Report on the Deliberation Results

December 1, 2010
Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau
Ministry of Health, Labour and Welfare

[Brand name]	Pradaxa Capsules 75 mg Pradaxa Capsules 110 mg (The proposed Japanese brand name will be changed.)
[Non-proprietary name]	Dabigatran Etexilate Methanesulfonate (JAN*)
[Applicant]	Nippon Boehringer Ingelheim Co., Ltd.
[Date of application]	March 4, 2010

[Results of deliberation]
In the meeting held on November 24, 2010, the First Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The product is not classified as a biological product or a specified biological product, the re-examination period 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)*

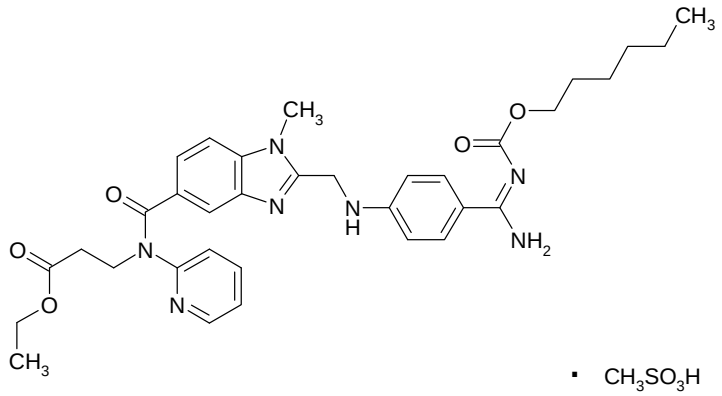
Review Report

November 16, 2010
Pharmaceuticals and Medical Devices Agency, Japan

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

[Brand name]	Pradaxa Capsules 75 mg Pradaxa Capsules 110 mg (The proposed Japanese brand name will be changed.)
[Non-proprietary name]	Dabigatran Etexilate Methanesulfonate
[Name of applicant]	Nippon Boehringer Ingelheim Co., Ltd.
[Date of application]	March 4, 2010
[Dosage form/Strength]	Hard capsules: Each capsule contains 75 mg or 110 mg of Dabigatran Etexilate Methanesulfonate
[Application classification]	Prescription drug (1) Drug with a new active ingredient

[Chemical structure]



Molecular formula:	$C_{34}H_{41}N_7O_5 \cdot CH_4O_3S$
Molecular weight:	723.86
Chemical name:	Ethyl 3-({[2-({[4-(amino{[(hexyloxy)carbonyl]imino}methyl)phenyl]amino}methyl)-1-methyl-1H-benzoimidazol-5-yl]carbonyl}(pyridin-2-yl)amino)propanoate monomethanesulfonate

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

Review Results

November 16, 2010

[Brand name]	Pradaxa Capsules 75 mg Pradaxa Capsules 110 mg (The proposed Japanese brand name will be changed.)
[Non-proprietary name]	Dabigatran Etexilate Methanesulfonate
[Name of applicant]	Nippon Boehringer Ingelheim Co., Ltd.
[Date of application]	March 4, 2010

[Results of review]

Based on the submitted data, it is concluded that the efficacy of Pradaxa Capsules 75 mg and Pradaxa Capsules 110 mg in reducing the risk of ischaemic stroke and systemic embolism in patients with non-valvular atrial fibrillation has been demonstrated and their safety is acceptable in view of their observed benefits. Through the post-marketing surveillance, it is considered important to collect the safety information including bleeding risk in patients who receive concomitant antiplatelet therapy, elderly patients, and patients with renal impairment; safety information regarding gastrointestinal disorder or gastrointestinal haemorrhage; and safety information on concomitant drugs that are considered to affect the plasma concentration of dabigatran etexilate, the safety at each dose, and onset of myocardial infarction.

As a result of its regulatory review, the Pharmaceuticals and Medical Device Agency has concluded that Pradaxa Capsules 75 mg and Pradaxa Capsules 110 mg may be approved for the following indication, and dosage and administration.

