Suspension		Suspension	
Dose	Low dose	High dose	Low dose	Low dose	High dose	High dose	Low dose	High dose	Low dose	High dose
N	4	5	4	11	4	5	11	5	6	4
$AUC_{0-\infty}$ (μg·h/L)	1320 (13.1)	1760 (20.7)	902 (31.2)	720 (24.1)	1540 (52.0)	1070 (37.5)	674 (25.5)	755 (39.0)	503 (20.6)	672 (29.4)
C_{max} (μg/L)	129 (11.4)	180 (12.0)	118 (11.0)	82.5 (37.4)	172 (25.9)	85.1 (15.8)	84.2 (36.0)	60.1 (33.4)	94.9 (28.3)	143 (14.7)
C_{24} (μg/L)	7.94 (35.4)	9.46 (55.6)	3.18 (73.9)	3.35 (57.6)	8.46 (98.5)	7.18 (96.1)	3.27 (65.0)	5.71 (129)	1.94 (33.5)	2.39 (39.9)

Geometric mean (geometric CV[%])
a) Values estimated from the PPK model

[1)] A PPK analysis was performed based on the plasma rivaroxaban concentration data from Study 12892 (59 patients, 206 timepoints), and a PPK model was developed. The pharmacokinetics of rivaroxaban was described by a 2-compartment model with first-order absorption and first-order elimination from the central compartment. The absorption rate of rivaroxaban administered as undiluted suspension was approximately 3.4 times lower than that of rivaroxaban administered as tablets or diluted suspension. The relative bioavailability of rivaroxaban at the 20 mg-equivalent dose, compared with the 10 mg-equivalent dose was 64.8%. The V_c and CL of rivaroxaban were described by body weight-based allometric equations, with allometric coefficients of 1 (fixed value) and 0.323 (model-estimated value), respectively. No covariates, other than body weight, were incorporated into the model.

6.2.2 Foreign phase I study (Study 17992, CTD 5.3.3.2.2, November 2015 to May 2018)

This study was conducted to evaluate the pharmacokinetics of rivaroxaban after a single oral dose of rivaroxaban dry syrup in 45 non-Japanese patients aged ≥2 months to <12 years with a history of thrombosis who had completed initial anticoagulant treatment. Rivaroxaban was administered during or within 2 hours after meal intake, according to the dosage regimen presented in Table 4. Table 5 shows the pharmacokinetic parameters of rivaroxaban calculated from PPK models, based on the plasma rivaroxaban concentration data from the study. The pharmacokinetic parameters in patients aged <2 years were calculated from the PPK model developed in Section "6.2.8 PPK analysis in pediatric patients aged <2 years," while those in patients aged ≥2 years were calculated from the PPK model developed in Section "6.2.7 PPK analysis in pediatric patients."

The calculation of the pharmacokinetic parameters from the PPK models revealed that the $AUC_{0-\infty}$ and C_{24} of rivaroxaban tended to be lower in patients with lower body weight, particularly at age <2 years, while the C_{max} remained constant irrespective of body weight.

Table 4. Dosage regimen for rivaroxaban in Study 17992

Body weight	Dose (mg)		
	Group A[a)]	Group B[b)]	Group C[c)]
≥3 kg to <4 kg	0.6	0.7	1.2
≥4 kg to <5 kg	0.8	0.9	1.6
≥5 kg to <6 kg	1.2	1.4	2.0
≥6 kg to <7 kg	1.4	1.8	2.4
≥7 kg to <8 kg	1.6	2.2	2.8
≥8 kg to <9 kg	1.8	3.2	3.2
≥9 kg to <10 kg	2.2	3.2	3.6
≥10 kg to <12 kg	2.4	3.4	4.0
≥12 kg to <20 kg	2.5	4.0	-
≥20 kg to <30 kg	3.8	5.0	-
≥30 kg to <40 kg	5.0	7.5	-
≥40 kg to <50 kg	7.5	7.5	-
≥50 kg	10	10	-

-, Not applicable
a) A single dose of rivaroxaban dry syrup, corresponding to the 10 mg equivalent dose (Table 2) administered as tablets or (undiluted or diluted) suspension in the phase I study (Study 12892).
b) A single dose of rivaroxaban dry syrup, corresponding to the 10 mg equivalent dose (Tables 7 and 8) administered as diluted suspension in the phase II studies (Studies 14373 and 14374).
c) A single dose of dry syrup of rivaroxaban at approximately 0.4 mg/kg.

Table 5. Pharmacokinetic parameters[a)] of rivaroxaban

	Group A			Group B			Group C
Age group	≥6 years to <12 years	≥2 years to <6 years	≥6 months to <2 years	≥6 years to <12 years	≥2 years to <6 years	≥6 months to <2 years	≥2 months to <2 years
N	9	7	6	6	6	9	2
$AUC_{0-\infty}$ (μg·h/L)	1050 (38.0)	619 (27.1)	498 (27.2)	1360 (31.2)	1020 (42.9)	770 (26.4)	457,[b)] 618
C_{max} (μg/L)	117 (21.7)	93.9 (15.3)	77.1 (10.3)	141 (24.8)	133 (19.8)	124 (23.7)	124,[b)] 170
C_{24} (μg/L)	4.54 (68.2)	2.22 (58.5)	0.424 (426)	6.65 (68.5)	3.97 (86.1)	0.635 (213)	0.00272,[b)] 0.00336

Geometric mean (geometric CV[%])
a) Values estimated from the PPK model
b) Values from individual patients

6.2.3 Foreign phase II study (Study 14373, CTD 5.3.5.1.1, February 2013 to September 2016)

This study was conducted to evaluate the pharmacokinetics of rivaroxaban after multiple oral doses of rivaroxaban as tablets or diluted suspension in 42 non-Japanese patients aged ≥6 years to <18 years with VTE. Rivaroxaban was administered after meal intake, according to the dosage regimens presented in Table 6. Table 7 shows the pharmacokinetic parameters of rivaroxaban calculated from a PPK model [see Section "6.2.7 PPK analysis in pediatric patients"], based on the plasma rivaroxaban concentration data from the study.

Table 6. Dosage regimens for rivaroxaban in Study 14373

Dosage form	Age	Body weight	Dose (mg)	Dosage regimen
Tablets	≥6 years to <18 years	≥14 kg to <20 kg	5.0	Once daily after breakfast
		≥20 kg to <30 kg	7.5	
		≥30 kg to <40 kg	10	
		≥40 kg to <50 kg	15	
		≥50 kg	20	
Suspension	≥6 years to <12 years	≥9 kg to <10 kg	3.2	Twice daily after breakfast and supper (approximately 12 hours apart)
		≥10 kg to <12 kg	3.4	
		≥12 kg to <20 kg	4.0	
		≥20 kg to <30 kg	5.0	
		≥30 kg to <50 kg	7.5	
		≥50 kg to <100 kg	10	

Table 7. Pharmacokinetic parameters[a)] of rivaroxaban

Age group	≥12 years to <18 years	≥6 years to <12 years	≥6 months to <2 years
Dosage form	Tablets	Tablets	Suspension
Dosage regimen	Once daily	Once daily	Twice daily
N	11	12	19
$AUC_{(0\text{-}24)ss}$ (μg·h/L)	2088 (20.3)	1437 (30.7)	2593 (24.1)
$C_{max,ss}$ (μg/L)	215 (19.2)	194 (13.1)	168 (14.0)
$C_{(24)ss}$ (μg/L)[b)]	17.5 (31.3)	10.9 (48.5)	46.1 (46.2)

Geometric mean (geometric CV[%])
a) Values estimated from the PPK model
b) $C_{(12)ss}$ for the twice-daily dosing regimen

6.2.4 Global phase II study (Study 14374, CTD 5.3.5.1.2, January 2015 to April 2017)

This study was conducted to evaluate the pharmacokinetics of rivaroxaban after multiple oral doses of rivaroxaban as diluted suspension in 40 patients aged ≥6 months to <6 years with VTE. Rivaroxaban was administered after meal intake, according to the dosage regimen presented in Table 8. Table 9 shows the pharmacokinetic parameters of rivaroxaban calculated using a PPK model [see Section "6.2.7 PPK analysis in pediatric patients"], based on the plasma rivaroxaban concentration data from the study.

Table 8. Dosage regimen in Study 14374

Dosage form	Body weight	Dose (mg)	Dosage regimen
Suspension	≥3 kg to <4 kg	0.7	Twice daily after breakfast and supper (approximately 12 hours apart)
	≥4 kg to <5 kg	0.9	
	≥5 kg to <6 kg	1.4	
	≥6 kg to <7 kg	1.8	
	≥7 kg to <8 kg	2.2	
	≥8 kg to <10 kg	3.2	
	≥10 kg to <12 kg	3.4	
	≥12 kg to <20 kg	4.0	
	≥20 kg to <30 kg	5.0	
	≥30 kg to <50 kg	7.5	

Table 9. Pharmacokinetic parameters[a)] of rivaroxaban

Age group	≥2 years to <6 years	≥6 months to <2 years
N	25	15
$AUC_{(0\text{-}24)ss}$ (μg·h/L)	1810 (32.5)	1390 (37.5)
$C_{max,ss}$ (μg/L)	146 (23.6)	133 (27.2)
$C_{(12)ss}$ (μg/L)	23.0 (65.2)	15.4 (66.5)

Geometric mean (geometric CV[%])
a) Values estimated from the PPK model

6.2.5 Foreign phase I/II study (Study 17618, CTD 5.3.5.2.1, November 2015 to December 2017)

The study was conducted to evaluate the pharmacokinetics of rivaroxaban after multiple oral doses of rivaroxaban as diluted suspension or dry syrup in 10 non-Japanese patients aged <6 months with arterial or venous thrombosis. Rivaroxaban was administered immediately before or during meal intake, according to the dosage regimen presented in Table 10. The rivaroxaban exposure ($AUC_{(0\text{-}24)ss}$ and $C_{(12)ss}$) observed in the first 5 patients was lower than the expected exposure. For this reason, the study protocol was amended in November 2016 to change the regimen of rivaroxaban from twice daily to three times daily. Table 11 shows the pharmacokinetic parameters of rivaroxaban calculated using a PPK model [see Section "6.2.8 PPK analysis in pediatric patients aged <2 years"], based on the plasma rivaroxaban concentration data from the study.

Table 10. Dosage regimen for rivaroxaban in Study 17618

Dosage form	Body weight	Dose (mg)	Before protocol amendment	After protocol amendment
Suspension or dry syrup	≥2.6 kg to <3 kg	0.5	Twice daily (approximately 12 hours apart)	Three times daily (approximately 8 hours apart)
	≥3 kg to <4 kg	0.6		
	≥4 kg to <5 kg	0.9		
	≥5 kg to <6 kg	1.2		
	≥6 kg to <7 kg	1.6		
	≥7 kg to <8 kg	1.9		
	≥8 kg to <9 kg	2.5		
	≥9 kg to <10 kg	2.7		
	≥10 kg to <12 kg	2.9		
	≥12 kg to <20 kg	3.2		-

Table 11. Pharmacokinetic parameters[a)] of rivaroxaban

Dosage regimen	Twice daily	Three times daily
N	5[b)]	5[c)]
$AUC_{(0\text{-}24)ss}$ (μg·h/L)	881 (24.0)	1011 (25.1)
$C_{max,ss}$ (μg/L)	95.7 (23.1)	81.1 (10.0)
$C_{(12)ss}$ (μg/L)	3.23 (50.3)	-
$C_{(8)ss}$ (μg/L)	-	8.51 (140)

Geometric mean (geometric CV%); -, Not applicable
a) Values estimated from the PPK model
b) Four patients received the suspension formulation and 1 patient received the dry syrup formulation.
c) All 5 patients received the dry syrup formulation.

6.2.6 Global phase III study (Study 14372, CTD 5.3.5.1.3, November 2014 to January 2019)

This study was conducted to evaluate pharmacokinetics of rivaroxaban after multiple oral doses of rivaroxaban as tablets or dry syrup in 316 patients aged birth to <18 years with acute VTE. Rivaroxaban was administered during or after meal intake, according to the dosage regimens presented in Table 12. Table 13 shows the pharmacokinetic parameters of rivaroxaban calculated using a PPK model [see Section "6.2.9 Comprehensive PPK analysis in pediatric patients"], based on the plasma rivaroxaban concentration data from the study.

Table 12. Dosage regimens for rivaroxaban in Study 14372

Dosage form	Body weight	Dose	Dosage regimen
Dry syrup	≥2.6 kg to <3 kg	0.8 mg	Three times daily During or within 30 minutes after breakfast, lunch, and supper (approximately 8 hours apart)
	≥3 kg to <4 kg	0.9 mg	
	≥4 kg to <5 kg	1.4 mg	
	≥5 kg to <7 kg	1.6 mg	
	≥7 kg to <8 kg	1.8 mg	
	≥8 kg to <9 kg	2.4 mg	
	≥9 kg to <10 kg	2.8 mg	
	≥10 kg to <12 kg	3.0 mg	
	≥12 kg to <20 kg	5.0 mg	Twice daily During or within 1 hour after breakfast and supper (approximately 12 hours apart)
Tablets or dry syrup	≥20 kg to <30 kg	5.0 mg	
	≥30 kg to <50 kg	15 mg	Once daily During or within 2 hours after breakfast
	≥50 kg	20 mg (15 mg for Japanese)	

Table 13. Pharmacokinetic parameters[a)] of rivaroxaban

Dosage regimen	Once daily		Twice daily				Three times daily		
Age group	≥12 years to <18 years	≥6 years to <12 years	≥12 years to <18 years	≥6 years to <12 years	≥2 years to <6 years	≥6 months to <2 years	≥2 years to <6 years	≥6 months to <2 years	<6 months
N	173	29	1	38	39	4	5	18	13
Dosage form	Tablets or dry syrup		Dry syrup	Tablets or dry syrup	Dry syrup		Dry syrup		
$AUC_{(0\text{-}24)ss}$ (μg·h/L)	2120 (26.4)	1960 (31.8)	1770[b)]	1960 (32.0)	2370 (42.2)	1640 (49.4)	2480 (30.9)	1890 (34.4)	1590 (29.6)
$C_{max,ss}$ (μg/L)	238 (20.0)	247 (23.1)	123[b)]	148 (25.5)	185 (31.8)	156 (39.8)	162 (25.4)	132 (27.2)	119 (24.1)
$C_{trough,ss}$ (μg/L)	20.7 (45.9)	15.4 (56.4)	30.5[b)]	27.5 (51.4)	30.6 (72.3)	12.6 (82.8)	41.2 (46.6)	26.2 (57.0)	18.5 (50.4)

Geometric mean (geometric CV[%])
a) Values estimated from the PPK model
b) Values from individual patients

6.2.7 PPK analysis in pediatric patients (Analysis 15145, CTD 5.3.3.5.9)

The PPK model[1)] developed based on the data from Study 12892 was updated using the plasma rivaroxaban concentration data (201 children, 737 time points), including preliminary data obtained from the foreign phase I studies (Studies 12892 and 17992), a foreign phase II study (Study 14373), a global phase II study (Study 14374), and a global phase III study (Study 14372). To assess the effect of dose on the pharmacokinetics of rivaroxaban, the model describes the relationship between relative bioavailability and dose/weight ratio, using a linear function to represent decreasing relative bioavailability with increasing dose/weight ratio. An assessment of the effects of dosage form on the pharmacokinetics of rivaroxaban revealed that the absorption rate of rivaroxaban administered as undiluted suspension was inferred to be lower than that following the administration of tablets, diluted suspension, or dry syrup. The V_c and CL of rivaroxaban were described with body weight-based allometric scaling. No covariates other than body weight were incorporated into the model.

Each parameter was then optimized based on another data set (276 children, 1014 time points), composed of the above data and additional data from the 5 clinical studies, to establish the final model.

6.2.8 PPK analysis in pediatric patients aged <2 years (Analysis 19397, CTD 5.3.3.5.14)

A PPK analysis was conducted based on the plasma rivaroxaban concentration data (29 children, 77 time points) from children aged <2 years enrolled in the foreign phase I studies (Studies 12892 and 17992), a global phase II study (Study 14374), and a foreign phase I/II study (Study 17618). The plasma rivaroxaban concentration data used in the PPK analysis included those collected at 19 timepoints, from 5 children aged <6 months.

The pharmacokinetics of rivaroxaban was described by a 1-compartment model with first-order absorption and first-order elimination. The CL and V of rivaroxaban were described with body weight-based allometric scaling, with estimated allometric coefficients of 0.931 and 1.41, respectively. No covariates other than body weight were incorporated into the model.

The established final model was used to predict the $AUC_{(0\text{-}24)ss}$ of rivaroxaban administered (at the doses presented in Table 14) three times daily in the fed state to children aged <2 years enrolled in each clinical study. The predicted $AUC_{(0\text{-}24)ss}$ values in individual patients were generally within the target AUC range (approximately from 1800 to 2000 μg·h/L, which was not lower than the median $AUC_{(0\text{-}24)ss}$ in the subgroup of adults with $AUC_{(0\text{-}24)ss}$ values corresponding to the lower 30% of the adult exposure range). The target exposure range was set when the dosing frequency was increased to three times daily, so that the trough plasma rivaroxaban concentration would be kept above a certain level to achieve adequate efficacy, while a marked increase in the peak plasma rivaroxaban concentration could be avoided because it might lead to an increased risk of bleeding.

Table 14. Doses for the three-times-daily dosing regimen for rivaroxaban

Body weight	Dose (mg)
<3 kg	-
≥3 kg to <4 kg	1.1
≥4 kg to <5 kg	1.4
≥5 kg to <6 kg	1.7
≥6 kg to <7 kg	1.9
≥7 kg to <8 kg	2.2
≥8 kg to <9 kg	2.5
≥9 kg to <10 kg	2.8
≥10 kg to <12 kg	-

-, Not applicable

6.2.9 Comprehensive PPK analysis in pediatric patients (Analysis 18376, CTD 5.3.3.5.12)

A PPK analysis was conducted based on the plasma rivaroxaban concentration data (524 children, 1988 time points) from the foreign phase I studies (Studies 12892 and 17992), a foreign phase II study (Study 14373), a global phase II study (Study 14374), a foreign phase I/II study (Study 17618), and a global phase III study (Study 14372), as well as a global phase III study in pediatric patients undergoing a Fontan procedure (Study 18226[2)]).

The pharmacokinetics of rivaroxaban was described by a 2-compartment model with first-order absorption and first-order elimination from the central compartment. The CL, Q, V_c, and V_p of rivaroxaban were described with body weight-based allometric scaling, with estimated allometric coefficients of 0.481, 0.761, 0.821, and 0.821, respectively.

This analysis employed the PPK model constructed in Section "6.2.7 PPK analysis in pediatric patients" as the base model. Factors selected as potential covariates that might affect the pharmacokinetics of rivaroxaban were body weight, age, history of a Fontan procedure, eGFR (Schwartz formula), eGFR (Rhodin formula), the ratio of the serum creatinine level to the upper limit of normal (ULN), and serum creatinine level (not more than vs. more than the ULN). Among these factors, body weight was identified as a covariate for CL and V_c for the final model, as with the base model. No other covariates were found to have a significant effect on the pharmacokinetics of rivaroxaban.

6.R Outline of the review conducted by PMDA

6.R.1 Differences in the pharmacokinetics or pharmacodynamics of rivaroxaban between Japanese and non-Japanese children

The applicant's explanation about the differences in the pharmacokinetics and pharmacodynamics of rivaroxaban between Japanese and non-Japanese children:

The dose of rivaroxaban in maintenance treatment for Japanese adult patients with VTE was set at three-fourth the dose for non-Japanese patients, because (i) there are differences in the anticoagulant treatments used in clinical practice, between in and outside of Japan; and (ii) exposure to rivaroxaban in Japanese adults has been

[2)] An open-label, active control, parallel-group study to evaluate the pharmacokinetics and pharmacodynamics of rivaroxaban in children who had undergone a Fontan procedure. The dose of rivaroxaban, when administered as a suspension twice daily, was selected to achieve an exposure comparable to that observed in non-Japanese adults receiving rivaroxaban 10 mg once daily.

shown to be approximately 1.3 times higher than that in non-Japanese adults. In the PPK analyses submitted for the previous applications and the PPK analysis based on the plasma rivaroxaban concentration data from 7 clinical studies, including a global study, in adult patients with VTE (CTD 5.3.3.5.7), body weight and CL_{cr} (Cochcraft-Gault formula) were selected as covariates for CL/F, while body weight or lean body weight was selected for V. Given the magnitude of the effects of these covariates on the pharmacokinetic parameters, as well as the relationship between CL_{cr} (Cockcraft-Gault formula) and body weight, the effects of body weight on the pharmacokinetics of rivaroxaban in adults were limited. Thus, the difference in the exposure to rivaroxaban observed between Japanese and non-Japanese adults cannot be explained solely by the difference in body size between these populations. In contrast, the effects of body weight on the pharmacokinetics of rivaroxaban are expected to be greater in childhood, during which the overall body size, organs, etc. develop markedly, compared with adulthood. For this and other reasons, the dosage regimen of rivaroxaban that will produce a similar exposure in Japanese and non-Japanese children should be selected based on the results of simulations using pediatric physiologically-based pharmacokinetics (PBPK) models that take into account the childhood development of overall body size, organs, etc., instead of simply setting the dose for Japanese children at three-fourth the dose for non-Japanese children, as in the case of adults [see Section "6.R.2 Dosage regimen in the global phase III study (Study 14372)"].

In the global phase III study (Study 14372), 4 Japanese pediatric patients (1 aged 4 years and 3 aged <1 year) receiving rivaroxaban had evaluable pharmacokinetic data. Figure 1 shows the exposure ($AUC_{(0\text{-}24)ss}$, $C_{max,ss}$, and $C_{trough,ss}$) to rivaroxaban estimated from a PPK model [see Section "6.2.9 Comprehensive PPK analysis in pediatric patients"], based on the plasma rivaroxaban concentration data from Study 14372. The $AUC_{(0\text{-}24)ss}$ and $C_{max,ss}$ values in 3 individual Japanese pediatric patients aged <1 year (with baseline body weights of 6.3, 6.2, and 2.7 kg) were distributed around the lower limit of the adult exposure ranges. This tendency was also observed in pediatric patients, irrespective of race, who received rivaroxaban three times daily (particularly in pediatric patients weighing <7 kg). However, this is a reasonable result, given that the dosage regimen for children weighing <12 kg was selected to achieve the target exposure, that was the median exposure in the subgroup of adults with exposure values corresponding to the lower 30% of the adult $C_{tough,ss}$ range. The $C_{trough,ss}$ values in 3 individual Japanese pediatric patients aged <1 year were distributed around the median of the adult exposure range, with no clear difference from the values in individual non-Japanese pediatric patients. The estimated $AUC_{(0\text{-}24)ss}$, $C_{max,ss}$, and $C_{trough,ss}$ values in a Japanese pediatric patient aged 4 years (with a baseline body weight of 12.7 kg) were similar to those in non-Japanese pediatric patients in the same body weight category.

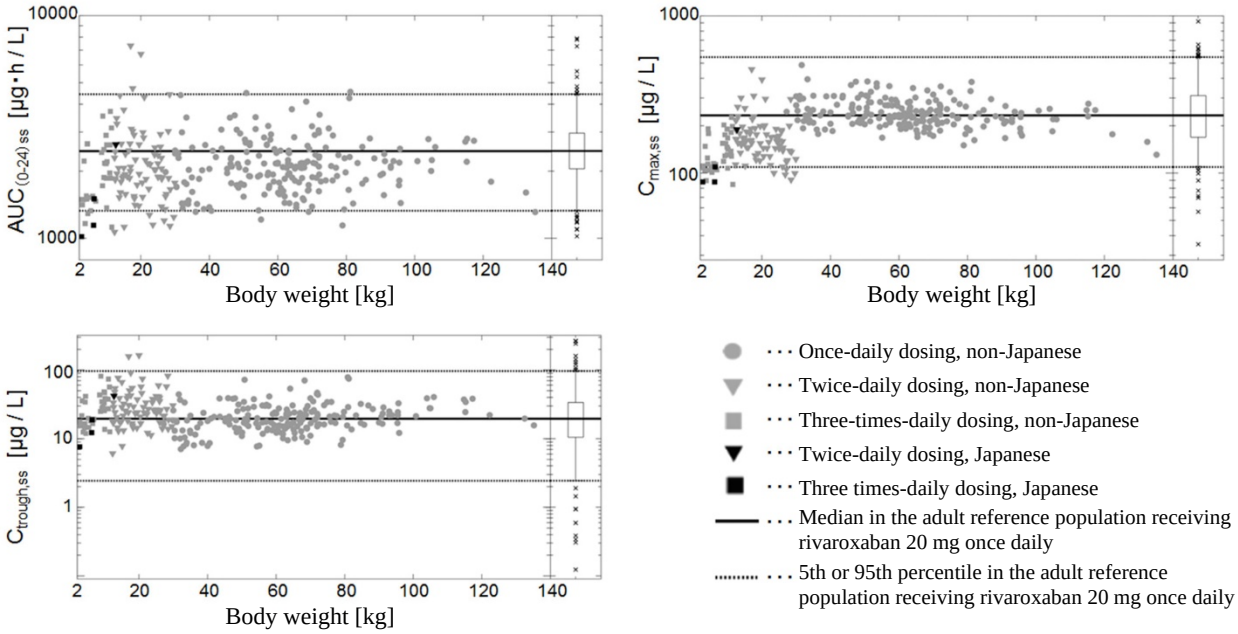

Figure 1. Exposure to rivaroxaban in Japanese and non-Japanese pediatric patients (Study 14372)

The relationship between plasma rivaroxaban concentration and pharmacodynamic parameters (ratios of prothrombin time [PT] and activated partial thromboplastin time [aPTT] to baseline values and anti-FXa activity) was similar in Japanese and non-Japanese children.

These results suggest no clear differences in the pharmacokinetics or pharmacodynamics of rivaroxaban administered at the body weight-adjusted dosage regimens, between Japanese and non-Japanese children.

PMDA's view:

The pharmacokinetics of rivaroxaban administered at a fixed dosage regimen has been shown to differ between Japanese and non-Japanese adults, and the causes for this difference remain unknown. This fact, along with limited data currently available regarding the pharmacokinetics of rivaroxaban in Japanese children, preclude an accurate interpretation of the study results. However, the submitted study results indicate no clear differences in the pharmacokinetics or pharmacodynamics of rivaroxaban administered at body weight-adjusted dosage regimens, between Japanese and non-Japanese children.

6.R.2 Dosage regimens in the global phase III study (Study 14372)

The applicant's explanation about the rationale for the dosage regimens used in Study 14372:

In Study 14372, the dosage regimens were selected to achieve an exposure to rivaroxaban in pediatric patients with VTE, which would be within the range of the exposure that had been demonstrated to be effective and safe in adult patients with VTE. The developmental maturation of the hemostatic system is still ongoing during childhood, and particularly the levels of coagulation factors in children change with age (*Blood Rev.* 2010;24:63-8, *Jpn J Thromb Hemost.* 2004;15:349-54). The pharmacodynamic response to rivaroxaban in children was investigated in an *ex vivo* plasma spiking study, with the aim of assessing the relationship between rivaroxaban concentrations (0 to 500 ng/mL) and pharmacodynamic parameters (PT, aPTT, anti-FXa activity,

and thrombin generation), in children aged birth to 16 years (birth to 28 days, 28 days to 23 months, 2 to 6 years, 7 to 11 years, and 12 to 16 years) (*Thromb Res.* 2012;130:804-7, *Blood Coagul Fibrinolysis.* 2014;25:237-40). The study showed that the relationship between rivaroxaban concentrations and pharmacodynamic parameters in pediatric patients aged ≥28 days did not largely differ from that in adult patients with DVT, while rivaroxaban caused a prolongation of PT, an increase in lag time as measured by thrombin generation and other changes in pediatric patients aged <28 days, compared with adult patients. Based on these results, the pharmacodynamic parameters of rivaroxaban were also assessed in clinical studies in pediatric patients with VTE.

