Report on the Deliberation Results

December 3, 2012
Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau
Ministry of Health, Labour and Welfare

[Brand name]	Eliquis Tablets 2.5 mg and 5 mg
[Non-proprietary name]	Apixaban (JAN*)
[Applicant]	Bristol-Myers K.K.
[Date of application]	December 21, 2011

[Results of deliberation]
In the meeting held on November 30, 2012, the First Committee on New Drugs concluded that the product may be approved and that this result should be reported to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The product is not classified as a biological product or a specified biological product, the re-examination period of the product is 8 years, and neither the drug substance nor the drug product is classified as a poisonous drug or a powerful drug.

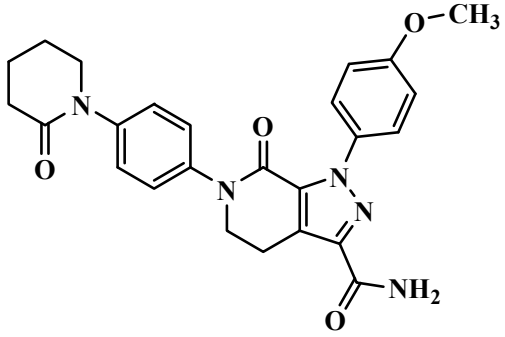
**Japanese Accepted Name (modified INN)*

Review Report

November 15, 2012
Pharmaceuticals and Medical Devices Agency

The results of a regulatory review conducted by the Pharmaceuticals and Medical Devices Agency on the following pharmaceutical product submitted for registration are as follows.

[Brand name]	Eliquis Tablets 2.5 mg and 5 mg
[Non-proprietary name]	Apixaban
[Applicant]	Bristol-Myers K.K.
[Date of application]	December 21, 2011
[Dosage form/Strength]	Film-coated tablets: Each tablet contains 2.5 or 5 mg of apixaban.
[Application classification]	Prescription drug (1) Drug with a new active ingredient
[Chemical structure]	



Molecular formula:	$C_{25}H_{25}N_5O_4$
Molecular weight:	459.50
Chemical name:	1-(4-Methoxyphenyl)-7-oxo-6-[4-(2-oxopiperidin-1-yl)phenyl] -4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*c*] pyridine-3-carboxamide

[Items warranting special mention]	None
[Reviewing office]	Office of New Drug II

Review Results

November 15, 2012

[Brand name]	Eliquis Tablets 2.5 mg and 5 mg
[Non-proprietary name]	Apixaban
[Applicant]	Bristol-Myers K.K.
[Date of application]	December 21, 2011

[Results of review]
Based on the submitted data, it is concluded that the efficacy of the product in the reduction of the risk of ischemic stroke and systemic embolism in patients with nonvalvular atrial fibrillation has been demonstrated, and its safety is acceptable in view of its observed benefits. It is important to collect, via post-marketing surveillance, information on the background factors of patients treated with low doses, information on the safety and efficacy, information on the safety in patients with renal impairment, elderly patients, patients with low body weight, and patients concomitantly administered with antiplatelet drugs, and information on the safety and efficacy when the product is discontinued or switched to or from other anticoagulant drugs.

As a result of its regulatory review, the Pharmaceuticals and Medical Devices Agency has concluded that the product may be approved for the following indication and dosage and administration.

[Indication]	Reduction of the risk of ischemic stroke and systemic embolism in patients with nonvalvular atrial fibrillation
[Dosage and administration]	The usual adult dosage of apixaban is 5 mg administered orally twice daily. The dose may be reduced to apixaban 2.5 mg twice daily depending on the age, body weight, and renal function of the patient.

Review Report (1)

October 5, 2012

I. Product Submitted for Registration

[Brand name]	Eliquis Tablets 2.5 mg and 5 mg
[Non-proprietary name]	Apixaban
[Applicant]	Bristol-Myers K.K.
[Date of application]	December 21, 2011
[Dosage form/Strength]	Film-coated tablets: Each tablet contains 2.5 or 5 mg of apixaban.
[Proposed indication]	Reduction of the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation
[Proposed dosage and administration]	The usual adult dosage of apixaban is 5 mg administered orally twice daily. The dose may be reduced to apixaban 2.5 mg twice daily, as appropriate.

II. Summary of the Submitted Data and Outline of Review by the Pharmaceuticals and Medical Devices Agency

The data submitted in the application and an outline of the review by the Pharmaceuticals and Medical Devices Agency (PMDA) are as shown below.

1. Origin or history of discovery and usage conditions in foreign countries, etc.

Apixaban is an orally active inhibitor of activated blood coagulation factor X (FXa) discovered by Bristol-Myers Squibb Company (US). Apixaban inhibits the blood coagulation system by selectively inhibiting FXa, thereby suppressing thrombus formation.

In foreign countries, Bristol-Myers Squibb Company (US) and Pfizer Inc. (US) jointly conducted the development of apixaban for the indications of "prophylaxis of venous thromboembolism," "treatment of venous thromboembolism (acute deep venous thrombosis and pulmonary embolism)," and "prophylaxis of stroke and systemic embolism associated with atrial fibrillation." First approved in the EU in May 2011 for the indication of "prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective hip or knee replacement surgery," apixaban is approved in 14 countries or regions including the EU as of [redacted].

In Japan, its development was initiated by Bristol-Myers K.K. in 20[redacted]. Based mainly on the results from the above global clinical trial, a marketing application for the product has now been submitted.

2. Data relating to quality

2.A Summary of the submitted data

2.A.(1) Drug substance

2.A.(1).1) Characterization

The drug substance is a white to pale yellow powder and has been characterized by description,

solubility, hygroscopicity, melting point, thermal analysis, pH of the solution, dissociation constant, partition coefficient, particle size, crystalline polymorphism, and forced degradation products.

The chemical structure of apixaban has been elucidated by elementary analysis, ultraviolet-visual spectrophotometry, infrared spectrophotometry (IR), nuclear magnetic resonance spectroscopy (^{1}H-NMR, ^{13}C-NMR), mass spectrometry, and single-crystal x-ray crystallography.

2.A.(1).2) Manufacturing process

[redacted] The following studies were performed using the quality-by-design (QbD) approach.

- Identification of genotoxic substances
- [redacted]
- Identification of manufacturing process parameters affecting CQA, according to the quality risk assessment and the design of experiments
- [redacted]

[redacted]

2.A.(1).3) Control of drug substance

The proposed specifications for the drug substance include content, description (appearance), identification (IR, liquid chromatography [HPLC]), purity (heavy metals [inductively coupled plasma-mass spectrometry], related substances [HPLC], residual solvents [gas chromatography]), particle size (laser diffraction), and assay (HPLC).

2.A.(1).4) Stability of drug substance

Stability studies conducted on the drug substance are as shown in Table 1. Results of the photostability testing showed the drug substance was photostable.

Table 1. Stability studies on drug substance

Study	Primary batch	Temperature	Humidity	Storage container	Storage period
Long-term	3 pilot-scale batches	5°C	–	Double-layered polyethylene bag + fiber drum	36 months
		25°C	60% RH		
		30°C	65% RH		
Accelerated		40°C	75% RH		6 months

-: Not specified

A retest period of [redacted] months has been proposed for the drug substance when stored in a double-layered polyethylene bag in a fiber drum at room temperature, based on the "Guideline on Evaluation of Stability Data," (PMSB/ELD Notification No. 0603004 dated June 3, 2003) (ICH Q1E Guideline).

2.A.(2) Drug product

2.A.(2).1) Description and composition of the drug product and formulation development

The drug product is a film-coated tablet containing 2.5 or 5 mg of the drug substance. The drug product contains, as excipients, anhydrous lactose, microcrystalline cellulose, croscarmellose sodium, sodium lauryl sulfate, magnesium stearate, hypromellose, lactose hydrate, titanium oxide, triacetin, and yellow ferric oxide (2.5 mg tablets) or iron sesquioxide (5 mg tablets).

2.A.(2).2) Manufacturing process

[redacted] The following investigations have been performed using the QbD approach.

- [redacted]
- Identification of manufacturing process parameters affecting the CQA, according to the quality risk assessment and the design of experiments
- [redacted]
- [redacted]

2.A.(2).3) Control of drug product

The proposed specifications for the drug product include content, description (appearance), identification (IR), uniformity of dosage units (content uniformity test [HPLC]), dissolution (HPLC), and assay (HPLC). [redacted]

- [redacted]
- [redacted]

If RTRT cannot be used as the release testing, specification tests are performed to check for release acceptability according to the pre-determined test procedures and the pre-defined criteria.

Dissolution was added to the specifications during the review process.

2.A.(2).4) Stability of drug product

Stability studies conducted on the drug product are as shown in Table 2. Results of the photostability test showed the drug product was photostable.

Table 2. Stability studies on drug product

Study	Primary batch	Temperature	Humidity	Storage container	Storage period
Long-term	3 pilot-scale batches	5°C	–	PVC/PVDC[a)] blister packaging	36 months
				HDPE[b)] bottle packaging	
		25°C	60% RH	PVC/PVDC[a)] blister packaging	
				HDPE[b)] bottle packaging	
		30°C	75% RH	PVC/PVDC[a)] blister packaging	
				HDPE[b)] bottle packaging	
Accelerated		40°C	75% RH	PVC/PVDC[a)] blister packaging	6 months
				HDPE[b)] bottle packaging	

-: Not defined
a): Polyvinyl chloride/polyvinylidene chloride
b): High-density polyethylene

The shelf life of 36 months has been proposed for drug product when stored at room temperature packaged in PVC/PVDC blisters or HDPE bottles, according to ICH Q1E Guideline.

2.B Outline of the review by PMDA

Based on the review of the submitted data and the responses to inquiries, PMDA concluded that the quality of the drug product is adequately controlled. The main issues in the review were as shown below.

2.B.(1) Parameters in the manufacturing process of the drug substance

PMDA asked the applicant to explain the criteria used in selecting the process parameters that are subject to a partial change approval application or to minor change notification, based on the results of the process risk assessment.

The applicant responded as follows:

[redacted]

PMDA considers as follows:

[redacted]

[redacted]

2.B.(2) Design space in the manufacturing process of drug substance

[redacted]

2.B.(3) Dissolution

[redacted]

The applicant explained as follows:

[redacted]The reconstructed model equation was validated using the commercial batches with the mean dissolution rate in [redacted] minutes of [redacted]% to [redacted]%. Results suggested that the equation was appropriate for predicting the dissolution rate of future commercial batches.

PMDA considers as follows:

[redacted] Based on the above, PMDA considered it is inappropriate to determine the release acceptability of the product based on the revised model equation of dissolution rate, and instructed the applicant to take the control strategy of releasing the product after confirming that the dissolution rate of the product conforms to the specifications by performing the dissolution test.

The applicant responded that they would take the control strategy of evaluating the conformity of the dissolution of the product to the specification based on the dissolution rate observed by the dissolution test, instead of the predicted value calculated from the model equation of the dissolution rate.

2.B.(4) Uniformity of dosage units

The applicant explained as follows regarding the testing method for ensuring the uniformity of dosage units:

[redacted]

There is a concern that the proposed acceptance criteria may not be able to ensure that no products widely deviate from the acceptance criterion for the uniformity of dosage units. Therefore, PMDA instructed the applicant to set the acceptance criteria for the number of tablets deviating from 100% ± 25% (75.0%-125.0%) of the labeled content as well.

[redacted]

3. Non-clinical data

3.(i) Summary of pharmacology studies

3.(i).A Summary of the submitted data

3.(i).A.(1) Primary pharmacodynamics

3.(i).A.(1).1) *In vitro* studies

3.(i).A.(1).1).(a) Affinity to human enzymes (Attached document 4.2.1.1.1 to 4.2.1.1.3)

Human activated blood coagulation factor X (FXa) and other human proteases were reacted with the synthetic substrate for each enzyme and with apixaban at different concentrations, and the inhibitory effect of apixaban against each human protease was investigated using, as the index, the absorbance or fluorescence intensity that changes with the degradation of the synthetic substrate. The inhibition constant (K_i) of apixaban against human FXa was 0.08 nM at 25°C and 0.25 nM at 37°C. Lineweaver-Burk plotting showed that apixaban inhibited human FXa in a competitive manner. Apixaban showed high selectivity for human FXa compared with other human proteases.

Using a rapid mixing stopped-flow method, phospholipids, FXa, activated blood coagulation factor V (FVa), a synthetic substrate, and apixaban were mixed, and the reaction velocity was measured over time. As a result, the binding rate constant (k_{on}) of FXa and apixaban in the formation of prothrombinase complex was 12 $\mu M^{-1}sec^{-1}$.

The dissociation constant of FXa-apixaban complex was calculated from the time-course of the recovery of FXa activity when the complex was diluted 100 times in the solution containing the synthetic substrate. The dissociation constant (k_{off}) was 0.0034 sec^{-1}.

Human FXa, human thrombin, and human trypsin were reacted with the synthetic substrate for each enzyme and with *O*-demethyl apixaban sulfate (M1), the main metabolite of apixaban in human blood, at different concentrations. As a result, M1 with concentration of <20 μM did not show any clear inhibitory effect against human FXa (K_i of approximately 58 μM), and inhibited neither human thrombin nor human trypsin up to 30 μM.

3.(i).A.(1).1).(b) Inhibition of prothrombinase activity (Attached document 4.2.1.1.1)

Phospholipid vesicles, FVa, calcium ion, and a synthetic substrate for thrombin were incubated and, after FXa and prothrombin were added to the mixture, the conversion of prothrombin to thrombin (prothrombinase activity) by FXa in prothrombinase complex was detected using, as the index, the change in absorbance that occurred with the degradation of the synthetic substrate of thrombin. Apixaban inhibited prothrombinase in a non-competitive manner with K_i of 0.63 nM at 25°C and 0.62 nM at 37°C.

3.(i).A.(1).1).(c) Affinity to FXa of animal origin (Attached document 4.2.1.1.4)

Blood coagulation factor X of rats, rabbits, and dogs was activated to FXa with Russell's viper venom, and the inhibitory effect of apixaban against these FXa samples was investigated using, as the index, the change in the absorbance with the degradation of the synthetic substrate. K_i of apixaban against rat, rabbit, and dog FXa was 1.4, 0.16, and 1.8 nM, respectively.

3.(i).A.(1).1).(d) Suppression of thrombin production (Attached document 4.2.1.1.1)

The inhibitory effect of apixaban against tissue factor (TF)-induced thrombin production in human platelet poor plasma was investigated using the thrombogram method (Hemker HC et al. *Pathophysiol Haemost Thromb.* 2003;33:4-15). Apixaban at 50 nM inhibited the rate of thrombin production by approximately 50% and, at 100 nM, suppressed the maximum thrombin production by approximately 50%.

3.(i).A.(1).1).(e) Blood coagulation test using human plasma (Attached document 4.2.1.1.5)

In human plasma samples, the concentration of apixaban required to increase by 2-fold the prothrombin time-international normalized ratio (PT-INR), activated partial thromboplastin time (aPTT), and coagulation time in HEPTEST assay was 1.9, 7.6, and 0.19 μM, respectively. Apixaban up to 20 μM did not prolong prothrombin time.

3.(i).A.(1).1).(f) Inhibition of the activity of FXa bound to blood clots (Attached document 4.2.1.1.6)

The inhibitory effect of apixaban against FXa bound to blood clots was investigated using the level of prothrombin fragment 1 + 2 as the index. Blood clots, prepared by the addition of calcium ion to human platelet poor plasma, were incubated in the buffer solution containing FVa and prothrombin in the presence or absence of apixaban. As a result, apixaban decreased the level of prothrombin fragment 1 + 2 by up to 73% to 78% with the 50% inhibitory concentration (IC_{50}) of 1.3 nM.

3. (i).A.(1).1).(g) Suppression of tissue factor-induced human platelet aggregation (Attached document 4.2.1.1.7)

In platelet rich human plasma, apixaban suppressed platelet aggregation mediated by TF-induced extrinsic blood clotting pathway (IC_{50} of 3.5 nM) in a concentration-dependent manner but did not suppress platelet aggregation induced by adenosine diphosphate (ADP), α-thrombin, thrombin receptor activating peptide (SFLLRN-NH_2), or collagen, which initiates directly platelet aggregation.

3.(i).A.(1).2) *In vivo* studies

3.(i).A.(1).2).(a) Effect on the appearance of thrombosis biomarkers in diabetic/obese mice (Attached document 4.2.1.1.8)

Apixaban (5, 50 mg/kg) or vehicle was administered twice daily, or apixaban (10, 100 mg/kg) or vehicle was administered once daily, orally for 3 days to male *db/db* mice (12 weeks of age, 38.3-56.7 g, n = 8). The concentrations of thrombin-antithrombin III complex and soluble CD40 ligand decreased to a greater extent in twice daily administration than in once daily administration.

3.(i).A.(1).2).(b) Effect in thrombosis and hemorrhage models of rats (Attached document 4.2.1.1.9)

The effect of apixaban was investigated in the following thrombosis and hemorrhage models of male Sprague-Dawley (SD) rats (12 weeks of age, 290-460 g).

i) Antithrombotic effect

The antithrombotic effect was investigated in the following 4 types of models.

a) Arteriovenous shunt thrombosis model

Apixaban (0.3, 1, 3 mg/kg/h) or vehicle was continuously administered intravenously to male SD rats (n = 6) and, at 1 hour after the start of administration, an arteriovenous shunt was made by connecting the carotid artery and the jugular vein with a Tygon tube with a silk thread inserted, and the weight of the thrombus attached to the silk thread was measured after 15-minute blood perfusion.

b) TF-induced congestive venous thrombosis model

Apixaban (0.3, 1, 3 mg/kg/h) or vehicle was continuously administered intravenously to male SD rats (n = 6-8) and, at 1 hour after the start of administration, the vena cava was exposed and ligated immediately at the level below the left renal vein. Then, thromboplastin-C reagent (0.1 mL) was administered into the femoral vein and, after 10 minutes, the vena cava was ligated at the level just above the branching of the femoral vein, and the weight of the thrombus within the vena cava

was measured immediately after the ligation.

c) Ferric chloride-induced vena cava thrombosis model
Apixaban (0.1, 0.3, 1, 3 mg/kg/h) or vehicle was continuously administered intravenously to male SD rats (n = 5-7) and, at 1 hour after the start of administration, a sheet of filter paper impregnated with 15% ferric chloride solution was placed on the abdominal vena cava for 1 minute, and the weight of the thrombus was measured after 1 hour.

d) Carotid artery thrombosis model
Apixaban (0.1, 0.3, 1, 3 mg/kg/h) or vehicle was continuously administered intravenously to male SD rats (n = 5-13) and, at 1 hour after the start of administration, a sheet of filter paper impregnated with 50% ferric chloride solution was placed on the right carotid artery for 10 minutes, and the weight of the thrombus was measured after 1 hour.

The result of a) to d) above demonstrated that the thrombus weight in each thrombus model decreased in an apixaban dose-dependent manner, showing a significant decrease in the apixaban ≥0.3 mg/kg/h groups compared with the vehicle group. The dose of apixaban required to suppress the thrombus weight by 50% (ID_{50}) was 1.20 mg/kg/h in the arteriovenous shunt thrombosis model, 1.55 mg/kg/h in the TF-induced congestive venous thrombosis model, 0.39 mg/kg/h in the ferric chloride-induced vena cava thrombosis model, and 0.72 mg/kg/h in the ferric chloride-induced vena carotid artery thrombosis model.

ii) Effect on hemorrhage
The effect on hemorrhage was investigated using the following 3 types of models.

a) Epidermal hemorrhage model
Apixaban (0.1, 0.3, 1, 3 mg/kg/h) or vehicle was continuously administered intravenously to male SD rats (n = 5-14). Before and at 1 hour after the start of administration of apixaban or vehicle, the tips of the cuticles of the right and left hind legs were cut, and the time to hemostasis was measured under the surface perfusion with Ringer's solution at 37°C.

b) Renal cortical hemorrhage model
Apixaban (0.1, 0.3, 1, 3 mg/kg/h) or vehicle was continuously administered intravenously to male SD rats (n = 6-8). Before and at 1 hour after the start of administration of apixaban or vehicle, the surface of the bilateral renal cortices exposed by the removal of the kidney capsule was superfused with Ringer's solution at 37°C, and the time to hemostasis was measured after incision of the renal cortex.

c) Mesenteric hemorrhage model
Apixaban (0.1, 0.3, 1, 3 mg/kg/h) or vehicle was continuously administered intravenously to male SD rats (n = 5-10). Before and at 1 hour after the start of administration of apixaban or vehicle, the surface of the jejunum was superfused with Ringer's solution at 37°C and, after the puncture of the artery that has branched perpendicularly from the mesenteric artery and runs along the jejunal surface, the time to hemostasis was measured.

Results of a) to c) above showed a significant (1.9-3.0 times) prolongation of bleeding time in the apixaban 3 mg/kg/h group in each hemorrhage model compared with the vehicle group. In the apixaban 1 mg/kg/h group, a significant increase in bleeding time was observed only in the mesenteric hemorrhage model, whereas in the apixaban 0.1 and 0.3 mg/kg/h groups, no significant prolongation of the bleeding time was observed in any of the models.

iii) Effect on blood coagulation parameters

Apixaban (0.1, 0.3, 1, 3 mg/kg/h) or vehicle was continuously administered intravenously to male SD rats (n = 9-16), and plasma apixaban concentration and prothrombin time (PT) at 75 to 120 minutes after the start of administration were measured. In the apixaban 0.1, 0.3, 1, and 3 mg/kg/h groups, plasma apixaban concentrations were 0.48 ± 0.07, 1.38 ± 0.11, 4.96 ± 0.39, and 12.35 ± 0.48 μM, respectively, and PT prolonged 1.24 ± 0.09, 1.93 ± 0.12, 2.75 ± 0.11, and 3.98 ± 0.18 fold, respectively, compared with the vehicle group. The PT prolongation was significant in the apixaban ≥0.3 mg/kg/h groups.

3.(i).A.(1).2).(c) Effect on rabbit thrombosis and hemorrhage models (Attached document 4.2.1.1.10)

The effect of apixaban was investigated using multiple thrombosis and hemorrhage models of anesthetized male New Zealand White (NZW) rabbits (13 weeks of age, 2-4 kg).

i) Arteriovenous shunt thrombosis model

Apixaban (0.03, 0.1, 0.3, 1, 3 mg/kg/h) or vehicle was continuously administered intravenously to male NZW rabbits (n = 3-7) and, at 1 hour after the start of administration, an arteriovenous shunt was made by connecting the femoral artery and the femoral vein with a Tygon tube with a silk thread inserted. The weight of the thrombus attached to the silk thread was measured after blood perfusion for 40 minutes and the plasma apixaban concentration at 80 minutes after the start of administration. The results showed that thrombus formation was suppressed in a manner dependent on apixaban dose and plasma concentration, with ID_{50} of 0.27 mg/kg/h and IC_{50} of 357 nM.

ii) Electrical stimulation-induced carotid arterial thrombosis model

Apixaban (0.01, 0.03, 0.1, 0.3, 1 mg/kg/h) or vehicle was continuously administered intravenously to male NZW rabbits (n = 6). At 1 hour after the start of administration, electric stimulation (4 mA, for 3 minutes) was applied to the carotid artery, and occlusive thrombus formation was assessed by the monitoring of blood flow for 90 minutes, after which the thrombus weight was measured. Also, PT and aPTT were measured before administration and at the end of the test. The intravenous administration of apixaban showed a dose-dependent prolongation of the patency of the carotid artery, with a 67% suppression of thrombosis formation in the apixaban 1 mg/kg/h group. ID_{50} and IC_{50} of the antithrombotic effect of apixaban, assessed based on the mean blood flow rate over 90 minutes, was 0.07 mg/kg/h and 106 nM, respectively. A slight prolongation of aPTT and a moderate prolongation of PT were observed in the apixaban ≥0.3 mg/kg/h groups.

iii) Silk thread-induced vena cava thrombosis model

Apixaban (0.03, 0.1, 0.3, 1 mg/kg/h) or vehicle was continuously administered intravenously to male NZW rabbits (n = 6). At 1 hour after the start of administration, a silk thread was inserted into the abdominal vena cava via the femoral vein to induce thrombus formation and, after 90 minutes, the weight of the thrombus adhering to the silk thread was measured. The intravenous administration of apixaban showed a dose-dependent suppression of thrombus formation, with ID_{50} being 0.11 mg/kg/h. In a separate experiment, a loading dose of apixaban or vehicle was intravenously administered at 30 minutes after the insertion of a silk thread, followed by a 2-hour maintenance dose (loading dose [mg/kg] + maintenance dose [mg/kg/h] of apixaban was 0.018 + 0.026, 0.06 + 0.09, 0.18 + 0.26, and 0.6 + 0.87), and the amount of thrombus adhering to the silk thread at 2 hours after the intravenous administration was measured (in the control group, the thrombus weight was measured at 30 minutes after the insertion of the silk thread). The thrombus weight in the vehicle group increased by 53 mg compared with the control group, whereas in the apixaban groups, the increase in thrombus weight was suppressed in a dose-dependent manner, with IC_{50} being 105 nM. The thrombus weight in the apixaban 0.6 mg/kg + 0.87 mg/kg/h group was lower than that in the control group.

iv) Epidermal (cuticular) hemorrhage model

Apixaban (1, 3 mg/kg/h) or vehicle was continuously administered intravenously to male NZW rabbits (n = 6). At 1 hour after the start of administration, the tips of the cuticles of the hind legs were cut, and the time to hemostasis was measured under the surface perfusion with Ringer's solution at 37°C. The bleeding time in the apixaban 3 mg/kg/h group was 228 ± 14 seconds, showing a significant prolongation compared with the vehicle group (172 ± 2 seconds), whereas the bleeding time in the apixaban 1 mg/kg/h group was not significantly different compared with the vehicle group.

3.(i).A.(1).2).(d) Effect on thrombosis and hemorrhage models of dogs (Attached document 4.2.1.1.11)

A loading dose of apixaban or vehicle was intravenously administered for 10 minutes to male and female mongrel dogs (7-14 months of age, 8-15 kg, n = 6-14), followed by the maintenance dosing until the end of the study (loading dose [mg/kg] + maintenance dose [mg/kg/h] of apixaban was 0.14 + 0.014, 0.28 + 0.028, 0.56 + 0.056, 1.12 + 0.112, 2.24 + 0.224, and 4.48 + 0.448), and the effect of apixaban was investigated in an arteriovenous shunt thrombosis model and an electrical stimulation-induced femoral vein thrombosis model. Also, before the administration of apixaban or vehicle and at 1 hour after the start of the maintenance dosing, plasma apixaban concentration, PT, aPTT, and bleeding time (time until no blood stain is adhered to filter paper after tongue incision) were measured.

In the arteriovenous shunt thrombosis model, an arteriovenous shunt was made by connecting the carotid artery and the jugular vein with a Tygon tube with a silk thread inserted. Following 30-minute perfusion, the thrombus adhering to the silk thread was measured before the administration of apixaban or vehicle and at 1 hour after the start of administration. A dose-dependent decrease in thrombus weight was observed in apixaban groups, with IC_{50} against thrombus formation being 3.3 μM.

In the electrical stimulation-induced femoral artery thrombosis model, the femoral artery was constricted, at 1 hour after the start of apixaban or vehicle administration, to decrease blood flow to 50%. Then, an electrode was inserted into the femoral artery and low current stimulation (100 μA) was applied continuously up to 3 hours, and the total arterial blood flow during 120 minutes after the start of the electrical stimulation and the patency duration until cessation of blood flow for at least 10 minutes were measured. In the apixaban group, significant increases in the patency duration and the total arterial blood flow were observed compared with the vehicle group. The patency duration increased 2-fold in the presence of 1.2 μM apixaban in the plasma. Also, administration of apixaban prolonged PT, aPTT, and bleeding time in a dose-dependent manner.

3.(i).A.(2) Secondary pharmacodynamics

3.(i).A.(2).1) *In vitro* binding to receptors, ion channels, etc. (Attached document 4.2.1.3.1, Reference data)

Binding of apixaban to 63 types of receptors, ion channels, transporters, and enzymes except human proteases was investigated. As a result, apixaban (1, 10 μM) did not inhibit the binding of radiolabeled ligands to any of the receptors, ion channels, etc., tested.

3.(i).A.(3) Safety pharmacology

Effects of apixaban on the cardiovascular, central nervous, and respiratory systems were evaluated in part of the safety pharmacology studies and toxicity studies.

3.(i).A.(3).1) Cardiovascular system

3.(i).A.(3).1).(a) *In vitro* studies (Attached document 4.2.1.3.2 to 4.2.1.3.5, Reference

data [non-GLP] 4.2.1.3.2, 4.2.1.3.3)

The Purkinje fibers isolated from male NZW rabbits (16-20 weeks of age, 2.5-3.0 kg) were stimulated at 1-second intervals. Apixaban (3, 10, 30 μM) did not affect the action potential duration of the cardiac muscle at 50% repolarization (APD_{50}), APD_{90}, overshoot, resting membrane potential, or maximum upstroke velocity (n = 3).

The Purkinje fibers isolated from female NZW rabbits (19-20 weeks of age, 2.9-3.1 kg) were stimulated at 1 or 0.5-second intervals. Apixaban (3, 10, 30 μM) did not affect APD_{60}, APD_{90}, resting membrane potential, action potential amplitude, or maximum upstroke velocity of the cardiac muscle (n = 5).

The Purkinje fibers isolated from male NZW rabbits (2.5-3.0 kg) were stimulated at 1-second intervals. M1 (3, 10, 30 μM) did not affect APD_{50}, APD_{90}, overshoot, resting membrane potential, or maximum upstroke velocity of the cardiac muscle (n = 3).

In HEK293 cells engineered to express human *ether-a-go-go*-related gene (hERG) channel, apixaban and M1, up to 30 μM, had little or no suppressive effect on hERG potassium current measured by the patch-clamp method.

3.(i).A.(3).1).(b) *In vivo* studies (Attached document 4.2.1.3.6 to 4.2.1.3.8, Reference data [non-GLP] 4.2.1.3.7, 4.2.1.3.8)

Apixaban (50 mg/kg) or vehicle was administered orally in a single dose to male and female beagle dogs (15-24 months of age, 9-13 kg, n = 2/sex/group), and systemic blood pressure and electrocardiogram were monitored by telemetry up to 20 hours after dosing. Also, hematological and clinical chemistry parameters at 24 hours after dosing and blood coagulation parameters at 4 hours after dosing were measured. Apixaban-related effect was not observed in symptoms, blood pressure, heart rate, cardiac contractility, electrocardiogram (ECG), hematological parameters, or clinical chemistry parameters, whereas PT and aPTT were prolonged 4.6- and 2.9-fold, respectively, compared with the baseline levels.

Apixaban (1.25, 4.0 mg/kg) or vehicle was administered intravenously in a single dose to male and female beagle dogs (27-44 months of age, 7.5-12.2 kg, n = 3/sex/group), and heart rate, systemic blood pressure, and ECG parameters (P amplitude, PR, RR, QRS, QT interval) were monitored by telemetry up to 20 hours after dosing. No apixaban-related symptoms were observed, neither were changes in hemodynamics or ECG parameters observed.

Apixaban (0.1, 0.3, 1, 3 mg/kg) or vehicle was administered intravenously by stepwise dose escalation at 30-minute intervals to male and female mongrel dogs under pentobarbital anesthesia (6.5-11.6 kg, n = 2/sex/group). As a result, 2 dogs in the apixaban 3 mg/kg group died after receiving apixaban, showing increased mean arterial pressure, heart rate, and myocardial contraction before death, from which myocardial ischemia was considered to be the cause of the death.

3.(i).A.(3).2) Central nervous and respiratory systems (Attached document 4.2.3.2.7)

Apixaban (5, 10, 20 mg/kg/day) or vehicle was administered orally once daily for 3 months to male and female beagle dogs (approximately 5-6 months of age, 6.4-9.8 kg, n = 6/sex/group), and the beagles dogs were monitored for mental conditions, gait, posture, central nervous function, peripheral nervous function, and body temperature. No changes suggestive of the effect on the nervous system were observed. Also, measurement of the respiratory rate and arterial oxygen saturation and chest (pulmonary sound) auscultation did not show any change suggestive of the effect on the respiratory system.

3.(i).A.(4) Pharmacodynamic drug interactions

3.(i).A.(4).1) Effect of concomitant use of an antiplatelet drug on antithrombotic effect and bleeding time (Attached document 4.2.1.4.1)

Using an electrical stimulation-induced carotid artery thrombosis model (n = 6) and an epidermal (cuticular) hemorrhage model (n = 6) of male NZW rabbits (13 weeks of age, 2-4 kg), the effect of concomitant use of apixaban with aspirin or clopidogrel sulfate (clopidogrel) on thrombus weight and epidermal bleeding time was investigated. Apixaban was administered at 0.04, 0.3, and 2.1 mg/kg/h, which are the doses that decrease the thrombus weight by 20%, 50%, and 80%, respectively, as calculated from the published report (Wong PC et al. *J Thromb Haemost.* 2008;6:1736-41). Aspirin was continuously administered at 1 mg/kg/h, the dose corresponding to the clinical dose, intravenously from 1 hour before the electrical stimulation or epidermal hemorrhage until the end of the study. Clopidogrel was administered orally at 3 mg/kg, the dose corresponding to the clinical dose, once daily for 3 days. The last dose of the drug was administered at 2 hours before the electrical stimulation or epidermal hemorrhage. Thrombus weight was measured at 90 minutes after the induction of thrombus formation by electrical stimulation (4 mA, for 3 minutes) of the carotid artery using a bipolar electrode. Epidermal bleeding time was measured as the time from the cutting of the tip of the cuticle until stenosis under surface perfusion with Ringer's solution at 37°C.

Thrombus weight in the apixaban 0, 0.04, or 0.3 mg/kg/h + aspirin group was 7.4 ± 0.5, 5.3 ± 0.3, and 3.6 ± 0.3 mg, respectively, showing that the thrombus weight in the apixaban + aspirin groups was significantly lower compared with the aspirin alone group. In contrast, the epidermal bleeding time in the 0, 0.04, or 0.3 mg/kg/h + aspirin group was 190 ± 7, 181 ± 9, and 225 ± 11 seconds, respectively, showing no significant difference between the apixaban + aspirin groups and the aspirin alone group.

Concomitant use of aspirin, clopidogrel, and apixaban (0.04 mg/kg/h) were investigated. As a result, thrombus weight in the aspirin + clopidogrel group was 5.3 ± 0.3 mg, whereas the weight in the 3-drug combination group was 0.7 ± 0.1 mg, which was significantly lower compared with the aspirin + clopidogrel group. Additionally, the epidermal bleeding time in 3-drug combination group receiving aspirin, clopidogrel, and 0.04, 0.3, or 2.1 mg/kg/h of apixaban was prolonged in an apixaban dose-dependent manner, showing a significant increase in all dose groups compared with the vehicle group.

3.(i).B Outline of the review by PMDA

The applicant discussed the fatal cases observed following intravenous administration of apixaban (3 mg/kg) to pentobarbital-anesthetized dogs, as follows:

Organic solvents (*N*,*N*-dimethylacetamide [DMA], ethanol, propylene glycol [PG]) were used in apixaban administration, and the cumulative dose of DMA and PG in intravenous administration of apixaban with stepwise dose escalation up to 3 mg/kg was approximately 240 and 950 mg/kg, respectively. It is reported that intravenous administration of DMA (236 mg/kg) to dogs and cats caused hypotension (Kim S-N. *Drug Metab Rev.* 1988;19:345-68) and that intravenous administration of PG (160-800 mg/kg) to dogs caused decreased heart rate and decreased blood pressure, followed by increased heart rate (Al-Khudhairi D et al. *Br J Anaesth.* 1986;58:897-902). It is also reported that after intravenous administration of pentobarbital (30 mg/kg) as the anesthetic agent used in the above study to dogs, decreases in cardiovascular and respiratory activities were shown, and tachycardia and myocardial depression were particularly noted (Manders WT et al. *Circulation Res.* 1976;39:512-7). Following oral dose of 50 mg/kg of apixaban or intravenous dose of 4.0 mg/kg of apixaban without using organic solvents to unanesthetized dogs, the maximum plasma concentration (C_{max}) was 29.1 and 22.1 μg/mL, respectively, which was higher than the C_{max} (15.8 μg/mL) achieved following intravenous administration to anesthetized dogs up to 3 mg/kg by stepwise dose escalation, but no effect on

the cardiovascular system was observed. In light of these findings, the death and the changes in the cardiovascular systems observed following intravenous administration of apixaban (3 mg/kg) to anesthetized dogs are unlikely to be related to apixaban.

Taking account of the explanation of the applicant, PMDA considers the fatal cases were unlikely to have been caused by apixaban. However, since ischemic heart diseases such as myocardial ischemia were observed as adverse events in clinical studies, PMDA considers that the risk of ischemic heart diseases in humans caused by apixaban should be investigated based on the results of clinical studies as well [see "4.(iii).B.(4).11) Risk of ischemic heart diseases"].

PMDA considers the antithrombotic effect of apixaban as follows:
The submitted data demonstrated that apixaban suppresses thrombosis formation through inhibition of FXa activity and apixaban is expected to suppress thrombus formation in humans. However, because of the antithrombotic effect, it is highly likely that apixaban makes patients prone to bleeding, and therefore it is critical to select the appropriate dosage and administration. The balance between the risk and benefit of the antithrombotic effect of apixaban in humans should be investigated based on the results of clinical studies.

3.(ii) Summary of pharmacokinetic studies

3.(ii).A Summary of the Submitted Data

Radioactivity concentrations in biological samples of mice, rats, dogs, and monkeys following administration of ^{14}C-labeled apixaban were measured in a liquid scintillation counter and expressed in apixaban equivalent.

Apixaban concentration in samples was measured using a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS). The lower limit of quantification of plasma apixaban concentration was 2 ng/mL in mice, 2 or 5 ng/mL in rats, 2 ng/mL in rabbits, and 2 or 5 ng/mL in dogs. The lower limit of quantification of apixaban concentration in the extracts of mouse and rat embryos was 2 ng/mL.

Pharmacokinetic parameters are expressed in mean values unless specified otherwise.

3.(ii).A.(1) Absorption

3.(ii).A.(1).1) *In vitro* studies

3.(ii).A.(1).1).(a) Study on membrane permeability using LLC-PK1 cells (Attached document 4.2.2.2.3)

Apixaban (final concentration, 2.5-100 μM) was added to P-glycoprotein (P-gp)-expressing LLC-PK1 cells and P-gp-non-expressing LLC-PK1 cells. As a result, the apparent efflux ratio (permeability coefficient from basolateral surface to apicolateral surface/permeability coefficient from apicolateral surface to basolateral surface) was 23 to 36 and 1.4 to 4.4, respectively. When ketoconazole, a P-gp inhibitor, was added to P-gp-expressing LLC-PK1 cells in the presence of apixaban at 5 or 50 μM (final concentration), IC_{50} was 5.4 and 2.9 μM, respectively.

3.(ii).A.(1).1).(b) Study on gastrointestinal permeability using isolated gastrointestinal tract (Attached document 4.2.2.2.1)

The permeability of apixaban from the mucosal membrane to the serous membrane was investigated using slices of the duodenum, jejunum, ileum, and colon isolated from rats. The permeability coefficient was 33, 73, 51, and 31 nm/sec, respectively. The permeability coefficient from the serous membrane to mucosal membrane of the jejunum was 170 nm/sec.

3.(ii).A.(1).2 Single-dose administration (Attached document 4.2.2.2.1, 4.2.2.2.6, 4.2.3.7.7.3)

Apixaban (0.5 mg/kg) was continuously administered intravenously for 60 minutes to male rats (n = 2). The total plasma clearance of apixaban (CLTp) was 4.3 mL/min/kg, and the distribution volume at steady state (V_{ss}) was 0.31 L/kg. Following a continuous intravenous dose of apixaban (0.2 mg/kg) for 60 minutes to male dogs (n = 2), CLTp was 0.87 mL/min/kg and V_{ss} was 0.30 L/kg.

Apixaban was suspended in 0.5% methylcellulose/Tween 80 (99:1, v/v) and administered orally in a single dose at 2 mg/kg to male rats (n = 2) or at 0.5 mg/kg to male dogs (n = 2). As a result, the absolute bioavailability (BA) was 34% and 88%, respectively.

Apixaban suspended in Labrafil/Tween 80 (99:1, v/v), the suspension used in assessing the toxicokinetics in repeat-dose toxicity studies, was administered orally in a single dose at 100 mg/kg to male rats (n = 2). As a result, the area under plasma concentration-time curve from time 0 to infinity (AUC_{inf}) was 580% higher than the AUC_{inf} achieved following administration of the same dose of apixaban using 0.5% methylcellulose/Tween 80 (99:1, v/v) as vehicle, accompanied by an increase in the time to the maximum plasma concentration (t_{max}).

Apixaban (20 mg/kg), the formulation manufactured using the drug substance with particle diameter of [redacted], [redacted] and [redacted] μm, were administered orally in a single dose to male and female dogs (n = 2/sex). C_{max} and the area under plasma concentration-time curve from time 0 to 24 hours after administration (AUC_{0-24}) increased by 102% to 155% when the particle size of the drug substance was changed from [redacted] μm to [redacted] μm.

3.(ii).A.(1).3 Repeated-dose administration (Attached document 4.2.3.2.4, 4.2.3.2.8)

Toxicokinetic data in repeat-dose toxicity studies in rats and dogs were submitted as pharmacokinetic data of apixaban in repeated-oral administration.

Apixaban (50, 200, 600 mg/kg) was administered orally once daily for 6 months to male and female rats (n = 3 or 4/sex/group). In males, C_{max} was 1.94, 1.94, and 3.27 μg/mL, respectively, and AUC_{0-24} was 9.78, 12.5, and 16.9 μg·h/mL, respectively, on Day 1, and C_{max} was 2.13, 3.05, and 4.48 μg/mL, respectively, and AUC_{0-24} was 16.6, 21.6, and 35.5 μg·h/mL, respectively, on Day 181; and in females, C_{max} was 2.13, 2.13, and 2.93 μg/mL, respectively, and AUC_{0-24} was 11.7, 16.0, and 18.6 μg·h/mL, respectively, on Day 1, and C_{max} was 3.93, 2.95, and 3.98 μg/mL, respectively, and AUC_{0-24} was 26.4, 27.2, and 34.4 μg·h/mL, respectively, on Day 181.

Apixaban (10, 30, 100 mg/kg) was administered orally once daily for 1 year to male and female dogs (n = 3-6/sex/group). In males, C_{max} was 7.87, 9.44, and 10.3 μg/mL, respectively, and AUC_{0-24} was 48.6, 66.5, and 93.1 μg·h/mL, respectively, on Day 1, and C_{max} was 9.73, 10.4, and 10.2 μg/mL, respectively, and AUC_{0-24} was 71.8, 92.2, and 99.4 μg·h/mL, respectively, on Day 360; and in females, C_{max} was 8.70, 13.7, and 12.1 μg/mL, respectively, and AUC_{0-24} was 55.5, 90.6, and 128.2 μg·h/mL, respectively, on Day 1, and C_{max} was 5.90, 9.97, and 12.5 μg/mL, respectively, and AUC_{0-24} was 40.8, 96.5, and 137.0 μg·h/mL, respectively, on Day 360.

3.(ii).A.(2) Distribution

3.(ii).A.(2).1 Protein binding and distribution in plasma/blood cells (Attached document 4.2.2.2.1, 4.2.2.3.3)

Apixaban (final concentration, 0.46-4.59 μg/mL) was added to pooled serums samples of rats, rabbits, dogs, cynomolgus monkeys, and chimpanzees. Results showed that the protein binding rate of apixaban was 95% to 96% in rats, 62% to 66% in rabbits, 91% to 94% in dogs, 52% to 64% in cynomolgus monkeys, and 94% to 95% in chimpanzees. Following the addition of apixaban (final concentration, 0.1-2.0 μg/mL) to mouse serum samples, the protein binding rate

of apixaban was 33% to 56%.

Following the addition of apixaban to dog blood samples, the plasma to blood ratio of apixaban concentration was 1.03.

3.(ii).A.(2).2) Tissue distribution following single-dose administration (Attached document 4.2.2.3.1, 4.2.2.3.2)

^{14}C-labeled apixaban (20 mg/kg) was administered orally in a single dose to male pigmented rats (n = 3/time point), and tissue radioactivity concentration was measured by the tissue isolation method at 1, 4, 12, 24, 48, 96, and 168 hours after dosing. The radioactivity concentration reached the maximum level within 4 hours after dosing in most of the tissues at 1 hour after dosing in the skeletal muscle (thoracic) and spleen, at 12 hours after dosing in the cecum and colon, and at 24 hours after dosing in the heart. The area under the radioactivity concentration-time curve from time 0 to infinity per gram of tissue or organ was highest in the stomach, followed in descending order by the small intestine, urinary bladder, thyroid gland, cecum, large intestine, adrenals, while the heart, bone marrow, and brain showed the lowest values. The area under the radioactivity concentration-time curve was similar between pigmented skin and non-pigmented skin. The elimination half-life of radioactivity ($t_{1/2}$), calculated in each tissue, was highest in the eyes (64.1 hours), followed in descending order by the cecum (63.5 hours), liver (57.6 hours), pigmented skin (52.4 hours), being longer in most tissues compared with the $t_{1/2}$ in the plasma (4.8 hours). $t_{1/2}$ of non-pigmented skin was 30.0 hours.