[Indication]

Reduction in the risk of ischaemic stroke and systemic embolism in patients with non-valvular atrial fibrillation

[Dosage and administration]

The usual adult dosage is 150 mg (two 75 mg capsules) of dabigatran etexilate administered orally twice daily. The dose should be reduced to 110 mg of dabigatran etexilate (one 110 mg capsule) twice daily, as needed.

Review Report (1)

October 25, 2010

I. Product Submitted for Registration

[Brand name]	Pradaxa Capsules 75 mg Pradaxa Capsules 110 mg (The proposed Japanese brand name will be changed.)
[Non-proprietary name]	Dabigatran Etexilate Methanesulfonate
[Name of applicant]	Nippon Boehringer Ingelheim Co., Ltd.
[Date of application]	March 4, 2010
[Dosage form/Strength]	Hard capsules: Each capsule contains 75 mg or 110 mg of Dabigatran Etexilate Methanesulfonate
[Proposed indication]	Reduction in the risk of stroke and systemic embolism in patients with atrial fibrillation
[Proposed dosage and administration]	The usual adult dosage is 150 mg (two 75 mg capsules) of Dabigatran Etexilate administered orally twice daily.
[Items warranting special mention]	None

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

A summary of 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.

Dabigatran Etexilate (dabigatran etexilate) Methanesulfonate is an oral pro-drug of a non-peptide, direct thrombin inhibitor developed by Boehringer Ingelheim International GmbH, Germany. Dabigatran etexilate methanesulfonate does not exhibit antithrombin activity, but is converted by esterase to dabigatran that is the active substance when absorbed from the gastrointestinal tract.

Dabigatran inhibits thrombogenicity by selectively and reversibly inhibiting thrombin, an important enzyme in the blood coagulation cascade.

Large-scale, multiregional clinical studies were conducted in foreign countries, and a marketing application for dabigatran was submitted in December 2009 in both the United States and Europe for the indication of reducing the risk of stroke and systemic embolism in patients with atrial fibrillation. On October 19, 2010, dabigatran gained its first approval in the US for the indication of “reducing the risk of stroke in patients with non-valvular atrial fibrillation.” On the other hand, dabigatran was approved for the indication of “primary prevention of venous thromboembolic events in adult patients who have undergone total hip

replacement surgery or total knee replacement surgery" in Europe in March 2008, and since then, it has been approved for the same indication in 74 countries as of May 2010.

In Japan, the drug development was started by Nippon Boehringer Ingelheim Co., Ltd. in 20[redacted]. A marketing application has been submitted based on the data from clinical studies in Japan and the above mentioned multiregional clinical studies involving Japanese.

2. Data relating to quality

2.A Summary of the submitted data

Pradaxa capsules 75 mg and Pradaxa capsules 110 mg (hereinafter collectively called "the proposed product") are hard capsules containing 86.48 and 126.83 mg, respectively, of dabigatran etexilate methanesulfonate (with a molecular formula of $C_{34}H_{41}N_7O_5 \cdot CH_4O_3S$, and a molecular weight of 723.86) (they are equivalent to 75 and 110 mg of dabigatran etexilate, respectively).

2.A.(1) Drug substance

2.A.(1).1) Characterization

(a) Structure

The chemical structure of the drug substance has been confirmed by elementary analysis, mass spectrometry, ultraviolet and visible absorption spectrum, infrared spectrophotometry (IR), hydrogen nuclear magnetic resonance spectrometry (^{1}H-NMR), and carbon nuclear magnetic resonance spectrometry.

(b) General properties

The general properties of the drug substance, including description, melting point, dissociation constant (pKa), partition coefficient, hygroscopicity, solubility, and crystalline polymorphism, have been determined. It is a yellow-white to yellow crystalline powder with a melting point around 180°C. [redacted] It was freely soluble in methanol, soluble in *N*,*N*-Dimethylacetamide, sparingly soluble in ethanol (99.9) and practically insoluble in water. Polymorphism was observed and two different crystalline forms (crystalline form I and II) were identified.

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

The drug substance is manufactured by the manufacturing process A or B.