In a foreign phase I study (Study 12892), which was the first clinical study involving pediatric patients with VTE, the dosages were selected based on the results of a simulation using a physiologically-based pharmacokinetic (PBPK) model in non-Japanese children.[3)] The relationship between body weight and exposure ($AUC_{0-\infty}$, C_{max}, and C_{trough}) to rivaroxaban, administered to children as a single oral dose of 0.14 or 0.3 mg/kg (equivalent to approximately 10 or 20 mg, respectively, in an adult weighing 70 kg) was predicted from a simulation using the PBPK model in non-Japanese children. The prediction suggested that the doses of 0.14 and 0.3 mg/kg in non-Japanese children, particularly those weighing <30 kg, would fail to achieve an exposure similar to that observed in healthy adults. Nevertheless, in view of the uncertainty of model-based predictions and the avoidance of excessive increases in plasma rivaroxaban concentrations, the dosage regimens presented in Table 2 were selected for Study 12892, based on the dosage regimens assessed in the above simulation.

In Study 12892, the exposure to rivaroxaban, administered as tablets to children aged ≥6 to <18 years (weighing ≥14 kg) at a 20 mg-equivalent dose (0.3 mg/kg) was similar to that observed in adults. The pharmacokinetics of rivaroxaban, administered as tablets or suspension to children, except those aged ≥6 months to <2 years, were well consistent with the results of the PBPK model-based prediction. Some of the children aged ≥6 months to <2 years (weighing 6 to 12 kg) had plasma rivaroxaban concentrations below the lower limit of quantification at 20 to 24 hours post-dose. This suggested that predicting the pharmacokinetics of rivaroxaban from a PBPK model-based analysis might be difficult in children aged ≥6 months to <2 years.

Based on the above, the same dosage regimen as those used in Study 12892 was employed for the use of rivaroxaban as tablets in children weighing ≥14 kg in phase II studies in children aged ≥6 months to <18 years (Studies 14373 and 14374). The plasma rivaroxaban concentrations at 20 to 24 hours post-dose in children with a lower body weight in Study 12892 tended to be lower than the results of the PBPK model-based prediction. Therefore, the twice-daily dosing regimen was selected for rivaroxaban administered as suspension, and the dose was to increase compared with that used in Study 12892. The dosage regimens selected for Studies 14373 and 14374 are presented in Tables 6 and 8, respectively.

[3)] In PBPK model-based analyses, PK-Sim (version 4.2) was used. A model in non-Japanese adults was initially developed, based on which a model in non-Japanese children was developed, taking into account age-related changes and variations in physical measures (height and body weight) and physiological characteristics (organ size, blood flow velocity, plasma protein levels, gastric emptying time, gastrointestinal transit time, etc.), as well as findings regarding the ontogeny of the elimination of rivaroxaban.

The results of Studies 14373 and 14374 showed that individual exposure ($AUC_{(0\text{-}24)ss}$, $C_{max,ss}$, and $C_{trough,ss}$) values (estimated based on the PPK model [see Section "6.2.7 PPK analysis in pediatric patients]) in children weighing ≥30 kg were generally within the adult exposure range. Individual $AUC_{(0\text{-}24)ss}$ values in children weighing <30 kg who received rivaroxaban as tablets once daily tended to be distributed below the median $AUC_{(0\text{-}24),ss}$ in adults. In contrast, the $AUC_{(0\text{-}24)ss}$ of rivaroxaban administered as diluted suspension twice daily, at a daily dose that was higher than the daily dose when administered as tablets once daily, was similar to that observed in adults. In children weighing <20 kg (particularly children weighing <12 kg), most of the individual $AUC_{(0\text{-}24),ss}$, $C_{max,ss}$, and $C_{trough,ss}$ values were distributed in the lower part of the adult exposure range or below that range. Based on the results of Studies 14373 and 14374, along with the following investigations, the dosage regimens presented in Table 12 were selected for a global phase III study in pediatric patients with VTE (Study 14372).

- In children weighing ≥40 kg, the dose of rivaroxaban for the once-daily dosing regimen would require no change from that in Study 14373. In Japanese children weighing ≥50 kg, which was the highest body weight category, the dose of 15 mg was selected for the once-daily dosing regimen, unlike the 20 mg set for non-Japanese children in the same body weight category in Study 14372, in view of the facts that: (i) Body weight does not substantially differ between Japanese and Caucasian children aged <15 years, while the body weight in Japanese children aged ≥15 years is approximately 15% to 20% lower than that in age-matched Caucasian children (*CDC Centers for Disease Control and Prevention, Clinical Growth Charts 2000, Health Phys.* 1997;72:368-83, etc.); and (ii) the maintenance dose of rivaroxaban in adult patients with DVT or PE differs between non-Japanese patients (20 mg once daily) and Japanese patients (15 mg once daily). Simulations using the PBPK model in non-Japanese children[3)] and the PBPK model in Japanese children[4)] indicated that the body weight-adjusted dosage regimen would provide similar pharmacokinetics in Japanese and non-Japanese children weighing <50 kg, and achieve an exposure similar to that observed in adults, and that the 20 mg once-daily dosing regimen in non-Japanese children weighing ≥50 kg and the 15 mg once-daily dosing regimen in Japanese children weighing ≥50 kg would provide similar pharmacokinetics, and achieve an exposure similar to that in adults.
- For children weighing ≥30 kg to <40 kg, the dosage regimen was increased from 10 mg once daily to 15 mg once daily, to achieve an exposure more closely consistent with that observed in adults.
- The results from the phase II study and predictions obtained using the PBPK model in non-Japanese children (CTD 5.3.3.5.5) indicated that twice-daily dosing in children weighing ≥12 kg to <30 kg would achieve an exposure more closely consistent with the exposure in adults. Thus, twice daily-dosing was selected as the dosage regimen for the body weight category in Study 14372. In children weighing ≥12 kg to <20 kg, the dose was increased from 4 mg, the dose used in the phase II study, to 5 mg.
- Based on the results of the foreign phase I/II study in children aged from birth to <6 months (Study 17618), three-times-daily dosing was selected for children weighing <12 kg to achieve an exposure more closely consistent with the adult exposure range. The results of a PPK model-based simulation in pediatric patients aged <2 years showed that rivaroxaban administered (at the doses presented in Table 14) three

[4)] In PBPK model-based analyses, PK-Sim (version 4.2) was used. Based on the model in non-Japanese adults, a model in Japanese adults, which took into account ethnic differences in physical measures (height and body weight), tubular secretion, and the absorption rate of rivaroxaban, was constructed as a base model, after which a model in Japanese children was constructed using a scaling technique similar to that used in the construction of the PBPK model in non-Japanese children.

times daily in the fed state would produce $AUC_{(0\text{-}24),ss}$ values that were generally within the target exposure range [see Section "6.2.8 PPK analysis in pediatric patients aged <2 years"). However, the limited availability of plasma rivaroxaban concentration data for the development of the above PPK model precluded an estimation of model parameters with sufficient accuracy. In addition, Table 14 included a body weight category for which the total daily dose exceeded twice the total daily dose for the twice-daily dosing regimen used in Study 17618. In view of these facts, the dose in children weighing <6 kg was to be set to minimize the increase from the dose used in Study 17618. Consequently, the dose of rivaroxaban for the three-times-daily dosing regimen for children weighing <6 kg was set at a dose that was approximately 50% higher than the dose used in Study 17618.

Figure 2 shows the exposure ($AUC_{(0\text{-}24)ss}$, $C_{max,ss}$, and $C_{trough,ss}$) to rivaroxaban estimated from a PPK model [see Section "6.2.9 "Comprehensive PPK analysis in pediatric patients"], based on plasma rivaroxaban concentration data from Study 14372, demonstrating that the dosage regimens selected for children in Study 14372 would achieve an exposure similar to the adult exposure. A visual assessment of the results from multiple-dose studies in pediatric patients with VTE (Studies 14373, 14374, 17618, and 14372) indicated that the relationship between plasma rivaroxaban concentrations and the ratios of PT and aPTT to baseline values in pediatric patients was similar to that in adult patients.

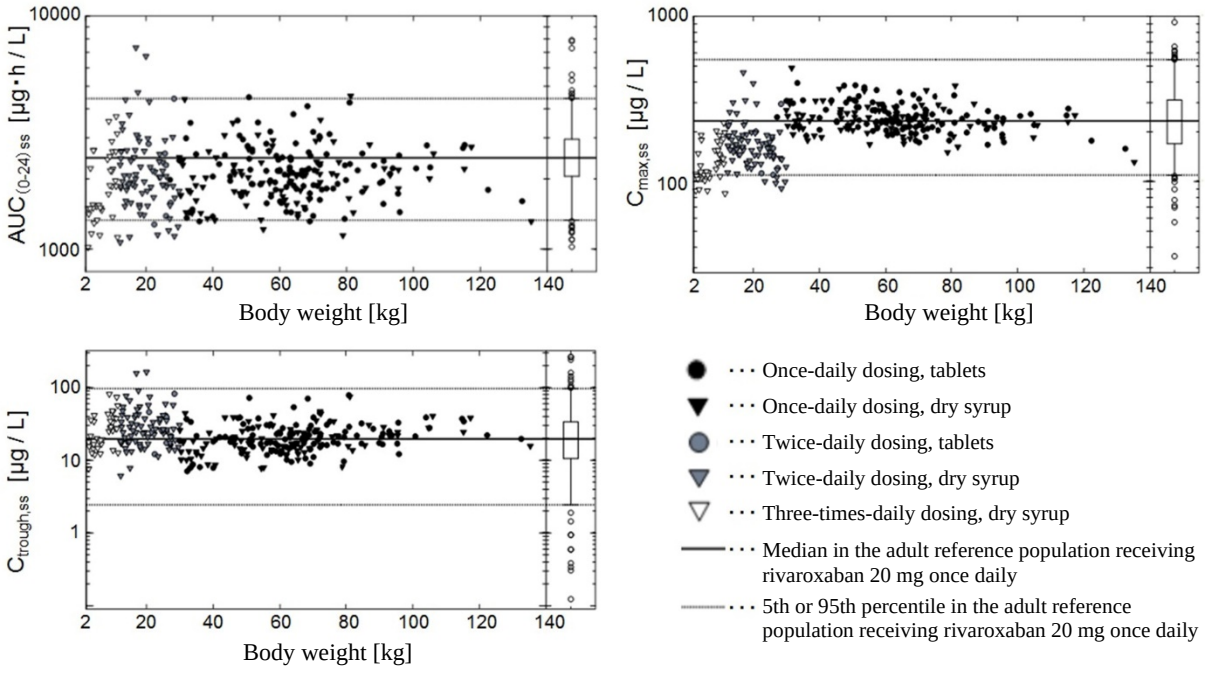

Figure 2. Relationships between body weight and (PPK model-estimated) pharmacokinetic parameters of rivaroxaban administered as multiple doses at the dosage regimens presented in Table 12 (Study 14372)

PMDA's view:

Based on the submitted study results and the applicant's investigations, the dosage regimens selected for Study 14372 were appropriate from the perspective of achieving a rivaroxaban exposure in children similar to that observed in adults. The dosage regimens in Japanese pediatric patients with VTE should be investigated further

based on the efficacy, safety, and other aspects of rivaroxaban observed in Study 14372 [see Section "7.R.7 Dosage and administration"].

6.R.3 Pharmacokinetic interactions

The proposed package insert for Xarelto Dry Syrup has included a precautionary statement that the use of 10 mg once-daily dosing should be considered when rivaroxaban is administered in combination with "fluconazole or fosfluconazole" or "clarithromycin or erythromycin," to children weighing ≥30 kg. PMDA asked the applicant to explain what action should be taken when the co-administration of rivaroxaban with these medications is required in children weighing <30 kg.

The applicant's explanation:

Drug-drug interaction studies in healthy adults showed that the concomitant use of fluconazole, clarithromycin, or erythromycin increased the C_{max} and AUC of rivaroxaban 1.3- to 1.4-fold and 1.3- to 1.5-fold, respectively, compared with those of rivaroxaban alone (see the data submitted for the initial application for "Xarelto Tablets 10 mg and Xarelto tablets 15 mg"). Based on the results of the drug-drug interaction studies, the package inserts for the tablet, fine granule (sachets), and OD tablet formulations of rivaroxaban have included a precautionary statement to the effect that in the maintenance treatment of patients with VTE using these medications, a dose reduction of rivaroxaban from the usual dosage regimen of 15 mg once daily, to 10 mg once daily should be considered, and that rivaroxaban should be used only if rivaroxaban therapy is deemed necessary after due consideration of the potential therapeutic benefits and possible risks.

The mean body weight in Japanese children aged 10 years is approximately 30 kg, regardless of gender (*Health Phys.* 1997;72:368-83, *Report on School Health Statistics 2019*, Change in mean body weight by age [from FY 1900 to 2019], https://www.e-stat.go.jp/dbview?sid=0003147023, last accessed on September 10, 2020), and the expression levels of major drug-metabolizing enzymes and drug transporters in children aged ≥10 years do not substantially differ from those in adults, and renal functions in such pediatric population are similar to those in adults (*Pharmaceutics.* 2011;3:253-72, *Drug Metab Dispos.* 2014;42:78-88, etc). In addition, from the viewpoint that rivaroxaban will be administered to children weighing ≥30 kg at the same dosage regimen as for adults [see Sections "6.R.2 Dosage regimens in the global phase III study (Study 14372)" and "7.R.7 Dosage and administration"], a precautionary statement similar to that for adults should be provided regarding the concomitant use of the above medications in Japanese children weighing ≥30 kg.

On the other hand, rivaroxaban is more rapidly eliminated in children weighing <30 kg than in children weighing ≥30 kg. Accordingly, a precautionary advice regarding pharmacokinetic interactions in children weighing <30 kg should be provided based on the results from pediatric clinical studies, rather than by simply applying findings from the use in adults to children. The effects of CYP3A4 inhibitors on the pharmacokinetics of rivaroxaban were assessed using a PPK analysis [see Section "6.2.9 Comprehensive PPK analysis in pediatric patients"], based on the plasma rivaroxaban concentration data from pediatric patients receiving multiple doses of rivaroxaban (0 patients receiving a strong CYP3A4 inhibitor, 11 patients receiving a moderate CYP3A4 inhibitor, and 31 patients receiving a weak CYP3A4 inhibitor) in clinical studies (Studies

14373, 14374, 17618, and 14372). The results of the assessment indicated that the concomitant use of a moderate CYP3A4 inhibitor had a significant effect on the CL of rivaroxaban. However, a small number of patients used a moderate CYP3A4 inhibitor in these studies, and the observed effects of the concomitant use of moderate CYP3A4 inhibitors on the CL of rivaroxaban could be mainly attributable to the lower CL value in 1 patient who used both a moderate CYP3A4 inhibitor and a CYP3A4 inducer. Thus, this assessment result is not reliable, and the effects of the concomitant use of moderate CYP3A4 inhibitors on the pharmacokinetics of rivaroxaban remains unclear. In addition, the effects of concomitant CYP3A4 inhibitors on the safety of rivaroxaban were assessed based on the results of Study 14372. The incidences of "clinically relevant non-major bleeding" in the rivaroxaban group were 1.2% (3 of 247 patients) in patients using no CYP3A4 inhibitor, 0% (0 of 3 patients) in patients using a strong CYP3A4 inhibitor, 3.6% (1 of 28 patients) in patients using a moderate CYP3A4 inhibitor, and 11.8% (6 of 51 patients) in patients using a weak CYP3A4 inhibitor, suggesting that "clinically relevant non-major bleedings" tended to be more frequent in patients receiving rivaroxaban in combination with a weak CYP3A4 inhibitor than in those receiving no CYP3A4 inhibitor. However, the concomitant use of CYP3A4 inhibitors is unlikely to substantially affect the safety profile of rivaroxaban in pediatric patients, because (i) "clinically relevant non-major bleedings" reported by 4 of the 7 patients receiving rivaroxaban in combination with a CYP3A4 inhibitor were less likely to be causally related to the concomitant use of the CYP3A4 inhibitors, in view of the temporal relationship between the onset of the event and the use of the CYP3A4 inhibitors, and (ii) "clinically relevant non-major bleedings" were not common in patients receiving rivaroxaban in combination with a moderate or strong CYP3A4 inhibitor. Thus, regarding the concomitant use of "fluconazole or fosfluconazole" or "clarithromycin or erythromycin" with rivaroxaban in children weighing <30 kg, the applicant will not simply use the precautionary advice for adults ("the dose reduction of rivaroxaban to two-thirds of the usual dose should be considered"), but will instead provide a precautionary statement that physicians should judge the appropriateness of the concomitant use of these medications with due consideration of the patient's condition and, if the concomitant use of any of such medications is deemed necessary, carefully initiate the combination therapy while closely monitoring the patient's condition.

PMDA's view:

According to the applicant, the pharmacokinetics of rivaroxaban does not seem to substantially differ between children weighing ≥30 kg and adults. It is therefore appropriate that a precautionary advice regarding the concomitant use of a CYP3A4 inhibitor is provided for the use in children weighing ≥30 kg, as in the case of adults. "Clinically relevant non-major bleedings" tended to occur more frequently in pediatric patients receiving rivaroxaban concomitantly with weak CYP3A4 inhibitors than in pediatric patients receiving rivaroxaban without concomitant CYP3A4 inhibitors. Given the temporal relationship between the onset of the events and the use of concomitant CYP3A4 inhibitors, however, there are no clear safety concerns in children weighing <30 kg when rivaroxaban at a body weight-adjusted dose to achieve an exposure similar to that observed in adults is administered in combination with CYP3A4 inhibitors. Nevertheless, only a small number of pediatric patients received rivaroxaban concomitantly with a moderate or strong CYP3A4 inhibitor in Study 14372. The possibility that the concomitant use of CYP3A4 inhibitors may increase the pharmacokinetics of rivaroxaban in children weighing <30 kg cannot be ruled out, although the degree of the increase cannot be

estimated from the currently available data. These situations preclude concluding that the dose adjustment for adults (i.e., reducing the dose of rivaroxaban to two-thirds the usual dose) will also be appropriate for children weighing <30 kg. Given these considerations, the use of "fluconazole or fosfluconazole" or "clarithromycin or erythromycin" in combination with rivaroxaban in children weighing <30 kg should be avoided, unless it is deemed medically necessary after due consideration of the potential therapeutic benefits and the possible risks. PMDA's conclusions will be finalized after taking into account the comments from the Expert Discussion.

6.R.4 Timing of dosing relative to meal intake, and dosing interval

The applicant's explanation about the rationale for recommending the administration of rivaroxaban in the fed state in the proposed dosage and administration:

In adults, the bioavailability of rivaroxaban at a dose of 20 mg in the fasted state is lower than that at 5 mg in the fasted state, and the AUC of rivaroxaban at a dose of 20 mg in the fed state is higher than that at 20 mg in the fasted state. These findings indicate that the saturation of the absorption of high-dose rivaroxaban can be improved by dosing in the fed state (see the data submitted for the initial application for "Xarelto Tablets 10 mg and Xarelto tablets 15 mg"). Since the dosage regimen of rivaroxaban for pediatric patients with VTE aimed to achieve an exposure similar to that observed in non-Japanese adults receiving rivaroxaban 20 mg once daily, the administration of rivaroxaban in the fed state was selected for clinical studies in pediatric patients, as in adult patients. For infants, dosing through feeding tubes or during feeding or meal intake was allowed to ensure the intake of rivaroxaban. In Study 14372, rivaroxaban was administered on the following dosing schedules with a certain time window for dosing in the fed state.

- Once-daily dosing: Administer during or within 2 hours after breakfast
- Twice-daily dosing: Administer during or within 1 hour after breakfast and supper
- Three-times-daily dosing: Administer during or within 30 minutes after breakfast, lunch, and supper

Study 14372 is considered to have included some pediatric patients with VTE receiving rivaroxaban during meal intake. The results of the study showed that the exposures to rivaroxaban in pediatric patients fell within the range of the exposure observed in adult patients with VTE. The body weight-adjusted doses of rivaroxaban administered either after meal intake (including dosing immediately after meal intake) or during meal intake are thus expected to achieve the target exposure. Therefore, dosing in the fed state has been recommended in the proposed dosage regimen for pediatric patients, as for adult patients. At the same time, the package insert will include a precautionary statement that rivaroxaban may be administered during a meal, and in such case, liquids or milk should be given immediately after rivaroxaban dosing to ensure the intake of rivaroxaban in children, as specified in the protocol for Study 14372.

The "Precautions Concerning Dosage and Administration" section in the proposed package insert has included a statement that rivaroxaban should be administered approximately 8 hours apart in the three-times-daily dosing regimen. PMDA asked the applicant to explain the compatibility between dosing in the fed state and dosing approximately 8 hours apart, in children weighing <12 kg who will require the three-times-daily dosing regimen.

The applicant's explanation:
In Study 14372, the dosing interval for the three-times-daily dosing regimen was set at approximately 8 hours to achieve the target exposure in pediatric patients weighing <12 kg. Most pediatric patients weighing <12 kg are <2 years of age. In particular, younger children weighing <12 kg require frequent feeding or between-meal snacks. Accordingly, the dosing of rivaroxaban in the fed state and approximately 8 hours apart is feasible. In Study 14372, no problems with the selected dosage regimens were reported. In Study 14372, the majority of patients assigned to the three-times-daily dosing regimen received rivaroxaban during the periods from 6 a.m.to 8 a.m., from 2 p.m.to 4 p.m., and from 8 p.m.to 11 p.m.

Based on the above, the rules for the timing of dosing relative to meal intake and the dosing interval used in Study 14372 are important for achieving the target rivaroxaban exposure. In view of the timing of meal intake in the target patient population of the three-times-daily dosing regimen and the results from Study 14372, dosing in the fed state and dosing approximately 8 hours apart are compatible, and the precautionary statements included in the proposed package insert are appropriate.

PMDA's view:
Based on the known findings about food effects on the pharmacokinetics of rivaroxaban, as well as the dosing rules for rivaroxaban, the actual dosing results, and the results of the assessment of the pharmacokinetics of rivaroxaban in Study 14372, the applicant has decided to recommend rivaroxaban dosing in the fed state in the "Dosage and Administration" section, and to inform healthcare professionals that rivaroxaban may be administered during meal intake, as allowed in Study 14372. The applicant's decision is appropriate. In addition, the applicant's proposal to include a statement that the dosing interval for the three-times-daily dosing regimen should be approximately 8 hours in the "Precautions Concerning Dosage and Administration" section is appropriate, in view of the applicant's explanation.

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

The applicant submitted efficacy and safety evaluation data, in the form of results data from the 4 clinical studies presented in Table 15 [For pharmacokinetics and pharmacodynamics, see Section "6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA"].

Table 15. Summary of key clinical studies

Data type	Geographic region	Study identifier	Phase	Patient population	N	Dosage regimen	Primary endpoints
Evaluation data	Foreign	14373	II	Patients aged ≥6 to <18 years with symptomatic or asymptomatic VTE	63	Body weight-adjusted dose of rivaroxaban (5 to 20 mg/day), administered orally once daily or twice daily for 30 days	Safety Efficacy PK/PD
	Global	14374	II	Patients aged ≥6 months to <6 years with symptomatic or asymptomatic VTE	46	Body weight-adjusted dose of rivaroxaban (0.7 to 7.5 mg per dose), administered orally twice daily for 30 days	Safety Efficacy PK/PD
	Foreign	17618	I/II	Patients aged <6 months with symptomatic or asymptomatic arterial or venous thrombosis	10	Body weight-adjusted dose of rivaroxaban (0.5 to 3.2 mg per dose or 0.5 to 2.9 mg per dose), administered orally twice daily or three times daily, respectively, for 7 days	PK/PD Safety Efficacy
	Global	14372	III	Patients aged birth to <18 years with acute VTE	491	Rivaroxaban group: Oral rivaroxaban at the following dosage regimens for 1 to 12 months: • 20 mg (15 mg for Japanese) once daily in patients weighing ≥50 kg, • 15 mg once daily in patients weighing ≥30 kg to <50 kg, • 5 mg twice daily in patients weighing ≥12 kg to <30 kg, • body weight-adjusted dose (2.4 to 9.0 mg/day), three times daily in patients weighing <12 kg Standard of care group: According to the local package inserts, start with unfractionated heparin (UFH), low molecular weight heparin (LMWH), or fondaparinux sodium, or switch to vitamin K antagonist (VKA) for 1 to 12 months	Efficacy Safety PK/PD

7.1 Phase I and II studies

7.1.1 Foreign phase I study (Study 12892, CTD 5.3.3.2.1, November 2010 to July 2015)

An open-label, uncontrolled study was conducted in 59 non-Japanese patients aged ≥6 months to <18 years who had completed anticoagulant treatment for VTE, but who were at risk for recurrent VTE. A single oral dose of rivaroxaban was administered as tablets or suspension within 2 hours after a meal.

The safety analysis revealed neither "major bleedings[5)]" nor "clinically relevant non-major bleedings[6)]" within 30 days after the administration of the study drug, with "trivial bleedings[7)]" reported in 3 of 59 patients (vessel puncture site bruise in 2 patients, and catheter site bruise in 1 patient). The incidence of adverse events occurring within 30 days post-dose was 27.1% (16 of 59 patients). A causal relationship to the study drug could not be ruled out in 4 of 59 patients (abdominal discomfort, dermatitis allergic, dyspepsia, and urticaria in 1 patient each). No adverse events resulting in death were reported. A serious adverse event (pelvic venous thrombosis) was reported in 1 of 59 patients, for which a causal relationship to the study drug was ruled out.

7.1.2 Foreign phase I study (Study 17992, CTD 5.3.3.2.2, November 2015 to May 2018)

An open-label, uncontrolled study was conducted in 47 non-Japanese patients aged ≥2 months to <12 years who had completed anticoagulant treatment for thrombosis. A single oral dose of rivaroxaban was administered as dry syrup during or within 2 hours after a meal.

5) Overt bleeding which falls under any of the following: (a) bleeding associated with a decrease in hemoglobin of ≥2 g/dL, (b) bleeding requiring a transfusion of ≥2 units of packed red blood cells or whole blood in adults, (c) bleeding in a critical organ (intracranial bleeding, intrathecal bleeding, intraocular bleeding, intrapericardial bleeding, intraarticular bleeding, intramuscular bleeding accompanied by compartment syndrome, or retroperitoneal bleeding), or (d) bleeding with a fatal outcome

6) Overt bleeding which does not meet the criteria for "major bleeding," but was associated with any of the following: (a) medical intervention, (b) unscheduled contact with a physician through a visit or telephone call, (c) discomfort for the child such as pain, (d) discontinuation (interruption) of the study treatment, or (e) impairment of activities of daily life

7) All other bleeding events which does not meet the criteria for "major bleeding" or "clinically relevant non-major bleeding"

The primary safety outcome was the composite endpoint of "major bleeding[5)]" and "clinically relevant non-major bleeding[6)]." The safety analysis revealed neither treatment-emergent (until 2 days after the last dose) "major bleedings" nor "clinically relevant non-major bleedings" with "trivial bleedings[7)]" reported in 2 of 47 patients (stoma site haemorrhage [1 patient] and vessel puncture site bruise [1 patient] in Group B). The incidence of treatment-emergent adverse events was 19.1% (9 of 47 patients; 2 of 22 patients in Group A, 7 of 23 patients in Group B, and 0 of 2 patients in Group C). A causal relationship to the study drug could not be ruled out in 3 of 47 patients (activated partial thromboplastin time prolonged [1 patient] and rash [1 patient] in Group A, and vessel puncture site bruise [1 patient] in Group B). No adverse events resulted in death, nor were any serious adverse events reported.