Following a single oral dose of ^{14}C-labeled apixaban (5 mg/kg) to male and female albino rats (n = 1/sex/time point), tissue radioactivity concentration was determined by whole-body autoradiography at 0.5, 1, 4, 8, 24, 72, 96, and 168 hours after dosing. Radioactivity concentration in the blood reached the maximum level at 1 hour after dosing, remaining at levels above the lower limit of quantitation (0.037 μg-eq/g) up to 8 hours after dosing. In most of the tissues as with blood, the radioactivity concentration reached the maximum level at 1 hour after dosing. At 1 hour after dosing, the radioactivity concentration was higher than the concentration in the blood in the following tissues of either or both males and females, excepting the content of the gastrointestinal tract, urine, and bile: urinary bladder, liver, kidney (medulla), kidney (cortical), adrenals, stomach, small intestine, and large intestine. In all tissues except the large intestine, cecum, and small intestine, the radioactivity concentration decreased below the lower limit of quantitation at 24 hours after dosing. The tissue/blood radioactivity ratio exceeded 10 before 8 hours after dosing in the following tissues, excepting the content of the gastrointestinal tract, urine, and bile: stomach, small intestine, cecum, liver, and urinary bladder. The radioactivity concentration in the central nervous system was the lowest and decreased below the lower limit of quantitation by 4 hours after dosing. No clear sexual difference was observed in the distribution of radioactivity.

3.(ii).A.(2).3) Placental transfer (Attached document 4.2.2.3.2, 4.2.3.5.2.6, 4.2.3.5.2.8)

Following a single oral dose of ^{14}C-labeled apixaban (5 mg/kg) to rats on Gestation day 18 (n = 1/time point), the radioactivity concentration in the placenta and amniotic membrane as well as in the blood, brain, kidney, and liver of fetuses reached the maximum level at 4 hours after dosing, with the maximum radioactivity concentration in fetal blood being 36% of the maximum radioactivity concentration in the blood of maternal rats. The radioactivity in the fetal brain decreased below the lower limit of quantitation (0.037 μg-eq/g) at 8 hours after dosing. At 24 hours after dosing, radioactivity was still detected in the amniotic membrane, but below the lower limit of quantitation in all fetal tissues.

Apixaban (3000 mg/kg) was administered orally once daily for 10 days to rats from Gestation day 6 (n = 6/time point). As a result, C_{max} of apixaban in the embryos on Gestation day 15 corresponded to 9% of C_{max} of apixaban in the plasma of maternal rats.

Apixaban (5 mg/kg) was administered intravenously once daily for 13 days to rabbits from Gestation day 7 (n = 5/time point). As a result, C_{max} and AUC_{0-t} of apixaban in the fetal plasma on Gestation day 19 corresponded to 0.9% and 1%, respectively, of C_{max} and AUC_{0-t} of apixaban in the plasma of maternal rabbits.

3.(ii).A.(3) Metabolism

3.(ii).A.(3).1) *In vitro* metabolism (Attached document 4.2.2.2.1, 4.2.2.4.1, 4.2.2.4.2)

Hepatocytes of mice, rats, dogs, and monkeys were incubated in the presence of ^{14}C-labeled apixaban (final concentration; 1, 10 μM) for 4 hours at 37°C. As a result, unchanged apixaban accounted for 74% to 93% of the radioactivity, and the following metabolites were identified: *O*-demethylated apixaban (M2), M1, hydroxyapixaban (M4), 3-hydroxyapixaban (M7), apixaban carboxylic acid (M6), and metabolites formed by the cleavage of the lactam ring mediated by oxidation or hydrolysis (M3 and M5, respectively). The metabolite that formed in the highest amount in each animal species was M2 (1.4% of total radioactivity) in dogs, M5 in mice and monkeys (1.0% and 7.6%, respectively), and M2 and M7 in rats (0.6% for each of both). M2 was detected in all animal species studied, whereas M1 was detected only in rats and monkeys.

^{14}C-labeled apixaban (final concentration, 50 μM) was added to Aroclor 1254-induced rat liver S9 fraction, and the mixture was incubated for 4 hours at 37°C. As a result, M2 accounted for 37% of the total radioactivity. In addition to M2, the following 6 metabolites were identified: M4, M7, M6, hydroxy *O*-demethylapixaban-1 (M8), apixaban oxidate-1 (M9), and hydroxy *O*-demethylapixaban-2 (M13). The radioactivity of each of these metabolites accounted for <7% of the total radioactivity.

When apixaban (final concentration; 10, 50 μM) was added to hepatocytes of dogs and rats in the presence of glutathione, no glutathione-adduct of apixaban was detected.

3.(ii).A.(3).2) *In vivo* metabolism (Attached document 4.2.2.4.5 to 4.2.2.4.9)

^{14}C-labeled apixaban (30 mg/kg) was administered orally in a single dose to male mice (n = 5). As a result, unchanged apixaban accounted for 97.25% and 75.15% of total plasma radioactivity at 1 and 4 hours after dosing, respectively. Radioactivity of metabolites M2, M7, M13, and *O*-demethylapixaban glucuronide-1 (M14) detected in the plasma at 1 and 4 hours after dosing accounted for <1% and 2.42% to 5.83%, respectively, of the total plasma radioactivity. Each of the metabolites recovered from the urine up to 48 hours after dosing accounted for <1% of the total radioactivity administered. M2 and M7 recovered from the feces up to 48 hours after dosing accounted for 5.87% and 3.48%, respectively, of the total radioactivity administered, whereas each of the other metabolites accounted for <1%.

^{14}C-labeled apixaban was administered in a single oral dose of 30 mg/kg (n = 15) or a single intravenous dose of 15 mg/kg (n = 3) to male rats. The main radioactive component in the plasma at each time point up to 48 hours after oral dose was unchanged apixaban. Each of the metabolites detected in the plasma accounted for ≤1.3% of the total plasma radioactivity. Each of the metabolites recovered from the urine up to 168 hours after the oral dose accounted for <1% of the total radioactivity administered. M2 and M7 recovered from the feces up to 168 hours after the oral dose accounted for 2.9% and 2.2%, respectively, of the total radioactivity administered, whereas each of the other metabolites accounted for <1%. Metabolites recovered from the urine up to 24 hours after the intravenous dose accounted for <1% of the total radioactivity administered. M2 and M7 recovered from the feces up to 24 hours after the intravenous dose accounted for 1.89% and 1.14%, respectively, of the total radioactivity administered, whereas each of the other metabolites accounted for <1%.

^{14}C-labeled apixaban (15 mg/kg) was administered intravenously in a single dose to bile duct-cannulated (BDC) male rats (n = 3). M1, M2, M7, and M9 recovered from the bile up to 24 hours after dosing accounted for 2.27%, 2.07%, 2.42%, and 1.29%, respectively, of the total radioactivity administered, whereas each of the other metabolites accounted for <1%.

^{14}C-labeled apixaban (30 mg/kg) was administered orally in a single dose to female rabbits (n = 3). Unchanged apixaban accounted for 9.06% and 8.85% of the total plasma at 1 and 4 hours, respectively, after dosing. M1, M2, and M14, which were the main metabolites in plasma, accounted for 23.40%, 29.17%, and 37.74%, respectively, of the total radioactivity at 1 hour after dosing, and 4.18%, 17.44%, and 53.32%, respectively, at 4 hours after dosing. M2 recovered from the urine up to 48 hours after dosing accounted for 1.34% of the total radioactivity administered, whereas each of the other metabolites accounted for <1%. M2 recovered from the feces up to 48 hours after dosing accounted for 13.40% of the total radioactivity administered, whereas each of the other metabolites accounted for <1%. ^{14}C-labeled apixaban (5 mg/kg) was administered intravenously in a single dose to female rabbits (n = 3). Unchanged apixaban accounted for 35.46% to 66.12% of the total plasma radioactivity at each time point up to 4 hours after dosing. M1, M2, and M14, which were the main metabolites in plasma, accounted for 9.63%, 23.74%, and 24.47%, respectively, of the total plasma radioactivity at 1 hour after dosing and 0.85%, 3.12%, and 85.85%, respectively, at 4 hours after dosing. M1, M2, and M14 recovered from the urine up to 48 hours after dosing accounted for 1.85%, 10.84%, and 1.37%, respectively, of the total radioactivity administered, whereas each of the other metabolites accounted for <1%. M1, M2, and M14 recovered from the feces up to 48 hours after dosing accounted for 2.22%, 43.88%, and 1.91%, respectively, of the total radioactivity administered, whereas each of the other metabolites accounted for <1%.

^{14}C-labeled apixaban (5 mg/kg) was administered orally in a single dose to male dogs (n = 3). Unchanged apixaban accounted for 78.2% to 95.9% of the total plasma radioactivity at each time point up to 48 hours after dosing. M2, the main metabolite in plasma, accounted for 1.1% to 2.5% of the total plasma radioactivity at each time point up to 48 hours after dosing. Each metabolite recovered from the urine up to 168 hours after dosing accounted for <1% of the total radioactivity administered. M2 and M7 recovered from the feces up to 168 hours after dosing accounted for 9.4% and 2.5%, respectively, of the total radioactivity administered, whereas each of the other metabolites accounted for <1%.

3.(ii).A.(4) Excretion

3.(ii).A.(4).1) Excretion in urine and feces (Attached document 4.2.2.4.5 to 4.2.2.4.7, 4.2.2.4.9, 4.2.2.5.2)

^{14}C-labeled apixaban (30 mg/kg) was administered orally in a single dose to male mice (n = 5). As a result, 15.15% and 83.89% of the total radioactivity administered were recovered from the urine and feces, respectively, within 48 hours after dosing, and 13.64% and 73.24% of the total radioactivity administered were recovered from the urine and feces, respectively, as unchanged apixaban.

^{14}C-labeled apixaban (30 mg/kg) was administered orally in a single dose to male rats (n = 3/group). As a result, 13.4% and 74.0% of the total radioactivity administered were recovered from the urine and feces, respectively, within 168 hours after dosing, and 12.1% and 65.9% of the total radioactivity administered were recovered from the urine and feces, respectively, as unchanged apixaban. Following the same dose in BDC rats (n = 3), 10.5% and 69.8%, respectively, of the total radioactivity administered were recovered from the urine and feces within 48 hours after dosing, and 9.4% and 64.6% of the total radioactivity administered were recovered from the urine and feces, respectively, as unchanged apixaban.

^{14}C-labeled apixaban (15 mg/kg) was administered intravenously in a single dose to male rats (n = 3). As a result, 20.72% and 12.71% of the total radioactivity administered were recovered from the urine and feces, respectively, within 24 hours after dosing, and 19.04% and 7.89% of the total radioactivity administered were recovered from the urine and feces, respectively, as unchanged apixaban. Following the same dose in BDC rats (n = 3), 46.55% and 24.91% of the total radioactivity administered were recovered from the urine and feces, respectively, within 24 hours after dosing, and 43.34% and 21.75% of the total radioactivity administered were recovered from the urine and feces, respectively, as unchanged apixaban.

^{14}C-labeled apixaban (30 mg/kg) was administered orally in a single dose to female rabbits (n = 3). As a result, 1.76% and 54.26% of the total radioactivity administered were recovered from the urine and feces, respectively, within 48 hours after dosing, and 0.04% and 39.38% of the total radioactivity administered were recovered from the urine and feces, respectively, as unchanged apixaban. ^{14}C-labeled apixaban (5 mg/kg) was administered intravenously in a single dose to female rabbits (n = 3). As a result, 24.80% and 62.44% of the total radioactivity administered were recovered from the urine and feces, respectively, within 48 hours after dosing, and 9.58% and 12.28% of the total radioactivity administered were recovered from the urine and feces, respectively, as unchanged apixaban.

^{14}C-labeled apixaban (5 mg/kg) was administered orally in a single dose to male dogs (n = 3). As a result, 8.8% and 73.7% of the total radioactivity administered were recovered from the urine and feces, respectively, within 168 hours after dosing, and 7.2% and 58.6% of the total radioactivity administered were recovered from the urine and feces, respectively, as unchanged apixaban.

3.(ii).A.(4).2) Excretion into bile (Attached document 4.2.2.4.7, 4.2.2.4.6)

^{14}C-labeled apixaban (30 mg/kg) was administered orally in a single dose to male BDC rats (n = 3). As a result, 2.6% of the total radioactivity administered was recovered from the bile within 48 hours after dosing. ^{14}C-labeled apixaban (15 mg/kg) was administered intravenously in a single dose to male BDC rats (n = 3). As a result, 23.03% of the total radioactivity administered was recovered from the bile within 24 hours after dosing.

3.(ii).A.(4).3) Excretion into milk (Attached document 4.2.2.3.4)

^{14}C-labeled apixaban (5 mg/kg) was administered orally in a single dose to maternal rats (n = 3/time point) on Lactation day 10 or 11. As a result, t_{max} of radioactivity in the plasma and milk was 0.5 and 6 hours, respectively, and $t_{1/2}$ was 4.32 and 3.67 hours, respectively. C_{max} and AUC_{inf} of radioactivity in milk were 8.6 and 30 times, respectively, those of radioactivity in the plasma. Apixaban accounted for 96.0% to 99.4% of radioactivity in milk; no metabolites were detected in milk.

3.(ii).A.(5) Other pharmacokinetic studies

3.(ii).A.(5).1) Effect of administration of activated charcoal (Attached document 4.2.2.7.1, 4.2.2.7.2)

A four-treatment, four-period crossover study was conducted in which apixaban (5 mg/kg) was administered orally in a single dose to fasted male dogs (n = 4), followed by a single oral dose of activated charcoal (250 mg/kg) 0.25, 1, or 3 hours after dosing, or no administration of activated charcoal in a crossover manner (with a washout period of ≥3 days between the treatment periods). When activated charcoal was administered at 0.25, 1, or 3 hours after dosing of apixaban, C_{max} of apixaban did not change, while AUC_{0-24} decreased by 24.3%, 18.7%, and 37.4%, respectively. t_{max} of apixaban was 4.0 hours when activated charcoal was not administered, while the value was 2.5 hours when activated charcoal was administered regardless of the timing of administration.

A five-treatment, five-period crossover study was conducted in which apixaban (5 mg/kg) was

administered orally in a single dose to fasted male dogs (n = 5), followed by (i) a single oral dose of activated charcoal (250 mg/kg) at 3 hours after dosing, (ii) a single oral dose of activated charcoal (250 mg/kg) at 5 hours after dosing, (iii) twice daily oral dose of activated charcoal (250 mg/kg) at 3 and 5 hours after dosing, (iv) a single oral dose of activated charcoal (2500 mg/kg) at 3 hours after dosing, and (v) no activated charcoal administration (with a washout period of ≥2 days between the treatment periods). C_{max} of apixaban was not changed by the administration of activated charcoal by any of the above methods, whereas AUC_{0-24} of apixaban was decreased by 15.5% by the administration of activated charcoal (250 mg/kg) at 3 hours after dosing of apixaban, 6.9% by the administration of activated charcoal (250 mg/kg) at 5 hours after dosing of apixaban, 21.5% by the administrations of activated charcoal (250 mg/kg) at 3 and 5 hours after dosing of apixaban, and 45.7% by the administration of activated charcoal (2500 mg/kg) at 3 hours after dosing of apixaban. t_{max} of apixaban was 4.5 hours without activated charcoal administration, while the value was 2.6 to 3.5 hours with activated charcoal administration regardless of the conditions of administration.

3.(ii).A.(5).2) Effect of hemodialysis (Attached document 4.2.2.7.3)

A four-treatment, four-period crossover study was conducted in which apixaban was administered in a single oral dose of 5 mg/kg, and a single intravenous dose of 1 mg/kg to fasted, jugular-catheterized male dogs (n = 4). Each dose was followed by hemodialysis for 4 hours from 5 minutes after dosing, and not followed by hemodialysis (with a washout period of ≥2 days between the treatment periods). The area under the plasma apixaban concentration-time curve from 0 to 4 hours after oral or intravenous administration decreased by 20% and 6%, respectively, in the treatment with hemodialysis compared with the treatment without hemodialysis, whereas no significant effect of hemodialysis on AUC_{0-24} was observed either in the oral administration or in the intravenous administration.

3.(ii).B Outline of the review by PMDA

3.(ii).B.(1) Absorption of apixaban

BA of apixaban differed depending on the vehicle used, and the applicant explained that the absorption of apixaban was improved when Labrafil/Tween 80 (99:1, v/v) was used as the vehicle in repeat-dose toxicity studies. In relation to this issue, PMDA asked the applicant to explain the reason(s) for the extremely small increase (<2-fold) in C_{max} and AUC_{0-24} of apixaban observed when the dose of apixaban was increased ≥10-fold in the toxicokinetics data of the 6-month repeat-dose toxicity study in rats and the 1-year repeat-dose toxicity study in dogs, and to explain whether or not the pharmacokinetics of apixaban within the dose range from 50 to 600 mg/kg (rats) and from 10 to 100 mg/kg (dogs) was appropriately evaluated.

The applicant responded as follows:

Upon oral administration to each animal species, apixaban was rapidly absorbed with t_{max} of 0.5 to 2 hours. The absolute BA of apixaban following oral administration was 34% in rats (2 mg/kg) and 88% in dogs (0.5 mg/kg), showing a favorable absorption when apixaban was administered orally at a low dose. When the dose was increased, however, the increase in the exposure level in rats and dogs was less than dose-proportional. When the formulation, manufactured using the drug substance with a large particle size, was administered to dogs, the exposure level of apixaban decreased by approximately 50%, which suggested that the dissolution velocity was the rate-limiting step of apixaban absorption. This appears to be the reason for the less than dose-proportional increase in the exposure level in the 6-month repeat-dose toxicity study in rats and in the 1-year repeat-dose toxicity study in dogs.

The study in rats showed that the rate of apixaban absorption was higher when Labrafil/Tween 80 was used as the vehicle compared with the rate achieved when 0.5% methylcellulose/Tween 80 (99:1, v/v) was used as the vehicle. When apixaban, suspended in 0.5% methylcellulose/Tween

80 (99:1, v/v), was orally administered to dogs at the dose of 0.5 mg/kg, t_{max} was 1.0 hour. In contrast, when apixaban, suspended in Labrafil/Tween 80 (99.5:0.5, v/v), was orally administered at a higher dose (20 or 30 mg/kg), t_{max} tended to increase to 1 to 4 hours, suggesting that apixaban was absorbed over a longer time period. The above results suggest that the correlation between the dose of apixaban and the exposure level was evaluated appropriately by using Labrafil/Tween 80 (99.5:0.5, v/v) as the vehicle in the 6-month repeat-dose toxicity study in rats and in the 1-year repeat-dose toxicity study in dogs.

PMDA considers as follows:
Since the dissolution velocity of apixaban is likely to be the rate-limiting step of the drug absorption, the pharmacokinetic profile in repeated-dose administration in non-clinical pharmacokinetic studies should have been investigated using the appropriate dose range where the low solubility of apixaban does not affect the pharmacokinetics. In the evaluation of pharmacokinetics of apixaban in humans, attention should be paid to a possible decrease in absorption rate at high doses due to the low solubility of apixaban.

3.(ii).B.(2) Distribution of apixaban in melanin-containing tissues
In pigmented rats, the elimination half-life of radioactivity after apixaban administration was the longest in the eyes. Therefore, PMDA asked the applicant to explain the affinity of apixaban to melanin, also taking account of the distribution of apixaban in pigmented tissues such as eyes observed in studies conducted on the tissue distribution of apixaban in pigmented rats by the tissue extraction method.

The applicant responded as follows:
The intraocular distribution of apixaban was investigated in non-clinical pharmacokinetic studies. In the tissue distribution study in pigmented rats, the exposure level of eyes, pigmented skin, and non-pigmented skin to radioactivity was 57.6, 55.4, and 50.0 μg-eq·h/g, respectively, showing similar values. In contrast, $t_{1/2}$ of radioactivity in these tissues was 64.1, 52.4, and 30.0 hours, which was longer compared with $t_{1/2}$ in the plasma (4.8 hours). However, the radioactivity concentration in the pigmented skin of pigmented rats and in the skin of albino rats was 0.692 and 0.675 μg-eq/g, respectively, at 1 hour after dosing and 1.01 and 0.370 μg-eq/g, respectively, at 4 hours after dosing, showing no marked difference. Given that the dose in pigmented rats (20 mg/kg) was 4 times that in albino rats (5 mg/kg), and that the lower limit of quantitation radioactivity in the tissue extraction method is lower than that in the quantitative whole-body autoradiography, the absence of marked differences observed in the radioactivity concentration between the pigmented skin of pigmented rats and the skin of albino rats suggest that apixaban does not bind to melanin. $t_{1/2}$ of radioactivity in the eye and the pigmented skin of pigmented rats (64.1 and 52.4 hours, respectively) was similar to that in organs with rapid blood flow, such as liver (57.6 hours), and only slightly longer than that in stomach (38.5 hours), large intestine (46.8 hours), and kidney (25.1 hours). The fact that $t_{1/2}$ of radioactivity in the eye is not markedly greater than that in other tissues also suggests that apixaban does not bind to melanin. Thus, results of tissue distribution studies in pigmented rats suggest that apixaban does not have the affinity for melanin.

PMDA considers as follows:
Given the distribution in, and the elimination rate from, pigmented tissues in pigmented rats as explained by the applicant, apixaban is unlikely to have a high affinity to melanin. However, the safety of apixaban in the eye following administration in humans will be continuously reviewed in the clinical section [see “4.(iii).B.(4).1).(c) Intraocular haemorrhage”].

3.(iii).A Summary of toxicology studies

Toxicology studies of apixaban conducted include single-dose toxicity, repeat-dose toxicity, genotoxicity, carcinogenicity, reproductive and developmental toxicity, comparative studies on pulverized drug substance, phototoxicity, and toxicokinetics evaluation of metabolites. The exposure level of metabolite M1 in dogs was similar to the clinical exposure level in humans, whereas in monkeys, the plasma concentration was generally below the lower limit of quantitation. Therefore, dogs were selected as the animal species to be used in non-rodent toxicity studies. Results of the comparative study on pulverized drug substance (Attached document 4.2.3.7.7.3) showed that AUC of the drug substance with the particle size of ≤[redacted] μm was approximately 2 times that of the drug substance with the particle size of [redacted] μm. Therefore, the pulverized drug substance with the particle size of <[redacted] μm was used in studies other than those conducted at the early stage of the development, i.e., single-dose toxicity studies, 3-month repeat-dose toxicity studies, bacterial reverse mutation assay, and rat micronucleus assay.

3.(iii).A.(1) Single-dose toxicity studies (Attached document 4.2.3.1.1 to 4.2.3.1.4)

Single oral dose toxicity studies were conducted in CD-1 mice (maximum dose 4000 mg/kg), SD rats (4510 mg/kg), beagle dogs (1500 mg/kg), and cynomolgus monkeys (300 mg/kg). No death occurred, neither were any changes in clinical conditions observed in mice, rats, or dogs.

Following a single oral dose of apixaban (30, 100, 300 mg/kg) to male and female cynomolgus monkeys (n = 3/sex/group), 1 female each died on the day of administration and at 2 days after dosing in the 300 mg/kg group, and 1 male in the 100 mg/kg group was sacrificed moribund because of an aggravated condition on the following day of dosing. In these fatal cases, decreased activity was observed before death, which was accompanied by gingival whitening, inguinal hemorrhage, as well as widespread hematoma covering the pelvic canal, area surrounding the reproductive organ, peritoneal cavity, and scrotum. These results suggested that the deaths were caused by serious hemorrhage at the site of blood sampling caused by accidental femoral artery injury during blood sampling and the FXa inhibitory activity of apixaban. Prolongation of PT and aPTT was observed in all dose groups, and swelling and discoloration were observed at and around the site of blood sampling in all dose groups except males in the 30 mg/kg group.

3.(iii).A.(2) Repeat-dose toxicity studies

Repeated oral dose toxicity studies were conducted in rats (treatment duration, 3 and 6 months) and in dogs (treatment duration, 3 months and 1 year). Prolongation of PT, aPTT, and bleeding time was observed in both animal species, but not considered as toxic findings because neither target organ toxicity nor clear hemorrhagic lesion associated with administration was observed. $AUC_{0\text{-}24}$ of apixaban (35.5 μg·h/mL in male rats, 34.4 μg·h/mL in female rats, 99.4 μg·h/mL in male dogs, 137.0 μg·h/mL in female dogs) following administration of apixaban at the no observed adverse effect level (NOAEL) (600 mg/kg in rats, 100 mg/kg in dogs) in rats (treatment duration, 6 months) and in dogs (treatment duration, 1 year) was 11 times (male and female rats), 32 times (male dogs), or 44 times (female dogs) the $AUC_{0\text{-}24}$ (3.1 μg·h/mL) observed when apixaban was administered at the recommended clinical dose (10 mg/day) to humans. Results of each study were as shown below.

3.(iii).A.(2).1) Repeat-dose toxicity studies in rats

3.(iii).A.(2).1).(a) Three-month repeated oral dose toxicity study (Attached document 4.2.3.2.3)

Apixaban (75, 150, 300 mg/kg/day) or vehicle was administered orally for 3 months to male and female SD rats (n = 25/sex/group). Death occurred in 1 male in the vehicle group, 1 male and female each in the 75 mg/kg/day group, 1 male and female each in the 150 mg/kg/day group, and 1 male in the 300 mg/kg/day group. All deaths were considered to be due to errors in administration. Prolongation of PT and aPTT, and decreased potassium level were observed in

males and females in the ≥75 mg/kg/day groups, increased fibrinogen was observed in males in the ≥75 mg/kg/day groups, and prolongation of bleeding time was observed in males and females in the ≥150 mg/kg/day groups. These changes were mild in severity and therefore considered to be of little toxicological significance. All of these changes were reversible after the 1-month recovery period. Changes in hematological parameters and in organ weight were also observed, but no changes were observed in actual blood count or in relative organ weight, neither were the observed changes associated with histopathological changes, from which the observed changes were considered to be of little toxicological significance. Based on the above, the NOAEL was determined to be 300 mg/kg/day in both males and females.

3.(iii).A.(2).1).(b) Six-month repeated oral dose toxicity study (Attached document 4.2.3.2.4)

Apixaban (50, 200, 600 mg/kg/day), vehicle, or distilled water was administered orally for 6 months to male and female SD rats (n = 25/sex/group). Death occurred in 2 males in the vehicle group, 4 females in the distilled water group, 1 female in the 50 mg/kg/day group, 1 male and 4 females in the 200 mg/kg/day group, and 2 females in the 600 mg/kg/day group. The death in 1 female in the 50 mg/kg/day group was considered unrelated to apixaban because localized brain injury associated with skull fracture/depression was observed in this rat. The death of 1 male and 2 females in the 200 mg/kg/day group was considered to be due to hemorrhage associated with blood sampling. For other fatal cases, although mild hemorrhage was observed in multiple tissues at necropsy, no direct cause of death could be identified. However, relationship with the blood sampling procedure was suggested because these death occurred within several days after blood sampling. Prolongation of PT and aPTT was observed in males and females in the ≥50 mg/kg/day groups. All these changes were reversible after the 1-month recovery period. The frequencies of erythrophagocytic image and hemosiderosis in mesenteric lymph node increased in treatment groups compared with the control group. However, since they were mild and not dose-dependent, they were considered to be of little toxicological significance. Increased albumin/globulin (A/G) ratio, decreased erythrocytic parameter values, etc., were also observed, but they were mild, transient changes and were therefore considered to be of little toxicological significance. Based on the above, the NOAEL was determined to be 600 mg/kg/day in both males and females.

3.(iii).A.(2).2) Repeat-dose toxicity studies in dogs

3.(iii).A.(2).2).(a) Three-month repeated oral dose toxicity study (Attached document 4.2.3.2.7)

Apixaban (5, 10, 20 mg/kg/day) or vehicle was administered orally for 3 months to male and female beagle dogs (n = 6/sex/group). Increased fibrinogen was observed in males and females in the ≥5 mg/kg/day groups, prolongation of PT and bleeding time was observed in males and females in the ≥10 mg/kg/day groups, and prolongation of aPTT was observed in males and females of the 20 mg/kg/day group. Decreased erythrocyte parameter values, etc., were also observed, but these changes, including the increased fibrinogen, were transient events observed only in Week 2, and were therefore considered to be of little clinical significance. Based on the above, the NOAEL was determined to be 20 mg/kg/day in both males and females.

3.(iii).A.(2).2).(b) One-year repeated oral dose toxicity study (Attached document 4.2.3.2.8)

Apixaban (10, 30, 100 mg/kg/day) or vehicle was administered orally for 1 year to male and female beagle dogs (n = 6/sex/group). Prolongation of PT and aPTT was observed in males and females in the ≥10 mg/kg/day groups. Mild and transient decreases in erythrocyte parameter values, etc., were also observed. However, since they were within the normal range and not correlated with the treatment duration, they were considered to be of little toxicological significance. Based on the above, the NOAEL was determined to be 100 mg/kg/day in both males and females.

3.(iii).A.(3) Genotoxicity studies (Attached document 4.2.3.3.1.1 to 4.2.3.3.1.3, 4.2.3.3.2.1, 4.2.3.3.2.2)

As genotoxicity studies, bacterial reverse mutation assay, chromosomal aberration assay using cultured mammalian cells (CHO cells), rat bone marrow micronucleus assay, and chromosomal aberration assay in rat peripheral lymphocytes were performed. In the chromosomal aberration assay in CHO cells, a significant increase in the number of cells with abnormal chromosomal structure was observed when cells were treated for 20 hours with apixaban in the absence of metabolic activation system. However, the change was within the range of the historical data and the results were not reproducible in the retesting. All other tests were negative. Based on the above, apixaban was considered to be non-genotoxic.

3.(iii).A.(4) Carcinogenicity

Carcinogenicity studies of 104 weeks were performed using mice and rats. No increase in neoplastic lesion associated with apixaban was observed in either study, from which apixaban was considered not to be carcinogenic.

3.(iii).A.(4).1) Mouse 104-week carcinogenicity study (Attached document 4.2.3.4.1.1)

To male CD-1 mice (n = 60/group), apixaban at 0 (2 groups), 150, 500, or 1500 mg/kg/day was administered for 105 weeks, and to female CD-1 mice (n = 60/group), apixaban at 0 (2 groups), 150, 500, or 3000 mg/kg/day was administered for 98 weeks (control group-2), 97 weeks (3000 mg/kg/day group), or 100 weeks (other groups). Apixaban was administered in a mixed diet. There was a significant increase in endometrial polyp in females in the 3000 mg/kg/day group (2 females in the control group-1, 3 females in the control group-2, 3 females in the 150 mg/kg/day group, 2 females in the 500 mg/kg/day group, 6 females in the 3000 mg/kg/day group). The endometrial polyp is a benign tumor often observed in CD-1 mice, and the incidence (10% in the 3000 mg/kg/day group) was within the range of the historical data (0%-20%). Based on the above results, apixaban was considered to be non-carcinogenic. Convulsions were observed frequently in males, but there was no correlation between the incidence and dose or exposure level. The incidence of convulsions in the 1500 mg/kg/day group was comparable to that observed in males in the control groups -1 and -2. In females, no convulsions were observed in the 3000 mg/kg/day group although the exposure level to apixaban was higher than in males. It is known that aged mice are prone to have convulsions in long-term administration studies with infrequent handling (e.g., *Lab Animal Sci.* 1999;49:468-9). Based on the above, convulsions were considered to be not related to apixaban.

3.(iii).A.(4).2) Rat 104-week carcinogenicity test (Attached document 4.2.3.4.1.2)

Apixaban (0 [2 groups], 50, 200, 600 mg/kg/day) was administered to male and female SD rats (n = 60/sex/group) for 104 weeks in a mixed diet. Apixaban did not increase the frequency of neoplastic lesions, from which apixaban was considered to be non-carcinogenic.

3.(iii).A.(5) Reproductive and developmental toxicity

As reproductive and developmental toxicity studies, study of fertility and early embryonic development to implantation (rats), studies for effects on embryo-fetal development (mice, rats, rabbits), and a study for effects on pre- and postnatal development, including maternal function (rats) were performed. In studies for effects on embryo-fetal development, no sufficient exposure level was obtained by oral administration in rabbits and thus, apixaban was administered intravenously to rabbits and orally to mice. In the study for effects on embryo-fetal development in mice, prolongation of PT and aPTT was observed in maternal animals. However, since these were changes caused by the pharmacological effect of apixaban and not accompanied by apparent hemorrhagic lesions, they were not considered to be toxic findings. In the study for effects on pre- and postnatal development, including maternal function in rats, a decreased frequency of copulation rate and accompanying decrease in the pregnancy rate were observed in F_1 females,

while no teratogenicity was observed. Apixaban was shown to be transferred to fetuses and excreted in milk in rats [see "3.(ii) Summary of pharmacokinetic studies"].

3.(iii).A.(5).1) Study of fertility and early embryonic development to implantation in rats (Attached document 4.2.3.5.1.1)

Apixaban (50, 200, 600 mg/kg/day) or vehicle was administered orally to male and female SD rats (n = 25/sex/group). Males were dosed from 14 days before mating until 1 day before necropsy and females were dosed from 15 days before mating until Gestation day 7. One female in the vehicle group and 1 male in the 600 mg/kg/day group died, but the deaths were considered to be due to errors in administration. One male in the 600 mg/kg/day group showed hind limb paralysis, cold feeling, and no-feces. The rat was sacrificed moribund and necropsied. As a result, splenic hypertrophy was observed. Although the cause of these changes was unknown, it was suspected that they were caused by a traumatic injury of some kind or other, considering the sudden occurrence of the hind limb paralysis within 3 minutes after administration 1 day before sacrificed moribund. Prolongation of PT and aPTT was observed in all treatment groups on Day 10, while apixaban had no effect on the reproductive performance of parent rats or on the early embryonic development. Based on the above, the NOAEL of apixaban was determined to be 600 mg/kg/day for general and reproductive toxicity of parent rats and for early embryonic development.

3.(iii).A.(5).2) Study for effects on embryo-fetal development in mice (Attached document 4.2.3.5.2.5)

Apixaban (600, 900, 1500 mg/kg/day), saline, or vehicle was administered orally to pregnant CD-1 mice (n = 25) from Gestation day 6 to Gestation day 15. Death occurred in 1 mouse in the saline group, 1 mouse in the vehicle group, 1 mouse in the 600 mg/kg/day group, 1 mouse in the 900 mg/kg/day group, and 2 mice in the 1500 mg/kg/day group. One mouse in the 600 mg/kg/day group was sacrificed moribund because of aggravated condition. All deaths were considered to be due to errors in administration. Prolongation of PT and aPTT was observed in all treatment groups on Gestation day 15, while no changes were observed in clinical conditions, etc., neither were apixaban-related changes observed in fetuses. Based on the above, the NOAEL of apixaban was determined to be 1500 mg/kg/day for maternal general and reproductive toxicity and for embryo-fetal development.

3.(iii).A.(5).3) Study for effects on embryo-fetal development in rats (Attached document 4.2.3.5.2.6)

Apixaban (100, 300, 1000, 3000 mg/kg/day) or vehicle was administered orally to pregnant SD rats (n = 25) from Gestation day 6 to Gestation day 15. One rat in the 1000 mg/kg/day group showed emaciation, decreased body weight, decreased activity, labored respiration, etc., and was therefore sacrificed moribund on Gestation day 15. Although the cause of these findings was unknown, they were considered not to be related to apixaban because no similar findings were observed in other groups. Red substances suggesting hemorrhage were observed in the perivaginal area at an increased frequency in the ≥100 mg/kg/day groups. They were considered to be due to the enhanced placental sign caused by the pharmacological action of apixaban. Changes in feces (change in fecal color to white or pale brown probably due to unabsorbed test substance, mucous stools) were observed in the ≥1000 mg/kg/day groups, while no apixaban-related changes were observed in fetuses. Based on the above, the NOAEL of apixaban was determined to be 3000 mg/kg/day for maternal general and reproductive toxicity and for embryo-fetal development.

3.(iii).A.(5).4) Study for effects on embryo-fetal development in rabbits (Attached document 4.2.3.5.2.7)

Apixaban (60, 180, 500, 1500 mg/kg/day) or vehicle was administered orally to pregnant NZW rabbits (n = 20) from Gestation day 7 to Gestation day 19. Abortion occurred in 1 rabbit each in the 180 and 1500 mg/kg/day groups, but since the event was not dose-dependent, it was considered unrelated to apixaban. No apixaban-related changes were observed in fetuses. Based on the above, the NOAEL of apixaban was determined to be 1500 mg/kg/day for maternal general and reproductive toxicity and for embryo-fetal development.

3.(iii).A.(5).5) Study for effects on embryo-fetal development in rabbits (Attached document 4.2.3.5.2.8)

Apixaban (1.25, 2.5, 5 mg/kg/day) or vehicle was administered intravenously to pregnant NZW rabbits (n = 27) from Gestation day 7 to Gestation day 19. Abortion occurred in 1 rabbit in the 2.5 mg/kg/day group, but was considered unrelated to apixaban because no abortion occurred in the maximum dose group. Prolongation of PT was observed in maternal rabbits in the ≥1.25 mg/kg/day groups, while no apixaban-related changes were observed in fetuses. Based on the above, the NOAEL of apixaban was determined to be 5 mg/kg/day for maternal general and reproductive toxicity and for embryo-fetal development.

3.(iii).A.(5).6) Study for effects on pre- and postnatal development, including maternal function in rats (Attached document 4.2.3.5.3.2)

Apixaban (25, 200, 1000 mg/kg/day) or vehicle was administered orally to pregnant SD rats (n = 25) from Gestation day 6 up to Lactation day 20. One rat each in the vehicle group and the 1000 mg/kg/day group died, and both deaths were considered to be due to errors in administration. Prolongation of PT was observed in the ≥25 mg/kg/day groups, and prolongation of aPTT and an increased frequency of vaginal discharge (red watery/mucoid), an enhanced placental sign, during late pregnancy were observed in the ≥200 mg/kg/day groups, while no effect was observed on the gestation period, maternal behavior, or viability of offspring. F_1 females showed a decreased copulation rate and an accompanying decrease in the pregnancy rate in the ≥200 mg/kg/day groups (copulation rate; 95.7% in the control group, 73.9%-79.2% in the apixaban groups: pregnancy rate; 95.7% in the control group, 65.2%-79.2% in the apixaban groups). However, these findings were considered unlikely to be extrapolated to humans for the following reasons: (i) these rates were similar to, or only slightly lower than, the lower limit of the historical data of the study facility (copulation rate 75%, pregnancy rate 62.5%), and (ii) AUC (43.4 μg·h/mL) in maternal rats in the 200 mg/kg/day group was ≥14 times the AUC (3.1 μg·h/mL) in humans receiving the recommended clinical dose (10 mg/day). Based on the above, the NOAEL of apixaban was determined to be 1000 mg/kg/day for general toxicity in maternal rats and F_1 males and females and for the reproductive toxicity of F_1 males, and 25 mg/kg/day for the reproductive toxicity of F_1 females.

3.(iii).A.(6) Other toxicity studies

3.(iii).A.(6).1) Evaluation of toxicokinetics of metabolites (Attached document 4.2.3.7.7.1, 4.2.3.7.7.2)

Apixaban was administered orally for 1 week to male and female SD rats (maximum dose of 600 mg/kg/day) and to male and female beagle dogs (maximum dose of 100 mg/kg/day), and plasma concentrations of apixaban and M1 were measured on Day 7. Compared with $AUC_{0\text{-}24}$ of M1 (0.94 μg·h/mL) following administration to humans at the recommended clinical dose, $AUC_{0\text{-}24}$ of M1 following administration of the maximum dose to rats and dogs (0.197 μg·h/mL in male rats, 0.095 μg·h/mL in female rats, 0.529 μg·h/mL in male dogs, 1.20 μg·h/mL in female dogs) was lower in rats but similar in dogs.

3.(iii).A.(6).2 Toxicity evaluation of impurities

Among impurities of apixaban, the acceptance criteria for related substance B exceed the qualification threshold (0.15%) specified by the "Revision of Guidelines on Impurities in New Drug Substances" (PMSB/ELD Notification No. 1216001 dated December 16, 2002) and the "Revision of Guidelines on Impurities in New Drug Products" (PMSB/ELD Notification No. 0624001 dated June 24, 2003). However, there was a safety margin of 67 to 334 fold, as calculated from the NOAEL of apixaban in toxicity studies using batches containing related substance B, from which the safety of related substance B was considered to be ensured.

3.(iii).A.(6).3 Phototoxicity test (Attached document 4.2.3.7.7.4)

Apixaban exhibits an absorption maximum at a wavelength of 278 nm with a molar absorption coefficient of 1.5894×10^4 $(mol/L)^{-1}$ cm^{-1}. The ultraviolet-visible absorption spectrum is not affected by pH. An *in vitro* 3T3 NRU phototoxicity testing was conducted. Based on the results, the applicant considered that apixaban is not phototoxic.

3.(iii).B Outline of the review by PMDA

In toxicity studies, no bleeding tendency was observed in animals treated with apixaban. Therefore, PMDA asked the applicant to explain whether or not the animal species used in toxicity studies were appropriate, and in particular, to explain whether or not it was appropriate that dogs were selected as non-rodents in the repeat-dose toxicity study just because the exposure level to M1, the metabolite without pharmacological activity, was similar between dogs and humans, despite the fact that the pharmacological effect of apixaban (hemorrhage) was observed in monkeys in the single-dose toxicity study. PMDA also asked the applicant to explain whether or not the toxicity of apixaban was evaluated appropriately from the toxicity studies conducted, by taking into account the above.

The applicant responded as follows:

In the toxicity studies in rats, mice, and dogs, apixaban was administered up to the dose that caused saturation of exposure. Although rats and dogs did not show bleeding from tissues or organs, they showed prolongation of bleeding time, PT, and aPTT (2-3.2 times longer compared with control group), which were changes almost equivalent to hemorrhage. Therefore, the toxicity of apixaban was evaluated appropriately by the toxicity studies in rats and dogs. In dogs, the exposure level to apixaban was higher than the level in humans receiving the recommended clinical dose, and the exposure level to M1 was similar to that in humans (Attached document 4.2.3.7.7.2), allowing the evaluation of the effect of M1. In contrast, in the single oral dose study conducted to evaluate toxicokinetics and tolerability in monkeys, the exposure level to apixaban was similar to that in humans even at the maximum dose that could be administered (300 mg/kg/day), and less than 7% of the exposure level achieved in dogs receiving the maximum dose (100 mg/kg/day) in the 1-year repeated oral dose toxicity study. In addition, the extent of PT and aPTT prolongation was milder compared with dogs. Furthermore, the plasma M1 concentration was generally below the lower limit of quantitation, precluding the evaluation of the effect of M1. For the above reasons, monkeys were not considered to be necessarily the animal species appropriate for evaluating the toxicity of apixaban. Death that occurred in 3 monkeys was considered to be due to serious hemorrhage caused by accidental femoral artery injury during blood sampling, and a possible enhancement of the severity of the hemorrhage by the pharmacological activity of apixaban cannot be ruled out, but they were considered not to be toxic changes directly caused by the drug.

PMDA considers as follows:

Although adverse events related to apixaban-induced bleeding were observed in clinical studies, bleeding tendency reflecting the FXa-inhibitory activity of apixaban was scarcely observed in toxicity studies, which suggests the possibility that there is a species difference in the sensitivity to the primary pharmacological effect of apixaban between humans and animals used in toxicity

studies and that other animal species should have been used. However, in the toxicity studies conducted, apixaban was administered up to the dose causing the saturation of exposure, suggesting that it is possible to evaluate the toxicity to a certain extent. However, given the species difference in the sensitivity to the primary pharmacological action of apixaban, the safety of apixaban should be thoroughly evaluated based on the results of clinical studies although there were no findings that raise a safety concern in toxicity studies.

4. Clinical data

4.(i) Summary of biopharmaceutic studies and related analytical methods

4.(i).A Summary of the submitted data

The concentrations of apixaban and *O*-demethyl apixaban sulfate (M1) in test samples were measured by validated liquid chromatography-tandem mass spectrometry (LC-MS/MS). The lower limit of quantitation of the assay method was 1 ng/mL for apixaban and 5 ng/mL for M1, in the plasma and urine samples.

Pharmacokinetic parameter values are expressed in mean ± standard deviation (SD) unless stated otherwise.

4.(i).A.(1) Bioequivalence

The formulation (2.5 mg tablets, 5 mg tablets) used in the global phase III study (Study CV185030) and the to-be-marketed formulation (2.5 mg tablets, 5 mg tablets) are identical between the tablets of the same strength, in the composition of the inner core but different in the components and contents of the film layer.

4.(i).A.(1).1) Dissolution tests

4.(i).A.(1).1).(a) Equivalence of the dissolution behavior between the formulation used in the global phase III study and the to-be-marketed formulation

Each pair of 2.5 mg tablets and of 5 mg tablets (the formulation used in the global phase III study and the to-be-marketed formulation) fulfilled the equivalence criteria for dissolution behavior under all test conditions required by the "Guidelines for Bioequivalence Studies for Formulation Changes of Oral Solid Dosage Forms" (PFSB/ELD Notification No. 1124004 dated November 24, 2006) (BE Guidelines for Formulation Changes).

4.(i).A.(1).1).(b) Equivalence of dissolution behavior of film-coated tablets and core tablets

For all of the 4 types of tablets, i.e., 2.5 and 5 mg tablets used in the global phase III study and 2.5 and 5 mg tablets intended for marketing, the dissolution behaviors of the core tablets and the film-coated tablets were the same in the tests conducted under the conditions specified by the BE Guideline for Formulation Changes.

4.(i).A.(1).2) BE between 2.5 mg tablets and 5 mg tablets intended for marketing

The difference in the formulation between 2.5 mg and 5 mg tablets intended for marketing corresponds to Level [redacted] stipulated in the "Guidelines for Bioequivalence Studies for Different Strengths of Oral Solid Dosage Forms" (PFSB/ELD Notification No. 1124004 dated November 24, 2006) (BE Guidelines for Different Strengths), and the dosage forms were considered to be bioequivalent based on the results of the dissolution test conducted according to BE Guidelines for Different Strengths.