Manufacturing process A

Step 1: [redacted]

[redacted]

Step 2 (part 1): [redacted]

Step 2 (part 2): [redacted]

Step 3 (part 1): [redacted]

Step 3 (part 2): [redacted]

Step 3 (part 3): [redacted]

Step 4: [redacted]

Step 5: The drug substance is packaged in a polyethylene bag, which is further packaged in an aluminum-laminated bag to be heat-sealed and placed into a fiber drum.

[redacted].

Manufacturing process B

Step 1: [redacted]

Step 2: [redacted]

Step 3: [redacted]

Step 4: [redacted]

Step 5: [redacted]

Step 6: The drug substance is packaged in a polyethylene bag, which is further packaged in an aluminum-laminated bag to be heat-sealed and placed into a fiber drum.

[redacted]

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

The drug substance specifications are description (appearance, solubility), identification (IR), heavy metals (color identification tests) and related substances (liquid chromatography [HPLC]) of the purity tests, residual solvents (gas chromatography [GC]), polymorphic forms (differential scanning calorimetry [DSC]), water content (Karl Fischer titration), residue on ignition (mass measurement), assay (HPLC) and particle size distribution (laser diffraction measurement).

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

The following stability studies were performed using lots produced at the commercial scale.

(a) Long-term stability study (25°C/60%RH, polyethylene bag/aluminum laminate/fiber drum, 24 months)

(b) Intermediate study (30°C /75%RH, polyethylene bag/aluminum laminate/fiber drum, 12 months)

(c) Accelerated study (40°C/75%RH, polyethylene bag/aluminum laminate/fiber drum, 6 months)

(d) Stress study—temperature stability (60°C, glass container [air-tight], 1 week)

(e) Stress study—humidity stability (25°C/75%RH, glass container [open], 1 week)

(f) Stress study—temperature and humidity stability (60°C/100%RH, glass container [air-tight], 1 week)

(g) Stress study—photostability (xenon lamp, quartz glass Petri dish, overall illumination 1.22 million lx h, integrated near ultraviolet energy 496 W h/m^2)

The long-term stability study (a) using the drug substance produced in the manufacturing process B (Drug substance B) was conducted up to 36 months. The intermediate study (b) was conducted using Drug substance B alone, while the stress study (g) was conducted using the drug substance produced by the manufacturing method A (Drug substance A) only.

Appearance, related substances, and strength were evaluated at all time points of each study, while water content was evaluated at all time points of all studies but the stress study (g), and particle size distribution was evaluated at all time points of the long-term stability study (a), the intermediate study (b), and the accelerated study (c). Mass change and crystalline polymorphism were evaluated at all time points of the stress study (d-f).

Increase in related substance BIBR 1154 and alteration in particle size distribution were observed in the long-term stability study (a). Increase in related substances BIBR and related substance A as well as alteration in particle size distribution were observed in the accelerated study (c). Considering the deviation observed in related substance A from the specification value in Drug substance B in the accelerated study (c), an intermediate study (b) was conducted. In the intermediate study (b), increase in related substance BIBR 1154 was observed but no change over time was found in related substance A. In the stress study (f), increase in related substance BIBR 1154, related substance A, related substance B, related substance C, and an unknown related substance, increase in water content, and decrease in strength were observed and found deviated from the specification values. Moreover in the stress study (f), mass increase and polymorphic transition from Form I to Form II were observed. No changes over time were observed in any test item in the stress studies (d, e, and f).

Based on the above results and according to the "Guideline on Evaluation of Stability Data" (PFSB/ELD Notification No. 0603004 dated June 3, 2003), a retest period of 36 months has been established for the storage of the drug substance at ≤30°C. The long-term stability study (a) using Drug substance A will continue for up to 36 months.

2.A.(2) Reference standards or materials

The proposed specifications for the drug substance reference material are description (appearance), identification (IR, ^{1}H-NMR), heavy metals (color identification tests) and related substances (HPLC), residual solvents (GC), polymorphic forms (DSC), water content (Karl Fischer titration), residue on ignition (mass measurement), and strength (mass balance).