7.1.3 Foreign phase II study (Study 14373, CTD 5.3.5.1.1, February 2013 to September 2016)

An open-label, uncontrolled study was conducted at 30 sites in foreign countries to evaluate the safety, efficacy, pharmacokinetics, and pharmacodynamics of rivaroxaban in non-Japanese patients aged ≥6 to <18 years with VTE (target sample size, 20 patients [10 patients aged ≥12 to <18 years and 10 patients aged ≥6 to <12 years]). Study 14373 was initiated as an open-label, randomized, parallel-group study using standard of care (low molecular weight heparin [LMWH], fondaparinux sodium, or a vitamin K antagonist [VKA]) as the comparator (sample size, 40 patients [20 per group]). However, due to poor patient recruitment and difficulty in making meaningful comparisons between the groups, the study protocol was amended in April 2015 to discontinue the allocation of patients to the standard of care group and assign all enrolled patients to the rivaroxaban group. For reference, the results from the standard of care group are also described below.

Key inclusion/exclusion criteria

Eligible patients were children aged ≥6 to <18 years with symptomatic or asymptomatic VTE[8)] that had been treated with LMWH, fondaparinux sodium, or VKA for ≥2 months (or ≥6 weeks for catheter-related VTE). Patients were excluded from the study if they had estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2 or platelet count $<50 \times 10^9$/L, or were scheduled to receive strong inhibitors of both CYP3A4 and P-glycoprotein (P-gp), or strong CYP3A4 inducers during the study treatment period.

Patients in the rivaroxaban group, after discontinuing the prior anticoagulant treatment, started treatment with oral rivaroxaban at the pre-specified doses (Table 6) and continued the treatment for 30 days. In the standard of care group, patients continued the prior anticoagulant treatment.

The blinded, central and independent adjudication committee assessed all cases of VTE, "asymptomatic deterioration of thrombotic burden" on imaging, and bleeding events.

All 64 enrolled patients (44 in the rivaroxaban group and 20 in the standard of care group) were included in the full analysis set (FAS). The FAS served as the population for efficacy analysis. Of these 64 patients, 63 (43 in the rivaroxaban group and 20 in the standard of care group) who received at least 1 dose of the study drug

[8)] Lower extremity DVT, vena cava thrombosis, pulmonary embolism, upper extremity DVT, subclavian vein thrombosis, cerebral vein or sinus thrombosis, or jugular vein thrombosis

were included in the safety analysis set. The safety analysis set was composed of 24 patients aged ≥12 to <18 years (11 in the rivaroxaban group and 13 in the standard of care group) and 39 patients aged ≥6 to <12 years (32 in the rivaroxaban group and 7 in the standard of care group).

Table 16 shows the efficacy results based on the incidences of "symptomatic recurrent VTE" and "asymptomatic deterioration of thrombotic burden" on imaging.

Table 16. Incidences of "symptomatic recurrent VTE" and "asymptomatic deterioration of thrombotic burden" on imaging (FAS)

	Rivaroxaban			Standard of care		
	Overall population (N = 43[c])	≥12 years to <18 years (N = 11)	≥6 years to <12 years (N = 32[c])	Overall population (N = 20)	≥12 years to <18 years (N = 13)	≥6 years to <12 years (N = 7)
Symptomatic recurrent VTE[a]	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Thrombotic burden assessment[b]						
Normalized	27.3 (9/33)	42.9 (3/7)	23.1 (6/26)	30.0 (3/10)	50.0 (2/4)	16.7 (1/6)
Improved	63.6 (21/33)	57.1 (4/7)	65.4 (17/26)	40.0 (4/10)	0 (0/4)	66.7 (4/6)
No relevant change	9.1 (3/33)	0 (0/7)	11.5 (3/26)	0 (0/10)	0 (0/4)	0 (0/6)
Deteriorated	0 (0/33)	0 (0/7)	0 (0/26)	0 (0/10)	0 (0/4)	0 (0/6)
Not evaluable	0 (0/33)	0 (0/7)	0 (0/26)	30.0 (3/10)	50.0 (2/4)	16.7 (1/6)

a) %(n). The assessment period was the study treatment period plus 30 days after the last dose.
b) %(n/N). Patients who had evaluable image data, both at baseline and at the end of the study treatment period were analyzed.
c) One patient withdrew consent before the start of the study treatment, and the remaining patients were included in the analysis.

The primary safety outcome was the composite of "major bleeding[5]" and "clinically relevant non-major bleeding [6]." The safety analysis revealed no treatment-emergent (until 2 days after the last dose) "major bleedings." Treatment-emergent "clinically relevant non-major bleedings" were reported in 4 of 43 patients in the rivaroxaban group (menorrhagia in 3 patients aged ≥12 to <18 years, gingival bleeding in 1 patient aged ≥6 to <12 years). No patients in the standard of care group reported such events.

The incidences of treatment-emergent adverse events were 62.8% (27 of 43 patients) in the rivaroxaban group and 50.0% (10 of 20 patients) in the standard of care group. The adverse events reported in ≥5% of patients in the rivaroxaban group were headache (16.3% in the rivaroxaban group vs. 0% in the standard of care group), abdominal pain (7.0% vs. 0%), menorrhagia (9.3% vs. 0%), vomiting (7.0% vs. 10.0%), fatigue (7.0% vs. 0%), and nasopharyngitis (7.0% vs. 0%).

No adverse events resulted in death or led to drug discontinuation.

The incidences of serious adverse events were 4.7% (2 of 43 patients; influenza B virus test positive and hypothalamo-pituitary disorder in 1 patient each, both aged ≥6 to <12 years) in the rivaroxaban group and 5.0% in the standard of care group (1 of 20 patients; multiple sclerosis relapse in 1 patient aged ≥12 to <18 years). A causal relationship to the study drug was ruled out for all of the events.

7.1.4 Global phase II study (Study 14374, CTD 5.3.5.1.2, January 2015 to April 2017)

An open-label, uncontrolled study was conducted at 27 sites in and outside of Japan to evaluate the safety, efficacy, pharmacokinetics, and pharmacodynamics of rivaroxaban in patients aged ≥6 months to <6 years with VTE (target sample size, 20 patients [10 patients aged ≥2 to <6 years and 10 patients aged ≥6 months to <2 years]). As with Study 14373, Study 14374 was initiated as an open-label, randomized, parallel-group study using standard of care (LMWH, fondaparinux sodium, or VKA) as the comparator (sample size, 40 patients [20 per group]). However, the study protocol was amended in April 2015 to discontinue the allocation of patients to the standard of care group and assign all enrolled patients to the rivaroxaban group. For reference, the results from the standard of care group are also described below.

Key inclusion/exclusion criteria

Eligible patients were children aged ≥6 months to <6 years with symptomatic or asymptomatic VTE[9)] that had been treated with LMWH, fondaparinux sodium, or VKA for ≥2 months (or ≥6 weeks for catheter-related VTE). Patients were excluded from the study if they had eGFR <30 mL/min/1.73 m^2 or platelet count <50 × 10^9/L, or were scheduled to receive strong inhibitors of both CYP3A4 and P-gp, or strong CYP3A4 inducers during the study treatment period.

Patients in the rivaroxaban group, after discontinuing the prior anticoagulant treatment, started treatment with oral rivaroxaban at the pre-specified dosage regimens (Table 8) and continued the treatment for 30 days. In the standard of care group, patients continued their prior anticoagulant treatment.

The blinded, central and independent adjudication committee assessed all cases of VTE, "asymptomatic deterioration of thrombotic burden" on imaging, and bleeding events.

All 46 enrolled and treated patients (40 in the rivaroxaban group and 6 in the standard of care group) were included in the FAS and used as the safety analysis set. The FAS served as the population for efficacy analysis. The FAS was composed of 31 patients aged ≥2 to <6 years (25 in the rivaroxaban group and 6 in the standard of care group) and 15 patients aged ≥6 months to <2 years (all in the rivaroxaban group).

Table 17 shows the efficacy results based on the incidences of "symptomatic recurrent VTE" and "asymptomatic deterioration of thrombotic burden" on imaging.

[9)] Lower extremity DVT, vena cava thrombosis, pulmonary embolism, right atrial thrombosis, upper extremity DVT, subclavian vein thrombosis, cerebral vein or sinus thrombosis, or jugular vein thrombosis

Table 17. Incidences of “symptomatic recurrent VTE” and “asymptomatic deterioration of thrombotic burden” on imaging (FAS)

	Rivaroxaban			Standard of care
	Overall population (N = 40)	≥2 years to <6 years (N = 25)	≥6 months to <2 years (N = 15)	≥2 years to <6 years (N = 6)
Symptomatic recurrent VTE[a)]	0 (0)	0 (0)	0 (0)	0 (0)
Thrombotic burden assessment[b)]				
Normalized	30.3 (10/33)	27.3 (6/22)	36.4 (4/11)	20.0 (1/5)
Improved	57.6 (19/33)	68.2 (15/22)	36.4 (4/11)	60.0 (3/5)
No relevant change	12.1 (4/33)	4.5 (1/22)	27.3 (3/11)	20.0 (1/5)
Deteriorated	0 (0/33)	0 (0/22)	0 (0/11)	0 (0/5)
Not evaluable	0 (0/33)	0 (0/22)	0 (0/11)	0 (0/5)

a) % (n). The assessment period was the study treatment period plus 30 days after the last dose.
b) %(n /N). Patients who had evaluable image data, both at baseline and at the end of the study treatment period were analyzed.

The primary safety outcome was the composite of “major bleeding[5)]” and “clinically relevant non-major bleeding[6)].” No patients reported treatment-emergent (until 2 days after the last dose) “major bleedings.” Treatment-emergent “clinically relevant non-major bleedings” were reported in 1 of 6 patients in the standard of care group (rectal haemorrhage).

The incidences of treatment-emergent adverse events were 62.5% (25 of 40 patients) in the rivaroxaban group and 66.7% (4 of 6 patients) in the standard of care group. The adverse events reported in ≥5% of patients in the rivaroxaban group were pyrexia (12.5% in the rivaroxaban group vs, 0% in the standard of care group), anaemia (7.5% vs. 0%), viral upper respiratory tract infection (7.5% vs. 16.7%), febrile neutropenia (5.0% vs. 16.7%), hypersensitivity (5.0% vs. 0%), ear infection (5.0% vs. 0%), nasopharyngitis (5.0% vs. 0%), upper respiratory tract infection (5.0% vs. 0%), subcutaneous haematoma (5.0% vs. 0%), neck pain (5.0% vs. 0%), and dermatitis allergic (5.0% vs. 0%).

No adverse events resulted in death or led to drug discontinuation.

The incidences of serious adverse events were 5.0% (2 of 40 patients; pyrexia and respiratory disorder in 1 patient each, both aged ≥6 months to 2 years) in the rivaroxaban group and 16.7% (1 of 6 patients; headache/optic atrophy, aged ≥2 to <6 years) in the standard of care group. A causal relationship to the study drug was ruled out for all of the events.

In Study 14374, 1 Japanese patient (aged ≥6 months to <2 years) was assigned to the rivaroxaban group. The efficacy results from the patient included no “symptomatic recurrent VTE” or “asymptomatic deterioration of thrombotic burden” on imaging. The safety results from the patient comprised the following adverse events: upper respiratory tract infection and cardiac failure congestive. The latter event was reported as a serious adverse event. A causal relationship to the study drug was ruled out for both the events. The patient reported no adverse events resulting in death or leading to drug discontinuation.

7.1.5 Phase I/II study (Study 17618, CTD 5.3.5.2.1, November 2015 to December 2017)

An open-label, uncontrolled study was conducted at 9 sites in foreign countries to evaluate the pharmacokinetics, pharmacodynamics, safety, and efficacy of rivaroxaban in non-Japanese patients aged birth to <6 months with arterial or venous thrombosis (target sample size, 8 patients).

Key inclusion/exclusion criteria

Eligible patients were children aged birth to <6 months with confirmed symptomatic or asymptomatic arterial or venous thrombosis,[10)] who had received anticoagulant treatment (LMWH, fondaparinux sodium, or VKA) for ≥5 days.[11)] Other key inclusion criteria included (a) gestational age at birth of ≥37 weeks, (b) oral feeding, or nasogastric or gastric tube feeding for ≥10 days, and (c) body weight >2600 g. Patients were excluded from the study if they had serum creatinine level >1.5 times the ULN, platelet count $<100 \times 10^9$/L, or were scheduled to receive strong inhibitors of CYP3A4 and P-gp (fluconazole is allowed), or strong CYP3A4 inducers during the study treatment period.

Patients discontinued the prior anticoagulant treatment, and then started the 7-day treatment with oral rivaroxaban immediately before or during a meal, using the dosage regimens presented in Table 10.

All cases of VTE, "asymptomatic deterioration of thrombotic burden" on imaging, adverse events, deaths, and other cardiovascular events and bleeding events were adjudicated by the blinded, central and independent adjudication committee.

All 10 enrolled and treated patients (5 in the twice-daily dosing group and 5 in the three-times-daily dosing group) were included in the FAS and used as the safety analysis set. The FAS served as the population for efficacy analysis. One patient (the three-times-daily dosing group) discontinued the study treatment due to consent withdrawal.

Table 18 shows the efficacy results based on the incidences of "symptomatic recurrent VTE" and "asymptomatic deterioration of thrombotic burden" on imaging.

[10)] This study initially enrolled patients with catheter-related arterial or venous thrombosis. However, arterial or venous thrombosis attributable to other causes also requires anticoagulant therapy. Therefore, the study protocol was amended in May 2016 to enroll patients with catheter-related or non-catheter-related arterial or venous thrombosis.

[11)] This study initially recruited patients who had received anticoagulant therapy for ≥2 weeks. However, most neonates and infants received a shorter duration of anticoagulant therapy in clinical practice. Therefore, the study protocol was amended in May 2016 to enroll patients with ≥5 days of anticoagulant therapy.

Table 18. Incidences of "symptomatic recurrent VTE" and "asymptomatic deterioration of thrombotic burden" on imaging (FAS)

	Twice daily (N = 5)	Three times daily (N = 5)
Symptomatic recurrent VTE[a)]	0 (0)	0 (0)
Thrombotic burden assessment[b)]		
Normalized	80.0 (4/5)	25.0 (1/4)
Improved	20.0 (1/5)	50.0 (2/4)
No relevant change	0 (0/5)	25.0 (1/4)
Deteriorated	0 (0/5)	0 (0/4)
Not evaluable	0 (0/5)	0 (0/4)

a) % (n). The assessment period was the study treatment period plus 30 days after the last dose.
b) % (n /N). Patients who had evaluable image data, both at baseline and at the end of the study treatment period, were analyzed.

The primary safety outcome was the composite of "major bleeding[5)]" and "clinically relevant non-major bleeding[6)]." No treatment-emergent (until 2 days after the last dose) "major bleedings" or treatment-emergent "clinically relevant non-major bleedings" were reported.

Treatment-emergent adverse events were reported in 2 of 10 patients (vomiting in 1 patient in the twice-daily dosing group, atrial thrombosis in 1 patient in the three-times-daily dosing group). A causal relationship to the study drug was ruled out for both of the events.

No adverse events resulted in death or led to drug discontinuation.

A serious adverse event was reported in 1 of 10 patients (atrial thrombosis in 1 patient in the three-times-daily dosing group), for which a causal relationship to the study drug was ruled out.

7.2 Phase III study

7.2.1 Global phase III study (Study 14372, CTD 5.3.5.1.3, November 2014 to January 2019)

An open-label, randomized, parallel-group study was conducted at 109 sites in and outside of Japan to evaluate the efficacy and safety of rivaroxaban versus those of the standard of care (unfractionated heparin [UFH], LMWH, fondaparinux sodium, or VKA), in patients aged birth to <18 years with acute VTE (target sample size, ≥170 patients[12)] [≥80 patients aged ≥12 to <18 years, ≥30 patients aged ≥6 to <12 years, ≥20 patients aged ≥2 to ≤6 years, and ≥20 patients aged birth to <2 years including ≥12 patients aged birth to <6 months]).

Key inclusion/exclusion criteria

Eligible patients were children aged <18 years with confirmed VTE,[13)] who had received anticoagulant treatment (UFH, LMWH, or fondaparinux sodium)[14)] ("initial treatment") for ≥5 days and required anticoagulant therapy for ≥90 days after the start of the study treatment (or anticoagulant therapy for ≥30 days for children aged <2 years with catheter-related VTE). Patients were excluded from the study if they had eGFR

[12)] The target sample size was set as the minimum target sample size, taking into account the rarity of pediatric VTE. To increase the estimation accuracy in comparisons between rivaroxaban and the standard of care, as many patients as possible were to be enrolled in the study during the allowable study period (date of completion of [redacted] agreed with [redacted] as of [redacted]).
[13)] Lower extremity DVT, vena cava thrombosis, right atrial thrombosis, pulmonary embolism, upper extremity DVT, subclavian vein thrombosis, jugular vein thrombosis, cerebral vein or sinus thrombosis, mesenteric vein thrombosis, portal vein thrombosis, renal vein thrombosis, or catheter-related VTE
[14)] The doses were titrated according to the local guidelines, etc.

<30 mL/min/1.73 m^2 (or serum creatinine levels beyond the pre-specified 97.5th percentile for children aged <1 year, or serum creatinine levels ≥0.93 mg/dL for Japanese children aged ≥1 to <2 years), platelet count <50 × 10^9/L, or were scheduled to receive strong inhibitors of both CYP3A4 and P-gp, or strong CYP3A4 inducers during the study treatment period. The study excluded children aged birth to <6 months who had (a) gestational age at birth of <37 weeks, (b) oral feeding, or nasogastric or gastric tube feeding for <10 days, and (c) body weight <2600 g.

In the study, patients were enrolled using a stepwise approach based on age group (≥12 to <18 years, ≥6 to <12 years, ≥2 to <6 years, and <2 years)[15] and, at ≤9 days after the start of the initial treatment, they were allocated to receive rivaroxaban or the standard of care at a ratio of 2:1, with stratification by age group and baseline presentation of VTE.[16]

In the rivaroxaban group, patients discontinued the prior anticoagulant treatment, and then started treatment with oral rivaroxaban at the dosage regimens presented in Table 12. In the standard of care group, patients received UFH, LMWH, fondaparinux sodium, or VKA according to the local package inserts. The dose of VKA was titrated to achieve an international normalized ratio of prothrombin time (PT-INR) of 2.0 to 3.0 (2.0 to 2.5 for Japanese patients). In patients aged ≥2 years and patients <2 years with non-catheter-related VTE, the study drug was administered for 3 months (the main treatment period). After that, whether treatment should be continued was determined by the investigators every 3 months, with a maximum duration of study treatment of 12 months (the extended treatment periods). In patients aged <2 years with catheter-related VTE, the study drug was administered for 1 month (the main treatment period). After that, whether treatment should be continued was determined by the investigators every 1 month, with a maximum duration of study treatment of 3 months (the extended treatment periods). The study treatment was followed by a 30-day follow-up period, irrespective of the duration of treatment. The median duration of treatment (range) in patients aged ≥2 years and those aged <2 years with non-catheter-related VTE was 97 (6 to 385) days in the rivaroxaban group and 98 (1 to 378) days in the standard of care group, whereas that in patients aged <2 years with catheter-related VTE was 58 (3 to 182) days in the rivaroxaban group and 63 (24 to 126) days in the standard of care group.

[15] Based on the results from Studies 14373, 14374, and 17618, patients were enrolled in the study by age group (in the descending order of age) for which safety had been confirmed and the dosage regimen for rivaroxaban had been decided.
[16] Either (a) or (b) below:
a) Lower extremity DVT, vena cava thrombosis, upper extremity DVT, subclavian vein thrombosis, right atrial thrombosis, pulmonary embolism, or catheter-related VTE
b) Cerebral vein or sinus thrombosis, jugular vein thrombosis, mesenteric vein thrombosis, portal vein thrombosis, or renal vein thrombosis

Table 12. Dosage regimens in Study 14372 (reposted)

Dosage form	Body weight	Dose	Dosage regimen
Dry syrup	≥2.6 kg to <3 kg	0.8 mg	Three times daily During or within 30 minutes after breakfast, lunch, and supper (approximately 8 hours apart)
	≥3 kg to <4 kg	0.9 mg	
	≥4 kg to <5 kg	1.4 mg	
	≥5 kg to <7 kg	1.6 mg	
	≥7 kg to <8 kg	1.8 mg	
	≥8 kg to <9 kg	2.4 mg	
	≥9 kg to <10 kg	2.8 mg	
	≥10 kg to <12 kg	3.0 mg	
	≥12 kg to <20 kg	5.0 mg	Twice daily During or within 1 hour after breakfast and supper (approximately 12 hours apart)
Tablets or dry syrup	≥20 kg to <30 kg	5.0 mg	
	≥30 kg to <50 kg	15 mg	Once daily During or within 2 hours after breakfast
	≥50 kg	20 mg (15 mg for Japanese)	

The blinded, central and independent adjudication committee assessed all cases of VTE, "asymptomatic deterioration of thrombotic burden" on imaging, deaths, and other cardiovascular events and bleeding events. The imaging test procedure was standardized across the study sites through the distribution of an imaging manual to each study site, the provision of pre-study training to the investigators, and by other means. Asymptomatic thrombotic burden was categorized[17)] by the central and independent adjudication committee, according to the clear-cut definition of thrombus state.

(a) Results from the overall study population

All 500 randomized patients (335 patients in the rivaroxaban group, 165 patients in the standard of care group) were included in the FAS and used as the population for efficacy analysis. Of these 500 patients, 491 patients (329 patients, 162 patients) who received at least 1 dose of the study drug were included in the safety analysis set. A total of 487 patients (328 patients, 159 patients) completed the main treatment period,[18)] of whom 218 patients (149 patients, 69 patients) entered the first extended treatment period,[19)] and 179 patients (123 patients, 56 patients) completed the first extended treatment period. Of these 179 patients, 91 patients (62 patients, 29 patients) entered the second extended treatment period,[20)] and 84 patients (57 patients, 27 patients) completed the second extended treatment period. Of these 84 patients, 48 patients (31 patients, 17 patients) were then included in the third extended treatment period,[21)] and all of the patients completed the third extended treatment period. A total of 10 patients (7 patients, 3 patients) discontinued the study treatment during the main treatment period. The reasons for discontinuation in the main treatment period were consent withdrawal in 5 patients (3

[17)] Normalized: no residual thrombus observed
Improved: thrombus still present, but partly recanalized or involving less venous segments
No relevant change: not recanalized and similar in extent
Deteriorated: thrombus extended, or new venous segment involved
Not evaluable or unknown: no repeat imaging conducted, no evaluable image available, or repeat imaging conducted >7 days before or after discontinuation of the study treatment

[18)] Patients who have completed the study were defined as patients who had their last visit after the scheduled day of completion of study treatment or patients who had final safety data.

[19)] The first extended treatment period was 3 months after the end of the main treatment period in patients aged ≥2 year and patients aged <2 years with non-catheter-related VTE, and 1 month after the end of the main treatment period in patients aged <2 years with catheter-related VTE.

[20)] The second extended treatment period was 3 months after the end of the first extended treatment period in patients aged ≥2 year and patients aged <2 years with non-catheter-related VTE, and 1 month after the end of the first extended treatment period in patients aged <2 years with catheter-related VTE.

[21)] The third extended treatment period was 3 months after the end of the second extended treatment period in patients aged ≥2 year and patients aged <2 years with non-catheter-related VTE.

patients, 2 patients), death in 1 patient (1 patient, 0 patients), the discretion of the treating physician in 1 patient (1 patient, 0 patients), protocol deviation in 1 patient (1 patient, 0 patients), onset of symptomatic recurrent VTE in 1 patient (1 patient, 0 patients), and lost to follow-up in 1 patient (0 patients, 1 patient). A total of 39 patients (26 patients, 13 patients) discontinued the study treatment during the first extended treatment period. The reasons for discontinuation were the discretion of the treating physician in 24 patients (16 patients, 8 patients), adverse events in 4 patients (4 patients, 0 patients), consent withdrawal in 2 patients (0 patients, 2 patients), poor compliance in 2 patients (2 patients, 0 patients), protocol deviation in 1 patient (1 patient, 0 patients), recovery in 1 patient (1 patient, 0 patients), and others in 5 patients (2 patients, 3 patients). A total of 7 patients (5 patients, 2 patients) discontinued the study treatment during the second extended treatment period. The reasons for discontinuation were the discretion of the treating physician in 4 patients (3 patients, 1 patient), lost to follow-up in 2 patients (1 patient, 1 patient), and adverse events in 1 patient (1 patient, 0 patients). A total of 28 patients (15 patients, 13 patients) discontinued the study during the follow-up period. The reasons for discontinuation were consent withdrawal in 10 patients (5 patients, 5 patients), lost to follow-up in 8 patients, (4 patients, 4 patients), discretion of the treating physician in 3 patients (2 patients, 1 patient), visiting before the scheduled date in 2 patients (0 patients, 2 patients), death in 1 patient (1 patient, 0 patients), patient's personal reason in 1 patient (0 patients, 1 patient), and others in 3 patients (3 patients, 0 patients).

The FAS was composed of 276 patients aged ≥12 to <18 years (184 patients, 92 patients), 101 patients aged ≥6 to <12 years (67 patients, 34 patients), 69 patients aged ≥2 to <6 years (47 patients, 22 patients), 30 patients aged ≥6 months to <2 years (21 patients, 9 patients), and 24 patients aged <6 months (16 patients, 8 patients).

Table 19 presents the incidence of "symptomatic recurrent VTE" during the main treatment period, which was the primary efficacy endpoint, while Figure 3 shows the Kaplan-Meier curves for the incidence of "symptomatic recurrent VTE" during the main treatment period. "Symptomatic recurrent VTE" during the extended treatment periods was reported in 0 of 149 patients in the rivaroxaban group and 1 of 69 patients in the standard of care group during the first extended treatment period, 1 of 62 patients and 1 of 29 patients, respectively during the second extended treatment period, and 0 of 31 patients and 0 of 17 patients, respectively during the third extended treatment period.