4.(i).A.(2) Food effect

4.(i).A.(2).1 To-be-marketed formulation (Study B0661019, Attached document 5.3.1.1.2; Studied period, September to October 2011)

A two-treatment, two-period crossover study was conducted in 22 foreign healthy adult subjects to investigate the pharmacokinetics of apixaban following a single oral dose of 5 mg tablets intended for marketing under fasted conditions or after taking a high fat diet (a ≥5-day washout period). The median time to the maximum plasma concentration (t_{max}) after a single oral dose of one 5 mg apixaban tablet under fasted condition or after a high fat diet was 3.0 and 2.0 hours, respectively, the maximum plasma concentration (C_{max}) was 121.3 (28%) and 103.2 (20%) ng/mL (geometric mean [coefficient of variation]), respectively, the area under the plasma concentration-time curve of apixaban from time 0 to infinity (AUC_{inf}) was 1229 (22%) and 971 (21%) ng·h/mL, respectively, the elimination half-life ($t_{1/2}$) was 9.9 ± 2.3 and 10.7 ± 3.0 hours, respectively, and the ratios (90% confidence interval [CI]) of the geometric mean of C_{max} and AUC_{inf} after a high fat diet to those under fasted condition were 0.8513 (0.7932-0.9135) and 0.7993 (0.7519-0.8497), respectively.

4.(i).A.(2).2 Formulation for foreign phase II studies (Study CV185008, Attached document 5.3.1.1.1; Studied period, [redacted] to [redacted] 20[redacted])

A two-treatment, two-period crossover study was conducted in 24 foreign healthy adult subjects to investigate the pharmacokinetics of apixaban following a single oral dose of 5 mg tablets intended for foreign phase II studies under fasted conditions or after taking a high fat diet (a ≥5-day washout period). In subjects receiving two 5 mg tablets, the ratios of the geometric mean of C_{max} and AUC_{inf} after a high fat diet to those under fasted condition were 1.10 (1.004-1.197) and 1.04 (1.004-1.086), respectively.

4.(i).B Outline of the review by PMDA

PMDA considers as follows regarding the bioequivalence (BE) between the formulation used in the global phase III study and the to-be-marketed formulation:

Both 2.5 and 5 mg tablets used in the global phase III study and those intended for marketing correspond to Level [redacted] in the formulation changes regarding the film layer, according to the BE Guidelines for Formulation Changes effective at the time of submission. However, PMDA deteremined that the formulation used in the global phase III study and to-be-marketed formulation are bioequivalent for the tablets of the same strength, based on the following reasons: (i) the dissolution behaviors of the core tablets and the film-coated tablets for both strengths were comparable under all test conditions specified in BE Guidelines for Formulation Changes, suggesting that the difference in the film layer does not affect the dissolution; (ii) for the tablets of the same strength, the composition of the inner core of the formulation for the global phase III study is identical with that of the to-be-marketed formulation; and (iii) for the tablets of the same strength, the dissolution behavior of the formulation for the global phase III study was comparable to that of the to-be-marketed formulation. Regarding the BE between the to-be-marketed formulation with different strengths, BE was demonstrated based on the results of the dissolution test conducted according to BE Guidelines for Different Strengths.

4.(ii) Summary of clinical pharmacology studies

4.(ii).A Summary of the submitted data

4.(ii).A.(1) *In vitro* tests using human biomaterials

4.(ii).A.(1).1 Plasma protein binding and plasma/blood cell partitioning (Attached document 4.2.2.2.1)

When apixaban (final concentration, 0.46 μg/mL) was added to human serum, the protein binding rate of apixaban was 87%. When apixaban (final concentration, 0.46-4.59 μg/mL) was added to a solution of human α_1-acidic glycoprotein (1 mg/mL), the protein binding rate of apixaban was 9%. When apixaban (final concentration, 0.46-4.59 μg/mL) was added to a solution of human

serum albumin (40 mg/mL), the protein binding rate of apixaban was 66%.

When apixaban was added to human blood, the ratio of plasma apixaban concentration to apixaban concentration in the blood was 1.09.

4.(ii).A.(1).2) *In vitro* metabolism (Attached document 4.2.2.2.1, 4.2.2.4.1, 4.2.2.4.3)

^{14}C-labeled apixaban (1, 10 μM) was added to human hepatocytes and the mixture was incubated at 37°C for 4 hours. As a result, unchanged apixaban accounted for 79% and 93%, respectively, of the total radioactivity administered, and the following 6 types of metabolites were identified: *O*-demethylated apixaban (M2), M1, hydroxyapixaban (M4), 3-hydroxyapixaban (M7), and metabolites formed by the cleavage of the lactam ring mediated by oxidation (M3) or hydrolysis (M5). M2 was the most predominant metabolite (0.8% of total radioactivity).

^{14}C-labeled apixaban (final concentration; 2.5, 25 μM) was added to microsomes derived from human liver, kidney, and small intestine, and to S9 fraction of human small intestine, and each mixture was incubated at 37°C for 1 hour. M2, M4, and M7 were detected in the liver microsomes and in the small intestinal microsomes, but only in small amounts. No metabolites were detected in the renal microsomes or in S9 fraction of the small intestine.

Apixaban (final concentration, 1-300 μM) was added to human liver microsomes and the mixture was incubated at 37°C for 20 minutes. The rates of M2, M4, and M7 formation increased in an apixaban concentration-dependent manner, and the rate of metabolite formation was not saturated even at 300 μM.

Apixaban (final concentration, 1-300 μM) was added to a human CYP3A4 gene-expressing system, and the mixture was incubated at 37°C for 1 hour. The rate of M7 formation increased in an apixaban concentration-dependent manner, becoming saturated within the concentration range examined. The dissociation constant of the enzyme-substrate complex (K_m) was 28.6 μM.

Apixaban was added to human hepatocytes or human liver microsomes in the presence of glutathione, and the mixtures were incubated at 37°C for 1 hour. As a result, no glutathione adduct of apixaban was detected.

4.(ii).A.(1).3) Studies on enzymes involved in metabolism (Attached document 4.2.2.4.3, 4.2.2.4.4, 5.3.2.3.1)

CYP isoforms involved in the metabolism of apixaban were investigated in the following studies: (i) a study on the rate of metabolite formation by each CYP isoform, using systems expressing genes of human CYP isoforms (CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C18, 2C19, 2D6, 2E1, 2J2, 3A4, 3A5, 3A7), (ii) a study on the rate of inhibition by inhibitors of CYP isoforms (CYP1A2, 2A6, 2C8, 2C9, 2C19, 2D6, 2E1, 3A4) in human liver microsomes, and (iii) a study on the correlation coefficient between the activity of each CYP isoform and the rate of metabolite formation, using human liver microsomes with known expression level of each CYP isoform (CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 3A4/5, 4A11). Results suggested that the formation of M2, M4, and M7 is mediated mainly by CYP3A4/5 and that the formation of M2 is mediated also by CYP1A2 and 2J2.

When M2 was added to human sulfotransferase (SULT) gene-expressing systems (SULT1A1*2, 1A2*1, 1A3, 1E, 2A1), M1 was formed in the highest amount by SULT1A1*2.

4.(ii).A.(1).4) Study on the membrane permeability using Caco-2 cells (Attached document 4.2.2.2.1, 4.2.2.2.2)

Apixaban (final concentration, 3-200 μM) was added to Caco-2 cells. As a result, the apparent efflux ratio (permeability coefficient from basolateral surface to apicolateral surface/permeability coefficient from apicolateral surface to basolateral surface) was 12 to 37. When cyclosporin A (50 μM) or ketoconazole (50 μM), which are inhibitors of P-glycoprotein (P-gp), was added, the apparent efflux ratio decreased by 84% and 93%, respectively. Addition of probenecid, an inhibitor of multidrug resistance-associated protein, did not change the apparent efflux ratio of apixaban.

4.(ii).A.(1).5) Study on the transport of apixaban by organic anion transporters and by organic anion transporting polypeptides using MDCKII cells and HEK-293 cells (Attached document 4.2.2.2.4)

^{14}C-labeled apixaban (1 μM) was added to MDCKII cells expressing, or not expressing, organic anion transporter (OAT) 1 or to HEK-293 cells expressing, or not expressing, OAT3, organic anion transporting polypeptide (OATP) 1B1, 1B3, or 2B1. As a result, little or no difference was observed in the velocity of ^{14}C-labeled apixaban transport between cells expressing any transporter or transporting peptide and non-expressing cells.

4.(ii).A.(1).6) Study of apixaban transport by human breast cancer resistance protein using MDCKII cells (Attached document 4.2.2.2.5)

^{14}C-labeled apixaban (final concentration, 1-100 μM) was added to MDCKII cells expressing human breast cancer resistance protein (BCRP). As a result, the apparent efflux ratio (permeability coefficient from basolateral surface to apicolateral surface/permeability coefficient from apicolateral surface to basolateral surface) was 11 to 19. When a similar test was carried out using BCRP non-expressing MDCKII cells, the apparent efflux ratio was 1 to 3.

^{14}C-labeled apixaban (final concentration, 5 μM) was added to BCRP-expressing MDCKII cells. The apparent efflux ratio was 12.6, but 1.49 in the presence of a BCRP inhibitor Ko134 (1 μM).

4.(ii).A.(2) Pharmacokinetics in healthy subjects

4.(ii).A.(2).1) Single-dose studies

4.(ii).A.(2).1).(a) Study in Japanese and Caucasian healthy adult subjects (Study CV185013, Attached document 5.3.3.1.6; Studied period, [redacted] 20[redacted] to [redacted] 20[redacted])

Apixaban was administered orally in a single dose to Japanese and Caucasian healthy adult male subjects at different doses with ≥5-day washout periods. Pharmacokinetic parameters of apixaban and of M1, the main metabolite in the plasma in the mass balance study, were as shown in Tables 3 and 4.

Table 3. Pharmacokinetic parameters of apixaban following a single-dose administration of apixaban (Adapted from submitted data)

	Dose (mg)	n	C_{max} (ng/mL)	t_{max}[a] (h)	AUC_{inf} (ng·h/mL)	$t_{1/2}$ (h)
Japanese	2.5	12	53.16 ± 8.39	3.50	472.21 ± 79.77 [b]	6.12 ± 1.21 [b]
	10	12	181.33 ± 40.71	3.00	1659.30 ± 294.97	8.11 ± 4.18
	25	12	373.42 ± 60.57	3.00	3453.88 ± 533.82	8.25 ± 2.47
	50	11	502.27 ± 141.99	4.00	4962.69 ± 1690.88	8.47 ± 1.71
Caucasians	2.5	12	45.60 ± 8.91	3.50	451.71 ± 69.53	8.87 ± 2.95
	10	12	220.17 ± 96.81	3.00	1966.71 ± 291.01	13.39 ± 6.15
	25	12	350.67 ± 62.38	3.50	3890.33 ± 731.63	12.70 ± 3.90
	50	12	508.08 ± 119.29	3.50	6259.80 ± 1473.22 [b]	16.12 ± 7.77 [b]

Mean ± SD, a: Median, b: n = 10

Table 4. Pharmacokinetic parameters of M1 following a single-dose administration of apixaban (Adapted from submitted data)

	Dose (mg)	n	C_{max} (ng/mL)	t_{max}[a] (h)	AUC_{inf} (ng·h/mL)	$t_{1/2}$ (h)
Japanese	2.5	12	9.66 ± 3.68	7.00	NC	NC
	10	12	32.53 ± 10.61	8.00	765.68 ± 213.70 [b]	9.99 ± 2.23 [b]
	25	12	60.39 ± 17.67	8.00	1237.79 ± 340.02 [c]	10.62 ± 2.81 [c]
	50	11	83.75 ± 26.80	8.00	1792.57 ± 628.76	11.21 ± 2.54
Caucasians	2.5	12	9.76 ± 2.78	8.00	NC	NC
	10	12	33.58 ± 10.68	8.00	883.92 ± 403.60 [d]	12.89 ± 3.57 [d]
	25	12	65.71 ± 21.81	9.00	1501.29 ± 650.06	13.53 ± 3.48
	50	12	83.29 ± 28.65	9.00	2162.32 ± 854.82 [e]	16.39 ± 6.09 [e]

Mean ± SD, a: Median, b: n = 6, c: n = 11, d: n = 8, e: n = 9
NC: Not calculated

4.(ii).A.(2).1).(b) Study in foreign healthy adult subjects (Study CV185001, Attached document 5.3.3.1.1; Studied period, [redacted] 20[redacted] to [redacted] 20[redacted])

Pharmacokinetic parameters of apixaban following a single oral dose of apixaban in foreign healthy adult subjects were as shown in Table 5.

Table 5. Pharmacokinetic parameters following a single-dose administration of apixaban (Adapted from submitted data)

	Dosing condition	Dose (mg)	n	C_{max} (ng/mL)	t_{max}[a] (h)	AUC_{inf} (ng·h/mL)	$t_{1/2}$ (h)
Solution	Fasted	0.5	6	9.28 ± 1.89	1.50	62.50 ± 9.91	3.57 ± 1.07
		1	6	24.59 ± 8.57	1.75	182.19 ± 57.14	4.25 ± 1.64
		2.5	6	55.52 ± 19.22	1.50	464.58 ± 188.56	6.79 ± 1.95
Tablets	Fasted	5	6	107.79 ± 27.35	3.25	1082.36 ± 404.60	15.19 ± 8.53
		10	6	190.60 ± 80.36	3.00	1387.90 ± 549.49	11.06 ± 5.75
		25	6	369.08 ± 62.48	3.00	4072.46 ± 785.70	26.80 ± 33.72
		50	7	700.25 ± 152.62	2.50	7785.15 ± 1959.40	19.72 ± 15.34
	Fed	10	6	189.88 ± 38.82	3.50	1990.78 ± 639.40	23.10 ± 18.85

Mean ± SD, a: Median
Fed administration of 10 mg was given to the same subjects who had received 10 mg fasted administration, after a ≥7-day washout period.

4.(ii).A.(2).1).(c) Study on intravenous administration in foreign healthy adult subjects (Study CV185020, Attached document 5.3.3.1.7; Studied period, [redacted] to [redacted] 20[redacted])

Apixaban (0.5, 1.25, 2.5, 3.75, 5 mg) was administered intravenously in a single dose to a total of 30 foreign healthy adult subjects (6 subjects per group). As a result, AUC_{inf} of apixaban was 147.10 ± 21.70, 373.09 ± 87.31, 736.72 ± 152.51, 1176.19 ± 124.87, and 1446.16 ± 184.99 ng·h/mL, respectively, total body clearance was 3.47 ± 0.54, 3.49 ± 0.71, 3.51 ± 0.67, 3.22 ± 0.31, and 3.50 ± 0.41 L/h, distribution volume at steady state (V_{ss}) was 17.09 ± 3.50, 19.36 ± 2.33, 21.99 ± 3.41, 23.71 ± 4.27, and 25.93 ± 4.26 L, and urinary excretion rate was 29.76% ± 7.65%, 30.14% ± 6.05%, 17.40% ± 9.05%, 27.15% ± 5.81%, and 27.48% ± 5.07%, respectively.

Subjects treated in the 2.5 mg group received a single oral dose of 5 mg apixaban after a ≥7-day washout period. AUC_{inf} of apixaban following a single oral dose was 1041.07 ± 447.29 ng·h/mL, and the absolute bioavailability was 67.52% ± 14.92%.

4.(ii).A.(2).2) Multiple dose studies

4.(ii).A.(2).2).(a) Study in Japanese healthy adult subjects (Study CV185046, Attached document 5.3.3.1.9; Studied period, [redacted] 20[redacted] to [redacted] 20[redacted])

Multiple oral doses of apixaban were administered twice daily (every 12 hours) for 7 days to Japanese healthy adult male subjects. Pharmacokinetic parameters of apixaban on Day 1 and Day 7 were as shown in Table 6.

Table 6. Pharmacokinetic parameters in multiple doses of apixaban (Adapted from submitted data)

Dosage and administration	Day	n	C_{max} (ng/mL)	t_{max}[a] (h)	AUC_{tau} (ng·h/mL)	$t_{1/2}$ (h)
2.5 mg twice daily	1	6	52.50 ± 12.97	3.00	350.19 ± 73.67	–
	7	6	85.07 ± 17.45	2.00	599.97 ± 102.56	8.41 ± 2.92
5 mg twice daily	1	6	129.58 ± 33.87	4.00	852.39 ± 197.23	–
	7	6	206.33 ± 26.36	3.50	1556.67 ± 178.17	10.10 ± 4.13
10 mg twice daily	1	6	196.67 ± 45.62	3.00	1429.79 ± 316.41	–
	7	6	368.00 ± 61.43	4.00	2789.37 ± 315.05	7.91 ± 1.32

Mean ± SD, a: Median

$t_{1/2}$ was calculated from the plasma apixaban concentration after dosing in the afternoon of Day 7. C_{max}, t_{max}, and AUC_{tau} were calculated from the plasma apixaban concentration after dosing in the morning of Day 1 and Day 7.

-: Not given because of the ongoing multiple doses

AUC_{tau}: AUC during the dosing interval

4.(ii).A.(2).2).(b) Study in foreign healthy adult subjects (Study CV185002A, Attached document 5.3.3.1.2; Studied period, [redacted] to [redacted] 20[redacted])

Multiple oral doses of apixaban were administered once daily or twice daily (every 12 hours) for 7 days to foreign healthy adult subjects. Pharmacokinetic parameters of apixaban on Day 1 and Day 7 were as shown in Table 7.

Table 7. Pharmacokinetic parameters in multiple doses of apixaban (Adapted from submitted data)

Dosage and Administration	Day	n	C_{max} (ng/mL)	t_{max}[a] (h)	AUC_{tau} (ng·h/mL)	$t_{1/2}$ (h)
2.5 mg twice daily	1	6	52.75 ± 14.36	3.50	363.79 ± 90.15	NC
	7	5	66.92 ± 25.02	3.00	491.23 ± 172.25	8.08 ± 1.80
5 mg twice daily	1	6	83.22 ± 15.17	3.50	611.04 ± 123.01	NC
	7	6	129.03 ± 12.78	4.00	1055.45 ± 93.19	11.70 ± 3.32
10 mg twice daily	1	6	239.53 ± 91.30	4.00	1673.42 ± 497.21	NC
	7	6	360.55 ± 162.15	3.00	2670.65 ± 1261.98	10.95 ± 2.92
25 mg twice daily	1	6	436.94 ± 106.50	3.50	3193.93 ± 800.37	NC
	7	6	728.71 ± 149.67	3.50	5908.77 ± 925.47	15.25 ± 7.15
10 mg once daily	1	6	181.13 ± 35.28	4.00	1615.74 ± 321.76	NC
	7	6	203.36 ± 29.87	3.50	2040.03 ± 325.16	14.87 ± 7.23
2.5 mg once daily	1	6	311.99 ± 38.09	4.00	2873.71 ± 197.77	NC
	7	6	435.83 ± 89.12	3.00	4307.70 ± 807.66	15.34 ± 4.32

Mean ± SD, a: Median
NC: Not calculated
$t_{1/2}$ in the twice daily group was calculated from the plasma apixaban concentration after dosing the afternoon of Day 7. C_{max}, t_{max}, and AUC_{tau} were calculated from the plasma apixaban concentration after dosing in the morning of Day 1 and Day 7.

4.(ii).A.(2).2).(c) Study in Chinese healthy adult subjects (Study CV185058, Attached document 5.3.3.1.10; Studied period, [redacted] to [redacted] 20[redacted])

Apixaban (10 mg) was administered in a single dose to 12 Chinese healthy adult subjects, which was followed by a 2-day washout period, then by twice daily multiple oral doses of apixaban (10 mg) for 6 days. On Day 6, only the morning dose was administered. As a result, the median t_{max} after the single-dose administration was 3.0 hours, C_{max} was 241.25 ± 61.88 ng/mL, AUC_{inf} was 2381.65 ± 645.20 ng·h/mL, and $t_{1/2}$ was 11.44 ± 3.57 hours. In multiple doses (after morning administration on Day 6), the median t_{max} of apixaban was 3.50 hours, C_{max} was 345.83 ± 83.19 ng/mL, AUC_{tau} was 2774.38 ± 658.79 ng·h/mL, and $t_{1/2}$ was 10.84 ± 4.90 hours.

4.(ii).A.(2).3) Mass balance study (Study CV185006, Attached document 5.3.3.1.4; Studied period, [redacted] to [redacted] 20[redacted])

^{14}C-labeled apixaban 20 mg (solution) was administered orally in a single dose to 10 foreign healthy adult male subjects (bile sample collection in 4 of the subjects). In subjects assigned to the bile collection group, bile samples were collected continuously from 3 hours until 8 hours after dosing of ^{14}C-labeled apixaban, and, at 7 hours after dosing, cholecystokinin (20 ng/kg) was administered intravenously to stimulate gallbladder contraction. In plasma samples collected at all time points (1, 6, 12, 24, and 48 hours after dosing), unchanged apixaban was the most predominant and M1 was the main metabolite. The percentage of unchanged apixaban relative to the total radioactivity in the plasma was the highest at 1 hour after dosing, which was 98.4% both in subjects who underwent bile collection and those who did not. At 48 hours after dosing, the percentage of unchanged apixaban relative to the total radioactivity was 58.5% in subjects without bile collection and 53.2% in those with bile collection, and M1 accounted for 41.5% and 46.8%, respectively. Other metabolites detected in the plasma were M2, M7, and *O*-demethyl apixaban sulfate-1 (M10), each of which accounted for <1% of the total radioactivity in the plasma at all time points examined. In subjects without bile collection and in those with bile collection, 24.5% and 28.8%, respectively, of the radioactivity administered was recovered from urine, and 56.0% and 46.7%, respectively, from feces by 216 hours after dosing. In subjects with bile collection, 2.4% of the radioactivity administered was recovered from the bile during the period from 3 to 8 hours after dosing. Unchanged apixaban was the most predominant among radioactive compounds recovered from urine by 216 hours after dosing, accounting for 21.5% of the

radioactivity administered in subjects without bile collection and 23.9% in subjects with bile collection. Metabolites recovered from urine were M1 and M7, with M1 accounting for 1.58% of the radioactivity administered in subjects without bile collection and 2.55% in subjects with bile collection, and M7 accounting for 1.46% of the radioactivity administered in subjects without bile collection and 1.85% in subjects with bile collection. Unchanged apixaban was the most predominant among radioactive compounds recovered from feces by 216 hours after dosing, accounting for 34.0% of the radioactivity administered in subjects without bile collection and 34.5% in subjects with bile collection. Main metabolites recovered from feces were M2 and M7, with M2 accounting for 12.2% of the radioactivity administered in subjects without bile collection and 5.09% in subjects with bile collection, and M7 accounting for 3.70% of the radioactivity administered in subjects without bile collection and 2.76% in subjects with bile collection. Unchanged apixaban was the most predominant among radioactive compounds recovered from bile during the period from 3 to 8 hours after dosing, accounting for 0.84% of the radioactivity administered. The main metabolite recovered from bile was M1, accounting for 0.96% of the radioactivity administered.

4.(ii).A.(3) Pharmacokinetics and pharmacodynamics in patients

4.(ii).A.(3).1) Population pharmacokinetic analysis (Attached document 5.3.3.5.1, 5.3.3.5.2)

4.(ii).A.(3).1).(a) Population pharmacokinetic analysis

A population pharmacokinetic (PPK) analysis was conducted using the plasma apixaban concentration data at 11,968 points obtained from a total of 4385 subjects in 12 Japanese and foreign studies conducted in healthy adult subjects, patients with renal impairment, patients with nonvalvular atrial fibrillation, and patients with acute coronary syndromes (Studies CV185002, CV185013, CV185018, CV185022, CV185023, CV185030, CV185046, CV185058, CV185959, CV185067, CV185070, and CV185074). The dosage regimens employed in the above 12 studies were single-dose administration at 2.5, 10, 20, 25, and 50 mg, and multiple-dose administration of 10 mg once daily, 20 mg once daily, 25 mg once daily, 2.5 mg twice daily, 5 mg twice daily, 10 mg twice daily, and 25 mg twice daily.

The distribution of background factors of the subjects analyzed include age 68 (18-94) years (median [minimum-maximum]); body weight 81.4 [32-198.2] kg; creatinine clearance (CL_{CR}) 79.3 [11.9-319.7] mL/min; sex, 3080 male subjects and 1305 female subjects; ethnicity, 3649 Caucasians, 652 Asians (401 Japanese subjects, 69 Korean subjects, 182 other subjects), 61 Black or African American, and 23 other subjects; and health condition, 270 healthy adult subjects, 3071 patients with atrial fibrillation, and 1044 patients with acute coronary syndromes. A potent CYP3A4 or P-gp inhibitor was concomitantly administered in 3 subjects and not in 4382 subjects, a moderate CYP3A4 or P-gp inhibitor was concomitantly administered in 718 subjects and not in 3667 subjects, and a potent CYP3A4 or P-gp inducer was concomitantly administered in 68 subjects and not in 4317 subjects.

The PPK model was constructed in 2 steps. The model in the first step was constructed based on the investigation of the basic model and of covariates using a data set of 11 studies (9036 points in 1543 subjects) out of the above 12 studies, excluding the global phase III study (Study CV185030). In the second step, the data of Study CV185030 (2932 points in 2932 subjects) were added to the dataset used in the first step, and CYP3A4 or P-gp inhibitors and inducers were examined as possible covariates using the model constructed in the first step, which resulted in the construction of the final model. The basic model of the pharmacokinetics of apixaban used was a 2-compatment model with the first-order absorption and the first-order elimination. From the final model, the apparent renal clearance (CL_R/F) and the apparent non-renal clearance (CL_{NR}/F) in typical patients with atrial fibrillation (65 years of age, non-Asian, male, body weight 70 kg, CL_{CR} 80 mL/min) were estimated to be 1.35 and 1.74 L/h, respectively, the apparent distribution volume of the central compartment (Vc/F) to be 30 L, the apparent clearance between

compartments to be 1.91 L/h, and the apparent distribution volume in the peripheral compartment to be 27 L.

As candidates of covariates of CL_{NR}/F, age, sex, and baseline body weight were investigated and, in the final model, age and sex were selected as the covariates. CL_{NR}/F was estimated to be 11.9% higher at the age of 50 years, and 8.5% lower at 80 years, compared with the value at 65 years, and 21.6% lower in female subjects compared with male subjects.

As candidates for covariates of the apparent oral clearance (CL/F), ethnicity (Caucasian, Black, Asian, other), disease (acute coronary syndromes, atrial fibrillation), time of administration (0 a.m. to 11 a.m., 11 a.m. to 5 p.m., 5 p.m. to 11 a.m.), concomitant use with a CYP3A4 or P-gp inhibitor, and concomitant use with a CYP3A4 or P-gp inducer were investigated and, as a result, ethnicity (Asian), disease (atrial fibrillation), and concomitant use with a CYP3A4 or P-gp inhibitor were selected as covariates in the final model. CLT/F was estimated to be 11.9% lower in Asians than in non-Asians, 13.9% lower in patients with atrial fibrillation than in healthy adult subjects, and 14.6% lower in subjects concomitantly administered with a moderate CYP3A4 or P-gp inhibitor than in subjects not concomitantly administered.

As candidates for covariates of Vc/F, baseline body weight and disease were investigated, and both were selected as covariates in the final model. Vc/F was estimated to be 23.3% lower in subjects weighing 50 kg, and 22% higher in those weighing 90 kg, compared with subjects weighing 70 kg, and 18% and 4% lower in patients with acute coronary syndromes and patients with atrial fibrillation, respectively, compared with healthy adult subjects.

As the candidate for the covariate of absorption rate constant (Ka), time of administration was investigated. As a result, time of administration was selected as the covariate in the final model. Ka was estimated to be 43% lower in nighttime administration compared with daytime administration.

Using the same dataset as used in the construction of the final model for the above analysis, Asians were classified into Japanese, Korean, and other Asian subjects, and an additional analysis was conducted using the model including the ethnicity (Japanese subjects, Korean subjects, other Asian subjects) as a covariate of CL/F. As a result, CL/F was estimated to be 15.1% lower in Japanese subjects compared with non-Asian subjects.

4.(ii).A.(3).1).(b) Exposure-response model

An exposure-response analysis was conducted on efficacy and safety using the data of a total of 3071 subjects consisting of 139 subjects in Study CV185067 and 2932 subjects in Study CV185030. Of the subjects analyzed, 389 subjects were ≥80 years of age, 313 subjects weighed ≤60 kg, 216 subjects had serum creatinine level of ≥1.5 mg/dL, 861 subjects received concomitant use with aspirin, 108 subjects received concomitant use with a non-aspirin antiplatelet agent, 401 subjects received concomitant use with a non-aspirin, non-steroidal antinflammatory drug (NSAID), and 229 subjects received concomitant use with an anticoagulant. The area under plasma concentration-time curve per day at steady state (AUC_{ss}) in each subject, estimated by the empirical Bayes method using the final model for PPK analysis, was used in the analysis.

In the exposure-response analysis of safety, the relationship between the exposure level and the time to the first bleeding event (major bleeding, major bleeding or clinically relevant non-major bleeding) was investigated. The relationship between the exposure level and clinical response of safety parameters was analyzed, using a proportional hazard model which assumed that the background hazard remained constant (did not change over time) and that the effect of apixaban on AUC_{ss} was linear with the daily apixaban dose. Results showed a tendency of increase in the

risk of major bleeding and the risk of major bleeding or clinically relevant non-major bleeding with the increase in the exposure level.

Effects of the following background factors on the hazard ratio of major bleeding were investigated: age ≥80 years, body weight ≤60 kg, serum creatinine ≥1.5 mg/dL, concomitant use with aspirin-containing drug, concomitant use with non-aspirin antiplatelet drug, concomitant use with non-aspirin NSAID, and concomitant use with anticoagulant. Results were as shown in Figure 1.

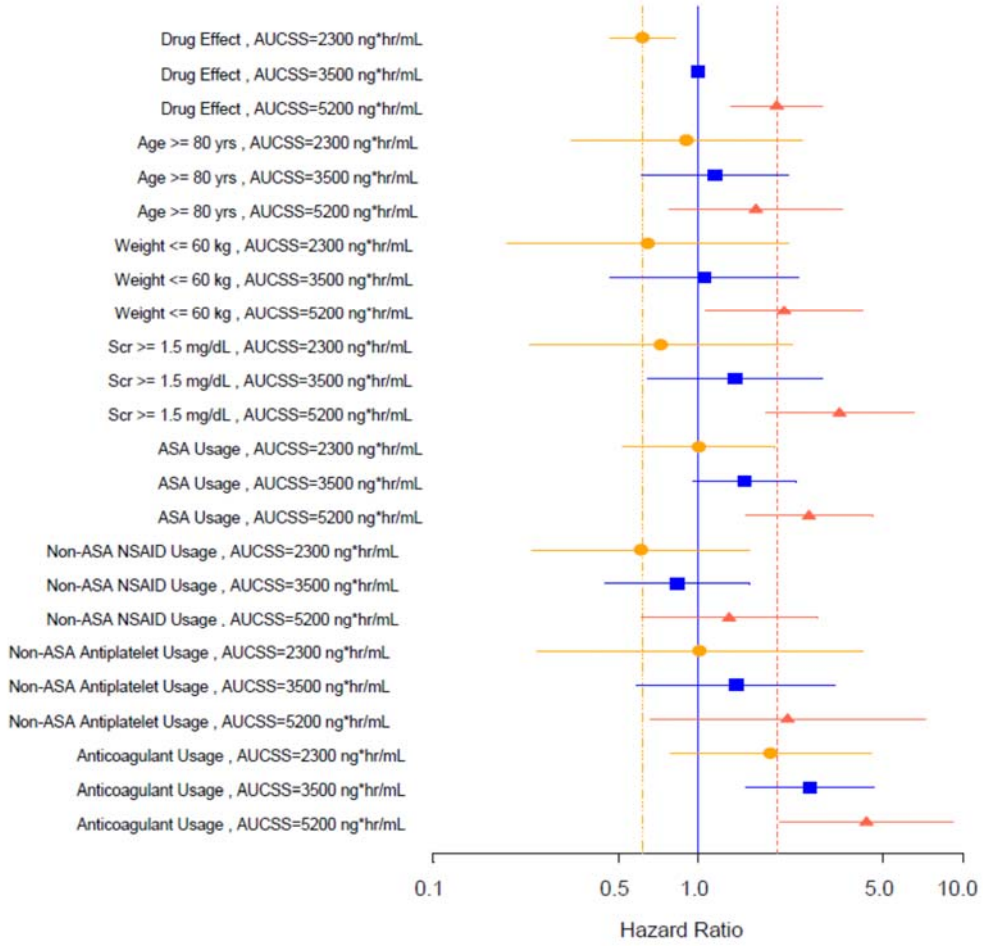


Figure 1. Hazard ratio of major bleeding estimated by exposure-response analysis using a full model

■: Estimated hazard ratio relative to the median exposure level in the study population (AUC_{ss} = 3500 ng·h/mL) (vertical solid line indicates hazard ratio 1).
●: Estimated hazard ratio relative to the median exposure level at the 10th percentile of the study population (AUC_{ss} = 2300 ng·h/mL) (vertical chain line indicates the hazard ratio at the exposure level at the 10th percentile of the study population).
▲: Estimated hazard ratio relative to the median exposure level at the 90th percentile of the study population (AUC_{ss} = 5200 ng·h/mL) (vertical chain line indicates the hazard ratio at the exposure level at the 90th percentile of the study population).
Control population: Patients with the same exposure level of apixaban as the median exposure level in the study population (AUC_{ss} = 3500 ng·h/mL) who were <80 years of age, weighed >60 kg, had serum creatinine level of <1.5 mg/dL, and did not use aspirin, NSAID, antiplatelet drug, or anticoagulant.

As regards efficacy, there was a tendency for a decrease in the risk of stroke or systemic embolism with the increase in the exposure level of apixaban. However, because of the limited number of events in the data analyzed, no clear relationship of these events with the exposure level of

apixaban could be confirmed.

4.(ii).A.(4) Pharmacokinetics in special patient populations

4.(ii).A.(4).1) Pharmacokinetics in subjects with renal impairment (Study CV185018, Attached document 5.3.3.3.1; Studied period, [redacted] 20[redacted] to [redacted] 20[redacted])

Apixaban (10 mg) was administered orally in a single dose to the following foreign subjects: 8 subjects with normal renal function (CL_{CR} estimated by Cockroft-Gault equation >80 mL/min), 10 subjects with mild renal impairment (CL_{CR}, >50 mL/min and ≤80 mL/min), 7 subjects with moderate renal impairment (CL_{CR}, ≥30 mL/min and ≤50 mL/min), and 7 subjects with severe renal impairment (CL_{CR}, <30 mL/min and not receiving hemodialysis). As a result, the median t_{max} of apixaban was 2.75, 4.00, 4.00, and 4.00 hours, C_{max} was 230.13 ± 57.25, 241.40 ± 79.39, 291.86 ± 52.97, and 226.57 ± 83.54 ng/mL, AUC_{inf} was 2592.35 ± 677.12, 3487.38 ± 1284.77, 4577.67 ± 1064.70, and 3708.35 ± 1832.96 ng·h/mL, renal clearance was 7.20 ± 2.36, 4.35 ± 2.32, 2.66 ± 2.36, and 2.14 ± 0.96 mL/min, cumulative urinary excretion rate up to 96 hours after administration was 10.42% ± 2.66%, 9.36% ± 6.23%, 7.18% ± 6.53%, and 4.65% ± 3.34%, and $t_{1/2}$ was 15.14 ± 7.56, 14.60 ± 7.27, 17.59 ± 5.99, and 17.25 ± 7.39 hours, respectively.

4.(ii).A.(4).2) Pharmacokinetics in subjects with hepatic impairment (Study CV185025, Attached document 5.3.3.3.3; Studied period, [redacted] 20[redacted] to [redacted] 20[redacted])

Apixaban (5 mg) was administered orally in a single dose to 16 foreign subjects with normal hepatic function and 8 each of foreign subjects with hepatic cirrhosis of Child-Pugh class A and B. As a result, the median t_{max} of apixaban was 3.25 in subjects with normal hepatic function, 3.00 in subjects with hepatic cirrhosis of Child-Pugh class A, and 2.50 hours in subjects with hepatic cirrhosis of Child-Pugh class B, C_{max} was 108.49 ± 31.91, 119.25 ± 30.13, and 127.15 ± 33.24 ng/mL, AUC_{inf} was 1130.79 ± 335.58, 1203.33 ± 335.73, and 1117.33 ± 396.40 ng·h/mL, and $t_{1/2}$ was 14.74 ± 7.03, 17.10 ± 16.76, and 14.83 ± 10.19 hours, respectively. The non-protein binding rate of apixaban in the serum samples collected from subjects with normal hepatic function, patients with hepatic cirrhosis of Child-Pugh class A and B was 7.1% ± 1.3%, 6.8% ± 1.4%, and 7.9% ± 1.8%, respectively.

4.(ii).A.(4).3) Study on the effect of age and sex (Study CV185022, Attached document 5.3.3.3.2; Studied period, [redacted] to [redacted] 20[redacted])

Apixaban (20 mg) was administered orally in a single dose to the following foreign subjects: 20 healthy young (18-40 years of age) male subjects, 20 young female subjects, 20 elderly (≥65 years of age) male subjects, and 19 elderly female subjects. As a result, the median t_{max} of apixaban was 3.00 hours in all treatment groups, C_{max} was 301.40 ± 85.84 in healthy young male subjects, 362.50 ± 129.69 in young female subjects, 321.30 ± 79.74 in elderly male subjects, and 377.58 ± 102.18 ng/mL in elderly female subjects, AUC_{inf} was 3230.31 ± 846.20, 3954.24 ± 1322.45, 4461.33 ± 1109.90, and 4847.81 ± 1018.28 ng·h/mL, and $t_{1/2}$ was 9.86 ± 2.98, 14.20 ± 6.03, 15.33 ± 6.89, and 15.58 ± 8.07 hours, respectively.

4.(ii).A.(4).4) Study on the effect of body weight (Study CV185059, Attached document 5.3.3.3.4; Studied period, [redacted] 20[redacted] to [redacted] 20[redacted])

Apixaban (10 mg) was administered orally in a single dose to 55 foreign healthy adult subjects (18 subjects weighing ≤50 kg, 18 subjects weighing ≥65 and ≤85 kg, 19 subjects weighing ≥120 kg). As a result, the median t_{max} was 3.0, 3.0, and 4.0 hours, C_{max} was 275.72 ± 70.76, 213.31 ± 51.62, and 148.81 ± 40.98 ng/mL, AUC_{inf} was 2525.76 ± 653.74, 2068.36 ± 487.72, and 1640.00 ± 512.96 ng·h/mL, and $t_{1/2}$ was 15.75 ± 9.78, 11.98 ± 5.35, and 8.76 ± 3.15 hours, respectively.

4.(ii).A.(5). Pharmacokinetic drug interactions

4.(ii).A.(5).1) Ketoconazole (Study CV185026, Attached document 5.3.3.4.3; Studied period, [redacted] to [redacted] 20[redacted])

A single dose of apixaban (10 mg) was administered orally to 18 foreign healthy adult subjects on Day 1, followed by once daily multiple oral doses of ketoconazole (400 mg) from Day 4 to Day 6, concomitant use of apixaban (10 mg) with ketoconazole (400 mg) orally on Day 7, and once daily multiple oral doses of ketoconazole (400 mg) on Day 8 and Day 9. The ratios (90% CI) of the geometric means of C_{max} and AUC_{inf} of apixaban in combination with ketoconazole to those in administration of apixaban alone were 1.62 (1.47-1.78) and 1.99 (1.81-2.18), respectively.

4.(ii).A.(5).2) Diltiazem hydrochloride (Study CV185032, Attached document 5.3.3.4.5; Studied period, [redacted] to [redacted] 20[redacted])

A single dose of apixaban (10 mg) was administered orally to 18 foreign healthy adult subjects on Day 1, followed by once daily multiple oral doses of diltiazem hydrochloride (diltiazem) (360 mg) from Day 4 to Day 10, concomitant use of apixaban (10 mg) with diltiazem (360 mg) orally on Day 11, and once daily multiple oral doses of diltiazem (360 mg) on Day 12 and Day 13. The ratios of the geometric means of C_{max} and AUC_{inf} of apixaban in combination with diltiazem to those in administration of apixaban alone were 1.31 (1.16-1.49) and 1.40 (1.23-1.59), respectively.

4.(ii).A.(5).3) Naproxen (Study CV185054, Attached document 5.3.3.4.9; Studied period, [redacted] 20[redacted] to [redacted] 20[redacted])

A two-treatment, two-period crossover study was conducted in 21 foreign healthy adult subjects in which apixaban (10 mg) was administered orally in a single dose on Day 1, after which subjects were randomly assigned in a crossover design to receive a single oral dose of naproxen (500 mg), and a concomitant treatment of a single oral dose of apixaban (10 mg) with naproxen (500 mg), on Day 4 and Day 11 (with a washout period of 7 days between the treatments). As a result, the ratios of the geometric means of C_{max} and AUC_{inf} of apixaban in combination with naproxen to those in administration of apixaban alone were 1.61 (1.42-1.83) and 1.54 (1.39-1.69), respectively.

4.(ii).A.(5).4) Rifampicin (Study CV185045, Attached document 5.3.3.4.7; Studied period, [redacted] to [redacted] 20[redacted])

A two-treatment, two-period crossover study was conducted in 20 foreign healthy adult subjects in which apixaban (5 mg) was administered intravenously in a single dose on Day 1, followed by a single oral dose of apixaban (10 mg) on Day 3, and by once daily multiple oral doses of rifampicin (600 mg) from Day 5 to Day 15. Subjects were assigned to receive apixaban (5 mg) intravenously, and apixaban (10 mg) orally, on Day 12 and Day 14 in a crossover design (with a washout period of 2 days between the treatments). The ratios of the geometric means of C_{max} and AUC_{inf} of apixaban in combination with rifampicin to those in intravenous administration of apixaban alone were 0.87 (0.77-0.98) and 0.61 (0.58-0.63), respectively, and the ratios of the geometric means of C_{max} and AUC_{inf} of apixaban in combination with rifampicin to those in oral administration of apixaban alone were 0.58 (0.52-0.65) and 0.46 (0.42-0.49), respectively. The absolute BA of apixaban in oral apixaban alone and in combination with rifampicin was 49% and 37%, respectively.

4.(ii).A.(5).5) Digoxin (Study CV185028, Attached document 5.3.3.4.4; Studied period, [redacted] to [redacted] 20[redacted])

Digoxin (0.25 mg) was administered orally 4 times daily to 24 foreign healthy adult subjects on Day 1, followed by once daily multiple oral doses of digoxin (0.25 mg) from Day 2 to Day 10, then by once daily multiple oral doses of apixaban (20 mg) and digoxin (0.25 mg) from Day 11 to Day 20. C_{max} and AUC_{inf} of digoxin were not affected by the concomitant use with apixaban.

4.(ii).A.(5).6) Atenolol (Study CV185033, Attached document 5.3.3.4.6; Studied period, ■ 20■)

A six-treatment, three-period crossover study was conducted in 15 foreign healthy adult subjects in which subjects were assigned to receive a single oral dose of apixaban (10 mg), a single oral dose of atenolol (100 mg), and concomitant use of apixaban (10 mg) with atenolol (100 mg) orally in a crossover design (with a washout period of 4 days between the treatments). The ratios of the geometric means of C_{max} and AUC_{inf} of apixaban in combination with atenolol to those in administration of apixaban alone were 0.82 (0.75-0.89) and 0.85 (0.78-0.92), respectively.

4.(ii).A.(5).7) Famotidine (Study CV185060, Attached document 5.3.3.4.10; Studied period, ■ 20■)

A two-treatment, two-period crossover study was conducted in 18 foreign healthy adult subjects in which a single oral dose of apixaban (10 mg) was administered with a washout period of 3 days between the treatment periods, followed by a single oral dose of famotidine (40 mg) and a single oral dose of apixaban (10 mg, 3 hours after the administration of famotidine), in a crossover design. C_{max} and AUC_{inf} of apixaban were not affected by famotidine.

The following studies on the pharmacokinetic drug interactions were also conducted: pharmacokinetics of apixaban, aspirin, and salicylate in concomitant use of apixaban with aspirin, pharmacokinetics of apixaban in concomitant use of apixaban with clopidogrel sulfate (clopidogrel), pharmacokinetics of a clopidogrel metabolite SR26334 and salicylate in concomitant use of apixaban with aspirin and clopidogrel, pharmacokinetics of apixaban in concomitant use of apixaban with enoxaparin sodium (enoxaparin). The pharmacokinetic parameters investigated were little affected in any of the concomitant uses [for pharmacodynamic interactions, see "4.(ii).A.(7) Pharmacodynamic interactions"].

4.(ii).A.(6). Pharmacodynamics

4.(ii).A.(6).1) Single-dose administration in Japanese and Caucasian healthy adult subjects (Study CV185013, Attached document 5.3.3.1.6; Studied period, ■ 20■ to ■ 20■)

A single dose of apixaban (2.5, 10, 25, 50 mg) or placebo was administered orally with a stepwise dose escalation to Japanese and Caucasian healthy adult subjects (with a washout period of ≥5 days between the treatments). Dose-dependent increases were observed in the international normalized ratio of prothrombin time (PT-INR), activated partial thromboplastin time (aPTT), and modified prothrombin time (mPT). The mean maximum PT-INR in Japanese and Caucasian subjects in each treatment group was 1.17 to 1.85 and 1.35 to 2.23, respectively, with the value in Japanese subjects being higher compared with Caucasian subjects, regardless of dose. No clear difference was observed in the maximum aPTT or mPT after dosing of apixaban between Japanese and Caucasian subjects at any doses studied. At 50 mg, aPTT was prolonged by approximately 20%, and mPT by >200%, compared with the placebo. After dosing of apixaban, prolonged time of thrombin formation to reach the peak level, decreased peak value, decreased capacity of intrinsic thrombin formation, and prolonged delay time were observed, but no clear difference was observed between Japanese and Caucasian subjects in the changes in any of the parameter values.