2.A.(3) Drug product

2.A.(3).1) Description and composition of the drug product

[redacted]

2.A.(3).2) Formulation development

[redacted]

The proposed products 75 mg and 110 mg have the content of identical formulation filling capsule size 1 and

capsule size 2, respectively.

2.A.(3).3) Manufacturing process

The drug product is manufactured in the following 5 steps.

[redacted]

Step 4 (encapsulation process): The content obtained in Step 3 is enclosed in hypromellose capsules by a capsule filling machine. [redacted]

Step 5 (packaging process):

(a) Double sided aluminum foil blister package: Using a blister packaging machine, capsules are placed in aluminum molded sheets which are covered with aluminum lid foils before heat-sealing.

(b) Press Through Pack (PTP)/aluminum pillow package: Using a blister packaging machine, capsules are placed in polyvinylidene chloride molded sheets which are covered with laminated aluminum lid foils before heat-sealing and packaged in aluminum bags with desiccants.

Step [redacted], Step [redacted], and Step [redacted] have been defined as critical process steps and in-process controls and action limits have been established in [redacted], Step [redacted], Step [redacted], and Step [redacted].

2.A.(3).4) Control of drug product

The proposed specifications for the drug product are description (appearance), identification (HPLC-ultraviolet-visible spectrophotometry [UV]), purity tests (related substance [HPLC]), loss on drying (gravimetry) of the content and capsules, uniformity of dosage unit (gravimetry), dissolution (UV) and assay

(HPLC).

2.A.(3).5） Stability of drug product

The following tests were conducted as stability studies using lots produced at a pilot scale.

(a) Long-term stability study (25°C/60%RH, PTP/aluminum pillow [with a desiccant] package, 12 months)

(b) Long-term stability study (25°C/60%RH, double sided aluminum foil blister package, 12 months)

(c) Accelerated study (40°C/75%RH, PTP/Aluminum pillow [with a desiccant] package, 6 months)

(d) Accelerated study (40°C/75%RH, double sided aluminum foil blister package, 6 months)

(e) Stress study—temperature and humidity stability (40°C/75%RH, exposed, 1 day)

(f) Stress study— temperature and humidity stability (60°C, exposed, 85 days)

(g) Stress study— photostability (Xenon lamp, exposed, overall illumination 1.2 million lx h, integrated near ultraviolet energy 200 W h/m^2 or up)

Appearance, loss on drying, strength, related substances, and dissolution were evaluated at all time points of each test. Microbial limit testing was performed at the start and at 12 months of the long-term stability study (a and b) and at the start and at 6 months of the accelerated study (c and d).

In the long-term stability study (a) and the accelerated study (c), the proposed product 75 mg exhibited a reduction of loss on drying in its content and capsule while the proposed product 110 mg exhibited a reduction of loss on drying in its content. An increase in related substance BIBR 1154 was found in the long-term stability study (b) and an increase in related substances BIBR 1154 and B was found in the accelerated study (d). In the stress study (e), an increase was found in related substance BIBR 1154 and related substance D as well as increase in the loss on drying in the content and the capsule. Increase in related substance BIBR 1154 and related substance A, as well as decrease in loss on drying in the content and the capsule were found in the stress study (f). No changes over time were found in the stress study (g).

Based on the above results, a shelf life of 24 months was adopted for the proposed product when stored in a PTP/aluminum pillow (with a desiccant) package and a double-sided aluminum foil blister package at room temperature according to the "Guideline on Evaluation of Stability Data" (PFSB/ELD Notification No. 0603004 dated June 3, 2003). The long-term stability study (a and b) will continue up to 36 months.

2.B. Outline of the review by PMDA

2.B.(1) Specifications for related substances in the drug substance

PMDA asked the applicant to set stricter specifications for related substance B taking into account the maximum value in the results of lot analysis. PMDA also cited, regarding the total amount of related substance E and F, the relatively smaller content of related substances in Drug substance B compared with Drug substance A when seeking the stricter specifications in Drug substance B based on the maximum value in the lot analysis results for Drug substance B, rather than on the lot analysis results for Drug substance A.