Table 19. Incidences of “symptomatic recurrent VTE” (main treatment period, FAS)

	Rivaroxaban	Standard of care	Hazard ratio [95%CI][a)]
Symptomatic recurrent VTE	1.2 (4/335)	3.0 (5/165)	0.40 [0.11, 1.41]
Location of index event			
Lower extremity	1.8 (2/112)	5.7 (3/53)	-
Lung	2.0 (1/49)	3.2 (1/31)	-
Upper extremity	2.6 (1/38)	0 (0/20)	-
Cerebral vein or sinus	0 (0/74)	2.3 (1/43)	-
Relation between the index event and catheter			
Cerebral vein and sinus thrombosis (CVST)	0 (0/74)	2.3 (1/43)	-
Non-catheter-related VTE (excluding CVST)	2.3 (4/171)	4.7 (4/85)	-
Catheter-related VTE	0 (0/90)	0 (0/37)	-

% (n/N)

a) Cox proportional hazards model stratified by index event (CVST vs. non-catheter-related VTE vs. catheter-related VTE)

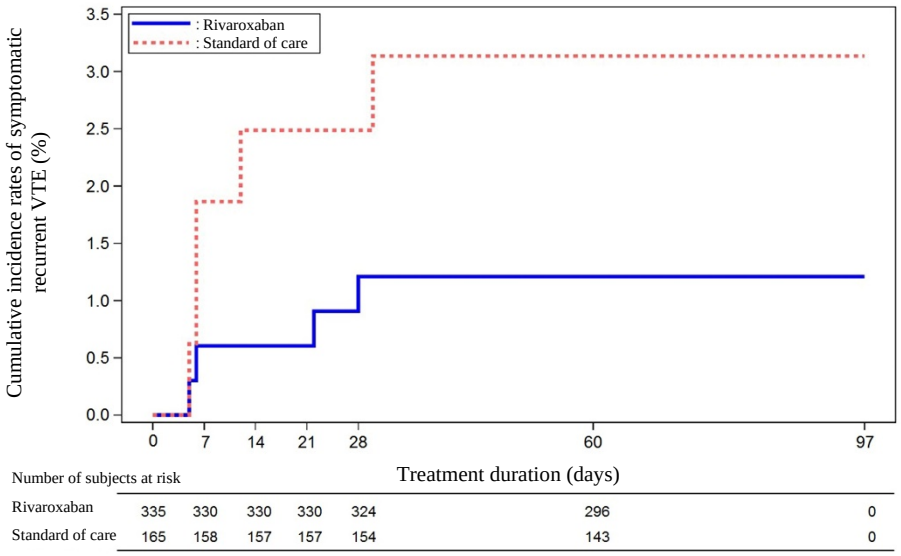

Figure 3. Cumulative incidence rates of “symptomatic recurrent VTE” (Kaplan-Meier curves; main treatment period, FAS)

Table 20 presents the incidences of the composite of “symptomatic recurrent VTE” and “asymptomatic deterioration of thrombotic burden” on imaging during the main treatment period, a secondary efficacy endpoint.

Table 20. Incidences of “symptomatic recurrent VTE” or “asymptomatic deterioration of thrombotic burden” on imaging (main treatment period, FAS)

	Rivaroxaban (N = 335)	Standard of care (N = 165)
“Symptomatic recurrent VTE” or “asymptomatic deterioration of thrombotic burden”	1.5 (5)	3.6 (6)
Thrombotic burden assessment[a)]		
Normalized	38.2 (128)	26.1 (43)
Improved	38.5 (129)	45.5 (75)
No relevant change	4.8 (16)	7.9 (13)
Deteriorated	0.3 (1)	0.6 (1)
Not evaluable or unknown	17.0 (57)	17.0 (28)

% (n)

a) Data from patients with no symptomatic recurrent VTE who had evaluable imaging data, both at baseline and at the end of the main treatment period

The primary safety outcome of the study was the composite of "major bleeding[5)]" and "clinically relevant non-major bleeding.[6)]" Table 21 presents the incidence of the composite of treatment-emergent[22)] "major bleeding" and "clinically relevant non-major bleeding" during the main treatment period, by bleeding site. The incidences of treatment-emergent "major bleeding" or "clinically relevant non-major bleeding" during the entire treatment period (the main treatment period plus the extended treatment periods) were 4.0% (13 of 329 patients) in the rivaroxaban group and 2.5% (4 of 162 patients) in the standard of care group.

Table 21. Incidences of bleeding events by bleeding category and site (main treatment period, safety analysis set)

	Rivaroxaban (N = 329)	Standard of care (N = 162)
Any bleeding event	36.2 (119)	27.8 (45)
"Major bleeding" or "clinically relevant non-major bleeding"	3.0 (10)	1.9 (3)
Major bleeding	0 (0)	1.2 (2)
Intracranial	0 (0)	0.6 (1)
Thorax	0 (0)	0.6 (1)
Clinically relevant non-major bleeding	3.0 (10)	0.6 (1)
Gastrointestinal tract	1.2 (4)	0 (0)
Genital tract	0.3 (1)	0 (0)
Injection site	0.3 (1)	0 (0)
Nasal cavity	0.6 (2)	0.6 (1)
Oral cavity	0.3 (1)	0 (0)
Urinary tract	0.3 (1)	0 (0)

% (n)

The incidences of treatment-emergent adverse events during the main treatment period were 83.3% (274 of 329 patients) in the rivaroxaban group and 75.3% (122 of 162 patients) in the standard of care group. Table 22 shows treatment-emergent adverse events reported in ≥4% of patients in either treatment group. The incidences of treatment-emergent adverse events during the entire treatment period (the main treatment period plus the extended treatment periods) were 86.9% (286 of 329 patients) in the rivaroxaban group and 79.0% (128 of 162 patients) in the standard of care group.

[22)] Adverse events occurring between randomization and the scheduled final dose of the study drug (until 2 days after the last dose if the study treatment was discontinued)

Table 22. Adverse events reported in ≥4% of patients in either treatment group (main treatment period, safety analysis set)

	Rivaroxaban (N = 329)	Standard of care (N = 162)
Headache	17.0 (56)	14.8 (24)
Epistaxis	11.2 (37)	11.1 (18)
Vomiting	10.6 (35)	8.0 (13)
Pyrexia	10.3 (34)	8.0 (13)
Nasopharyngitis	7.6 (25)	4.9 (8)
Diarrhoea	7.0 (23)	5.6 (9)
Pain in extremity	7.0 (23)	4.3 (7)
Menorrhagia	7.0 (23)	3.1 (5)
Nausea	6.4 (21)	4.3 (7)
Fatigue	6.1 (20)	3.7 (6)
Abdominal pain	5.5 (18)	5.6 (9)
Cough	4.9 (16)	6.2 (10)
Chest pain	4.6 (15)	3.7 (6)
Contusion	4.3 (14)	5.6 (9)
Rash	4.3 (14)	2.5 (4)
Constipation	2.4 (8)	6.8 (11)
ALT increased	2.1 (7)	4.3 (7)
Injection site bruising	0 (0)	4.3 (7)

% (n)

During the main treatment period, an adverse event resulting in death occurred in 0.3% (1 of 329) of patients in the rivaroxaban group (myxofibrosarcoma), for which a causal relationship to the study drug was ruled out. During the extended treatment periods, an adverse event resulting in death occurred in 0.3% (1 of 329) of patients in the rivaroxaban group (respiratory distress), for which a causal relationship to the study drug was ruled out.

The incidences of serious adverse events during the main treatment period were 21.6% (71 of 329 patients) in the rivaroxaban group and 19.8% (32 of 162 patients) in the standard of care group. Serious adverse events reported in ≥1% of patients in either treatment group were febrile neutropenia (2.1% in the rivaroxaban group, 0.6% in the standard of care group), vomiting (1.8%, 0%), pyrexia (1.2%, 1.2%), headache (0.9%, 1.9%), and seizure (0.3%, 1.2%). A causal relationship to the study drug could not be ruled out in 2.1% (7 of 329) of patients in the rivaroxaban group (retinal haemorrhage, haemorrhagic enterocolitis, gastric haemorrhage, procedural haemorrhage, urinary bladder haemorrhage, urinary retention, and haemorrhage in 1 patient each) and 1.2% (2 of 162) of patients in the standard of care group (subdural haemorrhage and oxygen saturation decreased in 1 patient each). The incidence of serious adverse events during the extended treatment periods were 4.0% (13 of 329 patients) in the rivaroxaban group and 3.7% (6 of 162 patients) in the standard of care group. The serious adverse event reported in ≥2 patients in either treatment group was pyrexia (0.6% in the rivaroxaban group, 0% in the standard of care group). A causal relationship to the study drug could not be ruled out in 1 of 162 patients in the standard of care group (haematoma).

During the main treatment period, adverse events led to treatment discontinuation in 3.3% (11 of 329) of patients in the rivaroxaban group (vomiting and epilepsy, thrombocytopenia and haematuria, hepatic function abnormal and urinary retention, urinary bladder haemorrhage and pulmonary haemorrhage, low cardiac output syndrome, large intestinal haemorrhage, procedural haemorrhage, pain in extremity, headache, haemorrhage, and vomiting in 1 patient each) and 1.9% (3 of 162) of patients in the standard of care group (injection site

haematoma and menorrhagia, subcutaneous haematoma, and subdural haemorrhage in 1 patient each). During the extended treatment period, adverse events led to treatment discontinuation in 1.2% (4 of 329 patients) of patients in the rivaroxaban group (anaemia and haemorrhagic ovarian cyst, nephropathy, rash, and mastoidectomy 1 patient each).

(b) Results from the Japanese subpopulation

All 6 randomized Japanese patients (4 in the rivaroxaban group, 2 in the standard of care group) were included in the FAS and used as the safety analysis set. The FAS in the Japanese subpopulation was composed of 1 patient aged ≥2 to <6 years (1 patient, 0 patients), 3 patients aged ≥6 months to <2 years (2 patients, 1 patient), and 2 patients aged <6 months (1 patient, 1 patient). All of the 6 patients completed the main treatment period. Of these patients, 3 patients aged <2 years with catheter-related VTE (1 patient, 2 patients) entered the first extended treatment period and completed the period, and 2 of these 3 patients (0 patients, 2 patients) entered the second extended treatment period and completed the period.

Table 23 presents efficacy results from the Japanese subpopulation. No "symptomatic recurrent VTE" or "asymptomatic deterioration of thrombotic burden" on imaging was reported by Japanese patients in either the rivaroxaban group or the standard of care group.

Table 23. Incidences of efficacy endpoints in the Japanese subpopulation (main treatment period, FAS)

	Rivaroxaban (N = 4)	Standard of care (N = 2)
Symptomatic recurrent VTE	0 (0)	0 (0)
Thrombotic burden assessment		
Normalized	25.0 (1)	0 (0)
Improved	50.0 (2)	0 (0)
No relevant change	25.0 (1)	50.0 (1)
Deteriorated	0 (0)	0 (0)
Not evaluable or unknown	0 (0)	50.0 (1)

% (n)

The safety analysis revealed no treatment-emergent "major bleeding" or "clinically relevant non-major bleeding" throughout the entire treatment period.

The incidences of treatment-emergent adverse events during the main treatment period were 75.0% (3 of 4 patients) in the rivaroxaban group (rectal haemorrhage, constipation, vomiting, and pyrexia in 1 patient; mouth haemorrhage, gastroenteritis, arthropod bite, upper respiratory tract inflammation, and skin abrasion in 1 patient; and constipation in 1 patient) and 100% (2 of 2 patients) in the standard of care group (atrial tachycardia, cholangitis, and eczema in 1 patient; and pyrexia and nasopharyngitis in 1 patient). A causal relationship to the study drug could not be ruled out for the mouth haemorrhage in the rivaroxaban group. No adverse events were reported during the extended treatment periods.

No adverse events resulting in death occurred in Japanese patients throughout the entire treatment period.

During the main treatment period, 1 Japanese patient in the standard of care group reported a serious adverse event (atrial tachycardia), for which a causal relationship to the study drug was ruled out.

During the main treatment, 1 patient in the rivaroxaban group discontinued the study treatment, due to an adverse event (vomiting) for which a causal relationship to the study drug was ruled out.

7.R Outline of the review conducted by PMDA

7.R.1 Clinical positioning

PMDA asked the applicant to explain the clinical positioning of rivaroxaban in the treatment of pediatric VTE, taking into account the association with treatment for adult VTE and existing drugs for the treatment of pediatric VTE.

The applicant's explanation:

Rivaroxaban has been approved for the treatment of VTE (DVT and PE) and the prevention of recurrent VTE in adults. The 3 factors of Vircho's triad (venous endothelial dysfunction, hypercoagulability, and stasis of flow) are associated with the pathogenesis of thrombosis, with no differences in the pathophysiology of thrombogenesis between children and adults. Children, as compared with adults, are considered to generally have a decreased risk of VTE, due to the lower accumulation of vascular disorders and the lower frequency of exposure to the risk factors for acquired thrombosis, including oral contraceptives, smoking, and malignancies (*Jpn J Thromb Hemost.* 2004;15: 349-54). The proportion of secondary VTE to all VTE events is higher in children than in adults (*Blood Rev.* 2010;24:63-8, *Jpn J Thromb Hemost.* 2008;22:215-25, *Blood.* 1994;83:1251-7). The potential etiology of pediatric VTE is thrombotic protein abnormalities resulting from serious underlying illnesses (e.g., cancers, congenital heart diseases, severe infections, nephrosis) or genetic abnormalities, combined with acquired risk factors (e.g., asphyxia, dehydration, prolonged bed rest, central venous catheterization, medications) (*Jpn J Thromb Hemost.* 2004;15:349-54). Furthermore, children have a smaller lumen diameter than adults, and are thought to be more prone to blood flow changes due to lumen narrowing by catheter placement. Catheterization for the sustained administration of fluids, nutrients, or medications in children with serious illnesses or conditions is thus the most common cause of thrombotic complication, which frequently affects the upper extremities (*Thromb Res.* 2006;118:3-12). These facts indicate that while there are some differences in risk factors and commonly affected sites between these populations, children and adults share the same pathophysiology of thrombogenesis and VTE pathology, in which the formation of thromboemboli impairs blood flow, resulting in organ dysfunction. As with adult VTE, the aim of treatment for pediatric VTE is to treat symptoms that are attributable to blood flow impairment, prevent the development and recurrence of thrombosis, and reduce the risk of post-thrombotic syndrome.

Outside of Japan, dalteparin, an LMWH preparation, has been approved for the prevention of recurrent VTE in children aged ≥1 month. The Antithrombotic Therapy in Neonates and Children: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-based Clinical Practice Guidelines (*Chest.* 2012;141:e737s-e801s) (hereinafter, referred to as "the ACCP guidelines for antithrombotic therapy in neonates and children") recommend initial treatment with UFH or LMWH for ≥5 days as the

standard of care in children with primary VTE (regardless of association with a central venous access device) (Grade 1B). The maintenance treatment following the initial treatment, recommended by the guidelines was continued treatment with LMWH or UFH, or oral anticoagulant therapy with VKAs (Grade 1B). At the same time, the guidelines advise that the long-term use of UFH should be avoided if alternatives to UFH are available, taking into account the risk of heparin-induced thrombocytopenia, bone effects, etc. (Grade 2C). The guidelines-recommended duration of ongoing anticoagulant therapy is 6 to 12 months in children with idiopathic VTE, 3 months in children with secondary VTE in whom the risk factor has resolved, or >3 months until the risk factor has resolved in children who have ongoing or reversible risk factors, such as active nephrotic syndrome or ongoing L-asparaginase therapy (Grade 2C). In children with recurrent idiopathic VTE, indefinite treatment with VKAs is recommended (Grade 1A). The American Society of Hematology 2018 Guidelines for Management of VTE: Treatment of Pediatric VTE (*Blood.* 2018;2:3292-316) (hereinafter, referred to as "the ASH guidelines for treatment of pediatric VTE") recommend the use of LMWH or VKAs in children with symptomatic DVT or PE, but also advise that the treatment should be determined depending on the patient's conditions and preferences, health service resources, and other factors.

In Japan, no guidelines provide specific recommendations for the treatment of pediatric VTE. The Guidelines for Drug Therapy in Pediatric Patients with Cardiovascular Diseases (the Japanese Circulation Society Joint Working Groups for Guidelines for Diagnosis and Treatment of Cardiovascular Diseases 2012;89-271) states that anticoagulant therapy for cardiovascular diseases in children has been chosen independently by each medical institution, based on limited information and experience, due to minimal available evidence about such treatment. The JCS 2018 Guideline on the Clinical Examinations for Decision Making of Diagnosis and Drug therapy in Pediatric Patients with Congenital Heart Disease and Cardiovascular Disorder (The Japanese Circulation Society) provides recommendations for antiplatelet and anticoagulant agents, which are based on Japanese and overseas treatment guidelines for adult VTE and overseas guidelines for pediatric thrombosis, and refers to UFH along with body weight-adjusted dosage regimens, as a medication that is commonly used for pediatric treatment. Fondaparinux sodium, which is approved for the treatment of PE and DVT in adults, has no established recommended dosage regimen in children. LMWH has not been approved for the treatment of VTE in either children or adults. In Japan, UFH is thus only the drug that is recommended for the initial treatment of pediatric VTE in clinical practice. Existing maintenance treatments for pediatric VTE include the continuous intravenous infusion of UFH in an inpatient setting and the use of warfarin, a VKA. Warfarin is an oral anticoagulant drug that is extensively used in the treatment and prevention of thromboembolism. The approvals for warfarin include a maintenance dosage for children (approved in February 2011) and a granule formulation that is applicable in children. However, UFH therapy requires continuous intravenous infusion. Warfarin therapy is prone to food effects and causes interactions with a wide range of drugs, and its efficacy in children changes depending on various factors such as the intake of milk fortified with vitamin K, breast feeding, and vitamin K deficiency due to impaired eating. Furthermore, treatment with UFH or warfarin involves invasive aPTT or PT-INR monitoring. Accordingly, for anticoagulant therapy in children, a drug has been sought that reduces the duration of parenteral anticoagulant treatment and requires no coagulation monitoring.

Study 14372 in pediatric patients with VTE demonstrated the efficacy and safety rivaroxaban that were similar to those of the standard of care after initial treatment. In addition, the results of Study 14372 were similar to those of a clinical study of rivaroxaban in adult patients with VTE [see Section "7.R.3.2 Efficacy evaluation in Study 14372"]. These facts indicate that rivaroxaban is expected to become a first-line maintenance treatment aiming at treating VTE and preventing recurrent VTE in pediatric patients who have completed initial treatment, irrespective of age, body weight, VTE site, whether or not it is catheter-related, and risk factors. However, in cases where there are concerns regarding a bleeding risk associated with invasive procedures during maintenance treatment with rivaroxaban, the temporary use of UFH should be considered. In addition, in cases where comorbidities are treated with drugs that may cause drug interactions with rivaroxaban, the use of warfarin may be considered.

PMDA's view:

Pediatric VTE is characterized by the fact that the proportion of secondary VTE to all VTE events is higher in children than in adults, and many cases of VTE occur in the upper extremities due to the use of central venous catheter for the treatment of underlying diseases. However, pediatric VTE and adult VTE share the same pathology, in which the formation of thromboemboli impairs blood flow, possibly resulting in serious outcomes, despite differences in risk factors and commonly affected sites. As the applicant has explained, the strategy for the treatment of VTE does not substantially differ between children and adults. In Japan, where no specific guidelines exist, pediatric VTE has been treated in clinical practice according to Japanese and overseas treatment guidelines for adult VTE and overseas guidelines for pediatric thrombosis, as stated by the recommendations for antiplatelet and anticoagulant agents by the JCS 2018 Guideline on the Clinical Examinations for Decision Making of Diagnosis and Drug therapy in Pediatric Patients with Congenital Heart Disease and Cardiovascular Disorder. In the maintenance treatment of VTE, warfarin is only the oral anticoagulant approved for pediatric use.

The results from Study 14372 in pediatric patients with VTE demonstrated the efficacy of rivaroxaban that is similar to that of the standard of care and the acceptable safety of rivaroxaban [see Sections "7.R.3 Efficacy" and "7.R.4 Safety"]. In view of this fact, it is meaningful to make rivaroxaban available for clinical use in the treatment of pediatric VTE and the prevention of recurrent VTE, because it will offer a new option of drugs used in the maintenance treatment for pediatric patients who have completed initial parenteral anticoagulation. However, rivaroxaban therapy requires safety management, with attention to the facts that no anticoagulation parameters that are to be monitored during rivaroxaban therapy have been established, and that no agents which neutralize the anticoagulant effect of rivaroxaban are currently available. As with warfarin, rivaroxaban is expected to become an option for maintenance treatment for pediatric patients with VTE who have completed initial parenteral anticoagulation. At the same time, due to the above-mentioned drawbacks of rivaroxaban therapy, along with the very limited available data on the efficacy and safety of rivaroxaban in Japanese children in Study 14372, physicians should be advised to make a decision on the initiation of rivaroxaban therapy in children, as in the case of adults, after carefully assessing the bleeding risks, etc. of each patient, and balancing the potential benefits with the possible risks.

7.R.2 Differences in intrinsic and extrinsic ethnic factors between Japanese and non-Japanese patients, and the appropriateness of Japan's participation in the global clinical study

PMDA asked the applicant to explain the differences in intrinsic and extrinsic ethnic factors, including health service resources available for the treatment of pediatric VTE among the countries/regions participating in Study 14372, and the appropriateness of the participation of Japan in the study.

The applicant's explanation:

Intrinsic ethnic factors

Due to the limited epidemiological data on pediatric VTE available both in and outside of Japan, drawing a definite conclusion regarding the difference in the morbidity of pediatric VTE is difficult. However, the morbidity of pediatric VTE is low both in and outside of Japan, with no substantial difference between the regions (*Jpn J Obset Gynecol NeonatalHematil.* 2012; 21:5-13, *Blood.* 1994;83:1251-7, etc). The hereditary thrombophilias in Caucasians, such as the factor V Leiden mutation and prothrombin-gene mutation, are not found in Asians, and the leading causes of thrombosis in Japanese are mutations relating to protein S or protein C deficiency. The frequencies of genetic mutations affecting the coagulation system differ among ethnicities *(Pediatr Int.* 2013;55:267-71). Nevertheless, the differences in the hereditary thrombophilias among ethnicities are unlikely to affect the recurrence of VTE in patients receiving an anticoagulant therapy. A phase III study in non-Japanese adult patients with DVT or PT (Studies 11702-DVT and 11702-PE; hereinafter, collectively called "Study 11702") and Study 14372 in pediatric patients with VTE revealed that hereditary thrombophilias did not clearly affect the prevention of "symptomatic recurrent VTE" during rivaroxaban therapy. Idiopathic VTE is uncommon in children. A majority of pediatric patients with VTE have risk factors, including serious underlying diseases (e.g., malignancies) and external risk factors such as the use of central venous catheter. There appears to be no substantial differences in the risk factors between Japanese and non-Japanese patients. The pharmacokinetics of rivaroxaban administered to adults at a fixed dose differ between Japanese and non-Japanese (see the data submitted for the initial application for "Xarelto Tablets 10 mg and Xarelto Tablets 15 mg"). However, no clear differences between Japanese and non-Japanese patients were found in the pharmacokinetics of rivaroxaban administered to children at body weight-adjusted doses.

Extrinsic ethnic factors

Outside of Japan, the standard of care for pediatric VTE is chosen between parenteral anticoagulants, such as LMWH, and VKAs, depending on the patient's conditions and preferences, health service resources, and other factors, whereas in Japan, no established guidance, such as academic guidelines for the treatment of pediatric VTE exists, and patients are treated according to the guidance prepared at each medical institution. In Japanese clinical practice, UFH is the only available initial treatment for pediatric VTE. All of the 6 Japanese patients participating in Study 14372 received initial treatment with UFH. In maintenance treatment for pediatric VTE, VKAs, including warfarin, which is widely used throughout the world, are commonly selected. Although the type of drugs used in the initial treatment of VTE varied between in and outside of Japan in Study 14372, the results of a subgroup analysis by the type of initial parenteral anticoagulant (UFH, LMWH, or fondaparinux sodium [some patients used multiple drugs]) revealed no substantial difference in the efficacy or safety of rivaroxaban (Table 24). In the standard of care group, anticoagulants were administered at the doses

recommended for the treatment of VTE by the local package inserts or relevant guidelines. For example, the dosage regimen of warfarin was adjusted to achieve an international normalized ratio (INR) of 2.0 to 3.0 outside Japan, or 2.0 to 2.5 in Japan.

Table 24. Efficacy endpoint results and the incidences of bleeding events by the type of initial parenteral anticoagulant (Study 14372, main treatment period, FAS for efficacy evaluation, safety analysis set for safety evaluation)

	Rivaroxaban			Standard of care		
Type of initial parenteral anticoagulant	UFH	LMWH	Fondaparinux sodium	UFH	LMWH	Fondaparinux sodium
Symptomatic recurrent VTE	2.5 (2/79)	1.3 (4/303)	0 (0/5)	5.1 (2/39)	3.3 (5/152)	0 (0/3)
"Symptomatic recurrent VTE" or "asymptomatic deterioration of thrombotic burden"	2.5 (2/79)	1.7 (5/303)	0 (0/5)	5.1 (2/39)	3.9 (6/152)	0 (0/3)
Thrombotic burden assessment						
Normalized	29.1 (23/79)	38.6 (117/303)	20.0 (1/5)	25.6 (10/39)	28.3 (43/152)	0 (0/3)
Improved	46.8 (37/79)	38.6 (117/303)	40.0 (2/5)	51.3 (20/39)	45.4 (69/152)	0 (0/3)
No relevant change	2.5 (2/79)	4.6 (14/303)	0 (0/5)	10.3 (4/39)	6.6 (10/152)	33.3 (1/3)
Deteriorated	0 (0/79)	0.3 (1/303)	0 (0/5)	0 (0/39)	0.7 (1/152)	0 (0/3)
Not evaluable or unknown	19.0 (15/79)	16.5 (50/303)	40.0 (2/5)	7.7 (3/39)	15.8 (24/152)	66.7 (2/3)
Any bleeding event	33.3 (26/78)	35.6 (106/298)	60.0 (3/5)	33.3 (13/39)	28.7 (43/150)	50.0 (1/2)
"Major bleeding" or "clinically relevant bleeding"	5.1 (4/78)	2.7 (8/298)	0 (0/5)	2.6 (1/39)	2.0 (3/150)	0 (0/2)
Major bleeding	0 (0/78)	0 (0/298)	0 (0/5)	2.6 (1/39)	1.3 (2/150)	0 (0/2)
Clinically relevant bleeding	5.1 (4/78)	2.7 (8/298)	0 (0/5)	0 (0/39)	0.7 (1/150)	0 (0/2)

% (n/N)

As noted above, some differences in ethnic factors, such as hereditary thrombophilias relating to the development of VTE, are found between Japanese and non-Japanese patients. However, these differences are unlikely to affect the evaluation of the efficacy or safety of rivaroxaban. In addition, there are no substantial differences in the strategy for the maintenance treatment of pediatric VTE (i.e., the optimal intensity of anticoagulant treatment must be continued) between in and outside of Japan. In view of these facts, the participation of Japan in Study 14372, in which pediatric patients with VTE were randomized to receive rivaroxaban or standard of care, was appropriate. Furthermore, due to the rarity of pediatric VTE, it was infeasible to conduct a clinical study solely in Japan to evaluate the efficacy and safety of rivaroxaban in the treatment of VTE. This also justifies evaluation of the efficacy and safety of rivaroxaban in Japanese pediatric patients participating in the global clinical study.

PMDA's view:

According to the applicant's explanation, no differences in intrinsic ethnic factors between Japanese and non-Japanese pediatric patients affect the evaluation of the efficacy of rivaroxaban. For extrinsic ethnic factors, the type of anticoagulants used for initial or maintenance treatment for VTE had been assumed to differ across geographic regions, but no sufficient information on the possible impact of these differences in the type of anticoagulants on the efficacy or safety evaluation of rivaroxaban were available prior to the study. Nevertheless, the participation of Japanese pediatric patients with VTE in Study 14372 was appropriate for the following reasons: (a) In Study 14372, standard treatments selected according to the local treatment guidelines were used as the initial treatment for all participants, or the maintenance treatment in the standard of care group;

and, (b) a subgroup analysis in the overall study population of Study 14372 revealed that differences in the type of initial parenteral anticoagulant were unlikely to have a substantial impact on evaluation of the efficacy of rivaroxaban. Although there were differences in some patient characteristics, such as age and the type of index events (CVST, non-catheter-related VTE, or catheter-related VTE) between the overall study population and the Japanese subpopulation of Study 14372, these differences were unlikely to substantially affect evaluation of the efficacy of rivaroxaban [see Section "7.R.3.2 Efficacy evaluation in Study 14372"]. Based on the above, PMDA has concluded that the efficacy of rivaroxaban in Japanese pediatric patients can be evaluated based on the results from the overall population of Study 14372. However, due to the small number of Japanese patients enrolled in Study 14372, the present review primarily assesses the results from the overall study population, and then confirms results from individual Japanese patients in as much detail as possible, to discuss the efficacy and safety of rivaroxaban in Japanese pediatric patients.