4.(ii).A.(6).2) Multiple-dose administration in Japanese healthy adult subjects (Study CV185046, Attached document 5.3.3.1.9; Studied period, ■ 20■ to ■ 20■)

Apixaban (2.5, 5, 10 mg) was administered orally twice daily for 7 days to Japanese healthy adult male subjects. The mean baseline level of PT-INR in each treatment group was 1.05 to 1.14, and the rate of increase in PT-INR on Day 7 from baseline was 11% ± 3%, 21% ± 3%, and 32% ± 6%, respectively, in the 2.5, 5, and 10 mg twice daily groups. The baseline aPTT in each group was

36 to 38 seconds, and the maximum rate of increase in aPTT on Day 7 from baseline was 13% ± 3%, 16% ± 3%, and 25% ± 4%, respectively. The mean baseline mPT in each group was 54 to 57 seconds, and the maximum rate of increase in mPT on Day 7 from baseline was 57% ± 20%, 111% ± 29%, and 173% ± 19%, respectively. The baseline activity to inhibit activated blood coagulating factor X (FXa) in the plasma (expressed in low-molecular-weight heparin unit) was below the lower limit of quantitation in all groups, whereas the activity was increased by apixaban administration, with the maximum FXa-inhibitory activity on Day 7 being 1.25 ± 0.35, 3.26 ± 0.47, and 5.48 ± 1.09 IU/mL, respectively.

4.(ii).A.(7). Pharmacodynamic interactions

4.(ii).A.(7).1) Aspirin (Study CV185002B, Attached document 5.3.3.1.3; Studied period, [redacted] to [redacted] 20[redacted])

Aspirin (325 mg) was administered orally once daily for 5 days to 17 foreign healthy adult subjects, after which subjects were randomized into 2 groups to orally receive aspirin (325 mg) once daily and apixaban (5 mg) or to orally receive aspirin (325 mg) once daily and placebo twice daily for 7 days. PT-INR, mPT, and aPTT were not affected by aspirin, whereas they increased after concomitant use with apixaban, with the maximum rate of change from the baseline being 18%, 56%, and 12%, respectively. Arachidonic acid-induced platelet aggregation was inhibited almost completely by the 5-day multiple oral doses of aspirin, and not affected by concomitant use with apixaban.

4.(ii).A.(7).2) Clopidogrel (Study CV185005, Attached document 5.3.3.4.1; Studied period, [redacted] to [redacted] 20[redacted])

Clopidogrel (75 mg) was administered orally once daily for 5 days to 35 foreign healthy adult subjects, after which the subjects were randomized into 3 groups to receive clopidogrel (75 mg) once daily and apixaban (5 mg) twice daily, to receive clopidogrel (75 mg) once daily and apixaban (10 mg) once daily, or to receive clopidogrel (75 mg) once daily and placebo orally for 5 days. Compared with concomitant use of placebo with clopidogrel, concomitant use of apixaban with clopidogrel had no effect on adenosine diphosphate (ADP)-, arachidonic acid-, or collagen-induced platelet aggregation. Neither was there a difference in the mean bleeding time among groups after 5-day concomitant use.

4.(ii).A.(7).3) Aspirin and clopidogrel (Study CV185015, Attached document 5.3.3.4.2; Studied period, [redacted] to [redacted] 20[redacted])

A combination of clopidogrel (75 mg), aspirin (162 mg), and apixaban (20 mg) or a combination of clopidogrel (75 mg), aspirin (162 mg), and placebo was administered orally once daily for 10 days to 30 foreign healthy adult subjects. Concomitant use of apixaban did not affect the inhibitory activity of clopidogrel and aspirin against ADP- or arachidonic acid-induced platelet aggregation.

4.(ii).A.(7).4) Enoxaparin (Study CV185055, Attached document 5.3.3.4.8; Studied period, [redacted] to [redacted] 20[redacted])

A four-treatment, four-period crossover study was conducted in 20 foreign healthy adult subjects. The subjects received a single oral dose of apixaban (5 mg), a single subcutaneous dose of enoxaparin (40 mg), concomitant treatment of a single oral dose of apixaban (5 mg) with a single subcutaneous dose of enoxaparin (40 mg), and a single oral dose of apixaban (5 mg) followed by a single subcutaneous dose of enoxaparin (40 mg) 6 hours after the administration of apixaban, in a crossover design (with a washout period of ≥3 days between the treatment periods). Little change was observed in PT-INR in any of the treatment groups. The maximum anti-FXa activity was 1.36 U/mL in administration of apixaban alone, 0.42 U/mL in administration of enoxaparin alone, 1.92 U/mL in concomitant use of apixaban with enoxaparin, and 1.56 U/mL in administration of apixaban followed by enoxaparin administration after 6 hours. Thus, the

maximum anti-FXa activity was higher in concomitant use of apixaban with enoxaparin compared with either of them alone. Compared with the maximum anti-FXa activity and the area under the effect-time curve observed when apixaban alone was administered, the values were higher by 42% and 52%, respectively, when the 2 drugs were concomitantly administered, and by 15% and 58%, respectively, when enoxaparin was administered at 6 hours after dosing of apixaban.

4.(ii).A.(8) Effect on QTc interval (Study CV185031, Attached document 5.3.3.1.8; Studies period, [redacted] to [redacted] 20[redacted])

A, four-treatment, four-period crossover, double-blind study was conducted in 40 foreign healthy adult subjects to investigate the effect of apixaban (10, 50 mg) administered orally once daily for 3 days on QTc interval, using moxifloxacin 400 mg (placebo on Day 1 and Day 2, moxifloxacin 400 mg on Day 3) and placebo as controls (with a washout period of ≥7 days between the treatment periods).

The median t_{max} after a dose of 10 and 50 mg of apixaban was 4 and 3 hours, respectively, C_{max} was 228.1 ± 62.5 and 585.5 ± 162.8 ng/mL, and AUC_{tau} was 2313.6 ± 731.6 and 6082.1 ± 1906.5 ng·h/mL, respectively. The difference in the adjusted mean change of QTcF (QTc interval corrected by Fridericia's formula) between apixaban (10, 50 mg) groups and the placebo group was maximum at 24 hours after administration at both doses; the difference (two-sided 90% CI) was 1.36 (-0.83 to 3.54) and 1.51 (-0.69 to 3.71) msec, respectively. The maximum difference (two-sided 90% CI) between the moxifloxacin group and the placebo group was 10.2 (8.1-12.4) msec.

4.(ii).A.(9) Effect of activated charcoal on the pharmacokinetics of apixaban (Study CV185104, Attached document 5.3.3.1.12; Studied period, [redacted] 20[redacted])

A six-treatment, three-period crossover study was conducted in 18 foreign healthy adult subjects. The subjects received a single oral dose of apixaban (20 mg), a single oral dose of apixaban (20 mg) followed by an aqueous suspension of activated charcoal 2 hours after the dosing of apixaban, and a single oral dose of apixaban (20 mg) followed by an aqueous suspension of activated charcoal 6 hours after the dosing of apixaban, in a crossover design (with a washout period of ≥4 days between the treatment periods). Relative to the ratios (90% CI) of the geometric mean of C_{max} and AUC_{inf} of apixaban in the apixaban alone group, those in the group receiving activated charcoal at 2 hours after dosing of apixaban were 0.999 (0.903-1.105) and 0.496 (0.450-0.547), and those in the group receiving activated charcoal at 6 hours after dosing of apixaban were 1.030 (0.939-1.130) and 0.723 (0.661-0.792), respectively.

4.(ii).B Outline of the review by PMDA

4.(ii).B.(1) Difference in pharmacokinetics and pharmacodynamics between Japanese and foreign subjects

The applicant explained the ethnic difference of the pharmacokinetics and pharmacodynamics of apixaban as follows:

The AUC_{inf} of apixaban after single-dose administration was shown to be similar among non-Asian, Japanese, and Chinese subjects, when adjusted for dose and body weight. Comparison of C_{max} and AUC_{inf} of apixaban based on the combined results obtained from multiple phase I studies showed that the exposure level to apixaban is similar among different ethnic groups (Asian subjects, Caucasian subjects, Black subjects, other subjects). As regards pharmacodynamics as well, the relationship between anti-FXa activity and plasma apixaban concentration showed a similar tendency throughout multiple phase I studies in Chinese, Japanese, and non-Asian subjects.

PMDA asked the applicant to explain whether or not it was appropriate to use the same dose both in Japanese and foreign patients with nonvalvular atrial fibrillation in Study CV185030 from the point of view of pharmacokinetics, based on the results of the pharmacokinetic analysis in the Japanese phase II study (Study CV185067).

The applicant presented Figure 2, which showed the time-course change of plasma apixaban concentration in non-Asian patients with nonvalvular atrial fibrillation predicted by the PPK model and the actual plasma apixaban concentration observed in Japanese patients with nonvalvular atrial fibrillation in Study CV185067, and explained as follows:
Although the plasma apixaban concentration observed at each dose in Study CV185067 tended to be slightly higher than the value predicted in non-Asian subjects, the observed value exceeded 95% CI of the value predicted in non-Asian subjects in only a small number of subjects. This tendency was consistent with the observation that CL/F in Japanese subjects was lower by approximately 15% compared with non-Asian subjects in the study of ethnic difference in PPK analysis. However, the incidence rates of events for efficacy and for safety in the Japanese subpopulation enrolled in Study CV185030 tended to be consistent with those observed in the entire study population. Furthermore, there were no apixaban-specific adverse events that occurred commonly in the Japanese subpopulation; no significant difference was observed in the adverse event profile between the entire study population and the Japanese subpopulation. Based on the above, the above-observed difference in the exposure level between Japanese and non-Asian subjects would not have a clinically significant effect.

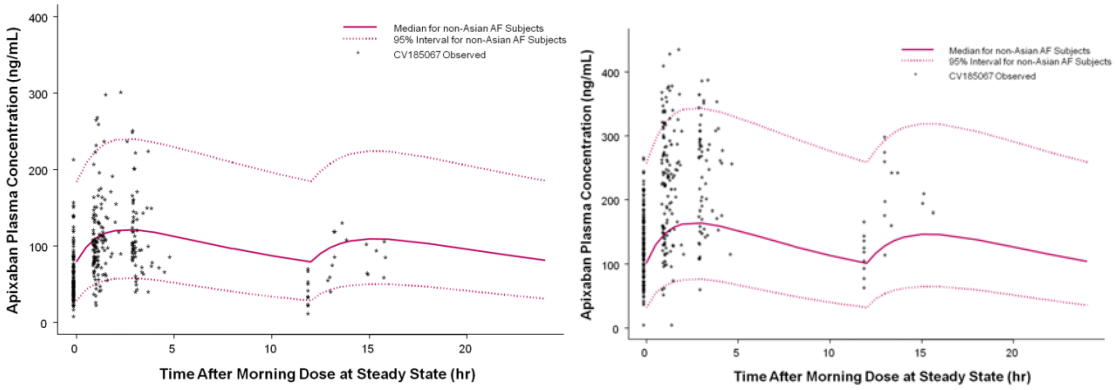


Figure 2. Plasma apixaban concentration observed in Japanese patients with nonvalvular atrial fibrillation in Study CV185067 and the CI of plasma apixaban concentration predicted by PPK analysis model of non-Asian patients with nonvalvular atrial fibrillation (left, 2.5 mg BID; right, 5 mg BID)

PMDA considers as follows:
Pharmacokinetic and pharmacodynamic studies in healthy subjects do not suggest any significant difference between Japanese and foreign subjects. In contrast, as shown in Figure 2, the plasma concentration after dosing of apixaban 5 mg was distributed over a higher range in Japanese patients with nonvalvular atrial fibrillation compared with the results obtained with the simulation of data in non-Asian patients with nonvalvular atrial fibrillation. Also, the difference in the exposure level between 2.5 mg and 5 mg doses appears to be larger in Japanese patients than in non-Asian patients. In addition, apixaban is required to adjust the dose based on the background factors possibly affecting the exposure level to the drug. Taking account of these factors, even if the dose setting in Study CV185030 based on the results of foreign clinical studies is justified, applying this dosage regimen to Japanese patients may be not optimal from the point of view of pharmacokinetics.

Whether or not the recommended dosage and administration derived from the results of Study CV185030 is applicable to Japanese patients should be determined based on the detailed investigation of the efficacy and safety in Japanese patients with nonvalvular atrial fibrillation in Study CV185030 [see "4.(iii).B.(3) Efficacy and dosage and administration of apixaban" and "4.(iii).B.(4) Safety"].

4.(ii).B.(2) Caution for use in patients with renal impairment

Results of the exposure-response analysis suggest that the hazard ratio of major bleeding in "typical patients with atrial fibrillation" (male, non-Asian, 65 years of age, body weight 70 kg, CL_{CR} 80 mL/min) may possibly be higher compared with patients who meet ≥2 of the dose reduction criteria for reasons of renal impairment alone. Therefore, PMDA asked the applicant to explain whether or not it is necessary to contraindicate the product, or require careful administration, in patients with decreased kidney function or to require dose reduction depending on the severity of CL_{CR}.

The applicant responded as follows:

In the analysis of the exposure-response relationship, the hazard ratio of major bleeding in "typical patients with atrial fibrillation" without covariates was estimated to be 2.0 if patients had severe renal impairment (CL_{CR} = 15 mL/min). This ratio was higher than the ratio (1.7) in "patients with advanced age and low body weight" which is a condition meeting the ≥2 of dose reduction criteria, but lower than the ratio in other combinations of dose reduction criteria, i.e., "patients with low body weight and high serum creatinine" (2.7) and " patients with advanced age and high serum creatinine" (2.9), and the ratio in patients who met all of the dose reduction criteria "patients with advanced age, low body weight, and high serum creatinine" (2.9). Of the total CL of apixaban, 27% is excretion from the kidney. In Study CV185018, which investigated the effect of mild to severe renal impairment on the pharmacokinetics of apixaban, the rate of increase in the exposure level of apixaban in patients with severe renal impairment (CL_{CR} 15.7-28.0 mL/min) was <50%. In PPK analysis, a 48% shrinkage occurred in CL/F estimate, showing that the SD of the individual CL/F estimate was 48% lower than the estimate of the individual variability (SD) of CL/F. This is possibly due to the low frequency of blood sampling in Study CV185030. Since the effect of the exposure level in the exposure-response analysis is taken into account in the linear model, using individual estimates causes the lower estimation of the exposure at the high exposure level compared with the exposure without shrinkage, resulting in an overestimation of the effect of the exposure level on bleeding. Also, data obtained from patients receiving dosage regimens exceeding twice daily 5 mg administration were not included in the construction of the exposure-response model. Therefore, consideration should be given to the uncertainty in the evaluation of bleeding risk at high exposure level based on the exposure-response model. Based on the above, it is appropriate to evaluate the effect of renal impairment on the apixaban-emergent bleeding risk on the basis of the results of the subpopulation analysis in Study CV185030. From the results of the subpopulation analysis in Study CV185030, it is not necessary to reduce the dose of apixaban in renal impairment patients with CL_{CR} ≥15 mL/min for reason of the impaired renal function alone, but it will be appropriate to require careful administration in patients with severe renal impairment (CL_{CR}, ≥15 mL/min and <30 mL/min). In patients with CL_{CR} of <15 mL/min, apixaban should be contraindicated because there is no use experience of nonvalvular atrial fibrillation in this patient group.

PMDA considers as follows:

It is understandable that there is a limitation to the quantitative evaluation of bleeding risk at the high exposure level using the exposure-response model based on the limited data. However, the PPK analysis based on the results of the clinical studies on apixaban and the analysis based on the exposure-response model have a clinical significance, given the data used and the process of model construction. Therefore, attention should be paid to the inference, derived from these analyses, that the severer the renal impairment, the higher the bleeding risk. From the point of view of safety, it is appropriate to contraindicate apixaban in patients with CL_{CR} of <15 mL/min. However, since it is shown that the exposure level of apixaban is increased in patients with renal impairment, caution should also be provided in using the product in patients with moderate renal impairment. The necessity for dose adjustment should be evaluated from the point of view of the

efficacy of apixaban as well, and will therefore be determined upon detailed review of the results of Study CV185030 [see "4.(iii).B.(3) Efficacy and dosage and administration of apixaban" and "4.(iii).B.(4).2) Administration in patients with renal impairment"].

4.(ii).B.(3) Concomitant use with CYP3A4 or P-gp inhibitor

PMDA instructed the applicant to investigate the necessity for requiring precautions or contraindications for concomitant use of drugs that increase the exposure level of apixaban (ketoconazole, diltiazem, naproxen) and for giving consideration to reducing the dose of apixaban in combination with these drugs, by taking account of the fact that, in the exposure-response model, the hazard ratio of the major event is estimated to be 3.5 when the dose of apixaban is increased 2-fold in typical patients with atrial fibrillation relative to the risk expected without the dose increase in the same patient group.

The applicant responded as follows:

As discussed in (2) above, the exposure-response model was constructed by using individual estimates, which may underestimate the exposure at the high exposure level and thereby the effect of exposure level on bleeding may be overestimated. In drug-drug interaction studies, concomitant use with CYP3A4 or P-gp inhibitors was shown to increase the exposure level of apixaban. Therefore, the incidence rates of stroke or systemic embolism in the apixaban group in Study CV185030 and in Study CV185048 (aspirin-controlled) conducted in foreign countries, and the incidence rates of major bleeding events according to the criteria of the International Society on Thrombosis and Haemostasis (ISTH) (the incidence rates of events in patients receiving concomitant use was calculated for the period of the combination therapy) were calculated for patients with and without concomitant use with moderate CYP3A4 or P-gp inhibitor (e.g., diltiazem, naproxen) or potent CYP3A4 or P-gp inhibitor (e.g., ketoconazole). Results showed that, in both studies, the efficacy and the safety of apixaban were similar between subjects who were concomitantly administered with moderate or potent CYP3A4 or P-gp inhibitor (2716 subjects in Study CV185030, 728 subjects in Study CV185048) and those who were not. Since the protocol of both studies prohibited the concomitant use with potent CYP3A4 and P-gp inhibitors, there were only 165 subjects in the apixaban group, including 5 Japanese subjects, who used a potent CYP3A4 or P-gp inhibitor in Study CV185030. Therefore, whereas neither systemic embolism nor major bleeding occurred during the combination therapy period, the effect of the concomitant use with drugs that potently and simultaneously inhibit CYP3A4 and P-gp on the efficacy and safety of apixaban could not be evaluated.

Based on the above, concomitant use with a moderate CYP3A4 or P-gp inhibitor does not affect the efficacy and safety of apixaban and that it is therefore unnecessary to provide caution against the use of these drugs. In contrast, concomitant use with a potent CYP3A4 or P-gp inhibitor increased the AUC_{inf} of apixaban approximately 2-fold in the drug-drug interaction study on ketoconazole, a drug that potently inhibits CYP3A4 and P-gp simultaneously and, in Study CV185030, no sufficient data were obtained for evaluating the incidence rates of the events. Therefore, the possibility of increased risk of major bleeding caused by combination therapy cannot be excluded. The proposed package insert has already provided cautions against the concomitant use with potent CYP3A4 or P-gp inhibitors in the "Precautions for concomitant use" section. For a further precaution, the "Clinical symptoms and measures" section will include the description "careful supervision such as close monitoring of the patient condition should be required during concomitant use with these drugs."

PMDA asked the applicant to explain the appropriateness of administering apixaban to patients who meet 1 or 2 of the dose reduction criteria in apixaban 2.5 mg twice daily administration (age ≥80 years, body weight ≤60 kg, serum creatinine ≥1.5 mg/dL) and also concomitantly receive a CYP3A4 or P-gp inhibitor.

The applicant responded as follows:
Regarding the effect of the increased exposure alone on the incidence rates of safety-related events, there is a limitation to the quantitative evaluation of major bleeding using the exposure-response model. Therefore, it is appropriate to investigate what precautions should be provided in the concomitant use with drugs that increase the exposure level of apixaban, based on the results of the subpopulation analysis and the use experience in Study CV185030 and on the results of drug-drug interaction studies. In patients who meet only 1 of the dose reduction criteria and concomitantly receive a drug that increases the exposure level of apixaban, there is no problem in administering apixaban without dose reduction, and it is unnecessary to provide caution against concomitant use with a moderate CYP3A4 or P-gp inhibitor. As regards concomitant use with a potent CYP3A4 or P-gp inhibitor, an appropriate caution will be provided in the "Precautions for concomitant use" section of "Interactions" in the package insert. In patients who meet at least 2 of the dose reduction criteria, a moderate CYP3A4 or P-gp inhibitor may be concomitantly administered by reducing the dose of apixaban to 2.5 mg twice daily. As for concomitant use with a potent CYP3A4 or P-gp inhibitor in such patients, appropriate administration will be done by providing a caution in the "Precautions for concomitant use" section of "Interactions" in the package insert.

PMDA considers as follows:
The hazard ratio of major bleeding estimated by the full model of exposure-response analysis suggests that the bleeding risk increases with the increase in the exposure level of apixaban. Therefore, the applicant's claim that caution is not provided against concomitant use with drugs that indicate increases of the exposure level of apixaban, is not appropriate. CYP3A4 and P-gp inhibitors that are shown to increase the exposure level of apixaban should be handled as drugs requiring precautions for concomitant use and, patient should be carefully monitored during concomitant use of apixaban with these drugs. Regarding the concomitant use with a potent CYP3A4 or P-gp inhibitor, there is a use experience in Study CV185030, albeit in a limited number of subjects, and since no serious bleeding events occurred in combination therapy, contraindication of these drugs is not necessarily warranted currently. However, results of Study CV185026 showed that the exposure level of apixaban was increased by approximately 2-fold when ketoconazole was concomitantly administered compared with the level observed in apixaban alone administration. Therefore, the therapeutic usefulness and risk should be thoroughly weighed against each other and caution should be provided, depending on the characteristics of patients, on considering the option of withholding the concomitant use with a potent CYP3A4 or P-gp inhibitor with apixaban or of reducing the dose of apixaban. A final decision on the appropriate caution statement regarding the concomitant use with CYP3A4 or P-gp inhibitors will be made, taking also account of comments raised in the Expert Discussion.

4.(iii) Summary of clinical efficacy and safety

4.(iii).A Summary of the submitted data

As the evaluation data, the results from a total of 35 studies (1 each of Japanese phase I study and Japanese phase II study, 29 foreign phase I studies, 2 foreign phase II studies, 1 foreign phase III study, 1 global phase III study in which Japanese patients participated) were submitted. Results of 7 Japanese and foreign studies were submitted as reference data [for BE and pharmacokinetics, see "4.(i) Summary of biopharmaceutic studies and related analytical methods" and "4.(ii) Summary of clinical pharmacology studies"]. The main study results are summarized below.

4.(iii).A.(1) Phase I studies

4.(iii).A.(1).1) Single-dose study in Japanese and Caucasian subjects (Protocol No. CV185013, Attached document 5.3.3.1.6 [[redacted] 20[redacted] to [redacted] 20[redacted]])

A randomized, double-blind, dose-escalation study was conducted at a single center in the US in order to investigate the pharmacokinetics of apixaban in Japanese and Caucasian subjects. Apixaban (2.5, 10, 25, 50 mg) or placebo was administered orally in a single dose to a total of 32 Japanese or Caucasian healthy adult male subjects (16 Japanese subjects, 16 Caucasian subjects) under fasting conditions (with a washout period of ≥5 days between the treatments).

Adverse events reported by Japanese subjects occurred in 2 subjects in the 2.5 mg group (infusion site pain; dry mouth, headache), 4 subjects in the 10 mg group (infusion site pain; hypoaesthesia; pharyngolaryngeal pain; alanine aminotransferase [ALT] increased, γ-glutamyl transpeptidase [γ-GTP] increased, pharyngolaryngeal pain, muscle tightness), 1 subject in the 25 mg group (lip dry), and 2 subjects in the placebo group (herpes virus infection, headache, diarrhoea, rhinorrhea, syncope, fall; diarrhoea, nausea, hepatic enzyme increased). Adverse events reported by Caucasian subjects occurred in 3 subjects in the 2.5 mg group (infusion site pain; vomiting, headache; dizziness), 6 subjects in the 10 mg group (dizziness; muscle spasms; hypoaesthesia, fatigue; headache; dyspepsia, headache; headache), 5 subjects in the 25 mg group (headache, asthenia, neck pain, bleeding time prolonged; hypoaesthesia, nausea; back pain; application site dermatitis; eye pruritus), 1 subject in the 50 mg group (chest pain), and 4 subjects in the placebo group (fatigue, headache, abdominal pain upper, disturbance in attention, dyspepsia; fatigue; muscle twitching, somnolence, rhinorrhoea, dizziness, toothache, cerumen impaction, gastroenteritis; myalgia, shoulder pain, dizziness). Neither serious adverse events nor deaths were observed.

There were no clinically significant variations in vital signs or ECG.

4.(iii).A.(1).2) Multiple dose study in Japanese subjects (Protocol No. CV185046, Attached document 5.3.3.1.9 [[redacted] 20[redacted] to [redacted] 20[redacted]])

A randomized, double-blind study was conducted at a single center in Japan in 24 Japanese healthy adult male subjects in order to investigate the safety and tolerability of apixaban. Apixaban (2.5, 5, 10 mg) or placebo was administered orally twice daily (morning, after a 10-hour fasting; evening, after a 3-hour fasting) for 7 days.

Adverse events were observed in 2 subjects in the 5 mg group (pain in extremity, blood triglycerides increased) and in 1 subject in the placebo group (dizziness). Neither serious adverse events nor deaths were observed.

There were no clinically significant variations in vital signs or ECG.

4.(iii).A.(2) Phase II studies

4.(iii).A.(2).1) Phase II study in Japanese patients with nonvalvular atrial fibrillation (Protocol No. CV185067, Attached document 5.3.5.1.7 [June 2008 to September 2009])

A randomized, double-blind, parallel group, comparative study was conducted at 23 centers in Japan in Japanese patients with nonvalvular atrial fibrillation in order to investigate the safety of apixaban (target sample size; 70 subjects per group, 210 subjects in total). Apixaban (2.5, 5 mg) was administered orally twice daily after breakfast and dinner, or warfarin (target PT-INR; 2.0-3.0 in patients aged <70 years, 2.0-2.6 in patients aged ≥70 years) was administered orally once daily after breakfast, for 12 weeks. The warfarin group received the treatment in an open-label fashion.

Subjects who had been receiving warfarin before the study were to discontinue the drug or receive

the drug at a reduced dose and, after PT-INR was confirmed to be <2.0, proceed to the 12-week treatment.

The main inclusion criteria were outpatients aged ≥20 years who were diagnosed with nonvalvular atrial fibrillation, based on atrial fibrillation (not explained by a reversible cause) on ECG observed during the run-in period or on 2 events of atrial fibrillation observed at ≥2-week interval within 12 months before the start of the run-in period. Subjects had also to have at least 1 of risk factors for stroke (cardiac failure congestive, hypertension requiring drug therapy, ≥75 years of age, diabetes mellitus, a history of cerebral infarction [including transient ischaemic attack (TIA)]). Exclusion criteria included cerebral infarction (within 4 weeks before proceeding to the treatment period), mitral valve stenosis, endocarditis infective, prosthetic valve replacement for valvular disease, and a history of non-cardiogenic cerebral infarction requiring continued treatment with aspirin >100 mg/day or concomitant use of aspirin with other antiplatelet drugs. In this study, patients were assigned to treatment groups by taking account of the medical institution and the history of warfarin treatment.

A total of 222 randomized patients (74 patients each in the apixaban 2.5 mg, apixaban 5 mg, and warfarin groups) were included in the full analysis set (FAS) and the FAS was used for the efficacy analysis. Of these patients, 218 patients who received at least 1 dose of the study drug (72 patients, 71 patients, 75 patients) were included in the study drug population and were included in the safety analysis population.

The period for safety evaluation was determined for each evaluation parameter: bleeding-related parameters, bleeding-related serious or non-serious adverse events, laboratory test values, vital signs, and ECG recording were to be evaluated from the first dose of the study drug until 2 days after the last dose; death caused by adverse events or serious adverse events was to be evaluated from the first dose of the study drug until 30 days after the last dose; and adverse events (including liver function test-related parameters and neurological events) were to be evaluated from the first dose of the study drug until 2 days after the last dose (for non-serious adverse events) or until 30 days after the last dose (for serious adverse events).

The primary safety endpoint used was “the composite endpoint of major bleeding or clinically relevant non-major (CRNM) bleeding.” Major bleeding was defined as clinically overt acute bleeding that met at least 1 of the following: “decrease in hemoglobin of ≥2 g/dL within 24 hours,” “transfusion of ≥2 units of packed red blood cells,” “bleeding that occurred in at least 1 of the critical site, i.e., intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular (with compartment syndrome), and retroperitoneal,” and “bleeding that was fatal.” CRNM bleeding was defined as a clinically overt acute or subacute bleeding that did not meet the criteria for major bleeding and that led to any of the following: “bleeding resulting in hospital admission,” “medical or surgical treatment for bleeding guided by the physician,” or “change in antithrombotic therapy.” The incidence of major bleeding or CRNM bleeding was 1.4% in the 2.5 mg group (1 of 72 patients; epistaxis), 1.4% in the 5 mg group (1 of 71 patients; gastrointestinal haemorrhage), and 5.3% in the warfarin group (4 of 75 patients; epistaxis, subarachnoid haemorrhage, blood urine present, conjunctival haemorrhage). The incidence of all bleeding events was 12.5% in the 2.5 mg group (9 of 72 patients; epistaxis in 4 patients, haemorrhoidal haemorrhage, haemorrhage subcutaneous, gingival bleeding, blood urine present, and eczema nummular in 1 patient each), 23.9% in the 5 mg group (17 of 71 patients; epistaxis in 4 patients, blood urine present in 3 patients, haematuria in 2 patients, gastrointestinal haemorrhage, conjunctival haemorrhage, haemorrhoidal haemorrhage, occult blood, contusion, purpura, gingival bleeding, haematochezia, bite, and traumatic haemorrhage in 1 patient each), and 17.3% in the warfarin group (13 of 75 patients; epistaxis and blood urine present in 4 patients each, subarachnoid haemorrhage, retinal haemorrhage, mouth haemorrhage, haematuria, conjunctival

haemorrhage, and contusion in 1 patient each).

The incidence of adverse events was 51.4% (37 of 72 patients) in the 2.5 mg group, 59.2% (42 of 71 patients) in the 5 mg group, and 46.7% (35 of 75 patients) in the warfarin group. Adverse events occurring in ≥2% of patients in any group were as shown in Table 8.

Table 8. Incidence of adverse events occurring in ≥2% of patients in any group: Study drug population (Adapted from submitted data)

MedDRA System Organ Class Preferred term (PT) (MedDRA version 12.0)	2.5 mg group (N = 72) n (%)	5 mg group (N = 71) n (%)	Warfarin group (N = 75) n (%)
Patients with adverse events	37 (51.4)	42 (59.2)	35 (46.7)
Cardiac disorders	3 (4.2)	2 (2.8)	0 (0)
Atrial fibrillation	0 (0)	2 (2.8)	0 (0)
Bradycardia	2 (2.8)	0 (0)	0 (0)
Gastrointestinal disorders	12 (16.7)	9 (12.7)	2 (2.7)
Diarrhoea	3 (4.2)	1 (1.4)	0 (0)
General disorders and administration site conditions	3 (4.2)	4 (5.6)	1 (1.3)
Fatigue	2 (2.8)	1 (1.4)	0 (0)
Oedema peripheral	0 (0)	2 (2.8)	0 (0)
Infections and infestations	11 (15.3)	10 (14.1)	10 (13.3)
Nasopharyngitis	8 (11.1)	8 (11.3)	7 (9.3)
Injury, poisoning and procedural complications	0 (0)	6 (8.5)	4 (5.3)
Contusion	0 (0)	2 (2.8)	1 (1.3)
Fall	0 (0)	2 (2.8)	0 (0)
Investigations	8 (11.1)	7 (9.9)	4 (5.3)
Blood bilirubin increased	2 (2.8)	1 (1.4)	0 (0)
Blood creatine phosphokinase increased	2 (2.8)	2 (2.8)	0 (0)
Blood urine present	1 (1.4)	3 (4.2)	4 (5.3)
Musculoskeletal and connective tissue disorders	3 (4.2)	3 (4.2)	1 (1.3)
Back pain	1 (1.4)	2 (2.8)	0 (0)
Nervous system disorders	2 (2.8)	4 (5.6)	8 (10.7)
Cerebral infarction	0 (0)	0 (0)	2 (2.7)
Renal and urinary disorders	0 (0)	2 (2.8)	2 (2.7)
Haematuria	0 (0)	2 (2.8)	1 (1.3)
Respiratory, thoracic and mediastinal disorders	9 (12.5)	5 (7.0)	6 (8.0)
Cough	2 (2.8)	1 (1.4)	0 (0)
Epistaxis	4 (5.6)	4 (5.6)	4 (5.3)
Oropharyngeal pain	2 (2.8)	0 (0)	0 (0)
Vascular disorders	1 (1.4)	0 (0)	3 (4.0)
Blood pressure inadequately controlled	0 (0)	0 (0)	2 (2.7)

Serious adverse events were reported by 1 patient in the 2.5 mg group (arterial stenosis limb), 5 patients in the 5 mg group (back pain; rectal cancer; benign prostatic hyperplasia; overdose, hypoglycaemia; accidental overdose), and 4 patients in the warfarin group (accidental overdose, subarachnoid haemorrhage, cerebral infarction, cerebral infarction [2 events]). No deaths were reported.

Adverse events leading to study drug discontinuation were reported by 4 patients in the 2.5 mg group (abdominal discomfort, diabetes mellitus inadequate control, diarrhoea, constipation), 4 patients in the 5 mg group (gastrointestinal haemorrhage, benign prostatic hyperplasia, atrial fibrillation, trigeminal neuralgia), and 4 patients in the warfarin group (subarachnoid haemorrhage, cerebral infarction, cerebral infarction, gastric ulcer).

The incidence of the primary efficacy endpoint, i.e., "the composite endpoint of stroke or systemic embolism" that occurred during the period from the date of randomization to the efficacy cut-off date (2 days after the last dose of the study drug, or Day 85 or Week 12 from the date of randomized assignment, whichever came later), was 0% (0 of 74 patients) in the 2.5 mg group, 0% (0 of 74 patients) in the 5 mg group, and 4.1% (3 of 74 patients) in the warfarin group. The incidence of "the composite endpoint of stroke, systemic embolism, or all-cause death" was 0% (0 of 74 patients) in the 2.5 mg group, 0% (0 of 74 patients) in the 5 mg group, and 4.1% (3 of 74 patients) in the warfarin group. All events reported by the 3 patients in the warfarin group were stroke. Neither myocardial infarction nor all-cause death was observed in any of the groups.

4.(iii).A.(2).2) Phase II study in foreign patients after elective total knee replacement surgery (Protocol No. CV185010, Attached document 5.3.5.1.1 [October 2004 to November 2005])

A randomized, double-blind, parallel group, comparative study was conducted at 100 centers in foreign countries to investigate the efficacy and safety of apixaban. Apixaban, enoxaparin, or warfarin was administered for 12 ± 2 days to foreign patients after elective total knee replacement surgery (target sample size, 150 patients per group). The warfarin group received the treatment in an open-label fashion. The initial dose of apixaban was to be administered orally at 12 to 24 hours after the closure of the skin wound, followed by once daily (5, 10, 20 mg) or twice daily (2.5, 5, 10 mg) oral administration. The initial dose of enoxaparin was to be administered subcutaneously at 12 to 24 hours after the closure of the skin wound, followed by twice daily subcutaneous administration at 30 mg. The initial dose of warfarin (5 mg) was to be administered orally in the evening of the surgery, followed by once daily oral administration at the dose adjusted to achieve PT-INR of 1.8 to 3.0.

The main inclusion criteria were patients aged between 18 and 90 years scheduled to undergo elective unilateral total knee replacement surgery who had no history or clinical suspicion of hereditary or acquired haemorrhagic diathesis or coagulation disorder and did not have a high risk of thromboembolic event.

Of a total of 1238 patients randomized (157 patients in the 5 mg QD group, 156 patients in the 10 mg QD group, 156 patients in the 20 mg QD group, 153 patients in the 2.5 mg BID group, 157 patients in the 5 mg BID group, 154 patients in the 10 mg BID group, 152 patients in the enoxaparin group, 153 patients in the warfarin group), 1217 patients who received the study drug (151 patients, 155 patients, 151 patients, 154 patients, 153 patients, 153 patients, 149 patients, 151 patients) were included in the study drug population and used for the safety analysis. Of the patients in this population, a total of 856 patients (97 patients, 105 patients, 110 patients, 111 patients, 105 patients, 110 patients, 109 patients, 109 patients) who underwent bilateral venography after the end of the study drug administration or reached the primary efficacy endpoint or died from the randomization to 2 days after the last dose of the study drug were included in the primary efficacy analysis population.

The primary efficacy endpoint was "the composite endpoint of venous thromboembolism (symptomatic or asymptomatic deep vein thrombosis, nonfatal pulmonary embolism) or all-cause death" that occurred during the period from randomization up to 2 days after the last dose of the study drug. The incidence of venous thromboembolism or all-cause death was 11.3% (11 of 97 patients) in the 5 mg QD group, 12.4% (13 of 105 patients) in the 10 mg QD group, 8.2% (9 of 110 patients) in the 20 mg QD group, 9.9% (11 of 111 patients) in the 2.5 mg BID group, 4.8% (5 of 105 patients) in the 5 mg BID group, 5.5% (6 of 110 patients) in the 10 mg BID group, 15.6% (17 of 109 patients) in the enoxaparin group, and 26.6% (29 of 109 patients) in the warfarin group.

As regards safety, the incidence of bleeding-related events that occurred during the period from the initial dosing of the study drug up to 2 days after the last dose was as shown in Table 9.

Table 9. Incidence of bleeding-related events: Study drug population (Adapted from submitted data)

	5 mg QD group (N = 151)	10 mg QD group (N = 155)	20 mg QD group (N = 151)	2.5 mg BID group (N = 154)	5 mg BID group (N = 153)	10 mg BID group (N = 153)	Enoxaparin group (N = 149)	Warfarin group (N = 151)
Major bleeding	4 (2.6)	1 (0.6)	5 (3.3)	0 (0)	4 (2.6)	4 (2.6)	0 (0)	0 (0)
Minor bleeding	1 (0.7)	9 (5.8)	10 (6.6)	6 (3.9)	6 (3.9)	11 (7.2)	6 (4.0)	8 (5.3)
Potentially important bleeding	0 (0)	1 (0.6)	0 (0)	0 (0)	0 (0)	0 (0)	2 (1.3)	0 (0)
Thrombocytopenia	0 (0)	1 (0.6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

n (%)

The incidence of adverse events that occurred during the period from randomization up to 2 days after the last dose of the study drug was 85.4% (129 of 151 patients) in the 5 mg QD group, 88.4% (137 of 155 patients) in the 10 mg QD group, 88.1% (133 of 151 patients) in the 20 mg QD group, 87.0% (134 of 154 patients) in the 2.5 mg BID group, 86.3% (132 of 153 patients) in the 5 mg BID group, 86.3% (132 of 153 patients) in the 10 mg BID group, 86.6% (129 of 149 patients) in the enoxaparin group, and 88.7% (134 of 151 patients) in the warfarin group. Adverse events with an incidence of ≥5% in any group were as shown in Table 10.

Table 10. Incidence of adverse events with an incidence of ≥5% in any group: Study drug population (Adapted from submitted data)

MedDRA System Organ Class Preferred term (PT) (MedDRA version 8.1)	5 mg QD group (N = 151) n (%)	10 mg QD group (N = 155) n (%)	20 mg QD group (N = 151) n (%)	2.5 mg BID group (N = 154) n (%)	5 mg BID group (N = 153) n (%)	10 mg BID group (N = 153) n (%)	Enoxaparin group (N = 149) n (%)	Warfarin group (N = 151) n (%)
Patients with adverse events	129 (85.4)	137 (88.4)	133 (88.1)	134 (87.0)	132 (86.3)	132 (86.3)	129 (86.6)	134 (88.7)
Blood and lymphatic system disorders	11 (7.3)	19 (12.3)	25 (16.6)	13 (8.4)	20 (13.1)	17 (11.1)	16 (10.7)	18 (11.9)
Anaemia	11 (7.3)	17 (11.0)	24 (15.9)	13 (8.4)	18 (11.8)	17 (11.1)	16 (10.7)	16 (10.6)
Cardiac disorders	12 (7.9)	9 (5.8)	4 (2.6)	13 (8.4)	10 (6.5)	9 (5.9)	7 (4.7)	18 (11.9)
Tachycardia	7 (4.6)	6 (3.9)	4 (2.6)	5 (3.2)	7 (4.6)	7 (4.6)	7 (4.7)	8 (5.3)
Gastrointestinal disorders	69 (45.7)	76 (49.0)	71 (47.0)	68 (44.2)	83 (54.2)	77 (50.3)	74 (49.7)	59 (39.1)
Constipation	26 (17.2)	37 (23.9)	32 (21.2)	15 (9.7)	26 (17.0)	28 (18.3)	36 (24.2)	29 (19.2)
Dyspepsia	5 (3.3)	1 (0.6)	6 (4.0)	4 (2.6)	11 (7.2)	3 (2.0)	8 (5.4)	5 (3.3)
Nausea	40 (26.5)	37 (23.9)	44 (29.1)	45 (29.2)	41 (26.8)	47 (30.7)	43 (28.9)	39 (25.8)
Vomiting	21 (13.9)	19 (12.3)	19 (12.6)	24 (15.6)	29 (19.0)	32 (20.9)	23 (15.4)	16 (10.6)
General disorders and administration site conditions	47 (31.1)	66 (42.6)	56 (37.1)	59 (38.3)	49 (32.0)	59 (38.6)	59 (39.6)	47 (31.1)
Fatigue	7 (4.6)	6 (3.9)	9 (6.0)	6 (3.9)	4 (2.6)	6 (3.9)	7 (4.7)	4 (2.6)
Oedema peripheral	17 (11.3)	28 (18.1)	23 (15.2)	17 (11.0)	14 (9.2)	20 (13.1)	26 (17.4)	14 (9.3)
Pyrexia	27 (17.9)	28 (18.1)	21 (13.9)	31 (20.1)	23 (15.0)	23 (15.0)	28 (18.8)	22 (14.6)
Injury, poisoning and procedural complications	43 (28.5)	51 (32.9)	52(34.4)	44 (28.6)	38 (24.8)	47 (30.7)	47 (31.5)	49 (32.5)
Contusion	3 (2.0)	4 (2.6)	5 (3.3)	6 (3.9)	5 (3.3)	3 (2.0)	7 (4.7)	9 (6.0)
Procedural pain	27 (17.9)	26 (16.8)	29 (19.2)	30 (19.5)	22 (14.4)	30 (19.6)	31 (20.8)	27 (17.9)
Investigations	36 (23.8)	39 (25.2)	32 (21.2)	49 (31.8)	34 (22.2)	42 (27.5)	32 (21.5)	44 (29.1)
Body temperature increased	10 (6.6)	15 (9.7)	15 (9.9)	16 (10.4)	10 (6.5)	14 (9.2)	8 (5.4)	12 (7.9)
Haemoglobin decreased	12 (7.9)	10 (6.5)	9 (6.0)	10 (6.5)	8 (5.2)	11 (7.2)	7 (4.7)	11 (7.3)
Musculoskeletal and connective tissue disorders	28 (18.5)	36 (23.2)	32 (21.2)	37 (24.0)	39 (25.5)	31 (20.3)	32 (21.5)	34 (22.5)
Arthralgia	13 (8.6)	18 (11.6)	16 (10.6)	20 (13.0)	23 (15.0)	18 (11.8)	13 (8.7)	18 (11.9)
Pain in extremity	7 (4.6)	9 (5.8)	8 (5.3)	8 (5.2)	5 (3.3)	4 (2.6)	10 (6.7)	8 (5.3)
Nervous system disorders	27 (17.9)	22 (14.2)	31 (20.5)	38 (24.7)	32 (20.9)	26 (17.0)	24 (16.1)	26 (17.2)
Dizziness	12 (7.9)	9 (5.8)	13 (8.6)	12 (7.8)	15 (9.8)	14 (9.2)	11 (7.4)	12 (7.9)
Headache	5 (3.3)	8 (5.2)	11 (7.3)	9 (5.8)	8 (5.2)	10 (6.5)	5 (3.4)	9 (6.0)
Psychiatric disorders	25 (16.6)	19 (12.3)	21 (13.9)	27 (17.5)	29 (19.0)	20 (13.1)	21 (14.1)	20 (13.2)
Insomnia	11 (7.3)	11 (7.1)	16 (10.6)	20 (13.0)	21 (13.7)	10 (6.5)	13 (8.7)	12 (7.9)
Renal and urinary disorders	14 (9.3)	17 (11.0)	15 (9.9)	18 (11.7)	23 (15.0)	23 (15.0)	17 (11.4)	18 (11.9)
Urinary retention	5 (3.3)	8 (5.2)	10 (6.6)	6 (3.9)	6 (3.9)	8 (5.2)	11 (7.4)	7 (4.6)
Skin and subcutaneous tissue disorders	29 (19.2)	28 (18.1)	28 (18.5)	28 (18.2)	30 (19.6)	37 (24.2)	28 (18.8)	31 (20.5)
Erythema	10 (6.6)	4 (2.6)	7 (4.6)	6 (3.9)	11 (7.2)	14 (9.2)	10 (6.7)	9 (6.0)
Pruritus	5 (3.3)	10 (6.5)	9 (6.0)	7 (4.5)	8 (5.2)	13 (8.5)	7 (4.7)	13 (8.6)
Vascular disorders	38 (25.2)	39 (25.2)	32 (21.2)	32 (20.8)	27 (17.6)	30 (19.6)	26 (17.4)	38 (25.2)
Deep vein thrombosis	20 (13.2)	21 (13.5)	12 (7.9)	17 (11.0)	12 (7.8)	12 (7.8)	16 (10.7)	26 (17.2)

Serious adverse events that occurred during the period from randomization up to 2 days after the last dose of the study drug were reported by 20 patients in the 5 mg QD group, 14 patients in the 10 mg QD group, 13 patients in the 20 mg QD group, 12 patients in the 2.5 mg BID group, 9 patients in the 5 mg BID group, 12 patients in the 10 mg BID group, 10 patients in the enoxaparin group, and 9 patients in the warfarin group. Death occurred in 2 patients in the 2.5 mg BID group (pulmonary embolism, cardiac arrest; myocardial infarction) and in 1 patient in the 20 mg QD

group (cachexia).