The applicant responded as follows: The specification for related substance B and the specification for the

total amount of related substance E and F in Drug substance B would be changed from [redacted]% to [redacted]% and [redacted]% to [redacted]%, respectively.

2.B.(2) Alkyl ester of methanesulfonate, a genotoxic substance

[redacted] On the other hand, the strength of alkyl ester of each methanesulfonate in the proposed product is ≤ [redacted] ppm in the results of lot analysis as well as of the stability study for the drug substance and the drug product. [redacted] ppm for the daily dose of 300 mg of dabigatran etexilate amounts to [redacted] μg/day, and this is lower than the accepted toxicological threshold value of 1.5 μg/day. This leads to a conclusion that the exclusion of alkyl ester of methanesulfonate in the specification is appropriate.

[redacted]

The applicant explained as follows:

Process parameters that could be involved in the generation of alkyl ester of methanesulfonate regarding the content and the capsule were investigated. [redacted]

PMDA accepted the applicant's responses in the sections 2.B.(1) and 2.B.(2) and concluded that there is no specific problem concerning the quality of the proposed product. While the tartaric acid used in the proposed product (confirming to the Japanese Pharmacopoeia) amounts to a new additive based on the unprecedented amount of consumption, PMDA has concluded that the possibility for safety problems caused by tartaric acid in the amount used in the proposed product would be extremely low and there should be no major problem in the use of tartaric acid in the proposed product.

3. Non-clinical data

3.(i) Summary of pharmacology studies

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

The pharmacology study of dabigatran etexilate was performed mainly with dabigatran ($C_{25}H_{25}N_7O_3$, with a molecular weight of 471.5), which is the active metabolite.

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

3.(i).A.(1).1) Mechanism of action

(a) Thrombin inhibitory activity (attached document 4.2.1.1-1)

Human platelet poor plasma were added and reacted with various concentrations of dabigatran, heparins, hirudin or vehicle for 1 hour, and then added and reacted with blood coagulation obtained by activating human platelet rich plasma or thrombin in 20 pM for another hour. Based on the amount of fibrinopeptide A generated by the reaction, the inhibitory activity of dabigatran, heparins, and hirudin for the thrombin bound with the coagulation (solid phase thrombin) and unbound thrombin (liquid phase thrombin) was assessed. The 50% inhibitory concentration (IC_{50}) of dabigatran, heparins, and hirudin against solid phase thrombin was 254.1, 98.7, and 3.1 nM, respectively, while IC_{50} against liquid phase thrombin was 186.3, 8.4, and 1.6 nM, respectively.

(b) Inhibitory activity against serine protease (attached document 4.2.1.1-2)

Inhibitory activity of dabigatran against various enzymes was evaluated by adding different concentrations of dabigatran to human thrombin, activated Blood Coagulation Factor X (Factor Xa), Factor VIIa/tissue factor complex, Factor XIa, plasma kallikrein, plasmin, double-strand urokinase, tissue plasminogen activator, activated protein C, granulocyte elastase, C1s esterase, or trypsin, based on the quantity of pigments liberated from the specific chromogenic substrate of each enzyme after the reaction. The inhibition constant of dabigatran to human thrombin (Ki) was 4.5 ± 0.2 nM. Trypsin among the serine proteases investigated was associated with the lowest Ki (50.3 ± 2.3 nM) while Ki to other serine proteases was ≥ 3520 ± 70 nM (Factor XIa).

3.(i).A.(1).2) Anticoagulant action (*In vitro* and *In vivo*)

(a) Anticoagulant action in humans and animals (attached document 4.2.1.1-3)

Activated partial thromboplastin time (aPTT), prothrombin time (PT), and ecarin clotting time (ECT) were measured following addition of various concentrations of dabigatran or vehicle to the plasma of humans, rats, rhesus monkeys, guinea pigs, pigs, dogs, and rabbits. The aPTT, PT, and ECT of the plasma of humans and different animals were prolonged dependent on the dose of dabigatran. Dabigatran concentrations required for prolonging aPTT and ECT twice that of the vehicle group (ED_{200}) were; 0.23 and 0.18 μM for humans, respectively; 0.46 and 0.10 μM for rats, respectively; 0.59 and 0.20 μM for rhesus monkeys, respectively.