7.R.3 Efficacy

7.R.3.1 Development program for treatment of pediatric VTE

The applicant's explanation about the clinical development program of rivaroxaban for the treatment of pediatric VTE:

The clinical development program of rivaroxaban for the treatment of pediatric VTE was planned based on the results from a phase III study in non-Japanese adult patients with DVT or PE (Study 11702), which demonstrated a benefit-risk balance of rivaroxaban that was non-inferior to that of standard of care. Due to the rarity of VTE in children and the limited number of pediatric patients with VTE (*J Pediatr.* 2011;159:663-9, *J Pediatr.* 2001;139:676-81, etc.), conducting a large-scale non-inferiority study was deemed infeasible. Pediatric VTE shares the same pathophysiology of thrombogenesis with adult VTE, although the risk factors for VTE and the most common sites of VTE differ between adults and children. Therefore, the development program was based on the premise that similar effects in pediatric and adult patients for the treatment of VTE is expected to be achieved by targeting rivaroxaban exposure in pediatric patients similar to that demonstrated to be effective in adult patients. The program was thus designed to establish the dosage regimens for children by age group, and to confirm that rivaroxaban had efficacy and safety in pediatric patients similar to those established in adult patients, by comparing the efficacy and safety of rivaroxaban with those of the standard of care in pediatric patients with VTE, on a feasible scale.

(a) Design of Study 14372

PMDA asked the applicant to explain the rationale for and the appropriateness of conducting Study 14372 as an open-label study.

The applicant's explanation:

Since the available anticoagulants for pediatric VTE differed among the countries/regions participating in Study 14372, standard of care was selected for the control group. In the standard of care group, the use of anticoagulants that are approved in individual countries/regions, as well as anticoagulants used widely throughout the world (VKAs and LMWH), was allowed. Because the procedure for coagulation monitoring varies depending on the type of anticoagulant, the use of a double-blind design in Study 14372 was considered

infeasible, and an open-label design was selected. To minimize information bias associated with an open-label design, the blinded, central and independent adjudication committee assessed all of the index events and all of the "symptomatic recurrent VTEs," "asymptomatic deterioration of thrombotic burden" on imaging, bleeding events, other cardiovascular events, and deaths that occurred during the study treatment period or within 30 days after the last dose of the study drug.

PMDA asked the applicant to explain the appropriateness of "symptomatic recurrent VTE" during the main treatment period selected as the primary efficacy endpoint in Study 14372, as well as the rationale for setting the main treatment period.

The applicant's explanation:
The objectives of Study 14372 were to find body weight-adjusted dosage regimens, thereby demonstrating that the efficacy and safety of rivaroxaban in pediatric patients with VTE are similar to those established in adult patients with VTE. "Symptomatic recurrent VTE" was selected as the primary endpoint of Study 14372, as with the case of the foreign phase III study in adult patients with DVT or PE (Study 11702). The main treatment period was defined as 3 months, because: (i) the duration of anticoagulant treatment recommended by the ACCP guidelines for antithrombotic therapy in neonates and children is ≥3 months in children with VTE who have ongoing risk factors for thrombosis, 6 to 12 months in children with idiopathic VTE, and 6 weeks to 3 months in children with catheter-related VTE; and, (ii) the minimum treatment duration in Study 11702, the study to be compared with Study 14732, was 3 months. In children aged <2 years with catheter-related VTE, the main treatment period was defined as 1 month. In addition, after completion of the main treatment period, continued treatment was allowed at the discretion of the investigator, in view of the results of a retrospective study in pediatric patients aged <2 years with VTE conducted at 12 sites in North America, Europe, and Israel (*Thromb J*. 2018;16:29). The study showed that 17% (8 of 46) of patients aged ≥6 months to <2 years and 24% (36 of 153) of patients aged <6 months received anticoagulation of a shorter duration than the guideline-recommended treatment duration (6 months). Based on the above, "symptomatic recurrent VTE" selected as the primary efficacy endpoint for Study 14372 was appropriate.

(b) Comparability with a clinical study in adult patients with VTE

The applicant's explanation about comparability with the results from a clinical study in adult patients with VTE:
VTE is uncommon in children compared with adults. An overseas study has reported that the annual incidence of pediatric VTE is estimated to be 20 to 100 times lower than that of adult VTE *(Arterioscler Thromb Vasc Biol*. 2014;34:2363-71). However, the incidence of "symptomatic recurrent VTE" after the development of an index event in the standard of care group was 3.0% (5 of 165 patients) in Study 14372, compared with 2.0% (82 of 4131 patients) in Study 11702, with no substantial difference between the studies. Although risk factors for VTE and the most common sites of VTE differ between children and adults, subgroup analyses of the efficacy endpoints (e.g., "symptomatic recurrent VTE," thrombosis burden assessment on imaging, etc.) by risk factor and the type (Table 25) or location of the index event (deep vein in a lower extremity, caval vein,

portal vein, renal vein, the right atrium, lung, deep vein in an upper extremity, jugular vein, and cerebral vein or sinuses) in Study 14372 revealed that these factors were unlikely to affect the efficacy of rivaroxaban.

Table 25. Incidences of efficacy endpoints by type of index event and risk factor for VTE (main treatment period, FAS)

	Rivaroxaban (N = 335)			Standard of care (N = 165)		
	CVST (N = 74)	Non-catheter-related VTE (N = 171)	Catheter-related VTE (N = 90)	CVST (N = 43)	Non-catheter-related VTE (N = 85)	Catheter-related VTE (N = 37)
Symptomatic recurrent VTE	0 (0)	2.3 (4)	0 (0)	2.3 (1)	4.7 (4)	0 (0)
"Symptomatic recurrent VTE" or "asymptomatic deterioration of thrombotic burden"	0 (0)	2.3 (4)	1.1 (1)	4.7 (2)	4.7 (4)	0 (0)
Thrombotic burden assessment						
Normalized	24.3 (18)	39.8 (68)	46.7 (42)	14.0 (6)	25.9 (22)	40.5 (15)
Improved	52.7 (39)	37.4 (64)	28.9 (26)	55.8 (24)	44.7 (38)	35.1 (13)
No relevant change	6.8 (5)	5.3 (9)	2.2 (2)	9.3 (4)	4.7 (4)	13.5 (5)
Deteriorated	0 (0)	0 (0)	1.1 (1)	2.3 (1)	0 (0)	0 (0)
Not evaluable or unknown	16.2 (12)	15.2 (26)	21.1 (19)	16.3 (7)	20.0 (17)	10.8 (4)

	Rivaroxaban (N = 335)				Standard of care (N = 165)			
		With risk factors				With risk factors		
	Without risk factors (N = 31)	Transient (N = 151)	Persistent (N = 62)	Transient and persistent (N = 90)	Without risk factors (N = 25)	Transient (N = 85)	Persistent (N = 25)	Transient and persistent (N = 25)
Symptomatic recurrent VTE	3.2 (1)	0 (0)	1.6 (1)	2.2 (2)	4.0 (1)	2.4 (2)	4.0 (1)	4.0 (1)
"Symptomatic recurrent VTE" or "asymptomatic deterioration of thrombotic burden"	3.2 (1)	0.7 (1)	1.6 (1)	2.2 (2)	4.0 (1)	3.5 (3)	4.0 (1)	4.0 (1)
Thrombotic burden assessment								
Normalized	51.6 (16)	38.4 (58)	29.0 (18)	40.0 (36)	32.0 (8)	24.7 (21)	24.0 (6)	32.0 (8)
Improved	35.5 (11)	38.4 (58)	46.8 (29)	34.4 (31)	44.0 (11)	50.6 (43)	44.0 (11)	36.0 (9)
No relevant change	6.5 (2)	5.3 (8)	6.5 (4)	2.2 (2)	0 (0)	7.1 (6)	8.0 (2)	20.0 (5)
Deteriorated	0 (0)	0.7 (1)	0 (0)	0 (0)	0 (0)	1.2 (1)	0 (0)	0 (0)
Not evaluable or unknown	3.2 (1)	17.2 (26)	16.1 (10)	21.1 (19)	20.0 (5)	14.1 (12)	20.0 (5)	8.0 (2)

% (n)

Unlike Study 11702 involving patients with symptomatic VTE, Study 14372 was designed to enroll both patients with symptomatic VTE and those with asymptomatic VTE, because "the ACCP guidelines for antithrombotic therapy in neonates and children" states that asymptomatic CVAD-related thrombosis causes PE, sepsis, and other conditions that may be fatal. A subgroup analysis by symptom of VTE in Study 14372 detected no development of "symptomatic recurrent VTE" in patients with asymptomatic VTE, and revealed no substantial differences in the thrombotic burden assessment on imaging or the incidence of bleeding events between the rivaroxaban group and the standard of care group. These results suggest that the presence of VTE symptoms has no large impact on evaluation of the efficacy or safety of rivaroxaban. Study 11702 in adult patients with DVT or PE was designed so that a high dose of rivaroxaban would be administered as an initial treatment. In contrast, Study 14372 adopted a design in which a diagnosis was made and consent for participation in the study was obtained while the patient was receiving initial parenteral anticoagulant therapy, after which the initial treatment was switched to maintenance treatment with rivaroxaban. This study design was selected, taking into account (i) the possibility that physicians may initiate anticoagulant treatment rather than making a diagnosis for patients with strongly suspected VTE in pediatric clinical practice, and (ii) the feasibility of conducting a clinical study in pediatric patients with acute VTE. The results from Study 11702 in

adult patients with DVT or PE showed no substantial differences in the incidence of "symptomatic recurrent VTE" or "major bleeding events" during the 21-day initial treatment period, between patients receiving initial treatment with rivaroxaban and those receiving initial treatment with enoxaparin and VKA for the first 5 days, indicating that the efficacy and safety of rivaroxaban administered as an initial treatment in adults are similar to those of enoxaparin or UFH, which is recommended as the initial parenteral anticoagulant treatment. The Guidelines for Diagnosis, Treatment, and Prevention of Pulmonary Thromboembolism and Deep Vein Thrombosis (JCS 2017) (the Japanese Circulation Society) equates rivaroxaban with parenteral anticoagulants and recommends it as initial treatments for acute VTE in adults. In Study 14372 in pediatric patients, the intensity of initial treatment with LMWH, UFH, or fondaparinux sodium was not specified, but the initial treatment was performed in accordance with overseas guidelines established for attaining the therapeutic range defined based on adult data. Evaluation of the efficacy or safety of rivaroxaban is thus not substantially affected by the difference in the types of drugs used for initial treatment in the rivaroxaban group between Studies 11702 and 14372.

Based on the results of the above investigations, the applicant believes that the results of Study 14372 are comparable to those of Study 11702, despite some differences in risk factors for VTE and the most common sites of VTE between adults and children, and in part of the study design between Study 14372 and Study 11702.

PMDA's view:
The clinical development program of rivaroxaban for the treatment of pediatric VTE adopted a strategy of designing a feasible-scale clinical study in pediatric patients with VTE, based on knowledge from clinical studies in adult patients with VTE, to demonstrate the efficacy and safety of rivaroxaban in children. This strategy is acceptable, taking into account the rarity of VTE in children, the similarity of the pathophysiology, disease course, and treatment goal for pediatric VTE and adult VTE, and the pharmacology of rivaroxaban. PMDA's view about the design of Study 14372 and the comparability of Study 14372 with a clinical study in adult patients with VTE are presented below.

(a) Design of Study 14372

In view of the currently available treatments for pediatric VTE in each country or region, the design of Study 14372 is appropriate, in which the standard of care was used as the comparator, and the control drug was allowed to be selected from multiple standard medications, without specifying a single drug as the comparator. In addition, the conduct of Study 14372 as an open-label study was inevitable, given the differences in blood coagulation monitoring procedures and dosing regimens between the drugs used in the standard of care group and rivaroxaban. Although an open-label study is associated with an increased risk of biases in interventions and assessments involved in the study, possible measures to reduce assessment biases, including assessment of the primary efficacy and safety endpoints by the blinded, central and independent adjudication committee, were taken in Study 14372. Taking this into account, the efficacy and safety of rivaroxaban in the treatment of pediatric VTE can be evaluated to a certain extent, based on the results of Study 14372.

In view of the goal of VTE treatment and the comparability with a foreign phase III study in adult patients with DVT or PE (Study 11702), the selection of "symptomatic recurrent VTE" as the primary endpoint in Study 14372 was appropriate. Defining the duration of the main treatment period as 3 months in patients aged ≥2 years with VTE and those aged <2 years with non-catheter-related VTE was justified from several viewpoints, including the recommendations by the "ACCP guidelines for antithrombotic therapy in neonates and children" and the comparability with Study 11702. In contrast, no definite rationale has been presented for the main treatment period of 1 month in patients aged <2 years with catheter-related VTE. However, in light of the information available at the time of planning of the study, defining a shorter duration for the main treatment period in such patient population was rational to a certain extent. In view of this, along with the fact that the investigators were allowed to decide whether treatment should be continued, evaluation based on the primary endpoints was acceptable.

(b) Comparability with a clinical study in adult patients with VTE

Despite the differences in the frequency of VTE, risk factors for VTE, and the most common sites of VTE between children and adults, subgroup analyses for the efficacy of rivaroxaban by risk factor, type of index event, and VTE location in Study 14372 revealed no substantial differences across the subgroups. The differences in the above factors are thus unlikely to affect the efficacy evaluation of rivaroxaban. The effects of the differences in the drugs used for initial treatment in the rivaroxaban group between Study 14372 and Study 11702 on the efficacy evaluation for rivaroxaban remains unclear. However, based on the applicant's explanation, all of the drugs used in both studies were beneficial as the initial treatment of VTE, and the results from Study 14372 and those of Study 11702 are comparable.

7.R.3.2 Efficacy evaluation in Study 14372

The applicant's explanation:

The point estimate for the hazard ratio of "symptomatic recurrent VTE" during the main treatment period, which was the primary efficacy endpoint, for the rivaroxaban group versus the standard of care group in Study 14372 was <1, suggesting that rivaroxaban is effective in the prevention of "symptomatic recurrent VTE" (Table 19). During the extended treatment periods, "symptomatic recurrent VTE" occurred in 1 of 149 patients in the rivaroxaban group and 2 of 69 patients in the standard of care group. Given that the results suggested a low incidence of "symptomatic recurrent VTE" and that asymptomatic VTE associated with the use of central venous catheter is common in children, the composite of "symptomatic recurrent VTE" and "asymptomatic deterioration of thrombotic burden" on imaging was selected as a secondary endpoint. The results of the secondary endpoint tended to be similar to those of the primary endpoint. The thrombotic burden assessment at the end of the main treatment period, relative to baseline, was classified as "normalized," "improved," "no relevant change," "deteriorated," or "not evaluable or unknown" (Table 20). More patients were classified as "normalized" in the rivaroxaban group than in the standard of care group, indicating a trend toward thrombus regression in the rivaroxaban group, compared with the standard of care group.

In foreign phase III studies in adult patients with acute symptomatic DVT or PE (Studies 11702-DVT and 11702-PE), the non-inferiority of rivaroxaban to standard of care, in terms of the incidence of "symptomatic

recurrent VTE" during the main treatment period, the primary endpoint, was verified. A pooled analysis of the studies (during the 3 months after the start of treatment) revealed that the incidences of "symptomatic recurrent VTE" were 1.7% (69 of 4150 patients) in the rivaroxaban group and 2.0% (82 of 4131 patients) in the standard of care group, with a hazard ratio [95% CI] of 0.82 [0.60, 1.13]. The point estimate of the hazard ratio of the primary endpoint in the study targeting pediatric patients with VTE for the rivaroxaban group versus the standard of care group was also <1. In view of these study results and other findings, rivaroxaban is non-inferior to standard of care in terms of efficacy in the treatment of pediatric VTE, as well as adult VTE. The incidence rates (mean treatment duration) of "symptomatic recurrent VTE" throughout the entire treatment period (≤12 months) were 3.49 events per 100 patient-years (207.6 days) in the rivaroxaban group and 3.94 events per 100 patient-years (203.8 days) in the standard of care group in Study 11702, as compared with 3.89 events per 100 patient-years (142.3 days) in the rivaroxaban group and 9.79 events per 100 patient-years (140.7 days) in the standard of care group in Study 14372, indicating no tendency for rivaroxaban to be inferior to standard of care, in terms of efficacy in the treatment of pediatric VTE throughout the entire treatment period.

Table 26 presents the results of comparisons of the incidence of "symptomatic recurrent VTE" during the 3 months after the start of treatment, between pediatric patients with non-catheter-related VTE affecting a lower extremity or lung, and similar adult patients with DVT or PE. There was no substantial numerical difference in the incidence of "symptomatic recurrent VTE" between adults and children treated with rivaroxaban, and the incidences of "symptomatic recurrent VTE" by location of the index event in both children and adults were not higher in the rivaroxaban group than in the standard of care group.

Table 26. Incidences of efficacy endpoints in pediatric patients with non-catheter-related VTE (lower extremity or lung) and adult patients with DVT or PE
(children: main treatment period, FAS; adults: 3 months after the start of treatment, ITT)

	Children Non-catheter-related VTE (lower extremity or lung)		Adults DVT/PE	
	Rivaroxaban	Standard of care	Rivaroxaban	Standard of care
Symptomatic recurrent VTE	2.3 (3/133)	6.3 (4/66)	1.7 (69/4150)	2.0 (82/4131)
Lung	2.1 (1/48)	3.7 (1/29)	1.6 (37/2419)	1.6 (38/2413)
Lower extremity	2.4 (2/85)	8.3 (3/37)	1.9 (32/1731)	2.6 (44/1718)

% (n/N)
Children, main treatment period; adults, 3 months after the start of treatment

Table 27 presents the patient characteristics and efficacy results of 6 individual Japanese patients (4 in the rivaroxaban group and 2 in the standard of care group) enrolled in Study 14372. Throughout the entire treatment period, no "symptomatic recurrent VTE" or "asymptomatic deterioration of thrombotic burden" on imaging was found in any of these Japanese patients. The asymptomatic thrombotic burden in the Japanese subpopulation tended to regress, and did not clearly differ from that in the overall study population. Since all of the Japanese patients enrolled in Study 14372 were aged 0.6 months to 4.2 years, the efficacy of rivaroxaban was not evaluated in Japanese patients aged ≥6 years. However, favorable efficacy results were generated both in the Japanese subpopulation and the overall study population of Study 14372. In addition, the results from the overall study population justified the dosage regimens, which were set to achieve an exposure similar to the exposure demonstrated to be effective in adults, and the appropriateness of the dosage regimens, within the range investigated in the study, was also suggested in Japanese children. In view of these study results and

other findings, the clinically significant efficacy of rivaroxaban can be promising in Japanese children aged ≥6 years, as well as in adults.

Table 27. Patient characteristics and efficacy results in Japanese patients (Study 14372, FAS)

	Age	Sex	Body weight (kg)	Index events		Initial treatment	Treatment duration	Symptomatic recurrent VTE (Entire treatment duration)	Thrombotic burden assessment
				Catheter-related/ non-catheter related	Location				
Rivaroxaban	[redacted]			Catheter-related	Jugular vein	UFH	66 days	None	Improved
				Catheter-related	Jugular vein	UFH	21 days	None	Improved
				Catheter-related	Jugular vein	UFH	29 days	None	No relevant change
				Catheter-related	Jugular vein	UFH	85 days	None	Normalized
Standard of care				Catheter-related	Deep vein in a lower extremity	UFH	91 days (VKA)	None	Not evaluable or unknown
				Catheter-related	Caval vein	UFH	82 days (VKA)	None	No relevant change

PMDA's view:

In Study 14372, the point estimate for the hazard ratio of "symptomatic recurrent VTE" during the main treatment period, which was the primary efficacy endpoint, for the rivaroxaban group versus the standard of care group was <1. This result suggested that rivaroxaban is non-inferior to standard of care in terms of efficacy in the treatment of pediatric VTE. In addition, in Study 11702, the point estimate of the hazard ratio of the "symptomatic recurrent VTE" during the 3 months after the start of treatment for the rivaroxaban group versus the standard of care group was also <1. These results and other findings indicate that similar efficacy results were generated from Studies 14372 and 11702. Thus, rivaroxaban has efficacy in the prevention of "symptomatic recurrent VTE" in pediatric patients with VTE, as well as adult patients with VTE.

In the Japanese subpopulation of Study 14372, the number of patients was very small, and no patients experienced "symptomatic recurrent VTE" or "asymptomatic deterioration of thrombotic burden." These facts precluded a precise assessment of the consistency of the results between the overall study population and the Japanese subpopulation. Nevertheless, the results from the Japanese subpopulation, along with the results (e.g., thrombotic burden assessment) from individual Japanese patients, support the efficacy of rivaroxaban in the Japanese subpopulation, as with the overall study population. Furthermore, as with other age groups, the efficacy of rivaroxaban is promising in Japanese patients aged ≥6 years with VTE, who were not enrolled in Study 14372, in view of the following findings: (i) The body weight-adjusted dosage regimens, which were set to achieve a rivaroxaban exposure similar to the exposure demonstrated to be effective in adults, have been justified in the overall study population [see Section "6.R.2 Dosage regimens in the global phase III study (Study 14372)]; (ii) no differences in the pharmacokinetics or pharmacodynamics of rivaroxaban administered at the body weight-adjusted dosage regimens were identified between Japanese and non-Japanese pediatric patients with VTE [see Section "6.R.1 Differences in pharmacokinetics and pharmacodynamics of rivaroxaban between Japanese and non-Japanese children]; and, (iii) the efficacy of rivaroxaban administered at the dosage regimens within the range investigated in the study has been suggested in Japanese patients.

7.R.4 Safety

PMDA's view:

No new safety concerns have been identified from post-marketing safety information regarding the use of rivaroxaban for the approved indications in or outside of Japan, except for the addition of thrombocytopenia as a serious adverse drug reaction, after the extension of the indication to include the treatment of adult VTE. Further, based on the incidence of adverse events in Study 14372 and the safety considerations presented below, and in view of its efficacy as described in Section "7.R.3 Efficacy," PMDA has concluded that rivaroxaban has acceptable safety in the treatment of pediatric VTE.

7.R.4.1 Bleeding

The applicant's explanation about the bleeding risks associated with treatment with rivaroxaban:

In Study 14372, the incidence of the composite endpoint of "major bleeding" and "clinically relevant non-major bleeding" during the main treatment period, which was the primary safety outcome, was higher in the rivaroxaban group than in the standard of care group (hazard ratio [95% CI], 1.58 [0.51, 6.27]) (Table 21). "Major bleedings" were reported in 2 patients in the standard of care group (subdural haemorrhage and traumatic haemothorax). "Clinically relevant non-major bleedings" were reported in 3.0% (10 of 329) of patients in the rivaroxaban group (mild in 6 patients [gastric haemorrhage, rectal haemorrhage, menorrhagia, epistaxis, procedural haemorrhage, and haematuria in 1 patient each], moderate in 4 patients [haematemesis, gastric haemorrhage, subcutaneous haematoma, and epistaxis in 1 patient each]) and 0.6% (1 of 162 patients) of patients in the standard of care group (moderate [epistaxis]). Only gastric haemorrhage and epistaxis were reported by ≥2 patients. Although gastrointestinal bleeding events were often reported, no specific bleeding events occurred more frequently than others. Bleeding events led to treatment interruption or discontinuation in 5 patients in the rivaroxaban group (gastric haemorrhage in 2 patients, and menorrhagia, procedural haemorrhage, and haematemesis in 1 patient each), all of which resolved with treatment or other measures. The incidence of bleeding events during the main treatment period was higher in the rivaroxaban group (36.2% [119 of 329 patients]) than in the standard of care group (27.8% [45 of 162 patients]); this was likely attributable to the fact that "trivial bleedings" were more common in the rivaroxaban group than in the standard of care group. "Trivial bleedings" led to treatment discontinuation or interruption in 11 of 113 patients in the rivaroxaban group and 2 of 44 patients in the standard of care group, most of which resolved or improved following treatment discontinuation or interruption, medical care, or other measures. During the extended treatment periods, "clinically relevant non-major bleedings" were reported in 3 patients (haemorrhagic ovarian cystoma, menometrorrhagia, and epistaxis) in the rivaroxaban group and 1 patient (epistaxis) in the standard of care group, all of which were moderate in severity. "Clinically relevant non-major bleedings" led to treatment discontinuation or interruption in 2 patients in the rivaroxaban group (haemorrhagic ovarian cystoma, epistaxis), which resolved with medical care or other measures. These results indicate that the bleeding risk associated with rivaroxaban therapy is not clearly higher than that of standard of care, and is acceptable.

In Study 11702 in adult patients with DVT or PT, the incidence of "major bleeding" during the 3 months after the start of treatment was 0.7% (28 of 4130 patients) in the rivaroxaban group and 1.2% (49 of 4116 patients) in the standard of care group, with a hazard ratio [95% CI] of 0.55 [0.35, 0.88]. The incidence of "clinically

relevant non-major bleeding" was 6.4% (266 of 4130 patients) in the rivaroxaban group and 6.0% (249 of 4116 patients) in the standard of care group. The incidence of bleeding events was 22.0% (908 of 4130 patients) in the rivaroxaban group and 21.9% (903 of 4116 patients) in the standard of care group. The incidence of "trivial bleeding" was 17.0% (702 of 4130 patients) in the rivaroxaban group and 17.1% (703 of 4116 patients) in the standard of care group. The incidences of bleeding events and trivial bleeding events were similar in the 2 treatment groups. The incidence of "major bleeding" did not substantially differ between the treatment groups, in both Study 14372 and Study 11702. The incidences of "clinically relevant non-major bleeding" and "trivial bleeding" were similar in the treatment groups in Study 11702, whereas the incidences were higher in the rivaroxaban group than in the standard of care group in Study 14372. However, the difference between the treatment groups was not clinically significant, in view of the measures taken for and the outcomes of the reported events. The incidence rates of the composite endpoint of "major bleeding" and "clinically relevant non-major bleeding" during the entire treatment period (up to 12 months) were 17.50 events per 100 patient-years in the rivaroxaban group and 19.02 events per 100 patient-years in the standard of care group in Study 11702, and 10.20 events per 100 patient-years in the rivaroxaban group and 6.50 events per 100 patient-years in the standard of care group in Study 14372. The incidence rates of "trivial bleeding" were 47.44 events per 100 patient-years in the rivaroxaban group and 47.43 events per 100 patient-years in the standard of care group in Study 11702, and 132.75 events per 100 patient-years in the rivaroxaban group and 99.89 events per 100 patient-years in the standard of care group in Study 14372. The incidences of these bleeding events during the entire treatment period showed similar tendencies to those during the main treatment period.

The most common sites of bleeding in the rivaroxaban group in Study 14372 (main treatment period) were skin, nasal cavity, genital tract, oral cavity, and gastrointestinal tract, in the decreasing order of frequency, which did not substantially differ from the sites of bleeding in the rivaroxaban group in Study 11702 (3 months after the start of treatment).