4.(iii).A.(2).3) Phase II study in foreign patients with acute symptomatic deep vein thrombosis (Protocol No. CV185017, Attached document 5.3.5.4.1 [December 2005 to February 2007])

A randomized, double-blind, parallel group comparative study was conducted at 64 centers in foreign countries in order to investigate the efficacy and safety of apixaban. Foreign patients with acute symptomatic deep vein thrombosis were to receive multiple oral doses of apixaban or to receive multiple doses of a vitamin K antagonist (VKA) in combination with a low molecular weight heparin (LMWH) or fondaparinux for 12 weeks (target sample size, 130 patients per group). There were no patients treated with fondaparinux. The LMWH/VKA group received the treatment in an open-label fashion. Apixaban was to be administered orally twice daily (5, 10 mg) or once daily (20 mg). VKA was to be administered orally once daily for 12 weeks at the dose adjusted to keep PT-INR at 2.5 (range, 2.0-3.0). LMWH was to be administered subcutaneously once or twice daily (for ≥5 days after the start of VKA).

The main inclusion criteria were patients aged between 18 and 90 years with confirmed acute proximal venous thrombosis or acute venous thrombosis of lower limb rapidly progressing in the upper one third of the lower limb vein (trifurcation area), without symptomatic pulmonary embolism. Subjects also had to have no active bleeding, no high risk of bleeding, and no history of other disease for which LMWH or VKA is contraindicated.

Of a total of 520 patients randomized (130 patients in the 5 mg group, 134 patients in the 10 mg group, 128 patients in the 20 mg group, 128 patients in the LMWH/VKA group), 511 patients who received the study drug (128 patients, 133 patients, 124 patients, 126 patients) were included in the safety analysis population. Of these, 476 patients (117 patients, 125 patients, 116 patients, 118 patients) who were considered as efficacy-evaluable based on the vein compression ultrasonography or lung perfusion scanning performed at baseline and at Week 12 of study drug administration or who experienced deep vein thrombosis or pulmonary embolism after study drug administration were included in the primary efficacy analysis population.

The primary efficacy endpoint was “the composite endpoint of symptomatic recurrent venous thromboembolism (recurrent deep vein thrombosis or fatal or nonfatal pulmonary embolism) or aggravation (increase) of thrombotic load assessed by compression ultrasonography of bilateral lower limb veins or lung perfusion scanning” that occurred during the period from the date of randomization up to 2 days after the last dose of the study drug. The incidence of symptomatic recurrent venous thromboembolism or aggravation of thrombotic load was 6.0% (7 of 117 patients) in the 5 mg group, 5.6% (7 of 125 patients) in the 10 mg group, 2.6% (3 of 116 patients) in the 20 mg group, and 4.2% (5 of 118 patients) in the LMWH/VKA group.

The safety evaluation period was from the first dose of the study drug up to 2 days (for non-serious adverse events) or 30 days (for serious adverse events) after the last dose of the study drug.

As regards safety, the incidence of “the composite endpoint of major bleeding or CRNM bleeding” was 8.6% (11 of 128 patients) in the 5 mg group, 4.5% (6 of 133 patients) in the 10 mg group, 7.3% (9 of 124 patients) in the 20 mg group, and 7.9% (10 of 126 patients) in the LMWH/VKA group.

The incidence of adverse events was 60.2% (77 of 128 patients) in the 5 mg group, 54.1% (72 of 133 patients) in the 10 mg group, 66.1% (82 of 124 patients) in the 20 mg group, and 57.1% (72 of 126 patients) in the LMWH/VKA group. Adverse events occurring in >3% of patients in any group were as shown in Table 11.

Table 11. Adverse events occurring in >3% of patients in any group: safety Analysis population (Adapted from submitted data)

MedDRA System Organ Class Preferred term (PT) (MedDRA version 10)	5 mg group (N = 128) n (%)	10 mg group (N = 133) n (%)	20 mg group (N = 124) n (%)	LMWH/VKA group (N = 126) n (%)
Patients with adverse events	77 (60.2)	72 (54.1)	82 (66.1)	72 (57.1)
Gastrointestinal disorders	21 (16.4)	17 (12.8)	23 (18.5)	16 (12.7)
Constipation	2 (1.6)	1 (0.8)	2 (1.6)	4 (3.2)
Diarrhoea	3 (2.3)	4 (3.0)	9 (7.3)	2 (1.6)
Nausea	4 (3.1)	2 (1.5)	5 (4.0)	2 (1.6)
Vomiting	2 (1.6)	4 (3.0)	4 (3.2)	1 (0.8)
General disorders and administration site conditions	13 (10.2)	11 (8.3)	10 (8.1)	9 (7.1)
Fatigue	4 (3.1)	0 (0)	2 (1.6)	1 (0.8)
Oedema peripheral	5 (3.9)	3 (2.3)	2 (1.6)	3 (2.4)
Infections and infestations	22 (17.2)	13 (9.8)	17 (13.7)	24 (19.0)
Cellulitis	1 (0.8)	0 (0)	1 (0.8)	5 (4.0)
Nasopharyngitis	8 (6.3)	3 (2.3)	1 (0.8)	3 (2.4)
Investigations	5 (3.9)	4 (3.0)	10 (8.1)	11 (8.7)
Blood creatine phosphokinase increased	0 (0)	2 (1.5)	4 (3.2)	1 (0.8)
Musculoskeletal and connective tissue disorders	10 (7.8)	23 (17.3)	15 (12.1)	18 (14.3)
Back pain	2 (1.6)	2 (1.5)	2 (1.6)	5 (4.0)
Pain in extremity	2 (1.6)	12 (9.0)	5 (4.0)	3 (2.4)
Nervous system disorders	16 (12.5)	16 (12.0)	22 (17.7)	8 (6.3)
Dizziness	4 (3.1)	2 (1.5)	6 (4.8)	1 (0.8)
Headache	11 (8.6)	9 (6.8)	11 (8.9)	4 (3.2)
Renal and urinary disorders	5 (3.9)	6 (4.5)	3 (2.4)	7 (5.6)
Haematuria	4 (3.1)	3 (2.3)	1 (0.8)	4 (3.2)
Respiratory, thoracic and mediastinal disorders	6 (4.7)	9 (6.8)	10 (8.1)	8 (6.3)
Dyspnoea	1 (0.8)	4 (3.0)	0 (0)	2 (1.6)
Skin and subcutaneous tissue disorders	8 (6.3)	5 (3.8)	13 (10.5)	11 (8.7)
Pruritus	2 (1.6)	0 (0)	4 (3.2)	1 (0.8)
Vascular disorders	6 (4.7)	10 (7.5)	6 (4.8)	7 (5.6)
Haematoma	1 (0.8)	3 (2.3)	1 (0.8)	4 (3.2)

Serious adverse events were reported by 16 patients in the 5 mg group, 11 patients in the 10 mg group, 20 patients in the 20 mg group, and 16 patients in the LMWH/VKA group. Death occurred in 4 patients in the 5 mg group (completed suicide; lung cancer, metastasis to brain; colon cancer; ovarian cancer), 2 patients in the 10 mg group (pancreatic neoplasm, multi-organ failure caused by bladder cancer recurrent), and 2 patients in the 20 mg group (seminoma, renal failure; pancreatic carcinoma).

Adverse events leading to study drug discontinuation were reported by 9 patients in the 5 mg group, 6 patients in the 10 mg group, 11 patients in the 20 mg group, and 5 patients in the LMWH/VKA group.

4.(iii).A.(3) Phase III studies

4.(iii).A.(3).1) Phase III study in patients with nonvalvular atrial fibrillation (ARISTOTLE) (Protocol No. CV185030, Attached document 5.3.5.1.2 [December 2006 to May 2011])

A randomized, double-blind, parallel group comparative study was conducted at 1053 centers in 40 countries including Japan in order to evaluate the non-inferiority of apixaban in efficacy to dose-adjusted warfarin. Japanese and foreign patients with nonvalvular atrial fibrillation received multiple oral doses of apixaban (5 mg) twice daily (2.5 mg twice daily if patients met at least 2 of the following: [a] age ≥80 years, [b] body weight ≤60 kg, [c] serum creatinine ≥1.5 mg/dL) or multiple oral doses of warfarin once daily (target PT-INR range, 2.0-3.0 [2.0-2.6 in Japanese subjects aged ≥70 years]) (target sample size; 9000 patients per group, 18,000 patients in total).

If patients had received VKA before randomization, VKA was to be discontinued or the dose was reduced before randomization, and the study drug was to be started after PT-INR decreased below 2.0. Patients were stratified at randomization by study center and by presence/absence of history of VKA administration before the study.

After randomization, patients were to receive either apixaban + warfarin placebo or apixaban placebo + warfarin.

The study was planned to be terminated when 448 patients reached the primary efficacy endpoint, i.e., stroke (ischemic, haemorrhagic, unidentified) or systemic embolism. Subjects who discontinued the treatment with the study drug before the accumulation of 448 cases of the primary efficacy endpoint were to be continued every-3-month phone follow-up until 30 days after the last dose of the study drug, or until the efficacy cut-off date (January 30, 2011), whichever came later.

The main inclusion criteria were patients aged ≥18 years with atrial fibrillation who had at least 1 of the risk factors of stroke ([a] ≥75 years of age, [b] history of stroke, TIA, or systemic embolism, [c] symptomatic cardiac failure congestive or left ventricular dysfunction with left ventricular ejection fraction (LVEF) of ≤40%, [d] diabetes mellitus, [e] hypertension requiring drug therapy). Main exclusion criteria included clinically overt mitral valve stenosis (moderate or severe), conditions requiring continuous anticoagulant therapy for any other reason (e.g., artificial cardiac valve), conditions requiring aspirin therapy of >165 mg/day, combination therapy of aspirin and thienopyridine, and severe renal impairment (serum creatinine >2.5 mg/dL or estimated CL_{CR} <25 mL/min).

4.(iii).A.(3).1).(a) Overall results of study

A total of 18,201 patients randomized (9120 patients in the apixaban group, 9081 patients in the warfarin group) were defined as the randomized population and were included in the primary efficacy analysis population. Of these, 18,140 patients (9088 patients, 9052 patients) who were treated with at least 1 dose of the study drug were included in the study drug population and were included in the safety analysis population. The study was discontinued in 4803 patients (2310 patients, 2493 patients). The main reasons for the discontinuation were request of the subjects (921 patients, 989 patients) and adverse events (679 patients, 738 patients).

The mean baseline $CHADS_2$ score was 2.1 in both groups. The percentage of subjects without a history of VKA administration was 42.9% (3912 of 9120 patients) in the apixaban group and 42.8% (3888 of 9081 patients) in the warfarin group.

In the randomized subjects, the dosage and administration of apixaban or apixaban placebo and related patient background factors were as shown in Table 12.

Table 12. Dosage and administration of apixaban or apixaban placebo and related patient background factors: Randomized population (Adapted from submitted data)

	Apixaban group (N = 9120)	Warfarin group (N = 9081)
Dosage and administration of apixaban or apixaban placebo[a]		
5.0 mg twice daily	8692 (95.3)	8678 (95.6)
2.5 mg twice daily	428 (4.7)	403 (4.4)
Factors requiring dose reduction		
Age ≥80 years	1225 (13.4)	1211 (13.3)
Body weight ≤60 kg	1018 (11.2)	967 (10.6)
Serum creatinine ≥1.5 mg/dL	626 (6.9)	615 (6.8)
Number of factors requiring dose reduction[a]		
0	6675 (73.2)	6681 (73.6)
1	2032 (22.3)	2014 (22.2)
2	402 (4.4)	379 (4.2)
3	11 (0.1)	7 (<0.1)

n (%)

a: Dosage and administration of apixaban or apixaban placebo were based on the allocation by the trial sites according to the information inputted into the interactive voice response system (IVRS). The number of factors requiring dose reduction was calculated based on the baseline values entered in the case report form (CRF). IVRS and CRF differed in the handling of birth date, body weight, and serum creatinine level, which resulted in discordance between the number of patients receiving 2.5 mg twice daily and the number of patients with ≥2 factors requiring dose reduction.

The mean treatment duration with the study drug was approximately 1.7 years both in the apixaban group and in the warfarin group, and the total exposure period was 15,534 patient-years in the apixaban group and 15,184 patient-years in the warfarin group. In the pre-determined analysis in subjects with all PT-INR values (during dose adjustment, during discontinuation, or during administration), the median time within therapeutic range (TTR) in subjects assigned to the warfarin group was 60.5%, or 66.0% if the first 7 days of the study and the days of discontinuation of warfarin were excluded.

i) Efficacy

The primary efficacy endpoint was the time to the first occurrence of "the composite endpoint of stroke (haemorrhagic, ischemic, or unidentified) or systemic embolism" during the period from the date of randomization up to the efficacy cut-off date. The secondary endpoints were the time to the first occurrence of "stroke (haemorrhagic, ischemic, or unidentified)," "systemic embolism," "all-cause death," "the composite endpoint of stroke (haemorrhagic, ischemic, or unidentified), systemic embolism, or major bleeding," "the composite endpoint of stroke (haemorrhagic, ischemic, or unidentified), systemic embolism, or all-cause death," "the composite endpoint of stroke (haemorrhagic, ischemic, or unidentified), systemic embolism, major bleeding, or all-cause death," "the composite endpoint of stroke (haemorrhagic, ischemic, or unidentified), systemic embolism, myocardial infarction, or all-cause death," and "the composite endpoint of stroke (haemorrhagic, ischemic, or unidentified), systemic embolism, or major bleeding in subjects without a history of treatment with warfarin." The incidence and incidence rate of each efficacy endpoint were as shown in Table 13. In the randomized population, the incidence rate of the primary efficacy endpoint was 1.27% per year (212 of 9120 patients) in the apixaban group and 1.60% per year (265 of 9081 patients) in the warfarin group. The hazard ratio (two-sided 95% CI) of the apixaban group relative to the warfarin group, calculated based on the Cox proportional hazard model (stratified by trial site and by presence/absence of history of VKA administration), was 0.79 (0.66-0.95), with the upper limit of the two-sided 95% CI being <1.38, the acceptable

non-inferiority margin.* In a similar manner, the hazard ratio (two-sided 99% CI) of the apixaban group relative to the warfarin group, calculated based on the Cox proportional hazard model, was 0.79 (0.62-1.00), with the upper limit of the two-sided 99% CI being <1.44, the acceptable non-inferiority margin.*

Table 13. Incidence and incidence rate of each efficacy endpoint from randomization until efficacy cut-off date: Randomized population (Adapted from submitted data)

	Apixaban group (N = 9120)	Warfarin group (N = 9081)
Stroke/systemic embolism (n [%])	212 (2.32)	265 (2.92)
Incidence rate (%/year)	1.27	1.60
Ischemic or unidentified stroke (n [%])	162 (1.78)	175 (1.93)
Incidence rate (%/year)	0.97	1.05
Haemorrhagic stroke (n [%])	40 (0.44)	78 (0.86)
Incidence rate (%/year)	0.24	0.47
Systemic embolism (n [%])	15 (0.16)	17 (0.19)
Incidence rate (%/year)	0.09	0.10
All-cause death (n [%])	603 (6.61)	669 (7.37)
Incidence rate (%/year)	3.52	3.94
Cardiovascular death (n [%])	308 (3.38)	344 (3.79)
Incidence rate (%/year)	1.80	2.02
Non-cardiovascular death (n [%])	196 (2.15)	208 (2.29)
Incidence rate (%/year)	1.14	1.22
Death of unknown cause (n [%])	99 (1.09)	117 (1.29)
Incidence rate (%/year)	0.58	0.69
Myocardial infarction (n [%])	90 (0.99)	102 (1.12)
Incidence rate (%/year)	0.53	0.61

Figure 3 shows the Kaplan-Meier curve of the occurrence of stroke or systemic embolism from the date of randomization up to the efficacy cut-off date.

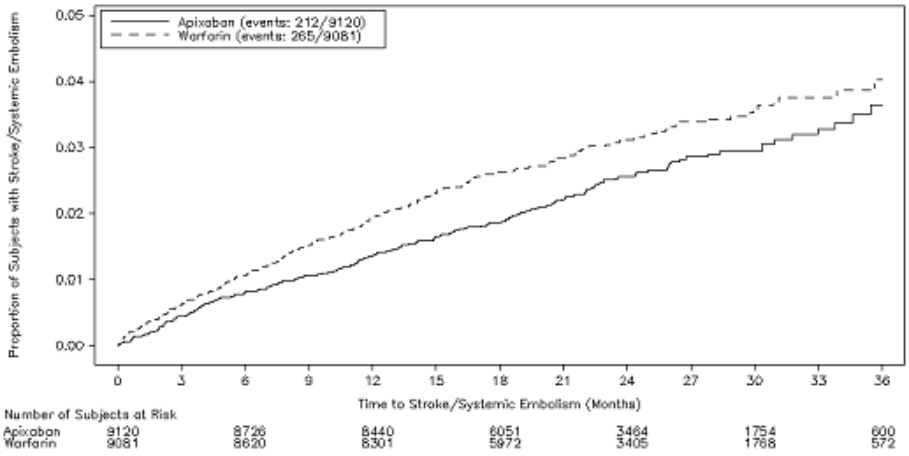


Figure 3. Kaplan-Meier curve of stroke or systemic embolism from randomization to efficacy cut-off date: Randomized population (Adapted from submitted data)

*As the primary analyses, the following 2 types of analyses were planned reflecting the different opinions of the regulatory agency of each region: (a) to investigate whether or not the upper limit of the two-sided 95% CI of the hazard ratio of apixaban group relative to warfarin group is lower than the acceptable non-inferiority margin (1.38), and (b) to investigate whether or not the upper limit of the two-sided 99% CI of the hazard ratio of apixaban group relative to warfarin group was lower than the acceptable non-inferiority margin (1.44).

ii) Safety

The evaluation period for each safety endpoint was the same as that in the Japanese phase II study (Study CV185067). The primary safety endpoint was the time to the first occurrence of "major bleeding according to ISTH criteria." The secondary endpoints were the time to the first occurrence of "the composite endpoint of major bleeding or CRNM bleeding according to ISTH criteria" and "all bleedings reported by the investigator." The incidence and incidence rate of each safety endpoint were as shown in Table 14.

Table 14. Incidence and incidence rate of safety endpoints: Study drug population (Adapted from submitted data)

	Apixaban group (N = 9088)	Warfarin group (N = 9052)
Major bleeding according to ISTH criteria (n [%])	327 (3.60)	462 (5.10)
Incidence rate (%/year)	2.13	3.09
Haemorrhagic death and fatal haemorrhagic stroke (n [%])	10 (0.11)	37 (0.41)
Incidence rate (%/year)	0.06	0.24
Bleeding at critical site (n [%])	91 (1.00)	158 (1.75)
Incidence rate (%/year)	0.59	1.04
Decrease in hemoglobin of ≥2 g/dL (n [%])	165 (1.82)	222 (2.45)
Incidence rate (%/year)	1.07	1.47
Transfusion of ≥2 units of packed red blood cells (n [%])	70 (0.77)	101 (1.12)
Incidence rate (%/year)	0.45	0.67
Major bleeding or CRNM bleeding according to ISTH criteria (n [%])	613 (6.75)	877 (9.69)
Incidence rate (%/year)	4.07	6.01
All bleedings (n [%])	2356 (25.92)	3060 (33.80)
Incidence rate (%/year)	18.08	25.82

The incidence of adverse events was 81.5% (7406 of 9088 patients) in the apixaban group and 83.1% (7521 of 9052 patients) in the warfarin group. Adverse events occurring in ≥3% of patients in either group were as shown in Table 15.

Table 15. Incidence of adverse events occurring in ≥3% of patients in either group: Study drug population (Adapted from submitted data)

MedDRA System Organ Class Preferred term (PT) (MedDRA version 14.0)	Apixaban group (N = 9088) n (%)	Warfarin group (N = 9052) n (%)
Patients with adverse events	7406 (81.5)	7521 (83.1)
Infections and infestations	3416 (37.6)	3495 (38.6)
Nasopharyngitis	763 (8.4)	779 (8.6)
Urinary tract infection	512 (5.6)	532 (5.9)
Bronchitis	503 (5.5)	516 (5.7)
Upper respiratory tract infection	436 (4.8)	456 (5.0)
Influenza	362 (4.0)	333 (3.7)
Pneumonia	324 (3.6)	385 (4.3)
Gastrointestinal disorders	2471 (27.2)	2641 (29.2)
Diarrhoea	585 (6.4)	584 (6.5)
Nausea	282 (3.1)	286 (3.2)
Respiratory, thoracic and mediastinal disorders	2115 (23.3)	2245 (24.8)
Dyspnoea	605 (6.7)	649 (7.2)
Epistaxis	560 (6.2)	685 (7.6)
Cough	495 (5.4)	505 (5.6)
Cardiac disorders	2055 (22.6)	1986 (21.9)
Atrial fibrillation	496 (5.5)	473 (5.2)
Cardiac failure	481 (5.3)	453 (5.0)
Musculoskeletal and connective tissue disorders	1984 (21.8)	2071 (22.9)
Arthralgia	447 (4.9)	463 (5.1)
Back pain	433 (4.8)	506 (5.6)
Pain in extremity	320 (3.5)	325 (3.6)
Nervous system disorders	1972 (21.7)	2044 (22.6)
Dizziness	663 (7.3)	709 (7.8)
Headache	482 (5.3)	485 (5.4)
General disorders and administration site conditions	1912 (21.0)	1912 (21.1)
Oedema peripheral	611 (6.7)	663 (7.3)
Fatigue	392 (4.3)	381 (4.2)
Chest pain	347 (3.8)	357 (3.9)
Injury, poisoning and procedural complications	1540 (16.9)	1839 (20.3)
Fall	321 (3.5)	395 (4.4)
Contusion	301 (3.3)	482 (3.3)
Vascular disorders	1212 (13.3)	1440 (15.9)
Hypertension	386 (4.2)	409 (4.5)
Haematoma	224 (2.5)	424 (4.7)
Renal and urinary disorders	881 (9.7)	945 (10.4)
Haematuria	338 (3.7)	408 (4.5)
Blood and lymphatic system disorders	463 (5.1)	477 (5.3)
Anaemia	270 (3.0)	265 (2.9)

The incidence of serious adverse events was 35.0% (3182 of 9088 patients) in the apixaban group and 36.5% (3302 of 9052 patients) in the warfarin group. Serious adverse events occurring in >1% of patients in either group were as shown in Table 16.

Table 16. Incidence of serious adverse events that occurred in ≥1% of patients in either group: Study drug population (Adapted from submitted data)

MedDRA System Organ Class Preferred term (PT) (MedDRA version 14.0)	Apixaban group (N = 9088) n (%)	Warfarin group (N = 9052) n (%)
Patients with serious adverse events	3182 (35.0)	3302 (36.5)
Cardiac disorders	1278 (14.1)	1231 (13.6)
Cardiac failure	310 (3.4)	301 (3.3)
Atrial fibrillation	301 (3.3)	287 (3.2)
Cardiac failure congestive	171 (1.9)	175 (1.9)
Angina unstable	112 (1.2)	87 (1.0)
Infections and infestations	598 (6.6)	622 (6.9)
Pneumonia	202 (2.2)	231 (2.6)
Nervous system disorders	458 (5.0)	465 (5.1)
Ischaemic stroke	91 (1.0)	76 (0.8)

Death occurred in 429 of 9088 patients (4.7%) in the apixaban group and in 468 of 9052 patients (7.9%) in the warfarin group during the period from the start of treatment with the study drug up to 30 days after the last dose. Serious adverse events leading to death and occurring in ≥0.1% of patients in either groups were sudden death (0.6% [57 of 9088 patients] in the apixaban group, 0.6% [50 of 9052 patients] in the warfarin group), cardiac failure (0.4% [37 of 9088 patients], 0.5% [43 of 9052 patients]), myocardial infarction (0.3% [29 of 9088 patients], 0.2% [21 of 9052 patients]), sudden cardiac death (0.3% [30 of 9088 patients], 0.2% [18 of 9052 patients]), cardiac arrest (0.3% [25 of 9088 patients], 0.2% [18 of 9052 patients]), pneumonia (0.3% [23 of 9088 patients], 0.3% [30 of 9052 patients]), death (0.2% [16 of 9088 patients], 0.3% [26 of 9052 patients]), ischaemic stroke (0.2% [14 of 9088 patients], 0.2% [15 of 9052 patients]), haemorrhagic stroke (0.1% [10 of 9088 patients], 0.3% [23 of 9052 patients]), and cardiac failure congestive (<0.1% [9 of 9088 patients], 0.2% [17 of 9052 patients]).

The incidence of adverse events leading to study drug discontinuation was 7.6% (688 of 9088 patients) in the apixaban group and 8.4% (758 of 9052 patients) in the warfarin group. Events reported by ≥10 patients in either group were ischaemic stroke (24 patients in the apixaban group, 17 patients in the warfarin group), haematuria (21 patients, 18 patients), gastrointestinal haemorrhage (20 patients, 19 patients), myocardial infarction (19 patients, 10 patients), epistaxis (17 patients, 14 patients), TIA (17 patients, 5 patients), cardiac failure (16 patients, 20 patients), anaemia (15 patients, 16 patients), pruritus (15 patients, 4 patients), rectal haemorrhage (12 patients, 6 patients), angina unstable (10 patients, 8 patients), pneumonia (6 patients, 21 patients), subdural haematoma (3 patients, 15 patients), and haematoma (4 patients, 13 patients).

4.(iii).A.(3).1).(b) Results in Japanese subpopulation

In Japan, this study was conducted at 40 centers from [redacted] 20[redacted] through [redacted] 20[redacted] (target sample size of Japanese patients, 300 patients). A total of 336 Japanese patients were randomized (161 patients in the apixaban group, 175 patients in the warfarin group), of whom, 335 patients (160 patients, 175 patients) received the study drug. The study was discontinued in 29 patients in the apixaban group and in 53 patients in the warfarin group. The main reasons for the discontinuation were adverse events (17 patients, 30 patients) and request of the subjects (7 patients, 17 patients). The mean baseline $CHADS_2$ score was 2.0 in both groups, and the percentage of subjects without a history of VKA administration was 16.1% (26 of 161 patients) in the apixaban group and 21.1% (37 of 175 patients) in the warfarin group.

In the randomized subjects, the dosage and administration of apixaban or apixaban placebo and related patient background factors were as shown in Table 17.

Table 17. Dosage and administration of apixaban or apixaban placebo and related patient background factors: Japanese subpopulation in randomized population (Adapted from submitted data)

	Apixaban group (N = 161)	Warfarin group (N = 175)
Dosage and administration of apixaban or apixaban placebo[a]		
5.0 mg twice daily	151 (93.8)	161 (92.0)
2.5 mg twice daily	10 (6.2)	14 (8.0)
Factors requiring dose reduction		
Age ≥80 years	14 (8.7)	20 (11.4)
Body weight ≤60 kg	58 (36.0)	67 (38.3)
Serum creatinine ≥1.5 mg/dL	8 (5.0)	6 (3.4)
Number of factors requiring dose reduction[a]		
0	90 (55.9)	95 (54.3)
1	62 (38.5)	67 (38.3)
2	9 (5.6)	13 (7.4)
3	0 (0)	0 (0)

n (%)

a: Dosage and administration of apixaban or apixaban placebo were based on the allocation by the trial site according to the information inputted into the IVRS. The number of factors requiring dose reduction was calculated based on the baseline values entered in the CRF. IVRS and CRF differed in the handling of birth date, body weight, and serum creatinine level, which resulted in discordance between the number of patients receiving 2.5 mg twice daily and the number of patients with ≥2 factors requiring dose reduction.

The median of the mean treatment duration with the study drug was approximately 2.0 years in the apixaban group and approximately 1.8 years in the warfarin group, and the total exposure period was 318.8 patient-years in the apixaban group and 305.9 patient-years in the warfarin group. The median TTR in the warfarin group was 67.0% if the target PT-INR level was set at 2.0 to 3.0 and 69.9% if the target level in elderly patients (≥70 years of age) was set at 1.6 to 2.6, calculated by excluding the first 7 days of the study and the days of discontinuation of warfarin.

i) Efficacy

The incidence and incidence rate of each efficacy endpoint from randomization until efficacy cut-off date were as shown in Table 18.

Table 18. Incidence and incidence rate of each efficacy endpoint from randomization until efficacy cut-off date: Japanese subpopulation in randomized population (Adapted from submitted data)

	Apixaban group (N = 161)	Warfarin group (N = 175)
Stroke/systemic embolism (n [%])	3 (1.86)	6 (3.43)
Incidence rate (%/year)	0.87	1.67
Ischemic or unidentified stroke (n [%])	3 (1.86)	4 (2.29)
Incidence rate (%/year)	0.87	1.11
Haemorrhagic stroke (n [%])	0 (0)	2 (1.14)
Incidence rate (%/year)	0	0.55
Systemic embolism (n [%])	0 (0)	0 (0)
Incidence rate (%/year)	0	0
All-cause death (n [%])	6 (3.73)	11 (6.29)
Incidence rate (%/year)	1.74	3.02
Cardiovascular death (n [%])	2 (1.24)	2 (1.14)
Incidence rate (%/year)	0.58	0.55
Non-cardiovascular death (n [%])	3 (1.86)	6 (3.43)
Incidence rate (%/year)	0.87	1.65
Death of unknown cause (n [%])	1 (0.62)	3 (1.71)
Incidence rate (%/year)	0.29	0.82
Myocardial infarction (n [%])	0 (0)	1 (0.57)
Incidence rate (%/year)	0	0.28

ii) Safety

The incidence and incidence rate of safety endpoints were as shown in Table 19.

Table 19. Incidence and incidence rate of safety endpoints: Japanese subpopulation in the study drug population (Adapted from submitted data)

	Apixaban group (N = 160)	Warfarin group (N = 175)
Major bleeding according to ISTH criteria (n [%])	4 (2.50)	18 (10.29)
Incidence rate (%/year)	1.26	5.99
Haemorrhagic death and fatal haemorrhagic stroke (n [%])	0 (0)	2 (1.14)
Incidence rate (%/year)	0	0.65
Bleeding at critical site (n [%])	1 (0.63)	7 (4.00)
Incidence rate (%/year)	0.31	2.30
Decrease in hemoglobin of ≥2 g/dL (n [%])	2 (1.25)	9 (5.14)
Incidence rate (%/year)	0.63	2.96
Transfusion of ≥2 units of packed red blood cells (n [%])	0 (0)	0 (0)
Incidence rate (%/year)	0	0
Major bleeding or CRNM bleeding according to ISTH criteria (n [%])	6 (3.75)	23 (13.14)
Incidence rate (%/year)	1.90	7.86
All bleedings (n [%])	51 (31.88)	82 (46.86)
Incidence rate (%/year)	20.95	40.13

The incidence of adverse events was 96.3% (154 of 160 patients) in the apixaban group and 96.6% (169 of 175 patients) in the warfarin group. Adverse events occurring in ≥3% of patients in either group were as shown in Table 20.

Table 20. Incidence of adverse events occurring in ≥3% of patients in either group: Japanese subpopulation in the study drug population (Adapted from submitted data)

MedDRA System Organ Class Preferred term (PT) (MedDRA version 14.0)	Apixaban group (N = 160) n (%)	Warfarin group (N = 175) n (%)
Patients with adverse events	154 (96.3)	169 (96.6)
Infections and infestations	98 (61.3)	99 (56.6)
Nasopharyngitis	85 (53.1)	78 (44.6)
Pneumonia	2 (1.3)	8 (4.6)
Gastroenteritis	5 (3.1)	4 (2.3)
Gastrointestinal disorders	80 (50.0)	88 (50.3)
Diarrhoea	14 (8.8)	19 (10.9)
Nausea	5 (3.1)	1 (0.6)
Constipation	14 (8.8)	14 (8.0)
Vomiting	5 (3.1)	2 (1.1)
Abdominal pain upper	10 (6.3)	6 (3.4)
Gingival bleeding	3 (1.9)	7 (4.0)
Periodontitis	9 (5.6)	5 (2.9)
Colonic polyp	7 (4.4)	12 (6.9)
Gastritis	7 (4.4)	6 (3.4)
Reflux oesophagitis	6 (3.8)	2 (1.1)
Dyspepsia	5 (3.1)	1 (0.6)
Haemorrhoids	5 (3.1)	4 (2.3)
Respiratory, thoracic and mediastinal disorders	36 (22.5)	51 (29.1)
Epistaxis	14 (8.8)	27 (15.4)
Cough	1 (0.6)	7 (4.0)
Oropharyngeal pain	5 (3.1)	1 (0.6)
Cardiac disorders	19 (11.9)	20 (11.4)
Atrial fibrillation	0 (0)	4 (2.3)
Cardiac failure	2 (1.3)	6 (3.4)
Musculoskeletal and connective tissue disorders	57 (35.6)	55 (31.4)
Arthralgia	7 (4.4)	12 (6.9)
Back pain	19 (11.9)	21 (12.0)
Pain in extremity	6 (3.8)	3 (1.7)
Osteoarthritis	3 (1.9)	7 (4.0)
Musculoskeletal stiffness	6 (3.8)	4 (2.3)
Myalgia	6 (3.8)	4 (2.3)
Periarthritis	5 (3.1)	1 (0.6)
Spinal osteoarthritis	5 (3.1)	4 (2.3)
Nervous system disorders	34 (21.3)	44 (25.1)
Dizziness	9 (5.6)	9 (5.1)
Headache	5 (3.1)	12 (6.9)
General disorders and administration site conditions	30 (18.8)	32 (18.3)
Oedema peripheral	9 (5.6)	12 (6.9)
Chest pain	5 (3.1)	3 (1.7)
Oedema	6 (3.8)	1 (0.6)
Chest discomfort	5 (3.1)	3 (1.7)
Injury, poisoning and procedural complications	46 (28.8)	61 (34.9)
Contusion	18 (11.3)	20 (11.4)
Laceration	3 (1.9)	9 (5.1)
Excoriation	2 (1.3)	7 (4.0)
Vascular disorders	16 (10.0)	19 (10.9)
Hypertension	10 (6.3)	9 (5.1)
Metabolism and nutrition disorders	30 (18.8)	27 (15.4)
Diabetes mellitus	8 (5.0)	10 (5.7)
Decreased appetite	6 (3.8)	2 (1.1)
Hyperuricaemia	5 (3.1)	6 (3.4)

MedDRA System Organ Class Preferred term (PT) (MedDRA version 14.0)	Apixaban group (N = 160) n (%)	Warfarin group (N = 175) n (%)
Skin and subcutaneous tissue disorders	42 (26.3)	57 (32.6)
Rash	3 (1.9)	11 (6.3)
Pruritus	8 (5.0)	5 (2.9)
Haemorrhage subcutaneous	11 (6.9)	14 (8.0)
Eczema	7 (4.4)	6 (3.4)
Purpura	1 (0.6)	6 (3.4)
Renal and urinary disorders	16 (10.0)	22 (12.6)
Haematuria	5 (3.1)	6 (3.4)
Eye disorders	26 (16.3)	29 (16.6)
Cataract	10 (6.3)	8 (4.6)
Conjunctival haemorrhage	8 (5.0)	7 (4.0)
Investigations	27 (16.9)	22 (12.6)
Occult blood positive	6 (3.8)	2 (1.1)
Blood uric acid increased	5 (3.1)	2 (1.1)
Reproductive system and breast disorders	15 (9.4)	10 (5.7)
Benign prostatic hyperplasia	11 (6.9)	6 (3.4)
Psychiatric disorders	8 (5.0)	8 (4.6)
Insomnia	7 (4.4)	4 (2.3)

The incidence of serious adverse events was 31.9% (51 of 160 patients) in the apixaban group and 34.3% (60 of 175 patients) in the warfarin group. Serious adverse events occurring in >1% of patients in either group were as shown in Table 21.

Table 21. Incidence of serious adverse events occurring in >1% of patients in either group: Japanese subpopulation in the study drug population (Adapted from submitted data)

MedDRA System Organ Class Preferred term (PT) (MedDRA version 14.0)	Apixaban group (N = 160) n (%)	Warfarin group (N = 175) n (%)
Patients with serious adverse events	51 (31.9)	60 (34.3)
Cardiac disorders	8 (5.0)	10 (5.7)
Cardiac failure	0 (0)	3 (1.7)
Atrial fibrillation	0 (0)	2 (1.1)
Cardiac failure congestive	2 (1.3)	1 (0.6)
Angina unstable	1 (0.6)	2 (1.1)
Infections and infestations	8 (5.0)	10 (5.7)
Pneumonia	2 (1.3)	6 (3.4)

During the period from the start of treatment with the study drug up to 30 days after the last dose, death occurred in 5 of 160 patients in the apixaban group (cause of death; traumatic injury, cardiac failure, malignant tumour, myocardial infarction, other non-cardiovascular death, and death of unknown cause in 1 patient each) and in 4 of 175 patients in the warfarin group (cause of death; malignant tumour, stroke, bleeding, and cardiac failure in 1 patient each). Serious adverse events leading to death were myocardial infarction, ventricular fibrillation, death, road traffic accident, metastatic hepatic cancer, subarachnoid haemorrhage, and completed suicide in the apixaban group; and angina unstable, cardiac failure congestive, lung neoplasm malignant, brain stem haemorrhage, upper gastrointestinal haemorrhage, pneumonia, and shock haemorrhagic in the warfarin group.

The incidence of adverse events leading to study drug discontinuation was 10.6% (17 of 160 patients) in the apixaban group and 17.7% (31 of 175 patients) in the warfarin group, and events

reported by ≥2 patients in either group were cerebral infarction (1 patient in the apixaban group, 3 patients in the warfarin group), cardiac failure (0 patients, 2 patients), cardiac failure congestive (2 patients, 0 patients), haemothorax (0 patients, 2 patients), and pneumonia (0 patients, 2 patients).

4.(iii).A.(3).2) Phase III study in patients with nonvalvular atrial fibrillation who have failed or are unsuitable for VKA therapy (AVERROES) (Protocol No. CV185048, Attached document 5.3.5.1.6 [August 2007 to ongoing])

A randomized, double-blind, parallel group comparative study was conducted at 526 centers in 36 foreign countries in order to verify the superiority of apixaban in efficacy to aspirin. Patients with nonvalvular atrial fibrillation who have failed or are unsuitable for VKA therapy received multiple oral doses of apixaban (5 mg) twice daily (2.5 mg twice daily if patients met at least 2 of the following: [a] age ≥80 years, [b] body weight ≤60 kg, [c] serum creatinine ≥1.5 mg/dL) or multiple oral doses of aspirin (81-324 mg) once daily (target sample size; 2800 patients per group, 5600 patients in total).

The double-blind period in this study was until accumulation of 226 cases of the primary endpoint, i.e., stroke (ischemic, haemorrhagic, or unidentified) or systemic embolism. Two interim analyses were planned in this study, and results of the first interim analysis (analysis of the primary efficacy endpoint was performed when approximately 50% of the expected number of events were accumulated with two-sided significance level of 0.00006 [set using the modified Haybittle-Peto boundary]) and the subsequent analysis performed 3 months later both demonstrated the superiority of apixaban to aspirin. Therefore, the data monitoring committee, based on the conclusion that apixaban was superior in efficacy to aspirin, recommended the premature termination of the study on March 31, 2010. As a result, the double-blind period of the study was ended on September 20, 2010.

The main inclusion criteria were patients aged ≥50 years with paroxysmal, persistent, or permanent atrial fibrillation confirmed during the screening period or within 6 months before enrollment who had ≥1 risk factor for stroke ([a] history of stroke or TIA, [b] age ≥75 years, [c] under hypertension treatment, [d] diabetes mellitus, [e] cardiac failure (NYHA cardiac function class ≥2 at enrollment), [f] LVEF ≤35% within 6 months before enrollment, [g] peripheral arterial disease) and were not currently receiving VKA therapy.

A total of 5598 patients randomized (2807 patients in the apixaban group, 2791 patients in the aspirin group) were included in the randomized population, and were included in the primary efficacy analysis population. Of these, 5578 patients (2798 patients, 2780 patients) who received at least 1 dose of the study drug were included in the study drug population, and were included in the safety analysis population. Of the subjects randomized to the apixaban group, 93.6% (2628 of 2807 patients) received 5 mg twice daily and 6.4% (179 of 2807 patients) received 2.5 mg twice daily. The study was discontinued in 558 patients in the apixaban group and in 649 patients in the aspirin group. Main reasons for the discontinuation were adverse events (174 patients, 260 patients) and the request of the subjects (156 patients, 171 patients). Of the randomized subjects, 39.6% were confirmed to be unsuitable for VKA therapy, and 60.4% were predicted to be unsuitable for VKA therapy although they had no history of treatment with VKA. In the randomized subjects, the dosage and administration of apixaban or apixaban placebo and related patient background factors were as shown in Table 22.

Table 22. Dosage and administration of apixaban or apixaban placebo and related patient background factors: Randomized population (Adapted from submitted data)

	Apixaban group (N = 2807)	Aspirin group (N = 2791)
Dosage and administration of apixaban or apixaban placebo[a]		
5.0 mg twice daily	2628 (93.6)	2609 (93.5)
2.5 mg twice daily	179 (6.4)	182 (6.5)
Factors requiring dose reduction		
Age ≥80 years	455 (16.2)	499 (17.9)
Body weight ≤60 kg	459 (16.4)	422 (15.1)
Serum creatinine ≥1.5 mg/dL	170 (6.1)	186 (6.7)
Number of factors requiring dose reduction[a]		
0	1911 (68.1)	1,872 (67.1)
1	714 (25.4)	735 (26.3)
2	176 (6.3)	180 (6.4)
3	6 (0.2)	4 (0.1)

n (%)

a: Dosage and administration of apixaban or apixaban placebo were based on the allocation by the study site according to the information inputted into the IVRS. The number of factors requiring dose reduction was calculated based on the baseline values entered in the CRF. IVRS and CRF differed in the handling of birth date, body weight, and serum creatinine level, which resulted in discordance between the number of patients receiving 2.5 mg twice daily and the number of patients with ≥2 factors requiring dose reduction.

The mean treatment duration with the study drug during the double-blind period was 59.5 weeks in the apixaban group and 59.1 weeks in the aspirin group, and the total exposure period was 3192.8 patient-years in the apixaban group and 3150.4 patient-years in the aspirin group.

The primary efficacy endpoint was the time to the first occurrence of "the composite endpoint of stroke (ischemic, haemorrhagic, or unidentified) or systemic embolism" during the period from the date of randomization up to the efficacy cut-off date of the double-blind period (May 28, 2010). The incidence rate of the primary efficacy endpoints in the randomized population was 1.62% per year (51 of 2807 patients) in the apixaban group and 3.63% per year (113 of 2791 patients) in the aspirin group, and the results of between-group comparison by log-rank test demonstrated the superiority of the apixaban group to the aspirin group ($P < 0.00001$; two-sided significance level at the interim analysis, 0.00006). The hazard ratio (two-sided 95% CI) of the apixaban group relative to the aspirin group, calculated based on the Cox proportional hazard model, was 0.45 (0.32-0.62). The incidence of efficacy endpoints was as shown in Table 23.

Table 23. Incidence of each efficacy endpoint from randomization until efficacy cut-off date: Randomized population (Adapted from submitted data)

	Apixaban group (N = 2807)	Aspirin group (N = 2791)
Stroke/systemic embolism	51 (1.82)	113 (4.05)
Ischemic stroke	31 (1.10)	86 (3.08)
Ischemic stroke with bleeding	4 (0.14)	9 (0.32)
Haemorrhagic stroke	6 (0.21)	9 (0.32)
Unidentified stroke	9 (0.32)	4 (0.14)
Systemic embolism	2 (0.07)	13 (0.47)

n (%)

Figure 4 shows the Kaplan-Meier curve of the occurrence of stroke or systemic embolism from the date of randomization up to the efficacy cut-off date.

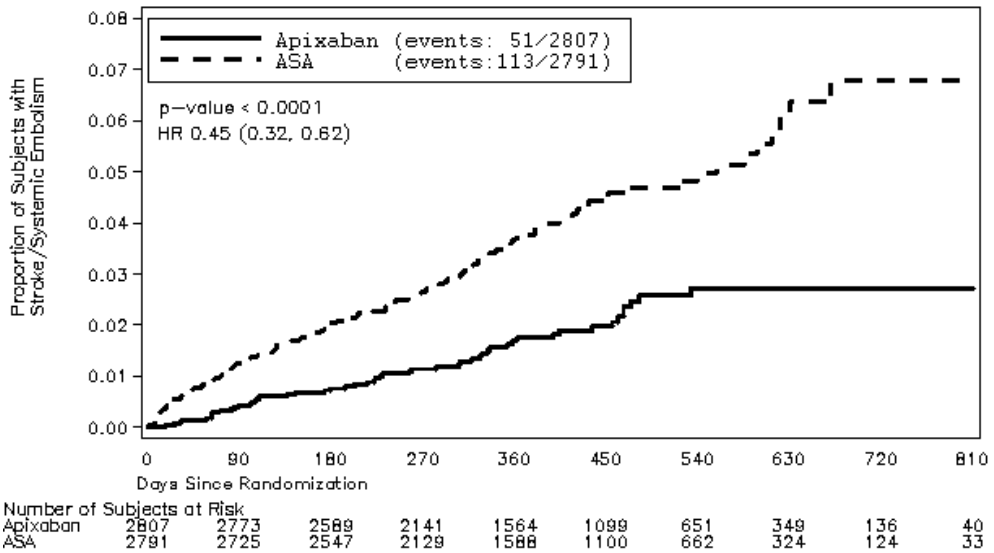


Figure 4. Kaplan-Meier curve of stroke or systemic embolism from randomization to efficacy cut-off date: Randomized population (Adapted from submitted data)

The primary safety endpoint was the time to the first occurrence of "major bleeding" during the double-blind period, and the secondary safety endpoints were "the composite endpoint of major bleeding or CRNM bleeding" and time to the first occurrence of "all bleedings." The incidences and incidence rates of safety endpoints were as shown in Table 24.