In Study 14372 (the main treatment period), haemorrhage intracranial was reported in 1 of 162 patients in the standard of care group (subdural haemorrhage in 1 patient aged 6 months), with no patient experiencing the event in the rivaroxaban group. In Study 11702 (3 months after the start of treatment), the incidences of haemorrhage intracranial were <0.1% (1 of 4130 patients) in the rivaroxaban group and 0.1% (5 of 4116 patients) in the standard of care group. These results indicated that the incidence of haemorrhage intracranial tended to be similar in pediatric and adult patients with VTE. An analysis of gastrointestinal haemorrhage in Study 14372 (the main treatment period) revealed incidences of "clinically relevant non-major bleeding" of 1.2% (4 of 329 patients) in the rivaroxaban group and 0% (0 of 162 patients) in the standard of care group, and incidences of "trivial bleeding" of 4.0% (13 of 329 patients) and 1.2% (2 of 162 patients), respectively. An analysis of gastrointestinal haemorrhage in Study 11702 (3 months after the start of treatment) revealed incidences of "major bleeding" of 0.3% (11 of 4130 patients) in the rivaroxaban group and 0.5% (19 of 4116 patients) in the standard of care group; those of "clinically relevant non-major bleeding" of 1.6% (68 of 4130 patients) and 1.1% (47 of 4116 patients), respectively; and those of "trivial bleeding" of 2.3% (93 of 4130 patients) and 1.6% (67 of 4116 patients), respectively. The incidence of gastrointestinal haemorrhage classified as "trivial bleeding," tended to be higher in pediatric patients with VTE than in adult patients with VTE;

however, all of the events resolved, and the difference in the incidence of these “trivial bleedings” was thus not clinically relevant. The package insert for rivaroxaban already includes precautionary advice regarding haemorrhage intracranial and gastrointestinal haemorrhage. The applicant thus believes that no additional precautions will be necessary for the use of rivaroxaban in the treatment of pediatric VTE. The incidence of menorrhagia in the rivaroxaban group of Study 14372 (the main treatment period) (7.0% [23 of 329 patients]) was higher than that in the standard of care group of the same study (3.1% [5 of 162 patients]), and in Study 11702 (3 months after the start of treatment), the incidence of menorrhagia in the rivaroxaban group (2.6% [109 of 4130 patients]) was higher than that in the standard of care group (1.2% [51 of 4116 patients]). Among patients who had menstruation at baseline in Study 14372, the incidence of menorrhagia was higher in the rivaroxaban group [26.7% (23 of 86 patients)] than in the rivaroxaban group [10.4% (5 of 48 patients)]. In Study 14372, one (aged 17.9 years) of 329 patients in the rivaroxaban group reported menorrhagia classified as “clinically relevant non-major bleeding,” for which a causal relationship to the study drug was ruled out, and the event resolved. Other reported menorrhagia events were classified as “trivial bleeding,” of which 12 events were mild and 11 events were moderate in severity, with no severe events. Menorrhagia led to treatment discontinuation in 2 patients, including the 1 patient having a “clinically relevant non-major bleeding.” The remaining 21 patients did not change the dose of the study drug. The events resolved in 20 patients, was resolving in 2 patients, and did not resolve in 1 patient. Approximately 84% to 90% of the patients required no procedure for menstruation control and continued the study treatment, and most of these patients recovered from the events. The applicant thus believes that no additional precautions regarding the development of menorrhagia will be necessary for the use of rivaroxaban in pediatric patients with VTE.

In the Japanese subpopulation composed of 6 patients (4 in the rivaroxaban group and 2 in the standard of care group), no “major bleedings” or “clinically relevant non-major bleedings” were reported. “Trivial bleedings” were reported in 2 of 4 patients in the rivaroxaban group, among whom a girl aged 7.8 months experienced rectal haemorrhage on Day 13 but recovered without treatment on the same day, and another girl aged 4.2 years experienced mouth haemorrhage on Day 36 but recovered without treatment on the same day. The incidences of these bleeding events in the Japanese subpopulation did not differ substantially from those in the overall study population.

PMDA’s view:

Bleeding is a risk related to the primary pharmacology of rivaroxaban. The primary safety outcome in Study 14372 was the composite endpoint of “major bleeding” and “clinical relevant non-major bleeding.” The incidence of the composite endpoint of “major bleeding” and “clinical relevant non-major bleeding” during the main treatment period was higher in the rivaroxaban group than in the standard of care group; however, no “major bleedings” were reported in the rivaroxaban group. “Clinically relevant non-major bleedings” were more frequently reported in the rivaroxaban group than in the standard of care group. Of the 10 patients experiencing such events in the rivaroxaban group, 5 required treatment interruption or discontinuation. All the events resolved with medical treatment or other measures. “Clinically relevant non-major bleeding events” are thus manageable through appropriate monitoring and treatment. At the same time, the following facts regarding the bleeding risk associated with the use of rivaroxaban should be noted: (i) The incidence of

bleeding events was higher in the rivaroxaban group than in the standard of care group in Study 14372, whereas the incidence of bleeding events did not tend to increase in the rivaroxaban group, compared with the standard of care group in Study 11702 in adult patients with DVT or PE; (ii) the number of Japanese patients evaluated in Study 14372 was extremely limited; (iii) no laboratory parameters for anticoagulation to be monitored during rivaroxaban therapy have been established; and, (iv) no agents that neutralize the anticoagulant effect of rivaroxaban are currently available. Based on the above, the applicant should provide appropriate information about the incidence of bleeding in pediatric patients with VTE, and include a precautionary statement in the package insert, that physicians with sufficient knowledge and experience in anticoagulant therapy in children should assess the bleeding risk for each patient, and carefully decide whether treatment with rivaroxaban should be initiated or whether the treatment should be continued once it is initiated. PMDA's conclusions will be finalized, taking into account the comments from the Expert Discussion.

7.R.4.2 Adverse events of special interest other than bleeding

The applicant's explanation:

In Study 14372, the incidences of the following adverse events defined as adverse events of special interest[23)] were assessed: liver disorder (ALT >5 × ULN and total bilirubin >2 × ULN), thrombocytopenia (platelet count $<50 \times 10^9$/L), and allergic reaction (allergic skin reaction, allergic systemic reaction).

The incidence of "potential" liver disorder-related events during the main treatment period was similar in the rivaroxaban group (5.5% [18 of 329 patients]) and the standard of care group (6.2% [10 of 162 patients]). A patient who had high hepatic enzyme levels at baseline in the rivaroxaban group experienced suspected/confirmed liver disorder-related events (drug-induced liver injury, ALT increased, and blood bilirubin increased), for all of which a causal relationship to the study drug was ruled out.

The incidence of "potential" cases of thrombocytopenia during the main treatment period was similar in the rivaroxaban group (5.2% [17 of 329 patients]) and the standard of care group (3.1% [5 of 162 patients]). A suspected/confirmed case of thrombocytopenia occurred in 1 patient in each of the treatment groups (thrombocytopenia in both patients). Twelve patients in the rivaroxaban group and 3 patients in the standard of care group experienced thrombocytopenia, when they were on the study treatment during the main treatment period; however, a causal relationship to the study drug was ruled out for all of the events. All of these 15 patients had persistent risk factors for VTE (active cancer in 11 patients, and osteosarcoma, rhabdomyosarcoma, congenital venous malformation, and major organ disease in 1 patient each). The investigators considered that the cases of thrombocytopenia in 13 of the 15 patients were related to chemotherapy with anticancer drugs, based on the changes over time in platelet count and the use of concomitant drugs. The case of thrombocytopenia reported by 1 of the remaining 2 patients in the rivaroxaban group was likely attributable to

[23)] For events extracted with the following Standardized MedDRA Queries (SMQs), the applicant classified events that might be adverse events of special interest as "potential" events, and events that were suspected or confirmed adverse events of special interest as "suspected/confirmed" events, based on MedDRA preferred terms or clinical laboratory results.
- Hepatic disorder: "Drug related hepatic disorders (SMQ)" (except for "Liver related coagulation and bleeding disturbances (SMQ)")
- Thrombocytopenia: "Haematopoietic thrombocytopenia (SMQ)"
- Allergic skin reaction or allergic systemic reaction: "Anaphylactic reaction (SMQ)," "severe cutaneous adverse reactions (SMQ)," "hypersensitivity (SMQ)," or "angioedema (SMQ)"

the use of levetiracetam, an antiepileptic administered before the start of the study treatment, or another adverse event (aplastic anaemia associated with bone marrow failure). The case of thrombocytopenia reported by the other patient in the rivaroxaban group was likely attributable to the use of UFH prior to the start of the study treatment. Among the patients experiencing thrombocytopenia during the study treatment, 6 of 12 patients in the rivaroxaban group and 2 of 3 patients in the standard of care group also had bleeding events, all of which were "trivial bleeding events" which were mild in severity. Of the patients with thrombocytopenia and bleeding events, 4 patients (7 events) in the rivaroxaban group and 1 patient (1 event) in the standard of care group experienced bleeding events when the platelet count decreased to $<50 \times 10^9$/L. The duration of these bleeding events in the rivaroxaban group was <1 day for 3 events in 3 patients, ≥1 to ≤3 days for 3 events in 1 patient, and 14 days for 1 event in 1 patient. In the rivaroxaban group, 116 patients with no thrombocytopenia reported a total of 189 bleeding events ("trivial bleedings," which were categorized as the same MedDRA preferred terms as those of the bleeding events reported in patients with thrombocytopenia). The duration of these bleeding events was <1 day for 90 events in 61 patients, ≥1 to ≤3 days for 14 events in 14 patients, >3 to ≤7 days for 26 events in 21 patients, >7 to ≤14 days for 9 events in 9 patients, >14 to ≤148 days for 16 events in 15 patients, and unknown for 34 events in 31 patients. These results suggested that the duration of bleeding did not tend to clearly increase in patients with thrombocytopenia. Post-marketing safety information from the specified use-results surveys in adult patients with non-valvular atrial fibrillation and those with PE or DVT revealed that rivaroxaban was used in combination with chemotherapy in 0.4% (45 of 10,664) of patients with non-valvular atrial fibrillation and 4.6% (100 of 2162) of patients with PE or DVT, and detected no thrombocytopenia reported as an adverse drug reaction in patients receiving rivaroxaban in combination with chemotherapy. These findings suggest that most of the thrombocytopenia cases reported in Study 14372 were related to chemotherapy, not rivaroxaban, and that the administration of rivaroxaban, which carries a risk of thrombocytopenia, did not increase the risk of bleeding in patients with a decreased platelet count due to chemotherapy. An additional precaution regarding the risk of thrombocytopenia is thus unnecessary.

The incidence of "potential" allergic reactions during the main treatment period was similar in the rivaroxaban group (9.1% [30 of 329 patients]) and the standard of care group (10.5% [17 of 162 patients]). The incidences of "suspected/confirmed" allergic reactions were 7.3% (24 of 329 patients) in the rivaroxaban group and 8.0% (13 of 162 patients) in the standard of care group. The common allergic reaction was rash (4.0% in the rivaroxaban group, 2.5% in the standard of care group). Allergic reactions occurred in patients of all age groups, except those aged ≥6 months to <2 years in the standard of care group, with no clear differences among the age groups.

The allergic reaction reported in the Japanese subpopulation was eczema in 1 patient in the standard of care group. There were no reports of hepatic disorder or thrombocytopenia in the Japanese subpopulation.

PMDA's view:

Hepatic disorder and allergic reaction are known risks associated with rivaroxaban therapy. Because the incidences of these events during the main treatment period in Study 14372 did not differ between the rivaroxaban group and the standard of care group, precautionary advice may also be provided for use in children,

similarly to that for use in adults. As with the approved indications, a causal relationship between thrombocytopenia and rivaroxaban cannot be ruled out, although the effects of other factors were also suggested in the study. Therefore, thrombocytopenia should continue to be listed in the "Clinically Significant Adverse Reactions" section of the package insert. Thrombocytopenia and bleeding should be carefully monitored when rivaroxaban is administered to patients on chemotherapy, for the following reasons: (i) A majority of pediatric VTE cases are considered to be secondary to the use of central venous catheter for chemotherapy in children with underlying cancer; and, (ii) rivaroxaban therapy in patients who are in a thrombocytopenic state due to chemotherapy-induced marrow depression promotes a bleeding tendency which may lead to a serious outcome. The package insert for rivaroxaban already includes appropriate precautionary advice regarding the risk of thrombocytopenia and bleeding, as well as measures to be taken for these events. The applicant's view that no additional precautionary advice will be necessary is thus appropriate. PMDA's conclusions will be finalized after taking into account the comments from the Expert Discussion.

7.R.4.3 Comparisons of the safety profile between adults and children

The applicant's explanation:

In Study 14372, the incidences of adverse events, serious adverse events, and adverse events leading to treatment discontinuation during the main treatment period did not substantially differ between the rivaroxaban group and the standard of care group. The incidences of adverse events for which a causal relationship to the study drug could not be ruled out were 27.4% (90 of 329 patients) in the rivaroxaban group and 16.7% (27 of 162 patients) in the standard of care group. The most common events were menorrhagia (6.1% [20 of 329 patients] in the rivaroxaban group, 2.5% [4 of 162 patients] in the standard of care group) and epistaxis (6.1% [20 of 329 patients], 4.9% [8 of 162 patients]). Two patients in the rivaroxaban group died. Of these 2 patients, one was a 17-year-old male patient with a history of myxofibrosarcoma in the thigh, who died on Day 34 (during the main treatment period) from recurrent myxofibrosarcoma. The other was a 13-year-old female patient with a history of Hodgkin's lymphoma, who died on Day 168 (during the follow-up period) from respiratory distress and deterioration of Hodgkin's lymphoma. Both of the deaths were attributable to cancer progression, and a causal relationship to the study drug was ruled out. The incidence of severe adverse events did not substantially differ between the rivaroxaban group (12.8% [42 of 329 patients]) and the standard of care group (14.2% [23 of 162 patients]). Most adverse events resolved or were resolving. Adverse events did not resolve in 19.8% (65 of 329) of patients in the rivaroxaban group and 22.8% (37 of 162) of patients in the standard of care group, with no substantial differences between the treatment groups. The proportion of patients who completed the main treatment period in Study 14372 was similar in the treatment groups and across different age groups. No particular safety concerns were identified from the Japanese subpopulation of the study.

The dry syrup formulation of rivaroxaban requires reconstitution of dry syrup powder for oral suspension, measurement of reconstituted suspension, and dosing procedures. In Study 14372, safety issues relating to medication errors were assessed. Seven cases of overdose of the dry syrup formulation occurred in 6 patients and 5 cases of underdose occurred in 5 patients. However, no adverse events associated with overdose or

underdose were reported. There were no reports of adverse events with clinical symptoms associated with the use of a dosing device for the dry syrup formulation.

PMDA asked the applicant to explain whether there was any trend characteristic to adverse events reported in pediatric patients with VTE, such as events specific to children (including their possible impacts on growth, development, or maturation) or events that occurred more frequently in pediatric patients with VTE than in adult patients with VTE, and to then consider the necessity of providing additional precautionary advice in the package insert.

The applicant's response:
To assess the differences in the safety profile of rivaroxaban between adult and pediatric patients with VTE, adverse events reported with a ≥2% higher incidence in the rivaroxaban group than in the standard of care group, throughout the entire treatment period in Study 14372 were compared with those in a foreign phase III study in non-Japanese adult patients with DVT or PE (Study 11702) (Table 28). The comparison detected no events specific to children, and revealed that the intergroup differences were similar in these studies. Among the adverse events reported with a ≥2% higher incidence in the rivaroxaban group than in the standard of care group throughout the entire treatment period in Study 14372, vomiting and pyrexia were more frequently reported in children than in adults. Most of these events reported in the rivaroxaban group of Study 14372 resolved, and a causal relationship to the study drug was ruled out. Febrile neutropenia and thrombocytopenia were likely attributed to chemotherapy for the underlying diseases, and a causal relationship to the study drug was ruled out for all of the reported events. Other adverse events infrequently led to treatment discontinuation, and the events reported in the rivaroxaban group were manageable, as indicated by the fact that most of the events resolved or were resolving with measures such as treatment interruption and medical care. An analysis of the incidence of adverse events by time to onset in Study 14372 revealed that no adverse events developed more frequently with time or occurred later.

Table 28. Adverse events with a ≥2% higher incidence in the rivaroxaban group than in the standard of care group in Study 14372, as well as the incidences of these adverse events in Study 11702 (safety analysis sets)

	Study 14372[a)]		Study 11702[b)]	
	Rivaroxaban (N = 329)	Standard of care (N = 162)	Rivaroxaban (N = 4130)	Standard of care (N = 4116)
Pyrexia	12.5 (41)	9.9 (16)	2.7 (111)	2.6 (108)
Vomiting	12.2 (40)	9.3 (15)	1.7 (69)	2.3 (96)
Nasopharyngitis	8.8 (29)	6.8 (11)	6.8 (279)	6.8 (278)
Pain in extremity	8.5 (28)	5.6 (9)	5.6 (230)	5.4 (221)
Nausea	7.3 (24)	4.9 (8)	3.7 (153)	3.9 (160)
Menorrhagia	7.0 (23)	3.7 (6)	3.0 (122)	1.6 (64)
Fatigue	6.4 (21)	3.7 (6)	2.2 (90)	1.7 (68)
Rash	5.5 (18)	2.5 (4)	2.3 (97)	2.2 (89)
Back pain	4.0 (13)	1.9 (3)	3.3 (138)	3.9 (162)
Gingival bleeding	4.0 (13)	0.6 (1)	2.3 (93)	2.5 (104)
Thrombocytopenia	3.6 (12)	1.2 (2)	0.1 (6)	0.2 (10)
Wound haemorrhage	4.0 (13)	1.2 (2)	1.4 (59)	1.6 (65)
Rhinorrhoea	4.3 (14)	1.2 (2)	0.2 (8)	0.3 (14)
Febrile neutropenia	2.7 (9)	0.6 (1)	<0.1 (2)	<0.1 (1)
Accidental underdose	2.4 (8)	0 (0)	0 (0)	0 (0)
Hypokalaemia	2.4 (8)	0 (0)	1.2 (48)	1.4 (59)
Pain	2.1 (7)	0 (0)	0.6 (23)	0.3 (14)

% (n)

a) MedDRA ver. 21.1; assessment period, 3 to 12 months (1 to 3 months for patients aged <2 years with catheter-related VTE); mean treatment duration, 142.3 days in the rivaroxaban group and 140.7 days in the standard of care group

b) MedDRA ver. 14.1; assessment period, 3 to 12 months; mean treatment duration, 207.6 days in the rivaroxaban group and 203.8 days in the standard of care group

From the market launch in 2008 to [redacted], post-marketing safety information was collected through publications and spontaneous reports in and outside of Japan. The safety information includes clinical experience from 292 children aged <18 years (16 children aged <1 month, 19 children aged ≥1 month to <2 years, 59 children aged ≥2 to <13 years, and 198 children aged ≥13 to <18 years; including 6 Japanese children). Among 192 children with indication data, 158 received rivaroxaban for a VTE-related reason (including 56 for embolism venous, 54 for DVT, and 34 for the prevention of VTE). Of 115 patients experiencing a serious condition, 32 had ≥1 case of bleeding events (MedDRA SMQ "haemorrhage terms (excl. laboratory terms) [narrow]"). No deaths were reported. No new important risks associated with rivaroxaban therapy have been identified from the post-marketing safety database.

Based on the above, the safety profile of rivaroxaban observed in the pediatric development program is generally consistent with its known safety profile in adults. The applicant therefore considers that no issues will require the inclusion of additional precautionary statements in the package insert.

PMDA's view:

In view of the following facts, the applicant's explanation that no safety concerns requiring additional precautionary advice regarding the use of rivaroxaban in pediatric patients with VTE have been identified so far is appropriate: (i) The results of Study 14372 identified no adverse events specific to children; and, (ii) some adverse events were more frequently reported in the rivaroxaban group than in the standard of care group in Study 14372, despite similar incidences of adverse events in the two treatment groups in Study 11702 in adult patients with DVT or PE (Table 28); however, all of these events were mild or moderate in severity, and most of the events resolved [see Sections "7.R.4.1 Bleeding events" and "7.R.4.2 Adverse events of special

interest other than bleeding"]. PMDA's conclusions will be finalized after taking into account the comments from the Expert Discussion.

7.R.4.4 Use in patients with renal impairment

PMDA asked the applicant to present the incidences of adverse events in clinical studies in pediatric patients with VTE conducted in and outside of Japan, by renal function (eGFR ≥30 to <60 mL/min/1.73 m^2, ≥60 to <90 mL/min/1.73 m^2, vs. ≥90 mL/min/1.73 m^2), and to then explain the appropriateness of the precautionary advice regarding the use of rivaroxaban in pediatric patients with moderate renal impairment included in the proposed package insert.

The applicant's explanation:

In a clinical pharmacology study in adult patients with renal impairment, the AUC of rivaroxaban in adults with mild (CL_{cr} = 50 to 79 mL/min), moderate (CL_{cr} = 30 to 49 mL/min), and severe (CL_{cr} <30 mL/min) renal impairment was 1.49-, 1.66-, and 1.79-fold higher, respectively, than that in those with normal renal function (see the data submitted for the initial application for "Xarelto Tablets 10 mg and Xarelto tablets 15 mg"). In 4 multiple dose studies in pediatric patients (Studies 14373, 14374, 14372, and 17618), most of the patients had normal renal function, and no clear difference in rivaroxaban exposure was noted between patients with normal renal function and a small number of patients with mild renal impairment (only 4 patients with an eGFR of ≥30 to <60). The limited number of patients with renal impairment precluded a conclusion regarding the effects of renal function on rivaroxaban exposure. The absence of the effects of renal function on rivaroxaban exposure in children, unlike adults, was analyzed from a physiological viewpoint in children aged ≥2 years, suggesting no substantial difference in the percent contribution of the kidney to the metabolism or elimination of rivaroxaban, between adults and children. Thus, the absence of the effects of renal function on rivaroxaban exposure in children cannot be rationally explained by the currently available findings.

The applicant's explanation about the safety in patients with renal impairment:

Study 14372 excluded patients aged ≥1 year with eGFR of <30 mL/min/1.73 m^2 and patients aged <1 year with serum creatinine levels above the protocol-specified 97.5th percentile. The rivaroxaban group included 286 patients with eGFR of ≥90 mL/min/1.73 m^2, 33 patients with eGFR of ≥60 to <90 mL/min/1.73 m^2, and 4 patients with eGFR of ≥30 to <60 mL/min/1.73 m^2. The standard of care group included 143 patients with eGFR of ≥90 mL/min/1.73 m^2, 16 patients with eGFR of ≥60 to <90 mL/min/1.73 m^2, and 2 patients with eGFR of ≥30 to <60 mL/min/1.73 m^2. The incidences of the composite of "major bleeding" and "clinically relevant non-major bleeding" during the main treatment period for patients with normal renal function (eGFR ≥90 mL/min/1.73 m^2) were 2.8% (8 of 286 patients) in the rivaroxaban group and 1.4% (2 of 143 patients) in the standard of care group, those for patients with mild renal impairment (eGFR of ≥60 to <90 mL/min/1.73 m^2) were 0% (0 of 33 patients) in the rivaroxaban group and 6.3% (1 of 16 patients) in the standard of care group, and those for patients with moderate renal impairment (eGFR of ≥30 to <60 mL/min/1.73 m^2) were 25.0% (1 of 4 patients) in the rivaroxaban group and 0% (0 of 2 patients) in the standard of care group. The bleeding event reported in the patient with moderate renal impairment in the rivaroxaban group was subcutaneous haematoma in the right neck, which was moderate in severity and resolved with surgical removal.

Alopecia and menorrhagia for which a causal relationship to the study drug could not be ruled out were reported with a ≥5% higher incidence in patients with eGFR of ≥60 to <90 mL/min/1.73 m^2 than in patients with eGFR of >90 mL/min/1.73 m^2, during the main treatment period in the rivaroxaban group. The incidence of alopecia was similar in the rivaroxaban group (0.7%) and the standard of care group (0.7%) in the subgroup of patients with an eGFR of ≥90 mL/min/1.73 m^2, whereas the incidence was higher in the rivaroxaban group (6.1%) than in the standard of care group (0%) in the subgroup of patients with an eGFR of ≥60 to <90 mL/min/1.73 m^2. However, the events reported by the 2 patients in the rivaroxaban group in the subgroup of patients with eGFR of ≥60 to <90 mL/min/1.73 m^2 were mild in severity, and required neither changes in the dosage regimen nor discontinuation of the study treatment; these events did not resolve in 1 patient, but resolved in the other patient. The incidences of menorrhagia were 5.6% in the rivaroxaban group and 2.1% in the standard of care group in the subgroup of patients with eGFR of ≥90 mL/min/1.73 m^2, and 12.1% and 6.3%, respectively, in the subgroup of patients with eGFR of ≥60 to <90 mL/min/1.73 m^2. Menorrhagia was thus more frequently reported in the rivaroxaban group than in the standard of care group, in both eGFR subgroups. The adverse event reported by ≥2 patients with eGFR of ≥30 to <60 mL/min/1.73 m^2 was cough, which resolved and for which a causal relationship to the study drug was ruled out in all of the patients. There were no reports of adverse events for which a causal relationship to the study drug could not be ruled out. Alopecia and menorrhagia have been listed in the "Other Adverse Reactions" section of the proposed package insert, and the incidences of these events by renal function showed no clinically significant differences between the treatment groups.

Post-marketing safety information from the specified use-results survey in adults patients with PE or DVT revealed that the incidences of bleeding events and major bleeding events by renal function were 18.2% (2 of 11 patients) and 18.2% (2 of 11 patients), respectively, in the subgroup of patients with CL_{cr} <30 mL/min, 8.5% (27 of 319 patients) and 2.5% (8 of 319 patients) in the subgroup of patients with CL_{cr} ≥30 to <50 mL/min, 7.8% (64 of 820 patients) and 3.0% (25 of 820 patients) in the subgroup of patients with CL_{cr} ≥50 to <80 mL/min, and 5.7% (53 of 928 patients) and 2.9% (27 of 928 patients) in the subgroup of patients with CL_{cr} of ≥80 mL/min. Bleeding events tended to occur more frequently in patients with CL_{cr} <30 mL/min. Patients who had CL_{cr} ≥30 to <50 mL/min at the onset of a bleeding event experienced bleeding events at doses of both 15 mg/day and 10 mg/day.

The applicant's investigation has identified no clear concerns about the use of rivaroxaban in patients with renal impairment. However, the evaluation of the pharmacokinetics and safety of rivaroxaban in pediatric patients with VTE who have renal impairment is limited. Thus, the use of rivaroxaban in pediatric patients with VTE and renal impairment requires the following precautionary advice, as with the case of adult patients with VTE and renal impairment: (i) rivaroxaban is contraindicated in patients with severe renal impairment, and (ii) the appropriateness of the use of rivaroxaban in patients with moderate renal impairment should be considered carefully.

PMDA's view:

The data on rivaroxaban exposure in patients with renal impairment in Study 14372 showed no clear tendency for renal function to affect the pharmacokinetics of rivaroxaban in children. However, as explained by the

applicant, there is no rational evidence demonstrating that the effects of renal function on the pharmacokinetics of rivaroxaban differ between children and adults. The limited experience with the use of rivaroxaban in pediatric patients with renal impairment in clinical studies precludes a strict evaluation of the safety of rivaroxaban in pediatric patients with renal impairment versus those with normal function. However, providing advice that differs from that for adult patients with VTE and renal impairment is not justified, at present. Therefore, the applicant's proposal to provide a precautionary statement that rivaroxaban is contraindicated in patients with severe renal impairment, and that the appropriateness of the use of rivaroxaban in patients with moderate renal impairment should be considered carefully, is appropriate. At the same time, in view of the following facts, the package insert should include a precautionary statement that physicians versed in anticoagulant therapy should carefully decide on the use of rivaroxaban, while taking into account its benefits and risks for each patient: (i) The incidence of bleeding events was higher in the rivaroxaban group than in the standard of care group in Study 14372 [see Section "7.R.4.1 Bleeding events"]; (ii) decreased renal function may increase the risk of bleeding, while clinical experience with the use of rivaroxaban in pediatric patients with VTE and moderate renal impairment is very limited; and, (iii) no anticoagulation parameters to be monitored during rivaroxaban therapy have been established. PMDA's conclusions will be finalized after taking into account the comments from the Expert Discussion.