Table 24. Incidence and incidence rate of safety endpoints during the double-blind period: Study drug population (Adapted from submitted data)

	Apixaban group (N = 2798)	**Aspirin group (N = 2780)**
Major bleeding (n [%])	45 (1.61)	29 (1.04)
Incidence rate (%/year)	1.41	0.92
Major bleeding or CRNM bleeding (n [%])	140 (5.00)	101 (3.63)
Incidence rate (%/year)	4.46	3.24
All bleedings (n [%])	325 (11.62)	250 (8.99)
Incidence rate (%/year)	10.85	8.32

The incidence of adverse events that occurred during the double-blind period was 65.5% (1833 of 2798 patients) in the apixaban group and 69.2% (1925 of 2780 patients) in the aspirin group. Adverse events occurring in ≥3% of patients in either group were atrial fibrillation (4.7% in the apixaban group, 4.6% in the aspirin group), dizziness (3.9%, 5.2%), dyspnoea (3.9%, 5.1%), headache (3.5%, 3.3%), cardiac failure (3.2%, 4.0%), nasopharyngitis (3.2%, 2.9%), oedema peripheral (3.1%, 3.8%), cough (3.0%, 3.5%), and hypertension (2.9%, 3.7%).

The incidence of serious adverse events was 23.5% (657 of 2798 patients) in the apixaban group and 28.9% (804 of 2780 patients) in the aspirin group, and serious adverse events occurring in >1% of patients in either group were atrial fibrillation (2.6%, 2.5%), cardiac failure (2.1%, 2.7%), cardiac failure congestive (1.4%, 1.0%), pneumonia (1.3%, 2.0%), ischaemic stroke (0.7%, 1.7%), and cerebrovascular accident (0.6%, 1.4%).

During the period from the start of treatment with the study drug up to 30 days after the last dose in the double-blind period, death occurred in 91 of 2798 patients (3.3%) in the apixaban group

and in 115 of 2780 patients (4.1%) in the aspirin group. Serious adverse events leading to death and occurring in >0.1% of patients in either group were death (0.5% in the apixaban group, 0.3% in the aspirin group), sudden death (0.3%, 0.4%), cerebrovascular accident (0.3%, <0.1%), pneumonia (0.3%, 0.2%), cardiac failure congestive (0.2%, <0.1%), cardiac failure (0.2%, 0.2%), myocardial infarction (0.2%, 0.3%), acute myocardial infarction (0.1%, 0.4%), ischaemic stroke (<0.1%, 0.3%), cardiac arrest (<0.1%, 0.3%), and respiratory failure (<0.1%, 0.3%).

The incidence of adverse events leading to treatment discontinuation was 9.5% (266 of 2798 patients) in the apixaban group and 13.0% (362 of 2780 patients) in the aspirin group. The main adverse events leading to treatment discontinuation were cerebrovascular disorder, ischaemic stroke, and atrial fibrillation in the apixaban group; and cerebrovascular disorder, ischaemic stroke, and TIA in the aspirin group.

4.(iii).B Outline of the review by PMDA

4.(iii).B.(1) Clinical positioning of apixaban

PMDA asked the applicant to compare and explain the clinical positioning of apixaban and existing drugs in anticoagulant therapy in Japanese patients with nonvalvular atrial fibrillation.

The applicant responded as follows:
Currently, warfarin, dabigatran etexilate methanesulfonate (dabigatran), and rivaroxaban are approved in Japan as drugs for anticoagulant therapy in patients with nonvalvular atrial fibrillation. "Guidelines for Pharmacotherapy of Atrial Fibrillation (JCS 2008)" (*Circ J*. 2008;72 Suppl IV:1581-638), "Guidelines for management of anticoagulant and antiplatelet therapy in cardiovascular diseases (JCS 2009)" (2008 report of Joint Working Group), and "Urgent statement on antithrombotic therapies for atrial fibrillation (2011)" ("Guidelines for Pharmacotherapy of Atrial Fibrillation [JCS 2008]" Working Group leader Satoshi Ogawa, "Guidelines for management of anticoagulant and antiplatelet therapy in cardiovascular diseases [JCS 2009]," Working Group leader Masatsugu Hori) recommend that patients with nonvalvular atrial fibrillation receive, as the basic anticoagulant treatment, warfarin or dabigatran depending on the risk of embolism (history of stroke or TIA, ≥75 years of age, cardiac failure congestive, hypertension, coronary artery disease, diabetes mellitus). Rivaroxaban was not yet approved at the time of the publication of the above guidelines. In warfarin treatment, monitoring with PT-INR measurement is essential. The efficacy of warfarin is affected not only by patient background factors such as age and complications but also by vitamin K-containing foods and drinks and by concomitant drugs. In addition, it takes several days before the onset and disappearance of the anticoagulant effect. Thus, it is not easy to control PT-INR because of the large inter- and intra- individual variability in the optimal dose. Because of these drawbacks, warfarin is not used effectively currently even in patients with disease conditions requiring warfarin treatment. Results of Study CV185030 suggested that apixaban is superior to the comparator drug warfarin in both efficacy and safety, with lower incidences of stroke, systemic embolism, and major bleeding. Other advantages of apixaban include the following; (a) there are no food effects, no clinically significant drug-drug interactions, and less individual variability in pharmacokinetics, etc., obviating the necessity of monitoring patient conditions during the treatment, (b) anticoagulant therapy is possible at a fixed dosage and administration, (c) the onset of the anticoagulant effect is faster compared with warfarin and the disappearance is predictable from the blood elimination half-life, and (d) renal excretion accounts for approximately 27% of the total body clearance, indicating the presence of multiple routes of metabolism and excretion. The drawback of apixaban is that there is currently no established method for neutralizing the anticoagulant effect of apixaban. As regards the clinical positioning of apixaban relative to dabigatran and rivaroxaban, although there are data of clinical studies on each drug using warfarin as the comparator, there are no data that directly compared dabigatran or rivaroxaban with apixaban within the same study, precluding the evaluation currently. Results of Study CV185048 conducted in foreign countries showed that the incidences of stroke and systemic embolism in the

apixaban group were significantly reduced without increase in the risk of intracranial haemorrhage compared with the aspirin group. These findings are expected to allow more active use of apixaban in antithrombotic therapy in the future. Thus, apixaban will become a new treatment option for the prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation.

PMDA considers the clinical positioning of apixaban as follows:
In Study CV185030, apixaban was compared with warfarin, the standard anticoagulant drug currently used for patients with nonvalvular atrial fibrillation, and results suggest the non-inferiority of apixaban to warfarin in efficacy and safety. Therefore, apixaban may be used for anticoagulant therapy in Japanese patients with nonvalvular atrial fibrillation [see "4.(iii).B.(3) Efficacy and dosage and administration of apixaban" and "4.(iii).B.(4) Safety"]. Given that the primary objective of Study CV185030 was to verify the non-inferiority of apixaban to warfarin in efficacy, the clinical positioning of apixaban should be evaluated based on the results of the evaluation of the non-inferiority of apixaban to warfarin in the primary endpoints.

On the other hand, only a limited number of Japanese patients were enrolled in Study CV185030. Therefore, in administering apixaban to Japanese patients, the following measures should be taken with consideration given to the fact that the efficacy and safety in Japanese patients have been investigated within an extremely narrow range: (i) careful evaluation of the appropriateness of using the drug to patients with a high risk of adverse reactions such as bleeding, and (ii) providing cautions based on the information collected after the market launch, as appropriate. Also, patient safety should be ensured with consideration given to the absence of an appropriate marker for monitoring the efficacy of apixaban and of any agent that neutralizes the anticoagulant effect of the drug. Apixaban has unique characteristics not shared by warfarin such as no need to restrict intake of vitamin K-containing food or to adjust the dose by monitoring PT-INR, but this does not necessarily prove the superiority of safety of apixaban to warfarin. Safety measures are required to avoid the underestimation of the apixaban-induced risks in clinical practice with the unwarranted assumption that apixaban is safer than warfarin based on the above characteristics of apixaban.

As regards the clinical positioning of apixaban relative to dabigatran and rivaroxaban, the efficacy and safety of these drugs have not been compared directly in the same clinical study, precluding a sufficient evaluation currently. However, these drugs are equivalent in that they should be selected based on the comparison of the above advantages and disadvantages with those of warfarin in anticoagulant therapy in patients with nonvalvular atrial fibrillation.

Based on the results of aspirin-controlled Study CV185048 conducted in foreign countries, the applicant claimed that apixaban is effective in patients with nonvalvular atrial fibrillation in whom aspirin is selected when warfarin is not tolerated. Although there certainly is a need for an antithrombotic drug that is substituted for warfarin in patients with nonvalvular atrial fibrillation in whom warfarin is not tolerated, treatment with apixaban cannot be actively recommended in these patients in Japan based on the results of Study CV185048, for the following reasons: (i) in Japan, aspirin therapy is hardly an established treatment method in patients with nonvalvular atrial fibrillation, and (ii) since no Japanese patients participated in Study CV185048, the data from the study cannot be handled as important reference information for the evaluation of efficacy of apixaban in Japanese patients.

Based on the above, apixaban may be supplied to clinical practices as a treatment option, together with approved drugs, for anticoagulant therapy in patients with nonvalvular atrial fibrillation, provided that appropriate safety measures are taken with consideration given to the disadvantages of apixaban and to the fact that the safety information in Japanese patients is limited.

4.(iii).B.(2) Indication of apixaban and target patients

PMDA considers the target patients of apixaban as follows:

In the Confirmatory study CV185030, the target subjects were patients with atrial fibrillation with at least 1 of the following risk factors: (a) ≥75 years of age, (b) history of stroke, TIA, or systemic embolism, (c) symptomatic congestive cardiac failure or left ventricular dysfunction with LVEF ≤40%, (d) diabetes mellitus, and (e) hypertension requiring drug therapy. Exclusion criteria included moderate or severe mitral valve stenosis and conditions requiring chronic anticoagulant therapy for reasons other than atrial fibrillation (e.g., artificial cardiac valve). Although the inclusion criteria also included a "history of systemic embolism" and "left ventricular dysfunction with LVEF ≤40%," these criteria were not fully consistent with $CHADS_2$ score. Therefore, patients who met only either of these criteria were regarded as patients with $CHADS_2$ score 0 in Study CV185030. Based on these criteria, basically, the target patients were not significantly different from the patient population with nonvalvular atrial fibrillation for whom anticoagulant therapy is recommended in Japan and other countries. Since whether anticoagulant therapy can be used or not would be determined in clinical practice through the comprehensive assessment of the risk of ischemic stroke based not only on $CHADS_2$ score but also on other patient characteristics, and that the individual factors in the above criteria are appropriate as the risk factors of stroke, it is assumed the target patients in Study CV185030 were selected appropriately.

Based on the above, Study CV185030 demonstrated the non-inferiority of apixaban to warfarin in preventing the occurrence of "stroke" and "non-central nervous system embolism" in Japanese patients and the safety profile of apixaban is acceptable [see "4.(iii).B.(3) Efficacy and dosage and administration of apixaban" and "4.(iii).B.(4) Safety"]. Therefore, as is in the case with approved drugs that are clearly indicated for ischemic stroke, the indication of apixaban should be "reduction of the risk of ischemic stroke and systemic embolism in patients with nonvalvular atrial fibrillation." The decision on the indication and the target patients will be finalized, also taking account of comments raised in the Expert Discussion.

4.(iii).B.(3) Efficacy and dosage and administration of apixaban

The applicant, based on the dosage and administration investigated in Study CV185030, submitted the following proposed dosage and administration and the "Precautions for Dosage and Administration" for the dose reduction to be included in the package insert (draft).

[Dosage and Administration]
The usual adult dosage of apixaban is 5 mg administered orally twice daily.
The dose may be reduced to apixaban 2.5 mg twice daily as necessary.

[Precautions for Dosage and Administration]

1. Patients who meet at least 2 of the following criteria have a high risk of bleeding and may show an increased blood apixaban concentration. In these patients, apixaban should be administered carefully, with consideration given to dose reduction to 2.5 mg orally twice daily.
   - Age ≥80 years
   - Body weight ≤60 kg
   - Serum creatinine ≥1.5 mg/dL

4.(iii).B.(3).1) Justification for the doses investigated in Study CV185030

The applicant explained the background and the reason for setting the dosage and administration of apixaban in Study CV185030 as follows:

Based on the results of Study CV185010 in patients after the total knee replacement, results of the interim analysis of Study CV185017 in patients with deep vein thrombosis, and results of the studies on other anticoagulant drugs in these patient populations, the dosage regimen of apixaban was determined as "5 mg twice daily." In Study CV185010, the data were compared between

each of the 6 apixaban groups (2.5 mg twice daily, 5 mg twice daily, 10 mg twice daily, 5 mg once daily, 10 mg once daily, 20 mg once daily) and the 2 control groups (enoxaparin, warfarin). As a result, the incidence of the composite endpoint of venous thrombosis or death as the primary endpoint was lower in all of the apixaban groups compared with the enoxaparin group, and the incidence of major bleeding was 0% to 3.3% in the apixaban groups and 0% both in the enoxaparin group and in the warfarin group. Based on the above results, 2.5 mg twice daily was selected as the apixaban dosage regimen for the prophylaxis of venous thrombosis. However, a decrease in efficacy poses a serious concern for patients with nonvalvular atrial fibrillation. In addition, in Study CV185017, the incidence of all bleeding events in the 3 apixaban groups combined (5 mg twice daily, 10 mg twice daily, 20 mg once daily) was 11.4% (44 of 385 patients), which was lower compared with the incidence in the control group (LMWH + VKA, 15.9% [20 of 126 patients]). Therefore, 5 mg twice daily, the dose higher than that for the prophylaxis of venous thrombosis, was selected as the usual dosage regimen in Study CV185030.

PMDA asked the applicant to explain the reason for concluding it appropriate to administer apixaban to Japanese patients as well at 5 mg twice daily, the usual dosage regimen in Study CV185030, taking account of the fact that, in the Japanese phase II study (CV185067), the incidence of all bleedings was higher in the apixaban 5 mg twice daily group than in the warfarin group.

The applicant responded as follows:
In Study CV185067, the incidence of the primary endpoint "major bleeding or CRNM bleeding" was lower in both the apixaban 2.5 mg twice daily and 5 mg twice daily groups compared with the warfarin group, whereas the incidence of all bleedings was higher in the apixaban 5 mg twice daily group than in the warfarin group. The higher incidence of all bleedings in the apixaban 5 mg twice daily group than in the warfarin group was due to the higher incidence of minor bleeding in the apixaban 5 mg twice daily group. Taking into account that the incidence of clinically significant bleedings, i.e., major bleeding and CRNM bleeding, was lower in all apixaban groups compared with the warfarin group and that minor bleeding is not a predictive factor of major bleeding or CRNM bleeding, the safety, in terms of bleeding, in any of the apixaban groups would be equivalent to, or higher than, that in the warfarin group. In Study CV185067, no events corresponding to the efficacy endpoint occurred in any apixaban group, with no difference in the efficacy being observed between the apixaban 2.5 mg twice daily group and the 5 mg twice daily group. Thus, based on the comprehensive evaluation of the safety and efficacy, it would be appropriate to select 5 mg twice daily, the same dosage regimen as used in foreign countries, as the usual dosage regimen in Japanese patients in Study CV185030.

PMDA considers as follows:
It is hard to say that the usual dosage regimen of apixaban in Study CV185030 (5 mg twice daily) was selected based on any clear evidence, for the following reasons: (i) it is based on the results of Studies CV185010 and CV185017, which were phase II studies of other diseases for which the risk-benefit assessment was done by criteria different from those for nonvalvular atrial fibrillation, and (ii) the dosage regimen was set under the condition where no clear dose-response relationship was seen either in efficacy events or in bleeding-related safety events. However, given that the incidence rate for stroke or systemic embolism in patients with nonvalvular atrial fibrillation is low, and that no appropriate surrogate marker has been established for the reduction of the risk of stroke or systemic embolism, it is acceptable that the usual dosage regimen in Study CV185030 was determined, as a start, based on the results of Studies CV185010 and CV185017, by taking account of the clinical efficacy of apixaban and the objective of treatment.

PMDA also considers as follows, regarding the appropriateness of setting the usual dosage regimen in Japanese patients in Study CV185030 as 5 mg twice daily, the same dosage regimen as used in foreign patients:

Study CV185067 in Japanese patients with nonvalvular atrial fibrillation was conducted with the primary objective of confirming the safety of apixaban in Japanese patients when administered at the same dosage regimen as used in Study CV185030, and was not on a sufficiently large scale to allow comparison of the rate for efficacy events between the apixaban group and the warfarin group. Therefore, it is impossible to determine the appropriateness, from the point of view of efficacy, of the usual dosage regimen of apixaban in Japanese patients based on the results of this study. On the other hand, since the incidences of major bleeding and CRNM bleeding in Study CV185067 were not higher in the apixaban group compared with the warfarin group, it is acceptable from the point of view of safety that the dosage regimen used in Study CV185067 was applied to Japanese subjects in Study CV185030. However, although minor bleeding is not considered to be an index directly predicting the risk of major bleeding or CRNM bleeding, it may be considered as an index for proneness to bleeding. Therefore, the higher incidence of all bleedings in the apixaban 5 mg twice daily group than in the warfarin group should not be made light of. Caution should be paid to the possibility that the bleeding risk due to apixaban may be higher in Japanese patients than in foreign patients.

Whether or not the usual dosage regimen in Study CV185030 is appropriate for Japanese patients as well has to be determined based on the results of Study CV185030 and on the risk-benefit balance in Japanese patients.

4.(iii).B.(3).2) Usual dosage regimen of apixaban in Study CV185030

The incidence rate and the incidence of the composite endpoint of stroke or systemic embolism, the primary efficacy endpoint, in Study CV185030 were 1.27% per year and 212 of 9120 patients, respectively, in the apixaban group and 1.60% per year and 265 of 9081 patients, respectively, in the warfarin group. The hazard ratio (two-sided 95% CI) of the apixaban group relative to the warfarin group, calculated based on the Cox-proportional hazard model, was 0.79 (0.66-0.95), with the upper limit of the two-sided 95% CI being less than 1.38, the acceptable non-inferiority margin. In a similar manner, the hazard ratio (two-sided 99% CI) of the apixaban group for the primary endpoint relative to the warfarin group, calculated based on the Cox proportional hazard model, was 0.79 (0.62-1.00), with the upper limit of the two-sided 99% CI being less than 1.44, the acceptable non-inferiority margin.

The applicant explained the rationale for the acceptable non-inferiority margin set for the primary endpoint in Study CV185030, as follows:
From the results of the meta-analysis of 6 placebo-controlled studies so far conducted in patients with atrial fibrillation, it was estimated that warfarin administration reduced the relative risk of the efficacy endpoint by 64% in Study CV185030, with the lower limit of the two-sided 95% CI of the relative risk being 47%. Based on these data, the excess risk for placebo over warfarin was calculated to be 2.78, with the lower limit of the two-sided 95% CI of the excess risk being 1.88. In order to demonstrate that apixaban is not inferior to warfarin to more than a certain extent, it is necessary to show that the upper limit of the two-sided CI of the relative risk of apixaban against warfarin does not exceed 1.88. In this study, however, a stricter acceptable non-inferiority margin was selected. Therefore, the acceptable non-inferiority margin was set at 1.44 and 1.38* so that at least half of the conservative estimate of the effect of warfarin would be shared by apixaban as well.

PMDA considers the efficacy of apixaban demonstrated in Study CV185030 as follows:
From the submitted data, the acceptable non-inferiority margin in Study CV185030 was appropriate for confirming the efficacy of apixaban. Results of Study CV185030 verified the non-

* The two different acceptable non-inferiority margins were set, reflecting the different opinions of the regulatory agency of each region.

inferiority of apixaban 5 mg twice daily (2.5 mg twice daily if patients met the dose reduction criteria) to warfarin in the reduction of the risk of stroke or systemic embolism. The incidence of each event composed of the primary efficacy endpoint in the apixaban group and in the warfarin group was 1.54% (140 of 9120 patients) and 1.50% (136 of 9081 patients), respectively, for ischemic stroke, 0.44% (40 of 9120 patients) and 0.86% (78 of 9081 patients) for haemorrhagic stroke, and 0.15% (14 of 9120 patients) and 0.23% (21 of 9081 patients) for stroke of unknown cause, showing the non-inferiority of apixaban to warfarin in anyof the efficacy events. Thus, the clinical significance of the efficacy of apixaban has been demonstrated by Study CV185030. As regards safety as well, there were no bleeding risks that occurred at a clearly higher frequency in the apixaban group than in the warfarin group in Study CV185030, although various cautions are warranted as described later. Based on the above, it is appropriate to set the usual dosage regimen of apixaban at 5 mg twice daily. The applicant claims that apixaban was verified to be not only non-inferior to warfarin in the primary efficacy endpoint, the major objective of Study CV185030, but also superior to warfarin in the primary endpoint. However, by placing emphasis on the fact that this study was designed with the sole and the ultimate purpose of evaluating the above major objective, the clinical positioning of apixaban should be evaluated based on the non-inferiority to warfarin in terms of the primary endpoint.

4.(iii).B.(3).3) Dose reduction criteria and the rationale for the reduced dose

PMDA asked the applicant to explain the rationale and the appropriateness of the reduced dose of 2.5 mg twice daily and the dose reduction criteria defined as patients who meet at least 2 of the following criteria: (a) age ≥80 years, (b) body weight ≤60 kg, and (c) serum creatinine ≥1.5 mg/dL.

The applicant explained as follows:

In anticoagulant therapy for reduction of the risks of stroke in patients with nonvalvular atrial fibrillation, it is known that there are patients with a high risk of bleeding and that advanced age, female sex, low body weight, decreased kidney function, etc., are risk factors for bleeding. Therefore, in conducting the clinical study, it is necessary to take measures to minimize the risk of bleeding in patients with a high risk of bleeding while maintaining the efficacy. Results of the clinical pharmacology study had shown that the advanced age, low body weight, and decreased kidney function affected the exposure level of apixaban, but one factor alone out of these 3 factors would not have a sufficiently large effect on the exposure level of apixaban as to pose a bleeding risk. However, the presence of multiple risk factors is likely to increase the exposure level of apixaban, and the bleeding risk itself is increased in patients with multiple risk factors. Therefore, it was decided that patients with ≥2 out of the 3 risk factors (advanced age, low body weight, decreased kidney function) were to receive apixaban at the reduced dose. Also, from the results of the exploratory PPK analysis in Study CV185010, the exposure level was predicted to increase by approximately 28% to 37% in patients with 2 of the factors (age ≥80 years, body weight ≤60 kg, serum creatinine ≥1.5 mg/dL), but not to increase ≥2-fold even in patients with all 3 factors. Therefore, from the aspect of the exposure level, it was considered unnecessary to decrease the dose to half the usual dose. However, by also taking account of the possible increase in the bleeding risk in patients with multiple risk factors in the clinical setting, the dose for patients with ≥2 risk factors was set at 2.5 mg twice daily, half the usual dose.

The reference data on the cut-off levels of individual risk factors are as shown below.

Age ≥80 years: Age is identified as an independent factor affecting the occurrence of a bleeding event (Pisters R. et al. *Chest.* 2010;138(5):1093-100). In the SPAF II study (*Arch Intern Med.* 1996;156:409-16) which compared warfarin and aspirin in their effect to prevent stroke in patients with atrial fibrillation, the incidence of intracranial haemorrhage in the warfarin group increased in the subpopulation of patients aged >75 years compared with the subpopulation of patients aged

≤75 years, and the mean age of the subpopulation of patients aged >75 years was 80 years. Based on such clinical experiences, the cut-off value for age was set at "≥80 years of age."

Body weight ≤60 kg: In Study CV185059 in healthy adult subjects, AUC of apixaban in subjects with body weight of ≤50 kg (defined as low body weight) was increased by 20% compared with subjects with body weight of 65 to 85 kg (defined as the reference). Therefore, the cut-off value for body weight was set at "≤60 kg." The subpopulation analysis of Study CV185030 showed that, in the warfarin group, patients with body weight of ≤60 kg had an increased risk for all of the following parameters: the primary efficacy endpoint, major bleeding, major bleeding or CRNM bleeding, and all bleedings. Thus, low body weight (≤60 kg) was appropriate as a risk factor.

Serum creatinine ≥1.5 mg/dL: Renal impairment was handled as a bleeding risk in American College of Chest Physicians (ACCP) Consensus Conference on Antithrombotic Therapy (*Chest.* 2001;119:1088S-121S) and the Position Paper (*Europace.* 2011;13:723-46), etc., of the Working Group on Thrombosis of European Heart Rhythm Association (EHRA) and European Society of Cardiology (ESC). Therefore, "serum creatinine ≥1.5 mg/dL," which is a criterion of moderate renal impairment, was selected as the cut-off level.

PMDA considers as follows:
It is appropriate that advanced age, low body weight, and decreased kidney function, all of which pose concerns of both increased exposure level and bleeding risk, were selected as factors to be considered for apixaban dose reduction. However, there is no sufficient rationale for the cut-off level for deciding apixaban dose reduction in patients with nonvalvular atrial fibrillation and for the reduced dose. Also, the rationale and the appropriateness for not requiring dose reduction in patients with only 1 risk factor are unclear. These insufficiencies are partly unavoidable because of the absence of an appropriate surrogate marker for assessing the reduction of the risks of stroke or systemic embolism in patients with nonvalvular atrial fibrillation, and the appropriateness of the dose reduction criteria should be evaluated based on the results of each dose selected according to the dose reduction criteria in Study CV185030.

4.(iii).B.(3).4) Appropriateness of dose reduction criteria and of reduced dose

The incidence rate of the primary efficacy endpoint in Study CV185030 was 1.25% per year in the apixaban group and 1.53% per year in the warfarin group in the subgroup receiving the usual dose (apixaban or apixaban placebo 5 mg twice daily) (the usual dose population), and 1.70% per year in the apixaban group and 3.33% per year in the warfarin group in the subpopulation receiving the reduced dose (apixaban or apixaban placebo 2.5 mg twice daily) (the reduced dose population), with the results of either subpopulation not being significantly different from those of the entire study population. As regards safety, the incidence rate of major bleeding was 2.09% per year in the apixaban group and 2.95% per year in the warfarin group in the usual dose population and 3.29% per year in the apixaban group and 6.71% per year in the warfarin group in the reduced dose population, the incidence rate of major bleeding or CRNM bleeding was 4.03% per year in the apixaban group and 5.86% per year in the warfarin group in the usual dose population and 4.97% per year in the apixaban group and 9.80% per year in the warfarin group in the reduced dose population, and the incidence rate of all bleedings was 17.84% per year in the apixaban group and 25.35% per year in the warfarin group in the usual dose population and 24.23% per year in the apixaban group and 38.77% per year in the warfarin group in the reduced dose population. Thus, even in the reduced dose population, the frequency of bleeding events in the apixaban group (2.5 mg) did not exceed that in the warfarin group.

PMDA considers as follows:

In Study CV185030, the efficacy and safety of apixaban in the reduced dose population, albeit consisting of only a limited number of patients, were not markedly discrepant with those observed in the entire study population. Since both the efficacy and the bleeding risk of apixaban are derived from the anticoagulant effect of apixaban, both too much and too little anticoagulant effect may impair the usefulness of apixaban. Therefore, it is inappropriate to lightly recommend the dosage regimen of apixaban that have not been assessed its risk-benefit balance in clinical study. If apixaban is supplied to clinical practices based on the conclusion that the results of Study CV185030 may be regarded as reflecting those of Japanese patients in general, and therefore that the dosage regimen used in Study CV185030 are applicable to Japanese patients, it is necessary currently to establish the same dose reduction criteria as those used for the dosage regimen in Study CV185030 which evaluated the efficacy and safety based on the occurrence of each of the individual events. The efficacy of apixaban in Japanese patients and appropriateness of the dose reduction criteria will be reviewed in "4.(iii).B.(6) Efficacy of apixaban in Japanese patients," also taking account of the results of the Japanese subpopulation in Study CV185030.

4.(iii).B.(3).5) Appropriateness of control group in Study CV185030

PMDA considers as follows:

Selection of warfarin as the comparator in Study CV185030 was appropriate in light of the Japanese and foreign guidelines, the usage conditions, and the timing of the clinical study. Also, based on the Japanese and foreign guidelines, it was considered appropriate that a randomized, double-blind, parallel group comparable study was conducted to compare the efficacy and safety between the apixaban group and the warfarin group, with the target PT-INR set at 2.0 to 3.0 (1.6-2.6 for Japanese patients aged ≥70 years).

In the evaluation of Study CV185030, however, attention should be paid to the fact that, in the Japanese subpopulation of the warfarin group, the annual incidence rate of major bleeding was relatively high, at 5.99% per year. PMDA therefore considered it necessary to investigate whether or not the Japanese subpopulation of the warfarin group had a higher risk of major bleeding than Japanese patients in routine clinical settings, and asked the applicant to provide a detailed explanation of the actual status of warfarin control in Study CV185030.

The applicant explained as follows:

TTR in the entire study population was 60.5%, or 66.0% if the first 7 days of study drug administration and the days of discontinuation of warfarin were excluded. In Japanese patients also, TTR was 67.0% when the first 7 days of study drug administration and the days of discontinuation of warfarin were excluded. In the Japanese subpopulation, TTR in subjects aged ≥70 years was 69.9% when the therapeutic range was set at 1.6 to 2.6, which was not significantly different from 67% calculated by setting the therapeutic range at 2.0 to 3.0. In subjects aged <70 years, TTR calculated by setting the therapeutic range at 2.0 to 3.0 was 68.2%. In routine clinical settings in Japan, PT-INR is often controlled targeted at 1.6 to 2.6 regardless of age out of concern over bleeding (*Circ J.* 2011;75:2087-94). When the target PT-INR was set at 1.6 to 2.6 in subjects aged <70 years in the Japanese subpopulation, TTR was 67.5%. The period during which PT-INR exceeded 3.0 was 10.8% of the entire period in the entire study population, and the period during which PT-INR exceeded the target level was 11.6% in the Japanese subpopulation.

Table 25 shows the incidence rate of bleeding in Japanese patients classified by age group with different target PT-INR (≥70 years of age, <70 years of age).

Table 25. Incidence rate of major bleeding or CRNM bleeding by age group in Study CV185030 (Adapted from submitted data)

	<70 years		≥70 years	
Major bleeding or CRNM bleeding	Apixaban group	Warfarin group	Apixaban group	Warfarin group
Entire study population	3.01 (225/4340)	4.27 (315/4371)	5.12 (388/4748)	7.78 (562/4681)
Japanese subpopulation	2.12 (3/71)	4.85 (7/79)	1.72 (3/89)	10.80 (16/96)

%/year (n/N)

PMDA considers as follows:
Since the warfarin management rule employed in Study CV185030 conformed to Japanese and foreign guidelines, the warfarin management in the control group of Study CV185030 was appropriate, by also taking account of the investigation of TTR. In clinical practice, however, warfarin management is not necessarily performed strictly according to the guideline because of the difficulty of warfarin management and concern about bleeding. Therefore, PT-INR may have been controlled at a slightly higher level in Study CV185030 than in routine clinical settings. Particularly in the Japanese subpopulation of Study CV185030, PT-INR might be controlled at a slightly higher level than in routine clinical settings in Japan, from the following facts: the percentage of the period during which PT-INR exceeded the target level was calculated by individual patients, in the majority of subjects, PT-INR exceeded the target level in >10% of the treatment period, and in contrast to clinical practice where PT-INR is controlled often within the range from 1.6 to 2.6 in patients aged <70 years, the median period during which PT-INR was controlled within the range from 2.0 to 3.0 was approximately 70% of the treatment period. These results suggest the possibility that the relationship between apixaban or warfarin and bleeding risk observed in Study CV185030 does not accurately reflect the relationship in routine clinical settings. This issue should be given careful attention in comparing the bleeding risk between apixaban and warfarin.

4.(iii).B.(3).6) Efficacy in Japanese patients

4.(iii).B.(3).6).(a) Appropriateness of collectively evaluating the data of Japanese subpopulation and those of non-Japanese patients in Study CV185030

The applicant explained, based on the similarity and difference of the intrinsic and extrinsic ethnic factors between Japanese and foreign patients, the appropriateness of collectively evaluating the data of the Japanese subpopulation and those of non-Japanese patients in Study CV185030 and extrapolating the results of the entire study population to Japanese patients, as follows:
As regards the intrinsic ethnic factors, data of healthy adult subjects (Studies CV185013 and CV185046) and of patients with nonvalvular atrial fibrillation (Studies CV185067 and CV185030) showed the similarity of the pharmacokinetic and pharmacodynamic profiles between Japanese and Caucasian patients, demonstrating that the ethnic difference did not affect the pharmacokinetics or pharmacodynamics of apixaban. Also, comparison of pharmacokinetics and pharmacodynamics of apixaban in Japanese patients with nonvalvular atrial fibrillation in Study CV185067 with those in foreign patients with nonvalvular atrial fibrillation did not show any clinically significant difference.

As regards extrinsic ethnic factors, there is no difference in the definition of the disease between Japan and Europe and the US, based on the comparison of the representative guidelines in Japan and Europe and the US, i.e., “Guidelines for Pharmacotherapy of Atrial Fibrillation (JCS 2008)” and “ACC/AHA/ESC 2006 Guidelines for the Management of Patients With Atrial Fibrillation,” respectively, (Japanese and foreign guidelines). Also, there is no significant difference in the diagnosis or prevalence of atrial fibrillation between Japan and foreign countries. Both Japanese and foreign guidelines recommend administering appropriate antithrombotic therapy to patients

with nonvalvular atrial fibrillation who have a risk of stroke including a history of cerebral infarction or TIA, diabetes mellitus, hypertension, cardiac failure congestive, and advanced age, and there is no difference between Japan and overseas in such recommendation. Also, based on the analysis of the frequency of cerebral infarction and cerebral haemorrhage, both Japanese and foreign guidelines recommend controlling PT-INR within the range from 2.0 to 3.0 as the index of warfarin therapy, which is no difference between Japan and overseas. However, in Japan, a lower target PT-INR level of 1.6 to 2.6 is recommended for patients aged ≥70 years, based on the results of prospective studies conducted in Japan. Since Study CV185030 was a global clinical trial, it had been anticipated that there would be some differences in the control status of PT-INR. As it turned out, PT-INR from 4 days after the start of study drug administration to 2 days after the last dose was <2.0 in 34.28%, ≥2.0 and ≤3.0 in 58.62%, and >3.0 in 7.10% of the Japanese subpopulation, and 29.20%, 57.09%, 13.71%, respectively, of the entire study population, showing no significant difference with each other. Although there are differences in the dietary habits between Japan and foreign countries, they are not considered to have any significant effect on the evaluation of the efficacy or safety of apixaban. In Study CV185030, the primary efficacy endpoint, major bleeding, and CRNM bleeding were evaluated by independent event assessment committees according to the definitions standardized across countries. Based on the above, the applicant considers that, despite some differences in the target PT-INR in the warfarin therapy between Japan and foreign countries, there is no significant difference in the control status of PT-INR between the Japanese subpopulation and the entire study population in Study CV185030, and that there is no difference in extrinsic ethnic factors that significantly affect the interpretation of the study results between Japan and foreign countries. Therefore, it would be appropriate to collectively evaluate the results of the Japanese subpopulation and those of the non-Japanese population in Study CV185030 and to extrapolate the data of the entire study to Japanese patients.

PMDA considers as follows:
As regards the applicant's claim on intrinsic ethnic factors, study data suggest that the plasma apixaban concentration following administration of apixaban 5 mg in patients with nonvalvular atrial fibrillation is higher in Japanese patients than in non-Asian patients and that the difference in the exposure level between apixaban 2.5 mg and 5 mg doses is larger in Japanese patients than in non-Asian patients, as discussed in "4.(ii).B.(1) Difference in pharmacokinetics and pharmacodynamics between Japanese and foreign subjects." As regards extrinsic ethnic factors, there are no significant differences, such as those affecting the evaluation of study data, in the disease concept of atrial fibrillation or treatment policy related to anticoagulant therapy between Japan and foreign countries. However, in Japan, the target PT-INR level for patients aged ≥70 years with nonvalvular atrial fibrillation is set at 1.6 to 2.6, a range slightly lower than that in foreign countries. Attention should be paid to such a difference in the target PT-INR between Japan and foreign countries. Thus, it is acceptable that Study CV185030 was conducted as a global clinical trial including Japanese patients, based on the following reasons: (i) among extrinsic ethnic factors that could affect the efficacy and safety of apixaban, anticoagulant therapy for atrial fibrillation shows no significant difference in the treatment policy or treatment option between Japan and foreign countries and Study CV185030 was conducted with consideration given to the difference in target PT-INR between Japanese and foreign patients aged ≥70 years, (ii) although the exposure to apixaban, which is an intrinsic ethnic factor, is slightly different between Japanese patients and foreign patients, no appropriate surrogate marker has been established, and (iii) the dose that was investigated in Study CV185067 and confirmed to be acceptably safe was selected as the dose to be investigated in Study CV185030.

4.(iii).B.(3).6).(b) Consistency of the data of the entire study population with those of the Japanese subpopulation in Study CV185030

The data of the entire study population and of the Japanese subpopulation in Study CV185030 were as shown below.

The incidence rates of stroke or systemic embolism from the date of randomization up to the efficacy cut-off date in the apixaban group and in the warfarin group were 1.27% per year and 1.60% per year, respectively, in the entire study population, and 0.87% per year and 1.67% per year, respectively, in the Japanese subpopulation. The incidence rates of ischemic or unidentified stroke in the apixaban group and in the warfarin group were 0.97% per year and 1.05% per year, respectively, in the entire study population, and 0.87% per year and 1.11% per year, respectively, in the Japanese subpopulation. The incidence rates of haemorrhagic stroke in the apixaban group and in the warfarin group were 0.24% per year and 0.47% per year, respectively, in the entire study population, and 0% per year and 0.55% per year, respectively, in the Japanese subpopulation. The incidence rates of major bleeding, the primary safety endpoint, in the apixaban group and in the warfarin group were 2.13% per year and 3.09% per year, respectively, in the entire study population, and 1.26% per year and 5.99% per year, respectively, in the Japanese subpopulation. The incidence rates of major bleeding or CRNM bleeding in the apixaban group and in the warfarin group were 4.07% per year and 6.01% per year, respectively, in the entire study population, and 1.90% per year and 7.86% per year in the Japanese subpopulation. The incidence rate of all bleedings in the apixaban group and in the warfarin group were 18.08% per year and 25.82% per year, respectively, in the entire study population, and 20.95% per year and 40.13% per year, respectively, in the Japanese subpopulation.

PMDA considers the efficacy of apixaban in Japanese patients as follows:
The applicant set the target sample size of Japanese subjects at 300 subjects from the point of view of feasibility. The actual number of Japanese subjects enrolled in Study CV185030 was 336 subjects (161 subjects in the apixaban group, 175 subjects in the warfarin group), which was an extremely small number compared with the total number of subjects in the entire study (approximately 1.9%). Therefore, it is very difficult to evaluate the consistency of the results of the entire population of Study CV185030 with those of the Japanese subpopulation. Nevertheless, there are no significant discrepancies between the results of the entire study population and those of the Japanese subpopulation regarding the composite endpoint (primary efficacy endpoint), each component of the composite endpoint, or bleeding events, as far as the data obtained in the study are concerned. In Study CV185067, stroke or systemic embolism occurred in 0 of 74 patients in the apixaban 5 mg twice daily group and in 3 of 74 patients in the warfarin group, which supports the efficacy results of apixaban observed in Study CV185030. These results raise the expectation that the efficacy of apixaban in Japanese patients will be not inconsistent with the efficacy observed in the entire study population. Therefore, it is appropriate to set the dosage and administration as 5 mg twice daily in Japanese patients as well. However, as discussed in "4.(iii).B.(3).5) Appropriateness of control group in Study CV185030," the possibility cannot be totally excluded that the control status of PT-INR in the warfarin group of Study CV185030 slightly deviated from that in routine clinical settings. In addition, PMDA has no other choice but to evaluate the efficacy in Japanese patients for regulatory review, based on the discussion of the results from the Japanese subpopulation consisting of a very limited number of patients. Taking account of the above, it is necessary to collect information on the efficacy and safety of apixaban in Japanese patients after the market launch, and to provide relevant information to clinical practices in an appropriate manner.

4.(iii).B.(3).6).(c) Appropriateness of dose reduction criteria in Japanese subjects
The applicant explained the reduced dose population in the Japanese subpopulation of Study CV185030, as follows:
In the Japanese subpopulation of Study CV185030, the percentage of subjects who received the reduced dose was 6.2% (10 of 161 subjects) in the apixaban group and 8.0% (14 of 175 subjects) in the warfarin group. Of the subjects who received the reduced dose in the apixaban group, 8 subjects met the criteria of both advanced age and low body weight, while the remaining 2 subjects met only one of these criteria but were considered to also meet the other criterion as a result of rounding off the value in putting into IVRS for randomization. There were no subjects

who met all of the 3 criteria in the Japanese subpopulation. The percentage of subjects who met the criteria for dose reduction was not significantly different from the percentage (4.6% [831 of 18,201 subjects]) in the entire study population. As regards patient background factors, there were no significant differences either in the mean age or age distribution between the entire study population and the Japanese subpopulation, whereas mean body weight was lower by approximately 19.5 kg in the Japanese subpopulation compared with the entire study population, with the percentage of subjects weighing ≤60 kg being approximately 11% in the entire study population and 36% to 38% in the Japanese subpopulation. As regards the severity of renal impairment, there were slightly higher percentages of patients with mild or moderate severity and a lower percentage of normal renal function in the Japanese subpopulation compared with the entire study population. In the reduced dose population in the Japanese subpopulation, the incidence rate and the incidence of the primary efficacy endpoint in the warfarin group were 3.57% per year and 1 of 14 subjects, respectively, and the incidence rate and incidence of major bleeding were 10.97% per year and 2 of 14 subjects, respectively, whereas no efficacy or safety event occurred in the apixaban (2.5 mg) group. Only a small number of patients in the Japanese subpopulation met the criteria for dose reduction and, as a result, there were a very limited number of the primary efficacy endpoint events and major bleeding events, precluding the accurate evaluation. Nevertheless, efficacy and safety data in the apixaban group relative to those in the warfarin group in the Japanese subpopulation do not tend to differ significantly from those observed in the entire study population. Based on the above, the applicant considered it appropriate to set the same dose reduction criteria in the Japanese subpopulation as those set for the entire study group.

PMDA considers as follows:
It is appropriate to reduce the dose of apixaban in patients with a high risk of bleeding. However, the parameters for dose reduction criteria and their cut-off level were determined based on the results of foreign clinical studies, and it is hard to say that there are sufficient data to support the claim that they are optimal for Japanese patients as well. Also, in Study CV185030, there were only 10 Japanese subjects who received apixaban at 2.5 mg twice daily according to the dose reduction criteria. Thus, the available data were so small that not only the efficacy but also the safety of apixaban was not evaluated sufficiently. However, given the average life expectancy of Japanese and the increase in the frequency of atrial fibrillation with the advance in age, it is very likely that treatment with apixaban is considered for patients aged ≥80 years in Japan. Also, given the mean body weight of Japanese, it is highly likely that apixaban is administered to patients weighing <60 kg in Japan. These facts suggest that quite a few patients meet the dose reduction criteria in clinical practice in Japan. Since there are no evidences to recommend any alternative dose reduction criteria or any other reduced dose, it is appropriate currently to set the same dose reduction criteria as those employed in Study CV185030 which evaluated the efficacy and safety of apixaban. On the other hand, despite the fact that a high percentage of Japanese patients are expected to have background factors requiring dose reduction in clinical practice in Japan, there are no robust data that demonstrate the efficacy of apixaban 2.5 mg even in the entire study population. In addition, this reduced dosage regimen has scarcely been investigated in Japanese patients. Taking account of these facts, it is necessary to carefully determine the appropriateness of selecting apixaban in patients in whom apixaban 5 mg is considered to lead to an unacceptably high bleeding risk. It is critical to collect information on the efficacy and safety of patients treated with the reduced dose, if any, in the post-marketing surveillance, and it is very important to provide the obtained information to clinical practices in an appropriate manner.

Based on the conclusions described in Sections 4.(iii).B.(3).1) to 4.(iii).B.(3).6) above, PMDA considers it appropriate to select apixaban 5 mg twice daily as the dosage and administration. Also, it is acceptable currently to set the same criteria for dose reduction and the same reduced dosage regimen as those employed in Study CV185030, but relevant information should be

collected after the market launch. The dosage and administration and the description in the "Precautions for Dosage and Administration" section in the package insert (draft) should be changed as shown below.

[Dosage and Administration]
The usual adult dosage of apixaban is 5 mg administered orally twice daily.
The dose may be reduced to apixaban 2.5 mg twice daily depending on the age, body weight, and renal function of the patient.

[Precautions for Dosage and Administration]
Patients who meet at least 2 of the following criteria have a high risk of bleeding and may show an increased blood apixaban concentration. In these patients, apixaban should be administered orally at 2.5 mg twice daily.
- Age ≥80 years
- Body weight ≤60 kg
- Serum creatinine ≥1.5 mg/dL

The specific descriptions of the "DOSAGE AND ADMINISTRATION" section and "Precautions for Dosage and Administration" section related to dose reduction will be finalized, also taking account of comments raised in the Expert Discussion.

4.(iii).B.(4) Safety
4.(iii).B.(4).1) Bleeding
The applicant explained the risk of bleeding caused by apixaban, as follows:
No annual incidence rates of events were higher in the apixaban group than in the warfarin group for any of the bleeding events evaluated (major bleeding, major bleeding or CRNM bleeding, all bleeding) either in the entire population of Study CV185030 or in the Japanese subpopulation. Of events corresponding to major bleeding, intraocular haemorrhage showed a higher incidence rate in the apixaban group than in the warfarin group, while all other events showed lower incidence rates in the apixaban group than in the warfarin group. Intraocular bleeding occurred only in a very small percentage of patients in both groups (0.31% in the apixaban group and 0.21% in the warfarin group among the entire population of Study CV185030), and the incidence of such events was not significantly different between the 2 groups, which suggests that this was not an increase in an apixaban-specific bleeding event. The total incidence of bleeding-related adverse events was 25.2% in the apixaban group and 32.7% in the warfarin group in the entire study population, and 38.1% in the apixaban group and 51.4% in the warfarin group in the Japanese subpopulation. Bleeding events with an incidence of ≥2% in the apixaban group in the entire population of Study CV185030 were epistaxis (6.2% in the apixaban group, 7.5% in the warfarin group), contusion (3.3%, 5.3%), haematuria (3.7%, 4.5%), and haematoma (2.5%, 4.7%), all of which showed lower incidences in the apixaban group than in the warfarin group. Bleeding events with an incidence of ≥2% in the apixaban group in the Japanese subpopulation of Study CV185030 were epistaxis (8.8%, 15.4%), contusion (11.3%, 11.4%), haematuria (3.1%, 3.4%), haemorrhage subcutaneous (6.9%, 8.0%), conjunctival haemorrhage (5.0%, 4.0%), and occult blood positive (3.8%, 1.1%). Bleeding events with an incidence of ≥2% in the apixaban 2.5 or 5 mg group in Study CV185067 were epistaxis (5.6% in the apixaban 2.5 mg group, 5.6% in the apixaban 5 mg group, 5.3% in the warfarin group), blood urine present (1.4%, 4.2%, 5.3%), and haematuria (0.0%, 2.8%, 1.3%). These results showed that although a certain percentage of patients treated with apixaban experienced bleeding events predictable from administration of anticoagulant drugs, there were no noteworthy bleeding sites or findings, etc., unique to apixaban.

PMDA asked the applicant to investigate the patient background factors prone to bleeding events.

The applicant responded as follows:

In order to search for effects of a total of 21 background factors comprising intrinsic factors (age, sex, race, ethnicity, body weight, body mass index, severity of renal impairment, number of risk factors of stroke, status of other diseases and organ dysfunction) and extrinsic factors (region, dose of apixaban, a history of treatment with warfarin/VKA, presence or absence of aspirin or clopidogrel administration at randomization) on the between-group difference in 3 bleeding endpoints, i.e., major bleeding, major bleeding or CRNM bleeding, and all bleedings that occurred in Study CV185030, interactions between each background factor and treatment group were investigated. As a result, significant interactions ($P < 0.05$) were observed between major bleeding and severity of renal impairment and diabetes mellitus, between major bleeding or CRNM bleeding and region and diabetes mellitus, and between all bleedings and sex and presence or absence of clopidogrel administration at randomization. However, the point estimate of the hazard ratio of apixaban relative to warfarin regarding each bleeding endpoint was <1 in any of the subgroups classified by each of these background factors, and there were no background factors that consistently showed significant interactions with all of the above 3 bleeding endpoints. Based on these results, the applicant determined that no background factors prone to apixaban-induced bleeding events were identified from this investigation.

In addition, when the incidence rate of all bleeding events in the apixaban group was compared between subpopulations classified by patient background factor, the incidence rate of all bleedings increased in patients with the background factors "advanced age," "renal disorder," or "concomitant use with aspirin" compared with patients without the factor, but the extent of the increase was smaller compared with the extent observed in the warfarin group. Above results suggest that these populations are not particularly prone to apixaban-induced bleeding events compared with warfarin-induced bleeding events. However, by taking account of the possibility of higher risk compared with the patient population without these background factors, cautions will be provided in the "Precautions" section of the package insert (draft).

PMDA considers as follows:
In Study CV185030, the incidence of bleeding events was lower in the apixaban group than in the warfarin group. Therefore, bleeding risk of apixaban is clinically acceptable in patients with background factors within the range of those in subjects enrolled in Study CV185030. On the other hand, in order to examine whether or not sufficient cautions are provided against clinically significant bleedings possibly caused by apixaban, including those common to both apixaban and warfarin, the following reviews were conducted.

(a) Intracranial haemorrhage
In Study CV185030, the incidence rate and the incidence of intracranial haemorrhage were 0.33% per year and 52 of 9088 patients, respectively, in the apixaban group and 0.80% per year and 122 of 9052 patients, respectively, in the warfarin group in the entire study population, and 0% per year and 0 of 160 patients, respectively, in the apixaban group and 1.97% per year and 6 of 175 patients, respectively, in the warfarin group in the Japanese subpopulation. In Study CV185067, subarachnoid haemorrhage was reported by 1 patient in the warfarin group only.

Based on the above, PMDA considers as follows:
Since intracranial haemorrhage is a clinically relevant event, full attention is required against the occurrence during the treatment with apixaban. The incidence rate of intracranial haemorrhage in the apixaban group in the clinical study was not higher compared with that in the warfarin group. Therefore, the risk of apixaban-induced intracranial haemorrhage is clinically acceptable in anticoagulant therapy for patients with nonvalvular atrial fibrillation. However, apixaban should be supplied to clinical practices with consideration given to the facts that no sufficient number of Japanese patients were enrolled for thoroughly assessing the risk of intracranial haemorrhage in Study CV185030 and that, in routine clinical settings, there are patients with diverse backgrounds

not investigated in the clinical study, and information should be collected on the occurrence of intracranial haemorrhage after the market launch.

(b) Haemorrhage of digestive tract

The applicant explained the incidence of haemorrhage of digestive tract in Study CV185030, as follows:

The incidence of haemorrhage of digestive tract (upper gastrointestinal haemorrhage, lower gastrointestinal haemorrhage, rectal haemorrhage) in the apixaban group and in the warfarin group were 4.02% (365 of 9088 patients) and 4.28% (387 of 9052 patients), respectively, in the entire study population, and 4.38% (7 of 160 patients) and 3.43% (6 of 175 patients), respectively, in the Japanese subpopulation. Of these, the incidence of haemorrhage of digestive tract that met the criteria for major bleed in the apixaban group and in the warfarin group were 1.30% (118 of 9088 patients) and 1.44% (130 of 9052 patients), respectively, in the entire study population, and 1.25% (2 of 160 patients) and 3.43% (6 of 175 patients) in the Japanese subpopulation. As regards individual types of events, both occult blood positive and melena occurred in a larger (by ≥2 patients) number of patients in the apixaban group than in the warfarin group, both in the entire study population and in the Japanese subpopulation. The characteristics of subjects who experienced haemorrhage of digestive tract were investigated. Results showed that the percentage of subjects with renal impairment (severe or moderate), the percentage of subjects who were receiving aspirin or clopidogrel at randomization, and the percentage of subjects with a history of digestive tract disease were higher compared with those in the entire study population, but there were no significant differences between the treatment groups. As regards the timing of occurrence, "all bleedings" occurred frequently during the early period of administration both in the apixaban group and in the warfarin group, whereas no specific high frequency period was noted for "major bleeding" and "major bleeding or CRNM bleeding." Based on the above, the applicant considers that the risk of minor bleeding is slightly higher during the early stage of apixaban administration, but that there are no additional cautions required against haemorrhage of digestive tract.

PMDA considers the risk of haemorrhage of digestive tract during apixaban administration, as follows:

In Study CV185030, apixaban was not particularly prone to induce haemorrhage of digestive tract compared to warfarin. However, haemorrhage of digestive tract occurred in the apixaban group both in the entire study population and in the Japanese subpopulation, indicating that it is an important event requiring caution, all the same. In Study CV185067, the incidence of haemorrhage-related adverse event gastrointestinal disorder was 1.3% (1 of 75 patients) in the warfarin group, 2.8% (2 of 72 patients) in the apixaban 2.5 mg twice daily group, and 5.6% (4 of 71 patients) in the apixaban 5 mg twice daily group. In order to detect haemorrhage of digestive tract at an early stage and take appropriate measures, awareness of the healthcare professionals, including patient education, and appropriate tests are important. For this purpose, it is necessary to provide caution against haemorrhage of digestive tract during apixaban administration. Also, information on the occurrence of haemorrhage of digestive tract should be collected after the market launch.

(c) Intraocular haemorrhage

PMDA, by taking account of the fact that the incidence of intraocular haemorrhage, among major bleeding that occurred in Study CV185030, was higher in the apixaban group (0.31% [28 of 9088 patients]) than in the warfarin group (0.21% [19 of 9052 patients]), instructed the applicant to investigate the possibility that intraocular haemorrhage is an adverse reaction characteristic to apixaban administration.

The applicant responded as follows:

No intraocular haemorrhage was reported in Study CV185067. In Study CV185030, intraocular haemorrhage occurred in 49 patients in the apixaban group and in 63 patients in the warfarin

group (2 patients and 3 patients, respectively, in the Japanese subpopulation). Intraocular haemorrhage classified as major bleeding was observed in 32 patients in the apixaban group and in 22 patients in the warfarin group (2 patients and 1 patient, respectively, in the Japanese subpopulation). Events reported by ≥4 patients in either group were diabetic retinopathy with bleeding (6 patients in the apixaban group, 4 patients in the warfarin group), vitreous haemorrhage of unknown cause (4 patients, 4 patients), and retinal detachment or retinal tear (4 patients, 1 patient). There were no between-group differences in patient backgrounds that could have affected the incidence of intraocular haemorrhage. Also, the incidence of intraocular haemorrhage classified as major bleeding was low. Based on these results, the applicant considers that there is no clear relationship between intraocular haemorrhage and the pharmacological action of apixaban, and that apixaban does not increase the occurrence of intraocular haemorrhage compared with warfarin.

PMDA considers that currently there are no data that strongly suggest that intraocular haemorrhage is a risk unique to apixaban. However, given that the study was not conducted in a sufficiently large number of Japanese patients and that intraocular haemorrhage is a clinically relevant event, information on the occurrence of intraocular haemorrhage should be collected as part of the activity of collecting bleeding-related information via post-marketing surveillance.

Based also on the conclusions (a) to (c) above, PMDA considers the risk of bleeding-related adverse events during apixaban administration, as follows:
From the incidence of major bleeding or CRNM bleeding and individual bleeding events in Study CV185030, the risk of clinically significant bleeding was not greater in the apixaban group than in the warfarin group. However, attention should be paid to the presence of apixaban-inducible bleeding risk per se. Patients treated with apixaban should be followed up at an appropriate frequency. At each return visit, patients should be checked for the occurrence of various bleeding symptoms, and periodical medical examination and blood tests should be performed to check for signs suggestive of anemia or bleeding and for renal function, etc., thereby to detect bleeding events. If a bleeding event is observed, prompt measures such as discontinuation of apixaban should be taken. As for controlling the bleeding risk during apixaban administration, due caution should be paid to the facts that there is no appropriate markers for monitoring the efficacy of apixaban and that there is no drug that neutralizes the anticoagulant effect of apixaban. In providing apixaban for use in clinical practice, it is essential to thoroughly inform physicians of these facts as well as the necessity of paying attention to bleeding risk during apixaban administration, as is the case with administration of similar drugs including warfarin. In the couse of the review, the applicant proposed to provide caution on bleeding in the "WARNINGS" section, as is the case with similar drugs. However, taking account of the above discussion, it is necessary to provide a more detailed caution statement on bleeding risk, in addition to the caution statement in the "WARNINGS" section. As for factors that increase or decrease apixaban-induced bleeding risk, since clinical studies have so far been conducted in patients with a limited range of backgrounds, such factors should be continuously investigated after the market launch, including the collection of information on indices that reflect the efficacy or bleeding risk of apixaban. Appropriateness of a caution statement against apixaban-induced bleeding risk will be finalized together with the issues to be discussed later, i.e., the caution statement for special populations and for concomitant use with antiplatelet drugs as well as the points to consider in switching drugs, also taking account of comments raised in the Expert Discussion.

4.(iii).B.(4).2) Administration in patients with renal impairment

In Study CV185030, the results of safety related to the efficacy events and bleeding events in patients classified by the severity of renal impairment, assessed by estimated CL_{CR}, (severe, ≤30 mL/min; moderate, >30 mL/min and ≤50 mL/min; mild, >50 mL/min and ≤80 mL/min; normal, >80 mL/min) were as shown in Table 26.

Table 26. Incidence rates of primary efficacy endpoint and safety endpoints in patients classified by the severity of renal impairment in Study CV185030 (Adapted from submitted data)

	Entire study population		Japanese subpopulation	
	Apixaban group	Warfarin group	Apixaban group	Warfarin group
Primary efficacy endpoint	N = 9120	N = 9081	N = 161	N = 175
Severe	2.79 (6/137)	5.06 (10/133)	0.00 (0/4)	0.00 (0/4)
Moderate	2.05 (48/1365)	2.47 (59/1382)	0.00 (0/37)	5.60 (4/40)
Mild	1.24 (87/3817)	1.69 (116/3770)	1.69 (3/85)	0.93 (2/101)
Normal	0.99 (70/3761)	1.12 (79/3757)	0.00 (0/35)	0.00 (0/30)
Safety endpoints	N = 9088	N = 9052	N = 160	N = 175
Major bleeding				
Severe	3.75 (7/136)	11.94 (19/132)	0.00 (0/4)	25.79 (2/4)
Moderate	3.16 (66/1357)	6.01 (123/1380)	1.35 (1/37)	11.94 (6/40)
Mild	2.45 (157/3807)	3.21 (199/3758)	1.25 (2/85)	4.16 (8/101)
Normal	1.46 (96/3750)	1.84 (119/3746)	1.33 (1/34)	3.96 (2/30)
Major bleeding or CRNM bleeding				
Severe	5.39 (10/136)	16.75 (26/132)	0.00 (0/4)	25.79 (2/4)
Moderate	5.52 (113/1357)	9.17 (185/1380)	1.35 (1/37)	16.34 (8/40)
Mild	4.47 (281/3807)	6.31 (381/3758)	2.54 (4/85)	5.40 (10/101)
Normal	3.18 (206/3750)	4.46 (282/3746)	1.33 (1/34)	5.94 (3/30)
All bleedings				
Severe	36.23 (48/136)	47.29 (57/132)	47.59 (2/4)	32.12 (2/4)
Moderate	23.51 (405/1357)	34.16 (546/1380)	19.34 (11/37)	63.10 (22/40)
Mild	18.97 (1025/3807)	26.97 (1313/3758)	20.86 (26/85)	36.37 (46/101)
Normal	15.22 (870/3750)	21.66 (1130/3746)	20.81 (12/34)	32.64 (12/30)

%/year (n/N)

In Study CV185030 which excluded patients with serum creatinine level of >2.5 mg/dL or patients with calculated CL_{CR} of <25 mL/min, the incidences of "major bleeding," "major bleeding or CRNM bleeding," and "all bleedings" tended to increase with the decrease in the renal function according to the classification by the severity of renal impairment. Taking account of these observations, PMDA asked the applicant to further explain the appropriateness of just providing a caution statement that apixaban is not recommended in "patients with serious renal disorder with creatinine clearance of <15 mL/min and patients on hemodialysis," instead of contraindicating the drug in this patient group, and the appropriateness of the caution statement for patients with renal impairment.

The applicant responded as follows:
Since Study CV185030 excluded patients with CL_{CR} of <25 mL/min, there are only limited use experience in patients with nonvalvular atrial fibrillation who have serious renal impairment (CL_{CR} ≤30 mL/min). Decreased kidney function per se is a factor that potentially increases bleeding risk, and plasma apixaban concentration after dosing of apixaban tends to increase with the decrease in renal function (results of the clinical pharmacology study in patients with renal impairment [Study CV185018] and of PPK analysis). Therefore, the applicant considers it appropriate to raise caution in the "Careful Administration" section for patients with severe renal impairment with CL_{CR} of ≥15 mL/min and <30 mL/min. For patients with renal failure with CL_{CR} of <15 mL/min, it will be appropriate to contraindicate apixaban because of the lack of use experience in such patients with nonvalvular atrial fibrillation.

PMDA considers as follows:
Attention should be paid to the fact that, in patients with renal impairment, not only plasma apixaban concentration increases, but also bleeding risk may generally increase. In Study

CV185030, there was no clear tendency of increase in bleeding risk in the apixaban group compared with the warfarin group in any subpopulation of renal impairment, although data were obtained from a narrow range of patient populations because of the limited number of patients with renal impairment enrolled in clinical studies of apixaban. Therefore, the bleeding risk of apixaban in the pertinent patient population is considered clinically acceptable. On the other hand, in Study CV185030 in which dose reduction was required in patients with serum creatinine of ≥1.5 mg/dL, bleeding risk was higher in patients with renal impairment than in patients with normal renal function. Therefore, the appropriateness of treatment with apixaban for patients with renal impairment should be carefully considered and, if deemed appropriate, apixaban should be administered with caution. Based on the above, and by also taking account of the submitted study data, it is appropriate that the applicant required careful administration in patients with severe renal impairment with CL_{CR} of ≥15 mL/min and <30 mL/min. Careful administration is necessary in patients with moderate renal impairment as well in light of the observations that the incidence rate of bleeding events is higher compared with patients with normal renal function or mild renal impairment or with the entire study population, and that plasma apixaban concentration tends to increase with the decrease in renal function. Also, the measure taken by the aplichat that apixaban should be contraindicated in patients with severe renal impairment with CL_{CR} <15 mL/min is appropriate. In the post-marketing surveillance, information on the efficacy and safety of apixaban in Japanese patients with renal impairment should also be collected including the use status and administered dose, taking account of the fact that only a limited number of Japanese patients with renal impairment were enrolled in clinical studies. An appropriate caution statement for patients with renal impairment will be finalized, also taking account of comments raised in the Expert Discussion.

4.(iii).B.(4).3) Administration in patients with low body weight

Incidence of bleeding events in patients classified by body weight (≤50 kg, >50 kg) in Study CV185030 were as shown in Table 27.

Table 27. Incidence rates of bleeding events by body weight in Study CV185030: Study drug population (Adapted from submitted data)

	Entire study population		Japanese subpopulation	
	Apixaban group	Warfarin group	Apixaban group	Warfarin group
Major bleeding				
All patients	2.13 (327/9088)	3.09 (462/9052)	1.26 (4/160)	5.99 (18/175)
≤50 kg	3.22 (13/271)	3.77 (13/239)	3.51 (1/14)	3.24 (1/16)
>50 kg	2.11 (313/8785)	3.07 (447/8785)	1.04 (3/146)	6.30 (17/159)
Major bleeding or CRNM bleeding				
All patients	4.07 (613/9088)	6.01 (877/9052)	1.90 (6/160)	7.86 (23/175)
≤50 kg	3.73 (15/271)	7.00 (24/239)	3.51 (1/14)	6.48 (2/16)
>50 kg	4.07 (595/8785)	5.98 (850/8785)	1.74 (5/146)	8.03 (21/159)
All bleedings				
All patients	18.08 (2356/9088)	25.82 (3060/9052)	20.95 (51/160)	40.13 (82/175)
≤50 kg	18.27 (63/271)	29.35 (81/239)	23.06 (5/14)	42.08 (9/16)
>50 kg	18.10 (2287/8785)	25.72 (2967/8785)	20.75 (46/146)	39.90 (73/159)

%/year (n/N)

The applicant explained the control of bleeding risk in administration of apixaban to patients with low body weight, as follows:

In the entire study population, the incidence rates for each category of bleeding events (major bleeding, major bleeding or CRNM bleeding, all bleedings) were lower in the apixaban group than in the warfarin group in all body weight subpopulations. The Japanese subpopulation showed no significant difference from the entire study group in the incidence rate of all bleedings,

suggesting that the results in the Japanese subpopulation are consistent with those in the entire study population. Therefore, it suffices to set the dose reduction criteria, even if consideration is given to the possibility that there are many low-body-weight Japanese patients treated with apixaban.

PMDA considers as follows:
In Study CV185030 which required dose reduction in patients with body weight ≤60 kg, the incidence of major bleeding in the apixaban group in the entire study population was higher in the subpopulation with body weight ≤50 kg than in the subpopulation with body weight >50 kg. In the Japanese subpopulation, the incidences of major bleeding, major bleeding or CRNM bleeding, and all bleedings all tended to be higher in the subpopulation with body weight ≤50 kg than in the subpopulation with body weight >50 kg, although the data were obtained from only an extremely limited number of patients. The body weight (mean ± SD) of patients in the apixaban group was 83.93 ± 20.779 kg in the entire population of Study CV185030, but 64.71 ± 11.634 kg in the Japanese subpopulation. In Study CV185030, the percentage of subjects weighing ≤50 kg was very small (as small as approximately 3%) in the apixaban group. Since it is likely that the percentage of patients with body weight ≤50 kg is higher in routine clinical settings in Japan than in Study CV185030, due caution should be paid to the tendency of higher bleeding risk in patients with low body weight. Based on the above, the "Careful Administration" section of the package insert should include patients with low body weight. Also, since only limited information is available on the efficacy and safety of apixaban in patients with low body weight, relevant information should be thoroughly collected via post-marketing surveillance.

4.(iii).B.(4).4) Use in the elderly
The incidences of adverse events in patients classified by age group in Study CV185030 were as shown in Table 28.

Table 28. Incidences of adverse events in Study CV185030 (classified by age group): Study drug population (Adapted from submitted data)

	Apixaban group			Warfarin group		
	<65 years of age	≥65 and <75 years of age	≥75 years of age	<65 years of age	≥65 and <75 years of age	≥75 years of age
Bleeding-related (%/year)						
Entire study population	N = 2723	N = 3529	N = 2836	N = 2732	N = 3501	N = 2819
Major bleeding	1.17	1.99	3.33	1.51	2.82	5.19
Major bleeding or CRNM bleeding	2.59	3.94	5.81	3.82	5.57	9.04
All bleedings	13.57	17.94	23.45	19.07	25.92	33.65
Japanese subpopulation	N = 41	N = 66	N = 53	N = 44	N = 71	N = 60
Major bleeding	1.12	0.79	1.96	2.31	4.94	10.82
Major bleeding or CRNM bleeding	1.12	1.58	2.99	2.31	6.74	14.92
All bleedings	17.21	19.05	27.67	29.44	48.62	39.72
Serious adverse events (%)						
Entire study population	29.6	34.5	40.9	29.7	36.1	43.5
Japanese subpopulation	24.4	28.8	41.5	15.9	36.6	45.0
Adverse events occurring in ≥10% of patients aged ≥75 years in either group (%)						
Entire study population	N = 2723	N = 3529	N = 2836	N = 2732	N = 3501	N = 2819
Nasopharyngitis	8.3	8.8	8.0	8.5	8.8	8.5
Contusion	1.8	3.0	5.1	4.2	4.5	7.3
Oedema peripheral	5.1	6.3	8.7	5.0	7.0	10.0
Constipation	1.2	1.8	3.8	1.6	2.4	3.4
Haemorrhage subcutaneous	0.1	<0.1	0.2	0.1	0.4	0.3
Back pain	4.0	5.1	5.1	5.1	5.9	5.7
Epistaxis	4.8	6.1	7.5	6.5	8.1	7.9
Diarrhoea	5.3	6.1	8.0	5.0	6.1	8.3
Japanese subpopulation	N = 41	N = 66	N = 53	N = 44	N = 71	N = 60
Nasopharyngitis	43.9	57.6	54.7	45.5	53.5	33.3
Contusion	2.4	6.1	24.5	11.4	8.5	15.0
Oedema peripheral	2.4	0.0	15.1	2.3	5.6	11.7
Constipation	0.0	10.6	13.2	9.1	9.9	5.0
Haemorrhage subcutaneous	9.8	1.5	11.3	2.3	11.3	8.3
Back pain	9.8	15.2	9.4	6.8	11.3	16.7
Epistaxis	9.8	7.6	9.4	15.9	16.9	13.3
Diarrhoea	9.8	10.6	5.7	11.4	11.3	10.0

The applicant explained as follows:
The annual incidence rates of bleeding events were lower in the apixaban group than in the warfarin group in all age groups and for all bleeding parameters. In the Japanese subpopulation, the results were consistent with those observed in the entire study population; the incidence rates were lower in the apixaban group than in the warfarin group. None of the observed adverse events or serious adverse events in the elderly population was specific to the apixaban group, and there were no specific events requiring caution in treatment with apixaban for elderly patients. Based on the above, the package insert (draft) will not recommend careful administration in elderly patients, and include the description "Elderly patients often have reduced renal function and blood apixaban concentrations may increase. Especially, if patients are aged ≥80 years, dose reduction should be carefully considered for those with decreased renal function (serum creatinine ≥1.5 mg/dL) and low body weight (≤60 kg)" in the "Use in the Elderly" section.

PMDA considers as follows:
Results of Study CV185030 did not suggest any increased bleeding risk in elderly patients in the apixaban group compared with those in the warfarin group. Therefore, apixaban may be

administered to elderly patients provided that due attention is paid to safety. On the other hand, the incidence rates of major bleeding, major bleeding or CRNM bleeding, and all bleedings all tended to be higher in the subpopulation of ≥75 years in the apixaban group than in the subpopulation of <75 years, and this tendency was consistent between the entire study population and the Japanese subpopulation, which requires attention. Also, it is clinically important that the incidence rate of major bleeding increases particularly in patients aged ≥75 years. Therefore, attention should be paid to the possibility that bleeding risk is further higher in elderly patients than in non-elderly patients. The appropriateness of treatment with apixaban should be considered by also taking account of factors other than age in individual patients and, when apixaban is administered, patients should be followed up while paying attention to possible bleeding events. Since elderly patients often have reduced renal function, such patients should be monitored for renal function at an appropriate frequency before and during apixaban administration. The applicant claims that, for elderly patients, it suffices to provide only a caution statement to the effect that the dose reduction of apixaban should be considered in patients who are ≥80 years of age and who meet certain criteria for body weight or renal function. However, results of clinical studies have shown that elderly patients have an elevated bleeding risk, and it is therefore inappropriate to provide a caution statement in the "Use in the Elderly" section alone, as proposed by the applicant. Based on the above, careful administration should be required in all elderly patients, instead of only patients aged ≥80 years. Elderly patients aged ≥75 years account for approximately 30% of patients enrolled in clinical studies conducted so far, and an even smaller number of patients in this age group were studied for the Japanese subpopulation. Since it is expected that, in clinical practice, elderly patients with more diverse treatment conditions and complications than those of patients enrolled in clinical studies are treated with apixaban, information should be adequately collected via post-marketing surveillance.

4.(iii).B.(4).5) Concomitant use with antiplatelet drug(s)

The applicant explained the safety in concomitant use of apixaban with antiplatelet drug(s), as follows:

In Study CV185030, the percentage of patients who used aspirin during the period of treatment with the study drug was 31.7% (2883 of 9088 patients) in the apixaban group and 30.3% (2746 of 9052 patients) in the warfarin group. Incidences of bleeding events in patients classified by concomitant use with aspirin in Study CV185030 were as shown in Table 29.

Table 29. Incidence rates of bleeding endpoints in Study CV185030 (classified by concomitant use with aspirin): Study drug population (Adapted from submitted data)

	Apixaban group		Warfarin group	
	With aspirin %/year (n/N*)	Without aspirin %/year (n/N**)	With aspirin %/year (n/N*)	Without aspirin %/year (n/N**)
Major bleeding	3.42 (112/3521)	1.78 (215/7345)	4.59 (140/3417)	2.70 (322/7342)
Major bleeding or CRNM bleeding	5.83 (187/3511)	3.58 (426/7334)	8.02 (238/3406)	5.48 (639/7333)
All bleedings	23.46 (637/3457)	16.60 (1719/7259)	35.14 (805/3349)	23.53 (2255/7232)

n/N*: "Number of subjects who experienced the first occurrence of each bleeding event during concomitant use with aspirin or by 2 days after the last dose of aspirin" / "number of subjects receiving concomitant use with aspirin during the period from the start of treatment with the study drug up to the first occurrence of each bleeding event, or up to 2 days after the last dose of the study drug"

n/N**: "Number of subjects who did not use aspirin at the first occurrence of each bleeding event" / "number of subjects who had a period in which they did not use aspirin during the period from the start of treatment with the study drug up to the first occurrence of each bleeding event, or up to 2 days after the last dose of the study drug"

In the Japanese subpopulation, the percentage of subjects who used aspirin during the period of treatment with the study drug was 28.8% (46 of 160 patients) in the apixaban group and 28.0% (49 of 175 patients) in the warfarin group. Incidences of bleeding events in patients classified by concomitant use with aspirin were as shown in Table 30.

Table 30. Incidence rates of bleeding endpoints in Japanese subpopulation of Study CV185030 (classified by concomitant use with aspirin): Study drug population (Adapted from submitted data)

	Apixaban group		Warfarin group	
	With aspirin %/year (n/N*)	Without aspirin %/year (n/N**)	With aspirin %/year (n/N*)	Without aspirin %/year (n/N**)
Major bleeding	1.33 (1/48)	1.24 (3/131)	8.98 (6/53)	5.13 (12/139)
Major bleeding or CRNM bleeding	1.33 (1/48)	2.08 (5/131)	12.31 (8/53)	6.59 (15/139)
All bleedings	35.74 (18/48)	17.10 (33/125)	47.39 (22/52)	37.99 (60/136)

n/N*: "Number of subjects who experienced the first occurrence of each bleeding event during concomitant use with aspirin or by 2 days after the last dose of aspirin" / "number of subjects receiving concomitant use with aspirin during the period from the start of treatment with the study drug up to the first occurrence of each bleeding event or up to 2 days after the last dose of the study drug"

n/N**: "Number of subjects who did not use aspirin at the first occurrence of each bleeding event" / "number of subjects who had a period in which they did not use aspirin during the period from the start of treatment with the study drug up to the first occurrence of each bleeding event, or up to 2 days after the last dose of the study drug"

Use of thienopyridines was prohibited at the time of enrolment in the study, but permitted during the study period if deemed necessary by the investigator because of acute coronary syndromes or percutaneous coronary intervention (PCI), etc. Concomitant use of aspirin + thienopyridine drug + study drug was given to 2.3% (211 of 9088 patients) in the apixaban group and 1.9% (170 of 9052 patients) in the warfarin group.

Incidences of bleeding events in patients classified by concomitant use with antiplatelet drug in Study CV185030 were as shown in Table 31.

Table 31. Incidence rates of bleeding endpoints in Study CV185030 (by concomitant use of aspirin + thienopyridine drug): Study drug population (Adapted from submitted data)

	Apixaban group		Warfarin group	
	With aspirin + thienopyridine drug %/year (n/N*)	Without aspirin + thienopyridine drug %/year (n/N**)	With aspirin + thienopyridine drug %/year (n/N*)	Without aspirin + thienopyridine drug %/year (n/N**)
Major bleeding	7.53 (4/208)	2.11 (323/9084)	20.80 (8/165)	3.04 (454/9043)
Major bleeding or CRNM bleeding	7.70 (4/204)	4.04 (609/9084)	20.91 (8/161)	5.96 (869/9043)
All bleedings	53.63 (21/178)	17.92 (2335/9083)	91.31 (23/143)	25.63 (3037/9042)

n/N*: "Number of subjects who experienced the first occurrence of each bleeding event during concomitant use with aspirin and thienopyridine drug, or by 2 days after the last dose of concomitant use with aspirin or thienopyridine drug" / "number of subjects receiving concomitant use of aspirin and thienopyridine drug during the period from the start of treatment with the study drug up to the first occurrence of each bleeding event, or up to 2 days after the last dose of the study drug"

n/N**: "Number of subjects who did not use aspirin and/or thienopyridine drug at the first occurrence of each bleeding event" / "number of subjects who had a period in which they did not use aspirin and/or thienopyridine drug during the period from the start of treatment with the study drug up to the first occurrence of each bleeding event, or up to 2 days after the last dose of the study drug"

In the Japanese subpopulation, there was concomitant use with 2 antiplatelet drugs in 1 patient in the apixaban group and 2 patients in the warfarin group, but neither major bleeding nor CRNM bleeding occurred in these patients during the period of combination therapy. The patient in the apixaban group underwent PCI after the start of concomitant use with 2 antiplatelet drugs and, during the period of combination therapy, experienced mild haematuria.

In the population receiving concomitant use with antiplatelet drugs, the incidence rates of bleeding endpoints were all lower in the apixaban group than in the warfarin group. However,

since the bleeding risk was higher in the population with combination therapy compared with the population without combination therapy, the applicant considered that caution statements related to bleedings should be included in "Important Precautions" and "Precautions for Concomitant Use" sections of the package insert (draft).

PMDA considers the safety in concomitant use of apixaban with antiplatelet drugs as follows:
Many of patients with nonvalvular atrial fibrillation are elderly and/or complicated with coronary artery disorders. Therefore, concomitant use of apixaban with 2 antiplatelet drugs, e.g., aspirin + thienopyridine drug, is conceivable. In Study CV185030, none of the patients receiving concomitant use with these 2 antiplatelet drugs were included, and there were only an extremely limited number of Japanese subjects, thus precluding sufficient evaluation of safety in concomitant use of apixaban with antiplatelet drugs. However, as far as the limited data available from the study are concerned, an increased risk of bleeding events in concomitant use with antiplatelet drug was suggested, warranting caution against bleeding in such combination therapy. Furthermore, since it was suggested that the incidence of bleeding events increased markedly when apixaban was concomitantly administered with aspirin and thienopyridine, in patients requiring concomitant use with these drugs, the appropriateness of treatment with apixaban should be evaluated even more carefully than in patients receiving aspirin alone. The incidence of bleeding events was increased by concomitant use with antiplatelet drugs in the warfarin group as well. Thus, there was no tendency of any clear increase in bleeding risk in the apixaban group by concomitant use with antiplatelet drugs compared with the warfarin group. In the clinical study in patients with acute coronary syndromes, many patients might have received apixaban in addition to 2 antiplatelet drugs, but the study was discontinued for safety reasons [see "4.(iii).B.(4).6) Clinical study in patients with acute coronary syndrome which was discontinued for safety reasons"]. Based on the above, particular caution should be exercised against bleeding risk in concomitant use of apixaban with antiplatelet drugs such as aspirin, and that concomitant use of apixaban with antiplatelet drugs should be done only to patients for whom the benefit of the concomitant use clearly outweighs the risk. In clinical studies, only a small number of patients received concomitant use of apixaban with antiplatelet drugs. Therefore, in the post-marketing surveillance, information should be adequately collected on patients receiving concomitant use of apixaban with antiplatelet drugs, if any, and should be reflected to risk control in a timely manner. When PCI is performed, it is plausible that apixaban is concomitantly administered with 2 antiplatelet drugs. It is necessary to provide sufficient caution requiring that the safety of such combination therapy be evaluated more carefully than when apixaban is concomitantly administered with 1 antiplatelet drug. Collecting information on such cases after the market launch is also important. Details of a caution statement related to concomitant use with antiplatelet drugs in the package insert will be finalized, also taking account of comments raised in the Expert Discussion.

4.(iii).B.(4).6) Clinical study in patients with acute coronary syndrome which was discontinued for safety reasons

The applicant explained the the reason for the premature termination of the global phase III study in patients with acute coronary syndrome (Study CV185068), as follows:
In Study CV185068, apixaban or placebo was administered to patients with acute coronary syndrome within 7 days after onset. Patients who showed stable clinical conditions after parenteral anticoagulant therapy for acute coronary syndrome event within 7 days after onset, and were receiving the standard treatment for acute coronary syndrome including antiplatelet therapy (monotherapy [aspirin or $P2Y_{12}$ antagonist] or 2-drug therapy [aspirin + $P2Y_{12}$ antagonist]) at the discretion of the attending physician were enrolled in the study. The target sample size had been set at 10,800. However, on November 14, 2010 when 7392 patients were randomized, an increase in the occurrence of clinically significant bleeding was observed in the apixaban group, whereupon the independent data monitoring committee advised the premature termination of the study and, as a result, Study CV185068 was terminated. The incidence of major bleeding or

CRNM bleeding was 3.19% (117 of 3672 patients) in the apixaban group and 1.24% (45 of 3643 patients) in the placebo group.

PMDA, by taking account of the fact that the dosage and administration of apixaban in Study CV185068 was 5 mg twice daily, which was the same as the usual dosage and administration proposed in the application, asked the applicant to investigate whether or not a similar risk as observed in Study CV185068 would occur in patients with nonvalvular atrial fibrillation when treated with apixaban.

The applicant responded as follows:
Usefulness of warfarin for prophylaxis of cerebral embolism and systemic embolism in patients with atrial fibrillation has been established. On the other hand, in patients with acute coronary syndrome, administration of antiplatelet drugs is recommended to prevent the reocclusion and restenosis after reperfusion therapy by "Guidelines for Management of Acute Coronary Syndrome without Persistent ST Segment Elevation (JCS 2007)" (2006 report of Joint Working Group) and by "Guidelines for the management of patients with ST-elevation myocardial infarction (JCS 2008)" (*Circ J.* 2008;72 Suppl IV:1347-443). Against these backgrounds, the following inclusion criteria were set in 2 clinical studies in patients with acute coronary syndromes (Studies CV185068 and CV185070). Thus, subjects experienced acute coronary syndrome within the past 7 days, had at least 2 of the risk factors (e.g., ≥65 year, diabetes mellitus, a history of myocardial infarction, ischemic cerebrovascular disease, peripheral vascular disease, cardiac failure or left ventricular contraction fraction <40%, renal impairment, nonrevascularized), and were receiving the standard treatment (aspirin monotherapy or 2-drug therapy of aspirin + thienopyridine drug). Therefore, the majority of enrolled patients (81% in Study CV185068 and 97% in Study CV185070 at the time of enrollment) were receiving aspirin + thienopyridine. In contrast, in Study CV185030, patients receiving aspirin + thienopyridine were excluded from the study in accordance with the exclusion criteria. If, after the start of treatment with the study drug, concomitant use with 2 antiplatelet drugs was required, whether or not they should be given was decided by the attending physician by assessing the risk and benefit for each patient. In Studies CV185068 and CV185070, since high risk patients with ≥2 of the above risks were enrolled as described above, the subjects in these studies were likely to have had a potentially high bleeding risk such as advanced arteriosclerosis compared with the subjects in Study CV185030. As regards the study design, an important difference is that whereas placebo was used as the comparator in studies in patients with acute coronary syndrome, warfarin was used as the comparator in studies in patients with atrial fibrillation. Thus, both study design and treatment strategy are different between the studies in patients with atrial fibrillation and those in patients with acute coronary syndrome. Therefore, the applicant considers that it is more appropriate to assess the risk and benefit of apixaban based on the results obtained from studies in patients with atrial fibrillation.

PMDA considers as follow:
It is important that the findings on safety obtained from studies that were discontinued because of concerns about the safety of apixaban be appropriately reflected in order to ensure the safety of target patients proposed in the application, despite the difference from the patient population investigated in the discontinued studies. In routine clinical settings, antiplatelet drugs may possibly be used in patients with nonvalvular atrial fibrillation, the target patients proposed in the application, and results of clinical studies have shown that bleeding risk increases when they are concomitantly administered with apixaban [see "4.(iii).B.(4).5) Concomitant use with antiplatelet drugs"]. Therefore, given the risk of bleeding, it is not recommendable to administer apixaban to patients complicated with acute coronary syndrome or to concomitantly administer apixaban with 2 antiplatelet drugs. In individual cases where such combination therapy is required, the appropriateness of treatment with apixaban should be carefully evaluated by thoroughly weighing the balance of risk and benefit. Thus, it is necessary to provide an appropriate caution statement related to the increased bleeding risk in concomitant use of apixaban with 2 antiplatelet drugs.

Specific details will be finalized, also taking account of comments raised in the Expert Discussion.

4.(iii).B.(4).7) Switching from warfarin to apixaban

The applicant explained the switching from warfarin to apixaban as follows:

In Study CV185030, subjects who had been using warfarin before randomization were to discontinue or reduce warfarin dose before randomization and to receive the study drug after PT-INR decreased to below 2.0. Among subjects who switched from warfarin to the study drug in the entire study population, efficacy events occurred during the period from the start of treatment with the study drug up to 7 days after administration in 2 of 4451 patients in the apixaban group and in 1 of 4467 patients in the warfarin group. There were no corresponding subjects in the Japanese subpopulation. In subjects of the entire study population who switched from warfarin to the study drug, the incidence rate (its corresponding incidence) of bleeding events that occurred during the period from the start of the treatment with the study drug up to 7 days after administration was 4.72% per year (4 of 4443 patients) in the apixaban group and 1.18% per year (1 of 4457 patients) in the warfarin group for major bleeding, 9.45% per year (8 of 4443 patients) in the apixaban group and 5.88% per year (5 of 4457 patients) in the warfarin group for major bleeding or CRNM bleeding, and 80.72% per year (68 of 4443 patients) in the apixaban group and 48.34% per year (41 of 4457 patients) in the warfarin group for all bleedings. Thus, the incidence rates of major bleeding, major bleeding or CRNM bleeding, and all bleedings were all higher in the apixaban group compared with the warfarin group. In the Japanese subpopulation, neither major bleeding nor major bleeding or CRNM bleeding was observed, but all bleedings were observed in 4 of 131 patients in the apixaban group and in 2 of 133 patients in the warfarin group. In Study CV185030, patients in both apixaban group and warfarin group discontinued or reduced warfarin dose and started receiving the study drug after PT-INR decreased to below 2.0. Therefore, the incidence rate of bleeding events may be higher in the apixaban group because sufficient anticoagulant condition was achieved more rapidly by apixaban than by warfarin. However, the risk of bleeding events observed in subjects with a history of treatment with warfarin during the early period of study treatment (within 3 months) was lower in the apixaban group than in the warfarin group, suggesting that the risk is acceptable. Switching from warfarin to apixaban had no undesirable effect from the point of view of either efficacy or safety, which shows that the switching from warfarin to apixaban as specified in Study CV185030 is a safe switching. Based on the above clinical study data, the applicant considers that switching from warfarin to apixaban will provide benefits outweighing risk relatively promptly, provided that apixaban is administered when PT-INR has decreased to below 2.0 after discontinuation of warfarin, according to the rule stipulated in Study CV185030. Therefore, the following description should be included in the "Important Precaution" section of the package insert (draft): "In switching from vitamin K antagonist (warfarin) to apixaban, administration of apixaban should be started when INR has decreased to below 2.0 after discontinuation of vitamin K antagonist."

PMDA considers as follows:

Switching from warfarin to apixaban carries two considerable disadvantages, i.e., the risk of bleeding due to excessive enhancement of anticoagulant effect and the risk of thromboembolism due to insufficiency in anticoagulant effect. Therefore, it is critical to provide information on the specific method for the switching in the package insert. In both Studies CV185067 and CV185030, administration of apixaban was started when PT-INR decreased to below 2.0 and no other switching methods were investigated. Therefore, although it should be kept in mind that the incidence of bleeding events from the start of the treatment with the study drug up to 7 days after administration in Study CV185030 was higher in patients who switched from warfarin to apixaban than in patients who continued to be treated with warfarin, currently there is no other choice but to employ the method which was used in Study CV185030 and for which efficacy and safety information is available. Specific details, etc., of the wording for the switching from warfarin to apixaban in the package insert will be finalized, also taking account of comments

raised in the Expert Discussion. Information on the previous treatment and on the timing of switching from warfarin to apixaban should be collected via post-marketing surveillance. Also, the method of switching from warfarin to apixaban as well as the efficacy and safety in patients after the switching should be evaluated in an appropriate manner.

4.(iii).B.(4).8) Switching from apixaban to warfarin

The applicant explained the switching from apixaban to warfarin as follows:
In Study CV185030, it was recommended that apixaban be switched to open-label warfarin according to the following method. By counting the visit day for the last dose as Day 1 of switching, warfarin (or VKA) was to be administered under open-label conditions in the afternoon of Days 1 to 3 of switching, 1 apixaban tablet was to be administered under blinded conditions in the afternoon of Days 1 and 2 of switching and in the morning of Days 2 and 3 of switching, and PT-INR was to be measured under open-label conditions on Day 3 or 4 of switching, after which the treatment policy was to be determined. Information on Day 1 and the last day of warfarin administration was not collected.

PMDA asked the applicant to explain the rationale for the rule "When apixaban is switched to a vitamin K antagonist (warfarin), administration of apixaban should be continued up to 48 hours after the first dose of vitamin K antagonist" specified in the "Important Precautions" section of the package insert (draft).

The applicant responded as follows:
The description "administration of apixaban should be continued up to 48 hours after the first dose of vitamin K antagonist" was entered on the assumption that 4 doses of apixaban would be administered continuously according to the rule specified in Study CV185030. However, in Study CV185030, the incidence rate of "stroke or systemic embolism" during the period from the efficacy cut-off date up to 30 days after the last dose of the study drug was higher in the apixaban group than in the group that continued to receive warfarin without switching. The higher incidence was possibly caused partly by the failure to achieve sufficient anticoagulant therapy. Since the time for PT-INR to reach the therapeutic range differs from patient to patient, it is important to monitor PT-INR in switching from apixaban to warfarin. Therefore, the caution statement in the "Important Precautions" section of the package insert (draft) will be modified to "In switching from apixaban to vitamin K antagonist (warfarin), both apixaban and warfarin should be concomitantly administered until INR exceeds the lower limit of the therapeutic range."

PMDA considers as follows:
Since there may be cases where switching from apixaban to warfarin is required in clinical practice, it is necessary to provide information on the specific switching method that is considered the most appropriate currently. However, in Study CV185030, no information is available on the date of starting warfarin or on the period of concomitant use of warfarin with apixaban. Therefore, the occurrences of efficacy and safety-related events immediately after switching, including the period of concomitant use of apixaban with warfarin, were not evaluated, precluding the assessment of efficacy and safety in patients who underwent the switching. Also, although incidences of thrombotic events and bleeding events at the time of switching from the study drug to open-label warfarin were both higher in the apixaban group than in the warfarin group, there are no means to confirm that this was caused by the switching under blinded conditions. Normally, the study should have been designed to collect the information on the first day of open-label warfarin in each patient, thereby to allow evaluation of efficacy and safety at the switching. Under the current situations, however, there is no appropriate method but to "concomitantly administer apixaban and warfarin until INR exceeds the lower limit of the therapeutic range," as proposed by the applicant for the description in the package insert, by taking account of the policy of switching from warfarin to apixaban and of the time until the disappearance of the efficacy of apixaban. Since no sufficient information has been available on efficacy or safety of switching

from apixaban to warfarin in routine clinical settings, it is desirable to follow up patients who switched from apixaban to warfarin for a specific period of time in the post-marketing surveillance, thereby to collect information on the timing of the switching and on efficacy and safety after the switching. Details of a caution statement on the switching from apixaban to warfarin and of the information collection in the post-marketing surveillance will be finalized, also taking account of comments raised in the Expert Discussion.