7.R.5 Efficacy and safety by age

The applicant's explanation:

Table 29 presents the results of the efficacy endpoints and bleeding events by age group in Study 14372. Across all of the age groups of ≥2 years, the incidences of "symptomatic recurrent VTE" and the secondary endpoints were lower in the rivaroxaban group than in the standard of care group. In the age group of <2 years, no events of the primary efficacy endpoint occurred in either of the treatment groups, and thrombotic burden assessment revealed that the proportion of patients categorized as "normalized" or "improved" in the rivaroxaban group was similar to that in the other age groups, and did not substantially differ from that in the standard of care group, with no patients categorized as "deteriorated" in this age group. The efficacy of rivaroxaban is thus also promising in patients aged <2 years. The incidence of the composite of "major bleeding" and "clinically relevant non-major bleeding" did not clearly differ across the age groups.

Table 29. Incidences of the efficacy endpoints and bleeding events by age group
(main treatment period; efficacy, FAS; safety, safety analysis set)

	Rivaroxaban (N = 335)				Standard of care (N = 165)			
	≥12 years to <18 years (N = 184)	≥6 years to <12 years (N = 67)	≥2 years to <6 years (N = 47)	<2 years (N = 37)	≥12 years to <18 years (N = 92)	≥6 years to <12 years (N = 34)	≥2 years to <6 years (N = 22)	<2 years (N = 17)
Symptomatic recurrent VTE	2.2 (4)	0 (0)	0 (0)	0 (0)	3.3 (3)	2.9 (1)	4.5 (1)	0 (0)
"Symptomatic recurrent VTE" or "asymptomatic deterioration of thrombotic burden"	2.2 (4)	0 (0)	2.1 (1)	0 (0)	4.3 (4)	2.9 (1)	4.5 (1)	0 (0)
Thrombotic burden assessment								
Normalized	36.4 (67)	41.8 (28)	36.2 (17)	43.2 (16)	26.1 (24)	23.5 (8)	27.3 (6)	29.4 (5)
Improved	40.2 (74)	40.3 (27)	38.3 (18)	27.0 (10)	46.7 (43)	47.1 (16)	40.9 (9)	41.2 (7)
No relevant change	4.9 (9)	6.0 (4)	4.3 (2)	2.7 (1)	4.3 (4)	11.8 (4)	9.1 (2)	17.6 (3)
Deteriorated	0 (0)	0 (0)	2.1 (1)	0 (0)	1.1 (1)	0 (0)	0 (0)	0 (0)
Not evaluable or unknown	16.3 (30)	11.9 (8)	19.1 (9)	27.0 (10)	18.5 (17)	14.7 (5)	18.2 (4)	11.8 (2)
	≥12 years to <18 years (N = 180)	≥6 years to <12 years (N = 67)	≥2 years to <6 years (N = 46)	<2 years (N = 36)	≥12 years to <18 years (N = 89)	≥6 years to <12 years (N = 34)	≥2 years to <6 years (N = 22)	<2 years (N = 17)
Any bleeding event	42.2 (76)	29.9 (20)	21.7 (10)	36.1 (13)	30.3 (27)	26.5 (9)	27.3 (6)	17.6 (3)
"Major bleeding" or "clinically relevant non-major bleeding"	1.7 (3)	3.0 (2)	6.5 (3)	5.6 (2)	2.2 (2)	0 (0)	0 (0)	5.9 (1)
Major bleeding	0 (0)	0 (0)	0 (0)	0 (0)	1.1 (1)	0 (0)	0 (0)	5.9 (1)
Intracranial	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	5.9 (1)
Thorax	0 (0)	0 (0)	0 (0)	0 (0)	1.1 (1)	0 (0)	0 (0)	0 (0)
Clinically relevant non-major bleeding	1.7 (3)	3.0 (2)	6.5 (3)	5.6 (2)	1.1 (1)	0 (0)	0 (0)	0 (0)
Gastrointestinal tract	1.1 (2)	0 (0)	2.2 (1)	2.8 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Genital tract	0.6 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Injection site	0 (0)	0 (0)	2.2 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Nasal cavity	0 (0)	1.5 (1)	2.2 (1)	0 (0)	1.1 (1)	0 (0)	0 (0)	0 (0)
Oral cavity	0 (0)	0 (0)	0 (0)	2.8 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Urinary tract	0 (0)	1.5 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

% (n)

An assessment of the incidences of the efficacy endpoints and bleeding events in Study 14372 by body weight category (≥30 kg, ≥12 to <30 kg, <12 kg) revealed no clear differences in the efficacy or safety of rivaroxaban across the body weight categories.

Table 30 presents the incidences of adverse events by age group. The incidences of adverse events did not clearly differ across the age groups. In the age group <2 years, adverse events leading to treatment discontinuation occurred more frequently in the rivaroxaban group (13.9% [5 of 36 patients]; vomiting, procedural haemorrhage, large intestinal haemorrhage, vomiting and epilepsy, and pulmonary haemorrhage and urinary bladder haemorrhage) than in the standard of care group (5.9% [1 of 17 patients]; subdural haemorrhage). A causal relationship to the study drug was ruled out in the rivaroxaban group, except for the treatment-related bleeding in 1 patient and vomiting in 1 patient. The incidences of adverse events, serious adverse events, and adverse events by severity in the age groups <2 years did not substantially differ from those in other age groups, suggesting that the safety of rivaroxaban in the age group <2 years is unlikely to substantially differ from that in other age groups, or the safety of the standard of care in the same age group.

Table 30. Summary of adverse events by age group (main treatment period, safety analysis set)

		Rivaroxaban (N = 329)				Standard of care (N = 162)			
		≥12 years to <18 years (N = 180)	≥6 years to <12 years (N = 67)	≥2 years to <6 years (N = 46)	<2 years (N = 36)	≥12 years to <18 years (N = 89)	≥6 years to <12 years (N = 34)	≥2 years to <6 years (N = 22)	<2 years (N = 17)
Adverse events		86.7 (156)	82.1 (55)	78.3 (36)	75.0 (27)	73.0 (65)	73.5 (25)	81.8 (18)	82.4 (14)
Adverse drug reactions		35.6 (64)	19.4 (13)	13.0 (6)	19.4 (7)	20.2 (18)	2.9 (1)	18.2 (4)	23.5 (4)
Death		0.6 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Serious adverse events		18.9 (34)	25.4 (17)	21.7 (10)	27.8 (10)	15.7 (14)	23.5 (8)	13.6 (3)	41.2 (7)
Adverse events by severity	Severe	12.8 (23)	16.4 (11)	10.9 (5)	8.3 (3)	11.2 (10)	17.6 (6)	9.1 (2)	29.4(5)
	Moderate	33.9 (61)	28.4 (19)	26.1 (12)	27.8 (10)	30.3 (27)	23.5 (8)	22.7 (5)	23.5(4)
	Mild	40.0 (72)	37.3 (25)	41.3 (19)	38.9 (14)	31.5 (28)	32.4 (11)	50.0 (11)	29.4(5)
Adverse events leading to treatment discontinuation		2.2 (4)	1.5 (1)	2.2 (1)	13.9 (5)	2.2 (2)	0 (0)	0 (0)	5.9 (1)

% (n)

In younger children in Study 14372, the incidence of the composite of "major bleeding" and "clinically relevant non-major bleeding" tended to be higher in the rivaroxaban group than in the standard of care group. In light of this result, PMDA asked the applicant to explain their opinion on whether a special precaution regarding the use of rivaroxaban in younger children would be necessary, taking into account the activities, comprehension, and other abilities of the patient population.

The applicant's explanation:

The differences in the incidence of the composite of "major bleeding" and "clinically relevant non-major bleeding" observed among the age groups in the rivaroxaban group are not clinically significant, due to the small number of younger children experiencing such events. In addition, all of the bleeding events resolved after discontinuation or interruption of the study drug, medical care, or other measures. Thus, these bleeding events are tolerable in younger children. Although the incidence of bleeding events tended to be slightly higher in the rivaroxaban group than in the standard of care group, except in the age group ≥2 to <6 years, the difference between the treatment groups was attributed mainly to the difference in the incidence of "trivial bleeding," and thus is not clinically significant. Most of the bleeding events reported in the rivaroxaban group were those associated with manipulations of nasogastric tubes or ureteral catheters, and epistaxis, haemorrhage subcutaneous, and gastrointestinal haemorrhage, about which precautionary advice has been provided for the approved indications. Mild bleeding due to a facial scratch was reported in 1 child aged <2 years, which was likely related to the activity or comprehension of the infant; however, the event was mild in severity and resolved. Thus, no particular caution will be necessary.

The efficacy and safety of rivaroxaban were evaluated in infants (7 patients in the rivaroxaban group and 5 in the standard of care group) enrolled in Study 14372. Among the 7 patients in the rivaroxaban group (age, 0.2 to 0.8 months; treatment duration, 29 to 175 days), the asymptomatic deterioration of thrombotic burden was classified as "normalized" in 4 of 7 infants, "improved" in 2 of 7 infants, and "no relevant change" in 1 of 7 infants. Bleeding events were reported in 2 of 7 infants, all of which were classified as "trivial bleedings" (urethral haemorrhage and diarrhoea haemorrhagic, and wound haemorrhage) and resolved without changes in the dose of the study drug. Adverse events were reported in 6 of 7 infants; however, no adverse events resulted in death or led to treatment discontinuation. Serious adverse events were reported in 3 of 7 infants (meningitis bacterial, urinary tract infection, wound infection and gastroenteritis rotavirus, and metabolic acidosis);

however, a causal relationship to the study drug was ruled out for all of these events. Among the 5 infants in the standard of care group (age, 0.4 to 0.9 months; treatment duration, 28 to 103 days), asymptomatic deterioration of thrombotic burden was classified as “normalized” in 1 of 5 infants, “improved” in 1 of 5 infants, “no relevant change” in 2 of 5 infants, and “not evaluable” in 1 of 5 infants. No bleeding events were reported. Adverse events were reported in 4 of 5 infants; however, no adverse events resulted in death or led to treatment discontinuation. Serious adverse events were reported in 3 of 5 infants (atrial tachycardia, seizure, and oxygen saturation decreased); however, a causal relationship to the study drug was ruled out, except for 1 event (oxygen saturation decreased). Although the small number of infants enrolled in the study precluded a precise evaluation, these results indicated that the efficacy of rivaroxaban tended to be non-inferior to that of standard of care and that its safety was manageable, despite slightly more frequently reported bleeding events in infants receiving rivaroxaban than in those receiving standard of care. The applicant therefore considers that rivaroxaban has promising efficacy and acceptable safety in infants, as well.

Study 14372 excluded patients aged <6 months with (a) a gestational age at birth of <37 weeks, (b) oral feeding, or nasogastric or gastric tube feeding for <10 days, or (c) body weight <2600 g. The package insert will include a statement that the efficacy and safety of rivaroxaban have not been established in such patients.

PMDA’s view:

Based on the results of the above assessment of the efficacy and safety of rivaroxaban by age group in Study 14372, the incidences of “symptomatic recurrent VTE” and bleeding events did not substantially differ across the age groups, except for the age group <2 years. Due to the small number of patients aged <2 years and the absence of reported events for the primary efficacy endpoint or the key secondary efficacy endpoint (the composite endpoint of “symptomatic recurrent VTE” and “asymptomatic deterioration of thrombotic burden” on imaging) in this patient population, the efficacy of rivaroxaban cannot be evaluated based solely on the results of these endpoints. However, the results of thrombotic burden assessment on imaging, along with the above findings, support the efficacy of rivaroxaban. According to a safety analysis, the incidence of bleeding events in the age group <2 years during the main treatment period tended to be higher in the rivaroxaban group than in the standard of care group. However, most of these bleeding events were treatment-related and were mild in severity (e.g., epistaxis). A causal relationship between the study drug and the events was ruled out. In addition, given that all of the bleeding events resolved, the safety of rivaroxaban is acceptable, as its efficacy is supported by the study results. No concerns regarding the efficacy or safety of rivaroxaban have been identified in any particular body weight category.

In view of the results from the 12 infants with VTE (7 in the rivaroxaban group and 5 in the standard of care group) enrolled in Study 14372 and the above explanation of the applicant, rivaroxaban has promising efficacy and acceptable safety in such patient population. The applicant’s proposal to provide information regarding the patient populations excluded from Study 14372 is appropriate.

Based on the above, rivaroxaban has promising efficacy, irrespective of age or body weight, and acceptable safety in the treatment of pediatric VTE, as long as appropriate information is provided [see Section "7.R.4.1 Bleeding"].

7.R.6 Indications

PMDA's view:

Although pediatric VTE develops at a slightly greater variety of sites than adult VTE (including DVT and PE), pediatric VTE and adult VTE share the same pathology, in which thrombus formation in a vein reduces blood flow. The use of different indications for children and adults, proposed by the applicant, is not rational.

In view of this fact, along with the range of the efficacy and safety results evaluated for adults, the applicant's proposed indications should be modified as follows:

PMDA's proposed indications (Underline denotes additions to the applicant's proposed text. Strikethrough denotes deletions from the applicant's proposed text.)

Xarelto Tablets 10 mg, Xarelto Tablets 15 mg, Xarelto Fine Granules 10 mg, Xarelto Fine Granules 15 mg, Xarelto OD Tablets 10 mg, Xarelto OD Tablets 15 mg

- Prevention of ischemic stroke and systemic embolism in patients with non-valvular atrial fibrillation
- Treatment of venous thromboembolism (deep vein thrombosis and pulmonary thromboembolism in adults) and prevention of its recurrence
- ~~Treatment of pediatric venous thromboembolism and prevention of its recurrence~~

Xarelto Dry Syrup for Pediatric 51.7 mg, Xarelto Dry Syrup for Pediatric 103.4 mg

Treatment of ~~pediatric~~ venous thromboembolism and prevention of its recurrence

7.R.7 Dosage and administration

7.R.7.1 Rationale for the dosage and administration

PMDA's view:

As was discussed in Section "6.R.2 Dosage regimens in the global phase III study (Study 14372)," the dosage regimen assessed in Study 14372 was appropriate, with the intention of achieving exposure in children similar to that observed in adults. The results of Study 14372 conducted using the dosage regimen successfully demonstrated that rivaroxaban had efficacy that was non-inferior to that of standard of care and acceptable safety in the overall study population. The results were consistent with results from clinical studies in adult patients with VTE. Thus, the dosage regimen used in Study 14372 has been clinically justified. An analysis of the Japanese subpopulation, despite the small number of patients, predicted similarities in the pharmacokinetics and efficacy of rivaroxaban in Japanese and non-Japanese children [see Sections "6.R.1 Differences in the pharmacokinetics and pharmacodynamics of rivaroxaban between Japanese and non-Japanese children" and "7.R.3.2 Efficacy evaluation in Study 14372"], with no particular safety problems in the Japanese subpopulation [see Section "7.R.4 Safety"]. Based on these results, the dosage regimen assessed in Study 14372 should be used in Japanese pediatric patients with VTE, as well.

In view of the discussion presented in Section "7.R.6 Indications," the proposed dosage and administration of rivaroxaban should be modified as follows:

PMDA's proposed indications (Underline denotes additions to the applicant's proposed text. Strikethrough denotes deletions from the applicant's proposed text.)

Xarelto Tablets 10 mg, Xarelto Tablets 15 mg, Xarelto Fine Granules 10 mg, Xarelto Fine Granules 15 mg, Xarelto OD Tablets 10 mg, Xarelto OD Tablets 15 mg

- Prevention of ischemic stroke and systemic embolism in patients with non-valvular atrial fibrillation
  The usual adult dosage is 15 mg of rivaroxaban administered orally once daily with food. In patients with renal impairment, the dosage should be reduced to 10 mg once daily, depending on the degree of renal impairment.
- Treatment of venous thromboembolism~~, deep vein thrombosis, and pulmonary thromboembolism~~ and prevention of its recurrences
  Adults
  The usual adult dosage is 15 mg of rivaroxaban administered orally twice daily with food for the first 3 weeks after the onset of deep vein thrombosis or pulmonary thromboembolism, followed by 15 mg of rivaroxaban administered orally once daily with food.
- ~~Treatment of pediatric venous thromboembolism and prevention of its recurrence~~
  Children
  The usual dosage in children weighing ≥30 kg is 15 mg of rivaroxaban administered orally once daily with food.

Xarelto Dry Syrup for Pediatric 51.7 mg, Xarelto Dry Syrup for Pediatric 103.4 mg

The usual dosage in children is determined based on body weight (see the table below). For children weighing ≥2.6 kg to <12 kg is the body weight-based dose of rivaroxaban administered orally three times daily with food. The dosage in children weighing ≥12 kg to <30 kg is 5 mg of rivaroxaban administered orally twice daily with food, and the dosage in children weighing ≥30 kg is 15 mg of rivaroxaban administered orally once daily with food.

Recommended dosage for the treatment of ~~pediatric~~ venous thromboembolism and the prevention of its recurrence

Body weight	Dose (1 mg of rivaroxaban corresponds to 1 mL of the suspension)			Total daily dose
	Once daily	Twice daily	Three times daily	
≥2.6 kg to <3 kg			0.8 mg	2.4 mg
≥3 kg to <4 kg			0.9 mg	2.7 mg
≥4 kg to <5 kg			1.4 mg	4.2 mg
≥5 kg to <7 kg			1.6 mg	4.8 mg
≥7 kg to <8 kg			1.8 mg	5.4 mg
≥8 kg to <9 kg			2.4 mg	7.2 mg
≥9 kg to <10 kg			2.8 mg	8.4 mg
≥10 kg to <12 kg			3.0 mg	9.0 mg
≥12 kg to <30 kg		5 mg		10 mg
≥30 kg	15 mg			15 mg

7.R.7.2 Switching from the initial treatment

PMDA asked the applicant to explain why the duration of the initial treatment for acute VTE was set at ≥5 to ≤9 days in Study 14372, as well as whether the proposed precautionary advice about the duration of initial treatment is appropriate.

The applicant's explanation:

The duration of initial treatment with parenteral anticoagulants (e.g., UFH) of ≥5 days for acute VTE is a global standard, both in adults and children (ACCP guidelines for antithrombotic therapy in neonates and children; Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: ACCP Evidence-based Clinical Practice Guidelines [*Chest.* 2012;141:e419S-e494S], Guidelines for Diagnosis, Treatment and Prevention of Pulmonary Thromboembolism and Deep Vein Thrombosis [2017 version] [The Japanese Circulation Society]). Accordingly, the duration of initial treatment was set at ≥5 days in Study 14732. The package insert will include a precautionary statement that rivaroxaban should be administered after 5 days of appropriate initial treatment (e.g., heparin) for acute VTE. In addition, the duration of initial treatment with UFH, etc. had to be within a given range, to accomplish proper comparisons between rivaroxaban therapy and standard of care, including VKA. The maximum duration of initial treatment was set at 9 days in the study. However, it is not necessary to specify the maximum duration of initial treatment in the package insert of rivaroxaban, because: (i) a 5-day course of intravenous UFH with warfarin therapy added on Day 1 to 5 was compared with a 10-day course of intravenous UFH with warfarin therapy added on Day 5 to 10 for the prevention of symptomatic recurrent VTE in adults, and the comparison showed similarity in the results, with no significant difference in the incidence of bleeding complications between the treatment courses (*N Engl J.* 1990;332:1260-1264); and, (ii) in Study 14372, a subgroup analysis by the duration of initial treatment (≤7 days vs. >7 days) showed no substantial difference in the efficacy or safety of rivaroxaban.

PMDA asked the applicant to explain the appropriateness of the time interval to switch from initial parenteral anticoagulant treatment to rivaroxaban therapy, taking into account the guidance and dosing methods used in Study 14372.

The applicant's explanation:

To switch from initial treatment to rivaroxaban therapy, the balance between the bleeding risk associated with the overlap in the pharmacology of parenteral anticoagulants and rivaroxaban, and the thrombosis risk due to prolonged time between initial treatment and rivaroxaban therapy should be considered. In Study 14372, the first dose of rivaroxaban was administered (a) ≥4 hours after stopping the infusion of UFH, (b) ≥12 hours after the last injection of LMWH with a twice-daily regimen, or (c) ≥24 hours after the last injection of fondaparinux sodium or LMWH with a once-daily regimen. This rule was established during the planning of a phase II study in patients with VTE that had been treated with anticoagulants for ≥2 months (or ≥6 weeks for catheter-related VTE) after the onset of VTE (Study 14373), focusing on the bleeding risk rather than the thrombosis risk. However, UFH, an anticoagulant assumed to be commonly used in initial treatment for pediatric VTE in Japan, is rapidly eliminated in adults, and the clearance of heparin is significantly greater in children, especially newborns, than in adults, with a half life in children comparable to or shorter than that in adults (*Blood Cells*

Mol Dis. 2017;67:41-7, *Pediatr Res.* 1981;15:1015-8). In view of these findings, switching from initial treatment to rivaroxaban therapy for children at a timing similar to that for adults is inferred to result in lower blood UFH concentrations in children than in adults, and is thus unlikely to increase safety concerns about additional pharmacological effects in children. Based on the above, the guidance, which has been adopted for the approved adult indications and has accumulated experience, is appropriate to maintain the desired anticoagulant effect of initial treatment after the onset of VTE in children. The following guidance should be employed for treatment of pediatric VTE: "To switch from injectable anticoagulants (e.g., heparin) to rivaroxaban, start the administration of rivaroxaban 0 to 2 hours prior to the next scheduled intravenous or subcutaneous administration of an anticoagulant or at the time when the continuous infusion of the anticoagulant is stopped."

PMDA's view:
It is appropriate that the duration of initial treatment with parenteral anticoagulants (e.g., UFH) after the onset of VTE was set at ≥5 days in Study 14372, referring to guidelines available in and outside of Japan, and that the maximum duration of initial treatment with UFH, etc. was defined in the study to properly compare rivaroxaban therapy with standard of care, including VKA. In view of the guidance regarding switching from initial treatment to rivaroxaban therapy used in Study 14372, and of recommendations by guidelines available in and outside of Japan, the package insert of rivaroxaban should specify solely the minimum duration (5 days) of parenteral anticoagulation (e.g., UFH) prior to rivaroxaban therapy, and the duration of initial parenteral anticoagulation beyond 5 days should be decided by treating physicians, according to the condition of each individual patient.

In clinical practice in Japan, initial treatment for pediatric VTE is assumed to involve a continuous infusion of UFH in an inpatient setting. According to the applicant's explanation, and in view of the fact that appropriate monitoring such as vital sign checks and blood tests is possible in an inpatient setting, switching from initial treatment to rivaroxaban therapy will be accomplished with no major problems, given that the following precautionary advice is provided: "To switch from injectable anticoagulants (e.g., heparin) to rivaroxaban, start the administration of rivaroxaban 0 to 2 hours prior to the next scheduled intravenous or subcutaneous administration of the anticoagulant, or at the time when the continuous infusion of the anticoagulant is stopped."

7.R.7.3 Treatment duration

PMDA asked the applicant to justify the rationale for the main treatment period and the maximum treatment duration selected in Study 14372, and explain the appropriateness of the recommended treatment durations in clinical practice (1 to 3 months for patients aged <2 years with catheter-related VTE and 3 to 12 months for other pediatric patients with VTE).

The applicant's explanation:
The ACCP guidelines for antithrombotic therapy in neonates and children and the ASH guidelines for the treatment of pediatric VTE recommend the durations of anticoagulation in children shown below, depending

on whether the VTE is primary or recurrent, idiopathic or secondary, and whether the patient has ongoing risk factors:

- In children with provoked VTE in whom the risk factor has resolved: 3 months (Grade 2C)
- In children who have persistent risk factors: >3 months (Grade 2C)
- In children with catheter-related VTE: 6 weeks to 3 months (Grade 2C)
- In children with primary idiopathic VTE: 6 to 12 months (Grade 2C)
- In children with recurrent idiopathic VTE: indefinite treatment (Grade 1A)

In Study 11702, which demonstrated the efficacy and safety of rivaroxaban in the treatment of adult patients with DVT or PE, a treatment duration of 3, 6, or 12 months was selected for each patient by the investigator (or subinvestigator), based on an assessment of the risk factors for thrombosis and the potential for bleeding. In line with the overseas guidelines' recommendations and from the viewpoint of comparability with the results of Study 11702 in adult patients with DVT or PE, the main treatment period of Study 14372 was set at 3 months in patients aged ≥2 years and patients aged <2 years with non-catheter-related VTE, or 1 month in patients aged <2 years with catheter-related VTE, and the maximum treatment duration was set at 12 months or 3 months, respectively [see Section "7.R.3.1 Development program for treatment of pediatric VTE"].

The actual treatment durations in Study 14372 are presented in Table 31.

Table 31. Duration of treatment with the study drug in Study 14372 (FAS)

Patients aged ≥2 years and those aged <2 years with non-catheter-related VTE			Patients aged <2 years with catheter-related VTE		
Treatment duration	Rivaroxaban (N = 304)	Standard of care (N = 151)	Treatment duration	Rivaroxaban (N = 25)	Standard of care (N = 11)
≥1 month	96.7 (294)	95.4 (144)	≥1 week	96.0 (24)	100.0 (11)
≥2 months	95.4 (290)	94.7 (143)	≥2 weeks	92.0 (23)	100.0 (11)
≥3 months	65.5 (199)	60.9 (92)	≥3 weeks	92.0 (23)	100.0 (11)
≥6 months	26.3 (80)	24.5 (37)	≥1 month	76.0 (19)	63.6 (7)
≥9 months	13.2 (40)	13.2 (20)	≥2 months	48.0 (12)	54.5 (6)
≥12 months	3.0 (9)	4.0 (6)	≥3 months	20.0 (5)	27.3 (3)

% (n)

Table 32 presents the results of key efficacy and safety endpoints during the main treatment period, in patients aged ≥2 years and those aged <2 years with non-catheter-related VTE versus patients aged <2 years with catheter-related VTE. In both patient populations, the efficacy and safety results obtained during the main treatment period did not tend to substantially differ between the rivaroxaban group and the standard of care group. In addition, the efficacy and safety results during the extended treatment periods did not tend to substantially differ from those in the main treatment period in both patient populations.

Table 32. Incidences of efficacy endpoints and bleeding events in patients aged ≥2 years and those aged <2 years with non-catheter-related VTE versus patients aged <2 years with catheter-related VTE
(main treatment period; efficacy, FAS; safety, safety analysis set)

	Patients aged ≥2 years and those aged <2 years with non-catheter-related VTE		Patients aged <2 years with catheter-related VTE	
	Rivaroxaban (N = 309)	Standard of care (N = 154)	Rivaroxaban (N = 26)	Standard of care (N = 11)
Symptomatic recurrent VTE	1.3 (4)	3.2 (5)	0 (0)	0 (0)
"Symptomatic recurrent VTE" or "asymptomatic deterioration of thrombotic burden"	1.6 (5)	3.9 (6)	0 (0)	0 (0)
Thrombotic burden assessment				
Normalized	37.9 (117)	26.0 (40)	42.6 (11)	27.3 (3)
Improved	40.5 (125)	46.8 (72)	15.4 (4)	27.3 (3)
No relevant change	4.9 (15)	6.5 (10)	3.8 (1)	27.3 (3)
Deteriorated	0.3 (1)	0.6 (1)	0 (0)	0 (0)
Not evaluable or unknown	15.2 (47)	16.9 (26)	38.5 (10)	18.2 (2)
Any bleeding event	36.2 (110/304)	29.1 (44/151)	36.0 (9/25)	9.1 (1/11)
"Major bleeding" or "clinically relevant non-major bleeding"	3.0 (9/304)	2.0 (3/151)	4.0 (1/25)	0 (0/11)
Major bleeding	0 (0/304)	1.3 (2/151)	0 (0/25)	0 (0/11)
Clinically relevant non-major bleeding	3.0 (9/304)	0.7 (1/151)	4.0 (1/25)	0 (0/11)

% (n)

In clinical practice, the duration of treatment with rivaroxaban is likely to be shorter than the main treatment period set in Study 14372, due to the physician's discretion, recurrent VTE, or adverse events. For instance, the ASH guidelines for treatment of pediatric VTE (*Blood Adv.* 2018;2:3292-316) recommends anticoagulation for ≤3 months rather than anticoagulation for >3 months, in pediatric patients with DVT or PE provoked by risk factors, allowing anticoagulant therapy of a shorter duration. In contrast, the ACCP guidelines for antithrombotic therapy in neonates and children recommends indefinite anticoagulation in pediatric patients with recurrent idiopathic VTE. This suggests that such patients may require continued anticoagulant therapy beyond the maximum treatment duration set in Study 14372.