4.(iii).B.(4).9) Discontinuation of apixaban before surgery and other invasive procedures

The applicant explained the timing of the discontinuation of apixaban before surgery or other invasive procedures, as follows:
If apixaban is discontinued after achievement of steady-state concentrations of the drug, plasma apixaban concentrations decrease by approximately 80% from the steady-state trough levels 2 days after the discontinuation. Therefore, by taking account of the linear relationship of the anti-FXa activity of apixaban with the plasma drug concentration, it is expected that discontinuing apixaban 2 days before elective surgery or other invasive procedures will sufficiently reduce the bleeding risk caused by apixaban. Based on the above, the following statement should be included in the "Important Precautions" section in the package insert (draft): "In patients undergoing elective surgery or other invasive procedures, apixaban should be discontinued 2 or 3 days before the treatment."

PMDA asked the applicant to explain the appropriateness of the timing of the discontinuation of the study drug associated with surgery and invasive procedures in Study CV185030.

The applicant responded as follows:
In Study CV185030, discontinuation of apixaban before elective surgery was basically left to the discretion in each region, but 3 methods were presented as the reference criteria depending on the severity of thrombotic risk. According to the reference criteria, warfarin or warfarin placebo was to be discontinued 4 days before the procedure regardless of the severity of thrombotic risk, and apixaban or apixaban placebo was to be discontinued 2 to 4 days before the procedure, depending on the severity of thrombotic risk. As regards the method of using unfractionated heparin or low-molecular-weight heparin before and after operation, the study protocol specified that such heparin preparations be used only after operation in low risk cases, and that in cases of moderate and severe risks, they be used until the post-operative INR comes within the therapeutic range. In patients in whom apixaban was discontinued in Study CV185030, the incidence of efficacy events in the apixaban group during the discontinuation period was 0.00% (0 of 273 patients) for discontinuation 2 days before the procedure, 0.00% (0 of 285 patients) for discontinuation 3 days before the procedure, and 0.12% (1 of 822 patients) for discontinuation ≥4 days before the procedure. In the Japanese subpopulation, the incidence was 0.00% (0 of 3 patients), 0.00% (0 of 3 patients), and 0.00% (0 of 14 patients), respectively. As regards safety, the incidence of bleeding events in the apixaban group during the discontinuation period was the following. The incidence of major bleeding was 1.47% (4 of 273 patients) for discontinuation 2 days before the procedure, 1.75% (5 of 285 patients) for discontinuation 3 days before the procedure, and 1.22% (10 of 822 patients) for discontinuation ≥4 days before the procedure. The incidence of major bleeding or CRNM bleeding was 2.20% (6 of 273 patients) for discontinuation 2 days before the procedure, 2.46% (7 of 285 patients) for discontinuation 3 days before the procedure, and 1.82% (15 of 822 patients) for discontinuation ≥4 days before the procedure. In the Japanese subpopulation, no events corresponding to major bleeding or CRNM bleeding occurred in any of the 3 patients each in whom apixaban was discontinued 2 or 3 days before the procedure, whereas CRNM bleeding occurred in 1 of 14 patients in whom apixaban was discontinued ≥4 days before the procedure.

PMDA considers as follows:
Essentially, in the confirmatory study, after verifying the efficacy and safety in patients who met

the pre-specified criteria, the information should be provided for use in clinical practice. However, given that, in Study CV185030, there were only a limited number of patients in whom apixaban had to be discontinued because of surgery or other invasive procedures, that there were an extremely limited number of corresponding patients in the Japanese subpopulation, and that it is unknown to what extent the reference criteria for apixaban discontinuation were followed before elective surgery, it is practically impossible to find a clear rule that could ensure the efficacy and safety in the discontinuation of apixaban before surgery or other invasive procedures. The applicant has proposed the discontinuation of apixaban "2 or 3 days before the procedure," but this is different from the reference rule set in Study CV185030. Taking account of the fact that, in this study, apixaban was discontinued ≥4 days before the procedure in the majority of patients, there is no justification for strongly recommending the discontinuation from 2 or 3 days before the procedure. In light of the observation that, at 2 days after the discontinuation of apixaban, plasma apixaban concentrations decrease by approximately 80% from the steady-state trough levels, it is considered theoretically appropriate currently to discontinue apixaban 2 to 4 days before the procedure in patients undergoing elective surgery or other invasive procedures. However, caution should also be provided to give consideration to the use of an alternative therapy (e.g., heparin) after the discontinuation of apixaban. Clinical studies have provided extremely limited information on apixaban discontinuation associated with surgery or other invasive procedures. Therefore, post-marketing information should be collected thoroughly on the relationship between the timing of apixaban discontinuation before surgery or other invasive procedures and the efficacy and safety, and precautions should be provided for use in clinical practice as necessary. Details of a caution statement on the timing of apixaban discontinuation before surgery or other invasive procedures will be finalized, also taking account of comments raised in the Expert Discussion.

4.(iii).B.(4).10) Hepatobiliary disorder

The applicant explained apixaban-induced hepatic function disorder as follows:

In Study CV185030, the incidence of liver-related adverse events in the apixaban group and in the warfarin group were 4.9% (445 of 9088 patients) and 5.2% (475 of 9052 patients), respectively, in the entire study population, and 5.0% (8 of 160 patients) and 6.3% (11 of 175 patients) in the Japanese subpopulation. The incidence of liver-related serious adverse events in the apixaban group and in the warfarin group were 0.6% (50 of 9088 patients) and 0.5% (48 of 9052 patients), respectively, in the entire study population, and 0.6% (1 of 160 patients) (metastatic hepatic cancer) and 1.1% (2 of 175 patients) (liver disorder, INR increased), respectively, in the Japanese subpopulation. As regards laboratory abnormalities, AST increased to >3 times the upper limit of normal in 1.2% (106 of 8790 patients) in the apixaban group and in 1.1% (99 of 8761 patients) in the warfarin group in the entire study population, and in 2.5% (4 of 158 patients) in the apixaban group and in 2.9% (5 of 175 patients) in the warfarin group in the Japanese subgroup. ALT increased to >3 times the upper limit of normal in 1.1% (100 of 8790 patients) in the apixaban group and in 1.0% (89 of 8759 patients) in the warfarin group in the entire study population, and in 1.3% (2 of 158 patients) in the apixaban group and in 1.7% (3 of 175 patients) in the warfarin group in the Japanese subgroup. No liver-related adverse events unique to the apixaban group were observed either in the entire study population or in the Japanese subpopulation in Study CV185030, with the results of the Japanese subpopulation and those of the entire study population being consistent. In Study CV185067, the incidence of liver-related adverse events was 4.2% (3 of 72 patients) in the apixaban 2.5 mg group (blood bilirubin increased in 2 patients, AST increased in 1 patient), 2.8% (2 of 71 patients) in the apixaban 5 mg group (blood bilirubin increased and AST increased in 1 patient each), and 0.0% (0 of 75 patients) in the warfarin group, but all of these adverse events were mild in severity. Based on the above, the applicant considered that there was no significant safety problem in the liver when apixaban was administered to Japanese patients.

PMDA considers apixaban-induced hepatic function disorder as follows:

Results obtained from the entire population of Study CV185030 did not suggest the presence of risk of hepatic function disorder unique to apixaban, and the results of the Japanese subpopulation were not significantly different from those of the entire study population. Therefore, currently it is not necessary to take any specific measures against the risk of apixaban-induced hepatic function disorder. However, hepatic function-related adverse reactions observed in Study CV185030 should be described appropriately in the ”Adverse Reactions” section in the package insert to raise caution.

4.(iii).B.(4).11) Risk of ischemic heart disease

The applicant explained the occurrences of ischemic heart disease in Study CV185030 as follows: The incidence of events belonging to the category of ischemic heart disease among adverse events reported in Study CV185030 in the apixaban group and in the warfarin group were 5.1% (459 of 9088 patients) and 4.6% (420 of 9052 patients), respectively, in the entire study population, and 4.4% (7 of 160 patients) and 1.7% (3 of 175 patients), respectively, in the Japanese subpopulation. In the entire study population, angina pectoris occurred in 1.6% (145 of 9088 patients) in the apixaban group and in 1.5% (133 of 9052 patients) in the warfarin group, angina unstable in 1.4% (127 of 9088 patients) in the apixaban group and in 1.1% (98 of 9052 patients) in the warfarin group, and myocardial infarction in 0.9% (86 of 9088 patients) in the apixaban group and in 0.8% (68 of 9052 patients) in the warfarin group. In the Japanese subpopulation, there were only a limited number of patients, precluding the evaluation of the incidence of each type of the disease. The overall incidence of adverse events classified as ischemic heart disease was higher in the apixaban group than in the warfarin group, but there was no significant difference in the incidence of individual events. The incidence rate of myocardial infarction assessed by the clinical event adjudication committee was 0.53% per year in the apixaban group and 0.61% per year in the warfarin group. Based on the above, the applicant considered that there was no evidence suggesting a higher risk of ischemic heart diseases in the apixaban group than in the warfarin group.

PMDA considers as follows:

Results of Study CV185030 did not show any evidence of a higher risk of ischemic heart disease in the apixaban group than in the warfarin group. Therefore, there is no need currently to add a caution statement related to the occurrence of ischemic heart disease. However, because of the extremely limited number of Japanese patients investigated in Study CV185030, information should be collected, with condiseration to the occurrence of ischemic heart disease-related adverse reactions, via post-marketing surveillance.

4.(iii).B.(4).12) Blood coagulation markers

The applicant explained the effect of apixaban on each blood coagulation parameter as follows: In Study CV185001 in foreign healthy adult subjects, the maximum PT-INR following a single oral dose of apixaban (0.5-50 mg) was 1.16 to 1.71 while the mean value observed following placebo administration was 1.22. The mean maximum aPTT was 32.6 seconds following placebo administration, whereas aPTT was <35 seconds following a single dose of apixaban at <25 mg and close to the reference level following a single dose of 25 or 50 mg. In Study CV185013 in which a single oral dose of apixaban (2.5-50 mg) was administered in Japanese and Caucasian healthy adult subjects, the mean maximum PT-INR in Japanese subjects was 1.06 in the placebo group, while in the apixaban groups, 1.17 at 2.5 mg, 1.30 at 10 mg, 1.37 at 25 mg, and 1.85 at 50 mg, showing a dose-dependent increase, but the difference between the placebo group and the 10 mg group was not significant. The relationship between plasma apixaban concentrations versus PT-INR, aPTT, mPT (modified prothrombin time), and bleeding time was investigated based on the combined data of phase I studies. Results showed that none of the above parameters examined have sufficient sensitivity as markers for an anticoagulant effect at around the clinical dose of apixaban.

As regards the distribution of the maximum PT-INR following administration of apixaban 5 mg twice daily in Study CV185010, the median value was around 1.6 with a large SD, at 0.41, showing a wide individual variability, which makes PT-INR inappropriate for predicting the clinical efficacy of apixaban. Regarding the apixaban group in Study CV185030, further investigation was conducted on PT-INR in subjects who had intracranial haemorrhage, major bleeding, major bleeding or CRNM bleeding, or all bleedings, as well as in subjects who did not have any bleeding events. In all subpopulations examined, the mean and median values of the first (baseline) and last PT-INR levels were at around 1.2. In the data of the Japanese subpopulation, there were no major outliners, showing the maximum PT-INR of around 1.6 even at the time of the occurrence of bleeding events. The last PT-INR was substantially different from the first PT-INR (first PT-INR <5, last PT-INR >5) in 4 subjects with bleeding events (major bleeding, all bleedings in 2 subjects each) and in 3 subjects without bleeding events, which suggests that it is practically impossible to predict bleeding events based on PT-INR value. In 6 patients who had major bleeding or CRNM bleeding in the Japanese subpopulation, PT-INR did not exceed 1.5 at the time of the occurrence of bleeding events, showing no correlation between PT-INR levels over time and the timing of bleeding events.

The above clinical study data showed that blood coagulation parameters such as PT-INR and aPTT are not sufficiently sensitive for measuring the pharmacological action of apixaban 5 mg twice daily in clinical use and that PT-INR cannot serve as a parameter to predict bleeding events. In addition, although the extent of the anti-FXa activity changes in a manner dependent on the plasma apixaban concentration after dosing of apixaban, it does not correlate with bleeding events. Therefore, the applicant considers that anti-FXa activity does not serve as a useful index for discontinuing the administration of apixaban.

PMDA considers as follows:
It should be well kept in mind that currently it is difficult to control apixaban-induced bleeding risk using a coagulation parameter as the index. The reasons for not requiring the monitoring of coagulation parameters in treatment with apixaban should be made available in clinical practice together with the information that apixaban is not safer than warfarin. Coagulation parameters that allow monitoring of efficacy and safety of apixaban need to be investigated. Taking account of the fact that, in Study CV185030, no sufficient information was collected for the investigation of coagulation parameters, it is desirable to collect information that allows the investigation of the relationship between measured coagulation parameters and the efficacy of apixaban or bleeding events after the market launch. The above decision will be finalized, also taking account of comments raised in the Expert Discussion.

4.(iii).B.(5) Post-marketing surveillance
In Study CV185030, there were only an extremely small number (161 patients) of Japanese patients in the apixaban group. Therefore, PMDA considers that it is necessary to continue to collect information on the efficacy and safety of apixaban via post-marketing surveillance. In particular, given that apixaban 2.5 mg twice-daily dose was administered to only 428 of 9120 patients in the entire Study CV185030 (10 of 161 Japanese patients), and that patients weighing ≤60 kg are required to receive the reduced dose, there is a possibility that, in clinical practice in Japan, the percentage of patients who meet the criteria for administration of apixaban 2.5 mg twice daily is higher than that observed for foreign patients. Taking account of this possibility, PMDA considered it necessary to set a sufficiently large number of patients to be surveyed in order to (1) appropriately evaluate the efficacy and safety of apixaban in patients receiving 2.5 mg twice daily and (2) ensure the evaluation in each subgroup classified by background factors, etc., of patients receiving 2.5 mg twice daily. With consideration given to these points, PMDA instructed the applicant to plan a post-marketing surveillance, etc.

The applicant explained as follows:

In Study CV185030, major bleeding, major bleeding or CRNM bleeding, and all bleedings were safety endpoints. Among these endpoints, major bleeding showed the lowest annual incidence rate. By focusing attention on major bleeding, the target sample size was set at 1000 patients for 2.5 mg twice daily dose and at 1600 patients for 5 mg twice daily dose as the numbers that allow detection of risk factors for major bleeding in each of the patient group receiving 2.5 mg twice daily and the group receiving 5 mg twice daily. Taking account of the expected percentage of patients requiring dose reduction in routine clinical practice, it is expected that 4495 patients eligible for 5 mg twice daily dose will be registered during the period when data of 1000 patients receiving 2.5 mg twice daily dose are collected. Therefore, in the post-marketing surveillance, the total target sample size will be set at 5500 patients in order to ensure 1000 patients receive the 2.5 mg twice daily dose and, if the number of patients receiving the 2.5 mg twice daily dose has not reached 1000 when 5500 patients are registered, then the surveillance will be continued until the target number of 1000 patients is achieved. The standard observation period for each patient is set at 2 years, which was the mean observation period in the Japanese subpopulation in Study CV185030.

PMDA considers as follows:
It is necessary not only to collect information on the incidence rate of overall bleeding adverse events associated with the use of apixaban in routine clinical practice after the market launch, but also to collect information that allows the evaluation of individual events and their severity, as well as their relation with dose and background risk factors. In addition, it is necessary to take appropriate safety measures after the market launch. It is essential to investigate, as background factors, patients with renal impairment, advanced age, low body weight, and antiplatelet drug combination therapy. Efficacy and safety should be evaluated in patients classified by these background factors. Since it is likely that, in clinical practice in Japan, the percentages of patients with low body weight and patients with advanced age are higher than those observed in clinical studies, many patients are expected to be treated at the lower dose. Therefore, it is important to collect efficacy and safety information in patients receiving the lower dose (2.5 mg twice daily) together with the information on the background factors of these patients. In addition, the following information which was extremely limited in clinical studies should be collected: (i) timing of switching from another anticoagulant drug to apixaban or vice versa, and the efficacy and safety during and after the switching, and (ii) timing of apixaban discontinuation before surgery or other invasive procedures and associated efficacy and safety. Also, information should be collected on the safety when CYP3A4 or P-gp inhibitors, etc., drugs that change the pharmacokinetics of apixaban, are concomitantly administered. Furthermore, it is desirable to collect information on blood coagulation parameters with consideration given to the timing of medications and of blood sampling.

Details of the post-marketing surveillance, etc., will be finalized, also taking account of comments raised in the Expert Discussion.

4.(iii).B.(6) Medication error of the study drug

Among serious protocol deviations in Study CV185030, medication errors of the study drug occurred in 7.3% of patients in the apixaban group but in only 1.2% in the warfarin group, showing a considerable difference in the frequency between the 2 groups.

The applicant explained the difference as follows:
For the assessment of the above percentage of medication errors, the possibility that active apixaban and active warfarin may have been coadministered mistakenly (i.e., active warfarin may have administered in the apixaban group and active apixaban administration in the warfarin group) was calculated based on the record of the bottle number entered into the electronic case report form (eCRF). Because a larger number of warfarin bottles than apixaban bottles were supplied to subjects, the percentage of medication errors was higher in the apixaban group. Based

on the information from eCRF, the percentage of medication errors was calculated by including the possibility that the allocated active drugmay have not been administered (i.e., apixaban placebo may have been administered in the apixaban group and warfarin placebo may have been administered in the warfarin group) in addition to the possibility of coadministration of the 2 active drugs. As a result, the percentage of medication errors was 8.6% in the apixaban group and 7.9% in the warfarin group. By assuming that all these calculated medication errors were actual errors in administration, the effect of excluding the cases of these errors on the results of Study CV185030 was evaluated by sensitivity analysis. Results showed that the medication error of the study drug did not affect the primary efficacy endpoint, major bleeding, or all-cause death.

In addition, by taking account of the fact that the information in eCRF of Study CV185030 contained not only the true medication errors caused by the error of supplying the study drug but also errors in transcribing the number of recovered bottles to eCRF, the applicant cross-checked the labels attached to the bottles of study drugs against the allocation table, thereby estimating the true percentage of medication errors, and performed sensitivity analysis based on the information obtained, according to the instructions of the foreign regulatory agency.

The applicant explained the results as follows:
Labels of study drugs kept in each medical institution were recovered, and the true percentage of medication errors was examined based on the recovered labels. The target number of the sample size for the label recovery was set at 32% of labels in the entire study population. As a result, labels could be recovered and their bottle numbers were legible (usable labels) in approximately 99.2% of the total sample size. The percentage of unrecovered or illegible labels (unknown labels) was 0.73% in the apixaban group and 0.85% in the warfarin group. By examining the usable labels concerning whether or not they were mistakenly administered based on the cross-checking against the allocation table, and by assuming that 50% of the unknown labels were mistakenly administered, the percentage of medication errors was calculated to be 0.467% in the apixaban group and 0.538% in the warfarin group. Also, based on the percentage of medication errors thus calculated, effects of these errors on the results of Study CV185030 were evaluated by sensitivity analysis. Results showed that the medication errors did not affect the primary efficacy endpoint, major bleeding, or all-cause death.

PMDA considers as follows:
Based on the results of the investigation of the true percentage of medication errors in Study CV185030 and the results of sensitivity analysis for effects of medication errors on the results of Study CV185030, medication errors in Study CV185030 did not significantly affect the evaluation of the efficacy or safety of apixaban. It was necessary to evaluate the results of Study CV185030 and their integrity, taking account of the percentage of medication errors estimated from the results of the cross-checking of the label of the study drug against the allocation table, which was conducted over the widest range among the investigations conducted by the applicant on the medication errors, and also taking account of the results of the sensitivity analysis performed based on the percentage of medication errors above. Therefore, the regulatory review time for the proposed product was extended due to the prolongation of the time for the relevant sensitivity analysis, etc.

III. Results of Compliance Assessment Concerning the Data Submitted in the New Drug Application and Conclusion by PMDA

1. PMDA's conclusion on the results of document-based GLP/GCP inspections and data integrity assessment

A document-based inspection and data integrity assessment were conducted in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the new drug application. As a result, PMDA concluded that there should be no problem with conducting a regulatory review based on the submitted product application documents.

2. PMDA's conclusion on the results of GCP on-site inspection

GCP inspection took place in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the new drug application (5.3.5.1.2, 5.3.5.1.7). As a result, noncompliance with the standard operating procedure for control of the study drug (supply and administration to subjects of the wrong study drug, loss of the study drug recovered from subjects) or protocol deviations (administration of prohibited concomitant drugs, use of laboratory values measured outside the screening period, noncompliance with rules related to the start of treatment with the study drug) were found at some study sites. Thus, there were cases requiring improvements. However, since the cases were handled appropriately, PMDA concluded that the clinical studies as a whole were conducted in compliance with GCP and that there should be no problem with conducting a regulatory review based on the submitted product application documents.

IV. Overall Evaluation

As a result of the review described above, based on the submitted data, PMDA considers that the efficacy of apixaban in preventing ischemic stroke and systemic embolism in patients with nonvalvular atrial fibrillation has been confirmed, and that its safety is acceptable in view of its observed benefits. Compared with warfarin, which has been used as the standard drug for anticoagulant therapy in patients with nonvalvular atrial fibrillation, apixaban has an advantage of not requiring dose adjustment by monitoring periodically blood coagulation activity, coupled with low interactions with other drugs or foods, etc. Taking account of these characteristics of apixaban, PMDA considers that apixaban is useful as an option for anticoagulant therapy in patients with nonvalvular atrial fibrillation in addition to approved drugs, although due caution should be exercised against bleeding risk caused by apixaban. Apixaban has to be administered under appropriate risk control upon thorough evaluation of the appropriateness of using apixaban in individual patients. Therefore, PMDA will further discuss the specific caution statement to increase the safety during apixaban therapy and the method for providing relevant information, also taking account of comments raised in the Expert Discussion. In addition, it is necessary to appropriately collect post-marketing information on the patients requiring dose reduction, efficacy and safety of apixaban at reduced dose, bleeding risk caused by apixaban, as well as safety in patients with renal impairment, advanced age, or low body weight.

PMDA considers that the product may be approved if it can be concluded based on comments from the Expert Discussion that there are no particular problems.

Review Report (2)

November 15, 2012

I. Product Submitted for Registration

[Brand name]	Eliquis Tablets 2.5 mg and 5 mg
[Non-proprietary name]	Apixaban
[Applicant]	Bristol-Myers K.K.
[Date of application]	December 21, 2011

II. Content of the Review

The outline of the comments from the Expert Discussion and the subsequent review by the Pharmaceuticals and Medical Devices Agency (PMDA) is described in the following sections. The expert advisors for the Expert Discussion were nominated based on their declarations, etc., concerning the product submitted for registration, 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) Clinical positioning of apixaban

Based on the result of Study CV185030, PMDA has concluded that apixaban is expected to be non-inferior to warfarin in efficacy and safety, and therefore that apixaban may be used as an anticoagulant therapy in patients with nonvalvular atrial fibrillation. However, in order to cope with the extremely limited information on the efficacy and safety in a small number of Japanese patients investigated in the confirmatory study, it is necessary to carefully evaluate the appropriateness of administering apixaban to patients with a high risk of adverse reactions such as bleedings, and to appropriately revise the caution statement according to the information collected after the market launch. PMDA has also concluded that supplying apixaban as an option for anticoagulant therapy in patients with nonvalvular atrial fibrillation has a certain clinical significance provided that appropriate safety measures are taken with consideration given to the fact that there is no appropriate markers for monitoring the efficacy of apixaban, nor were there any drugs available that neutralizes the anticoagulant effect of apixaban. The above conclusions of PMDA were supported by the expert advisors, together with the following comments:

- The conclusion of PMDA is appropriate.
- Apixaban should be used with consideration given to the facts that only a limited number of Japanese subjects were investigated in the confirmatory study and that apixaban has characteristics different from those of warfarin
- Safety measures are necessary lest the risk of apixaban should be underestimated with the mistaken assumption in clinical settings that apixaban is safer than warfarin.

(2) Indication of apixaban and patients to be treated

PMDA has concluded that target patients of Study CV185030 were appropriate as subjects for the confirmatory study, from the facts that, in clinical practice, the appropriateness of anticoagulant therapy was evaluated based on the comprehensive assessment of the risk of ischemic stroke, by taking account of $CHADS_2$ score and other patient background factors, and that individual factors of the inclusion criteria used in Study CV185030 were appropriate as risk factors of stroke. The above conclusion of PMDA was supported by the expert advisors. The expert advisors also supported the conclusion of PMDA that the indication should clearly state that the type of stroke for which apixaban is effective is ischemic stroke.

Based on the above discussion, PMDA has concluded that the indication for apixaban should be set as shown below.

[Indication]
Reduction of the risk of ischemic stroke and systemic embolism in patients with nonvalvular atrial fibrillation

(3) Efficacy and dosage and administration of apixaban

1) Usual dosage regimen in Study CV185030 (5 mg twice daily)

The expert advisors supported the following conclusions of PMDA: (i) it is acceptable that the dosage and administration of apixaban in Study CV185030 was determined based on the results of Studies CV185010 and CV185017 which were phase II studies in foreign patients with other diseases, taking account of the facts that the incidence rate of stroke or systemic thromboembolism in patients with nonvalvular atrial fibrillation is low and that no appropriate surrogate marker has been established in the reduction of the risk of stroke or systemic thromboembolism; and (ii) it is appropriate to set the usual dosage and administration of apixaban as 5 mg twice daily, because the results in the entire population of Study CV185030 have demonstrated the non-inferiority of apixaban to warfarin in terms of the primary efficacy endpoint, i.e., the incidence rate of stroke or systemic embolism, and in safety as well.

2) Dose reduction rule and reduced dose (2.5 mg twice daily)

The expert advisors supported the following conclusions of PMDA: (i) selection of advanced age, low body weight, and decreased kidney function as factors requiring consideration for the dose reduction of apixaban in Study CV185030 was appropriate in itself, and (ii) there is currently no other choice but to set the dose reduction rule as that employed in the dosage regimen in Study CV185030 which evaluated the efficacy and safety of apixaban based on the occurrences of events, taking account of the facts that results obtained from the subgroup receiving the reduced dose were not significantly inconsistent with those from the entire population of Study CV185030 and that there is no evidence to support any other dose reduction rule.

3) Efficacy in Japanese patients

The expert advisors supported the conclusion of PMDA that it is acceptable that Japanese patients participated in Study CV185030 because rules, etc. were set in this study with consideration given to some differences found between Japanese and foreign patients in the extrinsic and intrinsic ethnic factors that may affect the efficacy or safety of apixaban. The expert advisors also supported the conclusion of PMDA that the results of the Japanese subpopulation and those of non-Japanese population in Study CV185030 can be collectively evaluated and that apixaban is expected to be effective and safe in Japanese patients to the similar extent as observed in the entire study population for the following reasons: (i) the comparison of the available data between the apixaban group and the warfarin group shows that there is no significant discrepancies between the results of the entire population and those of the Japanese subpopulation in Study CV185030, although there were only an extremely limited number of Japanese patients enrolled in the study; and (ii) results of Study CV185067 also support the efficacy of apixaban observed in Study CV185030. Furthermore, the expert advisors supported the conclusion of PMDA that since further collection of information is necessary in order to decide whether or not the parameters set for the dose reduction rule and the cut-off values are appropriate for Japanese patients as well, it is necessary to provide a caution statement that whether or not apixaban is administered to patients in whom apixaban 5 mg twice daily may cause an unacceptable bleeding risk should be determined carefully, and therefore that it is critical to collect information on the efficacy and safety in such patients via post-marketing surveillance, and to appropriately provide information obtained to clinical practices.

4) Dosage and administration of apixaban

The expert advisors supported the conclusion of PMDA that the dosage and administration and the "Precautions for Dosage and Administration" section in the package insert should be set as shown below, taking account of the discussions in 1) to 3) above.

[Dosage and Administration]
The usual adult dosage of apixaban is 5 mg administered orally twice daily.
The dose may be reduced to apixaban 2.5 mg twice daily depending on the age, body weight, and renal function of the patient.

"Precautions for Dosage and Administration"
Patients who meet at least 2 of the following criteria have a high risk of bleeding and may show an increase in blood apixaban concentrations. In these patients, apixaban should be administered orally at 2.5 mg twice daily (see "Clinical Studies").

- Age ≥80 years (see "Use in the Elderly")
- Body weight ≤60 kg
- Serum creatinine ≥1.5 mg/dL

(4) Safety of apixaban

1) Bleeding

PMDA has concluded that the risk of apixaban-induced bleeding adverse events per se should be emphasized, although no clinically significant bleeding risk was observed in the apixaban group compared with the warfarin group in Study CV185030, with no bleeding events characteristic to apixaban being suggested currently. PMDA has also concluded that, after the start of treatment with apixaban, periodical examinations and tests should be performed appropriately so that possible occurrence of various bleeding symptoms can be detected and, in the event of bleeding, measures such as discontinuing apixaban should be taken promptly. PMDA has further concluded that it is critical to thoroughly inform physicians of the facts that there is no appropriate markers for monitoring the efficacy of apixaban and that there is no drug that neutralizes the anticoagulant effect of apixaban, and that since there is no sufficient information on the occurrences of serious clinical conditions such as intracranial haemorrhage, haemorrhage of digestive tract, and intraocular haemorrhages as well as on the factors that affect the apixaban-induced bleeding risk and indices that reflect the efficacy or bleeding risk of apixaban, these should be continuously investigated after the market launch. The above conclusions of PMDA were supported by the expert advisors, together with the following comments:

- Since apixaban is not considered safer than warfarin regarding bleeding, it is critical to advise adequate caution.
- Occurrences of bleeding and information related to bleeding risk should be collected via post-marketing surveillance, and such information should be provided to clinical practices in an appropriate manner.

Based on the above discussion, PMDA instructed the applicant to include in the package insert the following caution statement on bleeding risk during the treatment with apixaban: Periodical examinations and tests should be performed to check for possible occurrence of various bleeding symptoms after the start of treatment with apixaban and patients should be instructed to notify a physician if any sign of bleeding is seen.
The applicant followed these instructions appropriately.

2) Administration in patients with renal impairment

Taking account of the occurrences of bleeding events in patients with different levels of kidney function in Study CV185030 and of the tendency toward an increase in plasma apixaban concentrations with decreasing kidney function, PMDA has concluded that apixaban should be

contraindicated in patients with severe renal impairment with CL_{CR} <15 mL/min and patients with severe renal impairment with CL_{CR} ≥15 mL/min and <30 mL/min and patients with moderate impairment with CL_{CR} ≥30 mL/min and ≤50 mL/min should be included in the "Careful Administration" section. PMDA has also concluded that information on the efficacy and safety of apixaban in patients with renal impairment should be collected adequately via post-marketing surveillance. The above conclusions of PMDA were supported by the expert advisors, together with the following comments:

- In patients with renal impairment, it is necessary to pay attention to bleeding events. Although there is no sufficient evidence to determine the cut-off level of CL_{CR} for requiring careful administration, there are no data which show that apixaban is safer than other drugs in the same class, dabigatran and rivaroxaban, for which careful administration is required in patients with moderate renal impairment. Therefore, it is appropriate to require careful administration in patients with moderate renal impairment with CL_{CR} ≥30 mL/min and ≤50 mL/min."

Based on the above discussion, PMDA instructed the applicant to require careful administration in patients with renal impairment with CL_{CR} ≥15 mL/min and ≤50 mL/min, and the applicant followed the instructions appropriately.

3) Administration in patients with low body weight

Taking account of the occurrences of bleeding events in the subpopulations with body weight of ≤50 kg and body weight of >50 kg, the mean body weight of the entire study population and that of the Japanese subpopulation in the apixaban group in Study CV185030, as well as the expectation that the proportion of patients with low body weight of ≤50 kg in routine clinical settings in Japan is higher than that in Study CV185030, PMDA has concluded that careful administration should be required in patients with low body weight and that information should be collected on the efficacy and safety of apixaban in patients with low body weight via post-marketing surveillance. The above conclusion of PMDA was supported by the expert advisors.

Based on the above discussion, PMDA instructed the applicant to require careful administration in patients with low body weight, and the applicant appropriately followed the instructions.

4) Use in the elderly

Taking account of the occurrences of bleeding events in the subpopulations of patients aged ≥75 years and patients aged <75 years in the apixaban group in Study CV185030, PMDA considered that elderly patients should be included in the "Careful Administration" section and, specifically, that appropriateness of treatment with apixaban should be carefully evaluated in individual patients with consideration given to their characteristics other than age and that, during the treatment with apixaban, patients should be carefully followed up by paying attention to the possible occurrence of bleedings. Also, since it is assumed that, in clinical practice, apixaban will be administered to elderly patients with a greater variety of complications than experienced in clinical studies, PMDA concluded that information should be collected adequately from these patients via post-marketing surveillance. To the above conclusion of PMDA, the following comments were raised from expert advisors:

- In Japan, the majority of patients receiving apixaban will be ≥65 years of age, and requiring "careful administration" in the elderly patients without defining the age threshold may cause physicians to hesitate to administer apixaban in the elderly patients.
- Since apixaban is expected to be administered often to elderly patients in routine clinical settings, apixaban should be administered carefully by adjusting to the patient conditions.

PMDA explained that elderly patients have an increased bleeding risk, that since other drugs in the same class, dabigatran and rivaroxaban, also require "careful administration" in the elderly patients without defining the age threshold, there is no reason for setting the age threshold for apixaban alone, and that requiring "careful administration" in the elderly patients is unlikely to

compromize the usefulness of apixaban. The expert advisors finally agreed on requiring "careful administration" in the elderly patients.

Based on the above discussion, PMDA instructed the applicant to require careful administration in the elderly patients, and the applicant appropriately followed the instructions.

5) Concomitant use with antiplatelet drug

Within the range of data obtained in Study CV185030, bleeding events increased when apixaban was concomitantly administered with an antiplatelet drug. In addition, the global phase III study (Study CV185068) in patients with acute coronary syndromes, in which Japanese patients participated and 2 antiplatelet drugs were concomitantly administered in many subjects, was terminated prematurely according to the advice of the independent data monitoring committee because of the increased incidence of clinically significant bleedings in the apixaban group. Taking account of these results, PMDA has concluded that the package insert should contain the descriptions "the appropriateness of treatment with apixaban should be carefully evaluated in patients requiring concomitant use with 2 antiplatelet drugs" and "Study CV185068 was terminated because of increased inicidence of clinically significant bleedings" and that information should be collected on cases of concomitant use with antiplatelet drug via post-marketing surveillance and reflected appropriately in risk controlling. The above conclusions of PMDA were supported by the expert advisors, together with the following comments:

- Taking account of the premature termination of Study CV185068, prohibiting the use of apixaban in patients being treated with 2 antiplatelet drugs could be a possible option, but the conclusion of PMDA is appropriate since there is no evidence that warfarin is safe even concomitantly administered with antiplatelet drugs.
- The conclusion of PMDA is acceptable.

Based on the above discussion, PMDA instructed the applicant to include in the package insert the caution statements that "the appropriateness of treatment with apixaban should be evaluated carefully in patients requiring concomitant use with 2 antiplatelet drugs," and that "Study CV185068 was terminated prematurely because of increased incidence of clinically significant bleedings."

The applicant responded as follows:

Ccaution will be provided by including the following descriptions in the "Important Precautions" section of the package insert: "Patients requiring concomitant use with antiplatelet drugs have an increased bleeding risk, warranting caution and appropriateness of concomitant use of apixaban with these drugs should be carefully determined by assessing risks and benefits." Caution will also be provided regarding the concomitant use with antiplatelet drugs in "Precautions for concomitant use" section in "Interactions." Furthermore, the "Other Precautions" section will be added to provide the following information: "In a global clinical study in patients (including Japanese patients) with acute coronary syndromes, a patient population with disease different from the proposed indication, apixaban was concomitantly administered with 2 antiplatelet drugs, aspirin and a thienopyridine drug, and the study was terminated prematurely because of the increased incidence of clinically significant bleedings in the apixaban 5 mg twice daily group compared with the placebo group," and an in-house document summarizing the results of this study will be submitted as a reference.

PMDA considered that the applicant's explanation was appropriate.

6) Switching from warfarin to apixaban

PMDA has concluded that currently the only appropriate method available for switching from warfarin to apixaban is that proposed in the package insert by the applicant, i.e., "the administration of vitamin K antagonist is discontinued and administration of apixaban is started

when INR has decreased to below 2.0," which is the method stipulated in Studies CV185067 and CV185030, and that information should be collected on the previous therapy and the timing of switching from warfarin via post-marketing surveillance. The above conclusions of the PMDA were supported by the expert advisors.

7) Switching from apixaban to warfarin

PMDA has concluded that although there may be cases where switching from apixaban to warfarin is necessary in clinical practice, there is currently no method that can be strongly recommended, and the only appropriate method available is "apixaban is concomitantly administered with warfarin until INR exceeds the lower limit of the therapeutic range" as proposed in the package insert by the applicant, and that patients who switched from apixaban to warfarin in routine clinical settings should be followed up for a specific period of time in the post-marketing surveillance, and information on the timing of the switching and the efficacy and safety after the switching should be collected. The above conclusions of PMDA were supported by the expert advisors.

8) Discontinuation of apixaban before surgery and other invasive procesures

It is unknown how strictly the reference criteria for discontinuing apixaban were followed before surgery or other invasive procedures in Study CV185030, precluding the establishment of an appropriate rule for discontinuation of apixaban before surgery, etc. However, taking account of the change in plasma apixaban concentration over time and of the fact that apixaban was discontinued ≥4 days before the procedure in the majority of patients in Study CV185030, PMDA has concluded that it is possible currently to set the rule to discontinue apixaban administration 2 to 4 days before elective surgery or other invasive procedures based on the assessment of the thrombotic risk of patients, and that it is also desirable to provide a caution statement that consideration should be given to the use of an alternative therapy (e.g., heparin) after the discontinuation of apixaban. The above conclusions of PMDA were supported by the expert advisors, together with the comment that although it would be desirable to set a similar discontinuation criterion as that for other drugs in the same class, dabigatran and rivaroxaban (administration should be discontinued ≥24 hours before treatment, if possible), there is no other method but to set the same discontinuation criteria as the reference criteria used in Study CV185030. Also, PMDA has concluded that information should be collected on the relationship between the timing of discontinuing apixaban before surgery and other invasive procedures and the efficacy or safety via post-marketing surveillance. The above conclusion of PMDA was supported by the expert advisors.

Based on the above discussion, PMDA instructed the applicant to include the following description in the "Important Precautions" section of the package insert: "In patients undergoing elective surgery or other invasive procedures, administration of apixaban should be discontinued 2 to 4 days before the procedure depending on the bleeding risk and thrombotic risk of each patient, and the use of an alternative therapy (e.g., heparin) should be considered. In cases of emergency surgery or otherprocedures, the balance between the extent of the emergency and the increased bleeding risk should be carefully considered."

The applicant appropriately responded to the instructions.

(5) Concomitant use with CYP3A4 or P-gp inhibitor

PMDA has concluded that CYP3A4 or P-gp inhibitors, which have been shown to increase apixaban exposure, should be listed in the "Precautions for concomitant use" section, since the results of exposure-response analysis suggested that the bleeding risk increases with increasing exposure to apixaban. PMDA has also concluded that CYP3A4 or P-gp inhibitors are not contraindicated currently since no serious bleeding events occurred even when apixaban was

concomitantly administered with a potent CYP3A4 or P-gp inhibitor, but it is advised that avoiding the concomitant use of apixaban with a potent CYP3A4 or P-gp inhibitor, or reducing the apixaban dose in such a combination therapy, should be considered as a treatment option, depending on the patient characteristics, by carefully balancing the benefits and risks of the treatment with apixaba, because apixaban exposure was increased to approximately 2-fold after administraton of apixaban in combination with ketoconazole compared with apixaban alone in Study CV185026.

The above conclusions of PMDA were supported by the expert advisors.

Based on the above discussion, PMDA instructed the applicant to list CYP3A4 or P-gp inhibitors in the "Precautions for concomitant use" section because the concomitant use of apixaban with such a drug can increase apixaban exposure, and to provide a caution statement to give consideration to treatment options such as avoiding the concomitant use with a potent CYP3A4 or P-gp inhibitor, and reducing apixaban in such a combination therapy. The applicant responded to the instructions appropriately.

(6) Post-marketing surveillance, etc.

PMDA has concluded that information should be collected on the incidence rate of overall bleeding-related adverse events, as well as information that allows the identification of the relationship of the incidence rate with the types and severity of adverse events, dose, and background risk factors associated with the use of apixaban in routine clinical practice after the market launch and, based on such information, appropriate post-marketing safety measures should be taken. PMDA has also concluded that it is necessary to collect detailed information on patients with advanced age or low body weight, patients in whom the low dose (2.5 mg twice daily) was selected, patients who switched from another anticoagulant drug to apixaban, patients who switched from apixaban to another anticoagulant drug, patients in whom apixaban was discontinued before surgery or other invasive procedures, and patients who received concomitant use with a CYP3A4 or P-gp inhibitor, etc. The above conclusions of PMDA were supported by the expert advisors. In addition, the following comments were raised from the expert advisors:

- There is only limited use experience in Japanese patients. Since many Japanese patients have low body weight or are at an advanced age, it is expected that many of them will be treated at the low dose. There are no neutralizing drugs, nor are there methods for monitoring the efficacy of apixaban. A variety of usage conditions, such as switching of drugs, are expected in clinical practice. Therefore, it is necessary to conduct the post-marketing surveillance in a sufficiently large number of patients.
- Currently, there is only limited information on the relationship between the timing of discontinuation of apixaban before surgery or other invasive procedures and the safety or efficacy, as well as on the relationship between the specific method of switching to or from other anticoagulant drug and the safety or efficacy, and such information should be collected in an appropriate manner and, useful information, if available, should be provided promptly to clinical practice.
- The appropriateness of the number of patients surveyed in the post-marketing surveillance should be determined by taking account of the feasibility of evaluation of the efficacy and safety in patient subgroups with different background factors.

Based on the above discussion, PMDA instructed the applicant to plan the post-marketing surveillance that allows the investigation of matters such as the overall incidences of bleeding adverse events, types of the events, severity, relationship with dose and the reason for dose reduction (e.g., age, body weight, kidney function), and background risk factors; in particular, safety, including the risk of apixaban-induced bleeding in patients with advanced age, low body weight, and renal impairment; the safety and efficacy at the low dose (2.5 mg twice daily); and the background factors of patients in whom the low dose was selected. PMDA also instructed the

applicant to design the post-marketing surveillance that can collect the following information: the safety in patients receiving concomitant use with 1 or 2 antiplatelet drugs, if any; the safety, efficacy, etc., in patients who switched to or from warfarin; the timing of discontinuation of apixaban before surgery or other invasive procedures and the anticoagulant therapy (e.g., heparin) after the discontinuation of apixaban associated with the procedures, as well as their relationship with the safety, efficacy, etc.; the safety when apixaban is concomitantly administered with a drug included in the "Precautions for Concomitant Use" section, particularly a CYP3A4 or P-gp inhibitor which changes the pharmacokinetics of apixaban; the occurrence/non-occurrence of efficacy events, treatment/therapy taken for the efficacy events, and their outcome; and the time of apixaban administration and the time point of blood sampling for measuring blood coagulation parameters. In addition, PMDA instructed the applicant to include the following plans in the post-marketing surveillance: (i) to perform surveillance focused on new signals that raise concern about apixaban administration, if such signals are identified in the above surveys and investigations, (ii) to appropriately collect information on the method of apixaban administration for switching to or from warfarin and on the timing of the discontinuation of apixaban before surgery or other invasive procedures, and investigate the appropriate method and the timing for the switching, and (iii) to provide useful information, if collected, appropriately to clinical practices.

The applicant presented the outline of the draft plan for specified drug use-result surveys and the draft survey sheet that reflected the advice of medical experts and the indications of PMDA, and responded as follows:
The currently planned specified drug use-results surveys with the target number of patients of 5500 and with a 2-year observation period will be able to collect information on cases of major bleeding in each subpopulation classified by the main background factors (e.g., age, body weight, kidney function), and to investigate the relationship between each of these background factors and bleeding risk for each dose level of apixaban. In the case of a new signal raising concern about treatment with apixaban, a survey, etc., focusing on the concerned matter will be conducted. The applicant will also collect detailed information on the method of switching another anticoagulant drug to or from apixaban, and appropriately provide the information to clinical practices. A temporary discontinuation of apixaban due to surgery or other invasive procedures is also included in the items to be surveyed in the post-marketing surveillance, and any useful information obtained will be provided appropriately to clinical practices.

PMDA has concluded that the draft plan for the post-marketing surveillance submitted by the applicant is appropriate, although further detailed review is necessary. Thus, PMDA accepted the response of the applicant.

III. Overall Evaluation

As a result of the above review, PMDA has concluded that the product 2.5 mg and 5 mg may be approved with the following indication and the dosage and administration. The re-examination period is 8 years for both tablet forms. Neither the drug substance nor the drug product is classified as a poisonous drug or a powerful drug, and the product is not classified as a biological product or a specified biological product.

[Indication]	Reduction of the risk of ischemic stroke and systemic embolism in patients with nonvalvular atrial fibrillation
[Dosage and administration]	The usual adult dosage of apixaban is 5 mg administered orally twice daily. The dose may be reduced to apixaban 2.5 mg of twice daily depending on the age, body weight, and renal function of the patient.