Whenever possible, rivaroxaban therapy should be continued for at least the same period of time as the main treatment period set in Study 14372 to achieve the efficacy and safety of rivaroxaban observed in Study 14372. However, rivaroxaban therapy shorter or longer than the maximum treatment period in Study 14372 may be required at the discretion of physicians, based on risk-benefit assessment for each patient, as described above. Therefore, the proposed package insert will include a precautionary statement, as in the case of adult VTE, to the effect that "the duration of treatment with rivaroxaban should be decided, taking into account the risk of recurrent VTE and the bleeding risk for each patient. The administration of rivaroxaban should not be continued injudiciously." At the same time, information on the treatment duration assessed in the clinical study will be properly provided.

PMDA's view:

Since the results of Study 14372 have demonstrated the promising efficacy and acceptable safety of rivaroxaban, both in the main treatment period and the entire treatment period [see Sections "7.R.3 Efficacy" and "7.R.4 Safety"), the applicant's explanation that the minimum treatment period and the maximum treatment period set in Study 14372 can be recommended as the duration of rivaroxaban therapy for pediatric patients with VTE is appropriate. Although the overseas guidelines indicate the target treatment durations for pediatric VTE, the appropriateness of continued treatment should be assessed for each patient based on the risk

of recurrent VTE, including the presence of ongoing risk factors for VTE, and bleeding risk. Thus, the applicant should properly provide information on the treatment durations set in the clinical study, and present a similar precautionary statement to that effect for adult VTE in the package insert, rather than specifying a uniform treatment duration. PMDA's conclusions will be finalized after taking into account the comments from the Expert Discussion.

7.R.8 Post-marketing investigations

The applicant's explanation about the post-marketing investigations for rivaroxaban:

In Study 14372, bleeding events for which a causal relationship to rivaroxaban could not be ruled out were reported. In addition, the risk of bleeding events may be attributable to the pharmacology of rivaroxaban. In view of these facts, the safety specification in the risk management plan (draft), requiring particular investigation for the use of rivaroxaban for the treatment of pediatric VTE is "bleeding." The applicant plans to conduct a post-marketing database survey to evaluate the incidence of bleeding, etc. in pediatric patients treated with rivaroxaban for VTE in clinical practice. The observation period of the survey will be 3 years and 6 months, and the planned sample size will be 250 pediatric patients receiving rivaroxaban (the exposed group) and 250 pediatric patients receiving warfarin (the reference group). The planned sample size of 250 patients in each group is expected to provide a ≥95% probability of detecting bleeding events in ≥3 patients. The survey will also collect and evaluate the data, whenever possible, regarding the concomitant use of antiplatelet drugs or non-steroidal anti-inflammatory drugs, bleeding risks associated with the chronic use of rivaroxaban, and bleeding risks associated with switching from other oral anticoagulants to rivaroxaban. Further, the applicant plans to collect post-marketing information about the incidence of recurrent VTE, although the details are still under consideration.

The safety specifications other than bleeding, including hepatic disorder and jaundice, interstitial lung disease, thrombocytopenia, the concomitant use of CYP3A4 inhibitors, the concomitant use of CYP3A4 inducers, long-term safety, and safety in patients with prior use of other oral anticoagulants, are presumed to pose risks to pediatric patients as well as adult patients, and therefore require the collection and evaluation of post-marketing safety information. Either no evaluation, or limited evaluation was made on some patient populations in Study 14372. However, no particular risks or new findings have been identified in pediatric patients with VTE compared with adult patients with VTE, and no additional precautionary advice is required for adult indications in the post-marketing setting. For these and other reasons, safety information will be collected and evaluated through routine pharmacovigilance activities and early post-marketing phase vigilance, and if necessary, additional safety measures will be considered.

PMDA's view:

The post-marketing surveillance should include the collection of information about the concomitant use of CYP3A4 inhibitors and bleeding in patients with renal impairment, which were listed as important potential risks and important missing information during the review for the approved indications, and will also require attention in the use of rivaroxaban in pediatric patients with VTE, in addition to the investigations the applicant has proposed. The details of the post-marketing surveillance, including safety specifications and the

appropriateness of risk classification, pharmacovigilance activities, and risk minimization activities, will be finalized in accordance with the Risk Management Plan Guidance (PFSB/SD Notification No. 0411-1 and PFSB/ELD Notification No. 0411-2, both dated April 11, 2012), after discussions at the Expert Discussion.

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

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

The new drug application data were subjected to a document-based 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.

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

The new drug application data (CTD 5.3.5.1.3) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

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

On the basis of the data submitted, PMDA has concluded that rivaroxaban has efficacy in the treatment of pediatric VTE and the prevention of recurrent VTE, and that rivaroxaban has acceptable safety in view of its benefits. Rivaroxaban, an FXa inhibitor, is clinically meaningful because it offers a new treatment option for pediatric patients with VTE. The dosage and administration, the precautionary statement to be included in the package insert, post-marketing investigations, etc. should be further discussed.

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

Review Report (2)

November 13, 2020

Product Submitted for Approval

Brand Name	(a) Xarelto Tablets 10 mg, (b) Xarelto Tablets 15 mg (c) Xarelto Fine Granules 10 mg (d) Xarelto Fine Granules 15 mg (e) Xarelto OD Tablets 10 mg (f) Xarelto OD Tablets 15 mg (g) Xarelto Dry Syrup for Pediatric 51.7 mg (h) Xarelto Dry Syrup for Pediatric 103.4 mg
Non-proprietary Name	Rivaroxaban
Applicant	Bayer Yakuhin, Ltd.
Date of Application	February 14, 2020 for (a), (b), (c), (d), (g), and (h) September 11, 2020 for (e) and (f)

List of Abbreviations

See Appendix.

1. Content of the Review

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

1.1 Efficacy

The development program of rivaroxaban for the treatment of pediatric venous thromboembolism (VTE) aims to demonstrate the efficacy and safety of rivaroxaban in pediatric patients with VTE based on findings from adult patients with VTE, by comparing the results of Study 14372 in pediatric patients with VTE, with those of foreign phase III studies in adult patients with VTE (Studies 11702-DVT and 11702-PE; hereinafter, collectively called “Study 11702”). PMDA has concluded that this development program is acceptable, and PMDA’s conclusion was supported by the expert advisors.

In Study 14372, rivaroxaban was shown to be non-inferior to standard of care in terms of efficacy in the treatment of pediatric VTE, measured by the incidence of “symptomatic recurrent VTE” during the main treatment period, the primary efficacy endpoint. The efficacy of rivaroxaban observed in Study 14372 was

similar to that observed in Study 11702. The efficacy results, including results from individual patients, in the Japanese subpopulation of Study 14372 indicated that rivaroxaban in the Japanese subpopulation, are expected to be consistent with the efficacy results from the overall study population. Based on these results, PMDA has concluded that the submitted data have demonstrated the efficacy of rivaroxaban in Japanese pediatric patients with VTE. PMDA's conclusion was supported by the expert advisors.

The expert advisors commented that the results of subgroup analyses by geographic region (e.g., Asia including Japan) should be presented because of the very small number of Japanese patients enrolled in Study 14372. PMDA explained that the incidence of "symptomatic recurrent VTE" in Study 14372 had been demonstrated not to substantially differ among races, and then confirmed that the incidences of the efficacy endpoints also did not differ across geographic regions (Table 33).

Table 33. Incidences of efficacy endpoints by geographic region (Study 14372, main treatment period, FAS)

	Rivaroxaban				Standard of care			
Geographic region	North America (N = 117)	Europe (N = 170)	Asia (N = 15)	Others (N = 33)	North America (N = 62)	Europe (N = 84)	Asia (N = 6)	Others (N = 13)
Symptomatic recurrent VTE	1.7 (2)	1.2 (2)	0 (0)	0 (0)	1.6 (1)	2.4 (2)	16.7 (1)	7.7 (1)
"Symptomatic recurrent VTE" or "asymptomatic deterioration of thrombotic burden"	1.7 (2)	1.2 (2)	0 (0)	3.0 (1)	1.6 (1)	3.6 (3)	16.7 (1)	7.7 (1)
Thrombotic burden assessment								
Normalized	41.9 (49)	37.1 (63)	33.3 (5)	33.3 (11)	30.6 (19)	19.0 (16)	16.7 (1)	53.8 (7)
Improved	37.6 (44)	39.4 (67)	46.7 (7)	33.3 (11)	45.2 (28)	51.2 (43)	16.7 (1)	23.1 (3)
No relevant change	1.7 (2)	5.3 (9)	13.3 (2)	9.1 (3)	3.2 (2)	10.7 (9)	33.3 (2)	0 (0)
Deteriorated	0 (0)	0 (0)	0 (0)	3.0 (1)	0 (0)	1.2 (1)	0 (0)	0 (0)
Not evaluable or unknown	17.1 (20)	17.1 (29)	6.7 (1)	21.2 (7)	19.4 (12)	15.5 (13)	16.7 (1)	15.4 (2)

% (n)

1.2 Safety

(1) Bleeding

Based on the incidence of bleeding events in Study 14372, PMDA has concluded that the safety of rivaroxaban is clinically acceptable in view of the observed benefits of rivaroxaban. PMDA's conclusion was supported by the expert advisors. PMDA has also concluded that information about the incidence of bleeding events in pediatric patients with VTE should be properly provided, and that the package insert should include a precautionary statement that rivaroxaban should be used by or under the supervision of physicians with sufficient knowledge and experience in pediatric anticoagulation, in view of the following facts: (i) The incidence of bleeding events was higher in the rivaroxaban group than in the standard of care group in Study 14372; (ii) the number of Japanese patients evaluated in Study 14372 was extremely limited; (iii) no anticoagulation parameters to be monitored during rivaroxaban therapy have been established; and, (iv) no drugs have been proven to neutralize the anticoagulant effect of rivaroxaban. The expert advisors supported this PMDA's conclusion, as well.

(2) Adverse events of special interest other than bleeding

At the Expert Discussion, the expert advisors supported the PMDA's conclusion that precautionary advice regarding the development of hepatic disorder and allergic reactions, which is similar to that for adult patients, should be provided for the use of rivaroxaban in children.

The expert advisors commented that the package insert should include a precautionary statement that patients with thrombocytopenia are at an increased risk of bleeding, given that more pediatric patients with VTE are receiving chemotherapy or have heart failure or hepatic failure than adult patients with VTE and that these patients often present with thrombocytopenia.

PMDA instructed the applicant to more clearly state in the package insert that patients presenting with thrombocytopenia should be monitored carefully, and to consider the inclusion of precautions for the use of rivaroxaban in patients who are receiving chemotherapy or those with other risk factors in written materials for healthcare professions. PMDA confirmed that the applicant had responded to this instruction appropriately.

(3) Others

At the Expert Discussion, the expert advisors supported the PMDA's conclusions presented below.

- The applicant's explanation that no new safety concerns requiring additional precautionary advice has been identified in pediatric patients with VTE, as compared with adult patients with VTE, is appropriate.
- Due to the limited experience with the use of rivaroxaban in pediatric patients with renal impairment in Study 14372, the applicant has decided to provide precautions regarding the use of rivaroxaban in children, as in the case of adults; specifically, that rivaroxaban is contraindicated in patients with severe renal impairment, and that the appropriateness of the use of rivaroxaban in patients with moderate renal impairment should be considered carefully. The applicant's decision is appropriate.
- The following precautionary advice regarding the concomitant use of rivaroxaban with CYP3A4 inhibitors should be provided: In children weighing ≥30 kg, as for adults, a reduction in the dosage of rivaroxaban from 15 mg once daily to 10 mg once daily should be considered, or rivaroxaban should be administered only to patients who are considered eligible for the use of rivaroxaban, after due consideration of the potential benefits and possible risks of the combination therapy. In children weighing <30 kg, the use of rivaroxaban in combination with fluconazole or fosfluconazole, or clarithromycin or erythromycin, should be avoided, unless such combination is deemed absolutely necessary, after due consideration of the potential benefits and possible risks of the combination therapy.

1.3 Clinical positioning and indications

PMDA has concluded that rivaroxaban is clinically meaningful in the treatment of pediatric VTE and the prevention of recurrent VTE, because it offers a new option for maintenance treatment to patients who have completed initial parenteral anticoagulation. PMDA's conclusion was supported by the expert advisors.

PMDA has also concluded that the indications proposed in the Review Report (1) should be modified as shown below.

Indications

Xarelto Tablets 10 mg, Xarelto Tablets 15 mg, Xarelto Fine Granules 10 mg, Xarelto Fine Granules 15 mg, Xarelto OD Tablets 10 mg, Xarelto OD Tablets 15 mg

Adults

- Prevention of ischemic stroke and systemic embolism in patients with non-valvular atrial fibrillation
- Treatment of venous thromboembolism (deep vein thrombosis and pulmonary thromboembolism) and prevention of its recurrence

Children

- Treatment of venous thromboembolism and prevention of its recurrence

Xarelto Dry Syrup for Pediatric 51.7 mg, Xarelto Dry Syrup for Pediatric 103.4 mg
Treatment of venous thromboembolism and prevention of its recurrence

1.4 Dosage and administration

(1) Appropriateness of the dosage and administration, and treatment duration

The dosage regimen for children assessed in Study 14372 was appropriate, with the intention of achieving an exposure similar to that observed in adults. The results of Study 14372 successfully demonstrated that rivaroxaban had efficacy non-inferior to that of standard of care and acceptable safety, and were consistent with those of clinical studies in adult patients with VTE. Based on these facts and other findings, PMDA has concluded that the dosage regimen used in Study 14372 have been clinically justified. The expert advisors supported PMDA's conclusion. PMDA has also concluded that package insert should include the following precautionary statements that the duration of treatment with rivaroxaban should be decided, taking into account the risk of recurrent VTE and the bleeding risk for each patient, and that the administration of rivaroxaban should not be continued injudiciously. The expert advisors supported this PMDA's conclusion, as well.

(2) Timing of dosing relative to meal intake and dosing interval

The "Dosage and Administration" section specifies that rivaroxaban should be administered with food, and the "Precautions Concerning Dosage and Administration" section includes a statement that rivaroxaban should be administered approximately 8 hours apart on the three-times-daily dosing schedule. The expert advisors commented how dosing "approximately 8 hours apart" can be compatible with "three-times-daily dosing" and "with food," because such dosing requirements are usually suggestive of dosing after breakfast, lunch, and supper. These phrases may cause confusion in patients and their families.

Regarding the dosing interval recommended for the three-times-dosing regimen, PMDA asked the applicant to explain a dosing time window that is allowable in terms of the efficacy and safety of rivaroxaban.

The applicant's explanation:

- A comprehensive population pharmacokinetics (PPK) analysis in pediatric patients (Analysis 18376) revealed that the estimated pharmacokinetic parameters of rivaroxaban administered before or after the scheduled time were generally within the range of the exposure in the adult reference population. Rivaroxaban therapy in children weighing <12 kg, who are the intended population of the three-times-daily dosing regimen, targeted the median exposure in adult patients with an exposure corresponding to the lower 30% of the adult reference exposure range in the clinical study. Therefore, no pediatric patients

weighing <12 kg have had an exposure (C_{max}) to rivaroxaban beyond the median exposure in the adult reference population. In view of this fact, along with the distribution of exposure values observed in the clinical studies, rivaroxaban should be administered to pediatric patients approximately 8 hours apart, as specified in the clinical study.

- Rivaroxaban should be administered in a non-fasted state. Children weighing <12 kg (generally <2 years of age), who are the intended population of the three-times-dosing regimen, have frequent intake of milk or snacks other than regular meals, and the clinical study allowed nursing, milk feeding, and snacking. The administration of rivaroxaban in the non-fasted state, approximately 8 hours apart is thus possible.

As a result of the discussion at the Expert Discussion based on the above applicant's explanation, PMDA concluded that physicians should be fully aware that rivaroxaban should be administered after meal intake, including nursing and snacking, and should be informed collectively of the recommended dosing interval for each dosage regimen and dosing in the non-fasted state. The following dosage and administration of rivaroxaban was adopted finally.

Dosage and administration

(Underlines denote additions to the text in the Review Report (1). Strikethroughs denote deletions from the text in the Review Report (1).)

Xarelto Tablets 10 mg, Xarelto Tablets 15 mg, Xarelto Fine Granules 10 mg, Xarelto Fine Granules 15 mg, Xarelto OD Tablets 10 mg, Xarelto OD Tablets 15 mg

- Prevention of ischemic stroke and systemic embolism in patients with non-valvular atrial fibrillation
  The usual adult dosage is 15 mg of rivaroxaban administered orally once daily with food. In patients with renal impairment, the dosage should be reduced to 10 mg once daily, depending on the degree of renal impairment.
- Treatment of venous thromboembolism and prevention of its recurrence
  Adults
  The usual adult dosage is 15 mg of rivaroxaban administered orally twice daily with food for the first 3 weeks after the onset of deep vein thrombosis or pulmonary thromboembolism, followed by 15 mg of rivaroxaban administered orally once daily with food.
  Children
  The usual dosage in children weighing ≥30 kg is 15 mg of rivaroxaban administered orally once daily with food.

Xarelto Dry Syrup for Pediatric 51.7 mg, Xarelto Dry Syrup for Pediatric 103.4 mg

The usual dosage in children is determined based on body weight (see the table below). For children weighing from ≥2.6 kg to <12 kg, the body weight-based dose of rivaroxaban is administered orally three times daily ~~with food~~. The dosage in children weighing from ≥12 kg to <30 kg is 5 mg of rivaroxaban administered orally twice daily ~~with food~~, and the dosage in children weighing ≥30 kg is 15 mg of rivaroxaban administered orally once daily ~~with food~~. Xarelto should be administered in the non-fasted state, with a once-daily dosing schedule

of approximately 24 hours apart, a twice-daily dosing schedule of approximately 12 hours apart, or a three-times-daily dosing schedule of approximately 8 hours apart.

Recommended dosage of rivaroxaban for
treatment of venous thromboembolism and prevention of its recurrence

Body weight	Dose (1 mg of rivaroxaban corresponds to 1 mL of the suspension)			Total daily dose
	Once daily	Twice daily	Three times daily	
≥2.6 kg to <3 kg			0.8 mg	2.4 mg
≥3 kg to <4 kg			0.9 mg	2.7 mg
≥4 kg to <5 kg			1.4 mg	4.2 mg
≥5 kg to <7 kg			1.6 mg	4.8 mg
≥7 kg to <8 kg			1.8 mg	5.4 mg
≥8 kg to <9 kg			2.4 mg	7.2 mg
≥9 kg to <10 kg			2.8 mg	8.4 mg
≥10 kg to <12 kg			3.0 mg	9.0 mg
≥12 kg to <30 kg		5 mg		10 mg
≥30 kg	15 mg			15 mg

1.5 Risk management plan (draft)

In view of the discussion presented in Section "7.R.8 Post-marketing investigations" in the Review Report (1) and comments from the expert advisers at the Expert Discussion, PMDA has concluded that the safety specifications listed in Table 34 should be included in the present draft risk management plan for rivaroxaban, and that the applicant should conduct the additional pharmacovigilance activities and additional risk minimization activities summarized in Table 35. The details of the post-marketing database survey, including the procedure for information collection, will be further discussed.

Table 34. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
・Bleeding ・Concomitant use of antiplatelet drugs or non-steroidal anti-inflammatory drugs ・Hepatic disorder and jaundice ・Interstitial lung disease ・Thrombocytopenia	・Concomitant use of CYP3A4 inhibitors ・Concomitant use of CYP3A4 inducers	・Safety in adult patients with low body weight ・Safety in patients with renal impairment ・Long-term safety ・Safety in patients with prior treatment with other oral anticoagulants
Efficacy specification		
・Efficacy of rivaroxaban in the treatment of deep vein thrombosis (DVT) and pulmonary thromboembolism (PE) in clinical practice		

Underline denotes additions for the present application.

Table 35. Summary of additional pharmacovigilance activities, efficacy survey and studies, and additional risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimization activities
・Early post-marketing phase vigilance (pediatric VTE) ・Specified use-results survey (PE/DVT) - A survey on safety and efficacy in the treatment of PE or DVT in clinical practice - ・Post-marketing database survey (pediatric VTE)	・Disseminate information gathered from the early post-marketing phase vigilance (pediatric VTE) ・Organize and disseminate information for healthcare professionals (a proper use guide for the treatment of stroke prevention in atrial fibrillation) ・Organize and disseminate information for health care professionals (a proper use guide for the treatment of adult VTE) ・Organize and disseminate information for healthcare professionals (a proper use guide for the treatment of pediatric VTE) ・Organize and disseminate information for patients (a proper use brochure for patients receiving Xarelto for the treatment of atrial fibrillation) ・Organize and disseminate information for patients (a proper use brochure for patients receiving Xarelto for VTE) ・Organize and disseminate information for patients (a proper use brochure for patients receiving Xarelto and their families)
Efficacy surveys and studies	
・Specified use-results survey (PE/DVT) - A survey on safety and efficacy in the treatment of PE or DVT in clinical practice -	

Underline denotes activities relating to the indication in the present application.

2. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved with the indications and the dosage and administration as shown below with the following approval condition. The present application is intended for a new indication, a new dosage, and an additional dosage form. The re-examination period is 4 years for the new indication and the new dosage. Xarelto Dry Syrup for Pediatric 51.7 mg and Xarelto Dry Syrup for Pediatric 103.4 mg are not classified as biological products or specified biological products, or poisonous drugs or powerful drugs.

Indications

Xarelto Tablets 10 mg, Xarelto Tablets 15 mg, Xarelto Fine Granules 10 mg, Xarelto Fine Granules 15 mg, Xarelto OD Tablets 10 mg, Xarelto OD Tablets 15 mg

Adults

- Prevention of ischemic stroke and systemic embolism in patients with non-valvular atrial fibrillation
- Treatment of venous thromboembolism (deep vein thrombosis and pulmonary thromboembolism) and prevention of its recurrence

Children

- Treatment of venous thromboembolism and prevention of its recurrence

Xarelto Dry Syrup for Pediatric 51.7 mg, Xarelto Dry Syrup for Pediatric 103.4 mg

Treatment of venous thromboembolism and prevention of its recurrence

Dosage and Administration

Xarelto Tablets 10 mg, Xarelto Tablets 15 mg, Xarelto Fine Granules 10 mg, Xarelto Fine Granules 15 mg, Xarelto OD Tablets 10 mg, Xarelto OD Tablets 15 mg

- Prevention of ischemic stroke and systemic embolism in patients with non-valvular atrial fibrillation

The usual adult dosage is 15 mg of rivaroxaban administered orally once daily with food. In patients with renal impairment, the dosage should be reduced to 10 mg once daily, depending on the degree of renal impairment.

- Treatment of venous thromboembolism and prevention of its recurrence

  Adults

  The usual adult dosage is 15 mg of rivaroxaban administered orally twice daily with food for the first 3 weeks after the onset of deep vein thrombosis or pulmonary thromboembolism, followed by 15 mg of rivaroxaban administered orally once daily with food.

  Children

  The usual dosage in children weighing ≥30 kg is 15 mg of rivaroxaban administered orally once daily with food.

Xarelto Dry Syrup for Pediatric 51.7 mg, Xarelto Dry Syrup for Pediatric 103.4 mg

The usual dosage in children is determined based on body weight (see the table below). For children weighing from ≥2.6 kg to <12 kg, the body weight-based dose of rivaroxaban is administered orally three times daily. The dosage in children weighing from ≥12 kg to <30 kg is 5 mg of rivaroxaban administered orally twice daily, and the dosage in children weighing ≥30 kg is 15 mg of rivaroxaban administered orally once daily. Xarelto should be administered in the non-fasted state, with a once-daily dosing schedule of approximately 24 hours apart, a twice-daily dosing schedule of approximately 12 hours apart, or a three-times-daily dosing schedule of approximately 8 hours apart.

Recommended dosage of rivaroxaban for
treatment of venous thromboembolism and prevention of its recurrence

Body weight	Dose (1 mg of rivaroxaban corresponds to 1 mL of the suspension)			Total daily dose
	Once daily	Twice daily	Three times daily	
≥2.6 kg to <3 kg			0.8 mg	2.4 mg
≥3 kg to <4 kg			0.9 mg	2.7 mg
≥4 kg to <5 kg			1.4 mg	4.2 mg
≥5 kg to <7 kg			1.6 mg	4.8 mg
≥7 kg to <8 kg			1.8 mg	5.4 mg
≥8 kg to <9 kg			2.4 mg	7.2 mg
≥9 kg to <10 kg			2.8 mg	8.4 mg
≥10 kg to <12 kg			3.0 mg	9.0 mg
≥12 kg to <30 kg		5 mg		10 mg
≥30 kg	15 mg			15 mg

Approval Condition

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

Appendix

List of Abbreviations

ACCP	American College of Chest Physicians
ACCP guidelines for antithrombotic therapy in neonates and children	Antithrombotic Therapy in Neonates and Children Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-based Clinical Practice Guidelines (*Chest.* 2012; 141: e737s-e801s)
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
ASH	American Society of Hematology
ASH guidelines for treatment of pediatric VTE	American Society of Hematology 2018 Guidelines for management of venous thromboembolism: treatment of pediatric venous thromboembolism (*Blood*. 2018; 2: 3292-3316)
AUC	Area under the plasma concentration-time curve
BE	Bioequivalence
CI	Confidence interval
CL	Total body clearance
CL_{cr}	Creatinine clearance
CL/F	Apparent total body clearance
C_{max}	Maximum observed plasma concentration
C_{trough}	Trough concentration
CV	Coefficient of variation
CVST	Cerebral vein and sinus thrombosis
CYP	Cytochrome P450
DVT	Deep vein thrombosis
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
FAS	Full analysis set
FXa	Activated factor X
INR	International normalized ratio
ITT	Intent to treat
LC/MS/MS	Liquid chromatography coupled with tandem mass spectrometry
LMWH	Low molecular weight heparin
OD	Orally disintegrating
PBPK	Physiologically-based pharmacokinetics
PD	Pharmacodynamics
PE	Pulmonary embolism
PK	Pharmacokinetics
PPK	Population pharmacokinetics
P-gp	P-glycoprotein
PMDA	Pharmaceuticals and Medical Devices Agency
PT	Prothrombin time
PT-INR	Prothrombin time-international normalized ratio
Q	Intercompartmental clearance
Rivaroxaban	Rivaroxaban
UFH	Unfractionated heparin
V	Volume of distribution
V_c	Central volume of distribution
VKA	Vitamin K antagonist
V_p	Peripheral volume of distribution
VTE	Venous thromboembolism