(b) Platelet aggregation activity in human platelet rich plasma (attached document 4.2.1.1-4)

Effect of dabigatran or vehicle against platelet aggregation induced by collagen, adenosine diphosphate

(ADP), or arachidonic acid was investigated with human platelet rich plasma. Dabigatran did not affect the platelet aggregation induced by collagen, ADP, or arachidonic acid. Moreover, dabigatran exhibited an inhibitory effect on the platelet aggregation induced by thrombin using human platelets subjected to gel filtration (IC_{50}, 1.04×10^{-8} M).

(c) Anticoagulant action in rats (attached document 4.2.1.1-5)

Following single, rising, intravenous doses of 1 or 3 mg/kg of dabigatran to male CHBB:THOM rats (280-350 g) (n = 2-4/group) or single intraduodenal administration of dabigatran 20 mg/kg or vehicle to animals (n = 3/group), aPTT was measured pre-dose and at 5, 15 (only after single intraduodenal administration), 30, 60, 120, and 180 minutes post-dose. At 5 minutes post-dose, the aPTT values in the dabigatran 1 and 3 mg/kg groups were 15-fold and 45-fold, respectively, the pre-dose value. At 30 minutes post-dose, the aPTT of dabigatran in the 20 mg/kg group was 1.5-fold the pre-dose value.

Following single oral administration of 10, 20, 50, or 100 mg/kg of dabigatran etexilate methanesulfonate or vehicle to male CHBB:THOM rats (280-350 g) (n = 3-4/group), aPTT was measured pre-dose and at 30, 60, 120, 180, and 300 (only for the 100 mg/kg group) minutes post-dose. As a result, aPTT was prolonged in a dose-dependent manner and the highest aPTT values were achieved at 30 minutes post-dose from the pre-dose value in all dabigatran groups. aPTT in the 100 mg/kg group at 30 minutes post-dose was approximately 13-fold the pre-dose value and even at 300 minutes post-dose, it was approximately 2.2-fold the pre-dose value.

(d) Anticoagulant action in dogs (attached document (4.2.1.1-7)

Male and female beagle dogs (12-14 kg) received an intravenous dose of 0.3 or 1 mg/kg of dabigatran etexilate (n = 2-3/sex/group or an oral dose of 10, 50, or 100 mg/kg of dabigatran etexilate (n = 3-4/sex/group). aPTT was measured pre-dose and at 5, 15, 30, 60, 120, and 240 minutes after the intravenous administration, while for oral administration, it was measured pre-dose and at 0.5, 1, 2, 4, 6.3, and 8 hours post-dose in the 10 mg/kg group; pre-dose and at 0.5, 1, 2, 4, 6, 8, and 24 hours post-dose in the 50 mg/kg group; and pre-dose and at 0.5, 1, 2, 4, 6, 8, 10, and 24 hours post-dose in the 100 mg/kg group. Dabigatran prolonged aPTT while dabigatran etexilate showed a mild prolongation of aPTT.

(e) Anticoagulant action in rhesus monkeys (attached document 4.2.1.1-8)

Male and female rhesus monkeys (3-8 kg) received a single intravenous dose of 0.15, 0.3, or 0.6 mg/kg of dabigatran (n = 3-4/sex/group) or a single oral dose of 1, 2.5, or 5 mg/kg of dabigatran etexilate methanesulfonate (n = 3-4/sex/group). aPTT was measured pre-dose and at 5, 15, 30, 60, 120, 240, and 480 minute post-dose. The aPTT at 5 minutes post-dose in the dabigatran 0.15, 0.3, and 0.6 mg/kg groups was approximately 2, 3, and 5-fold, respectively, the pre-dose values (21.4 ± 0.35, 22.2 ± 0.59, and 21.2 ± 0.47 seconds, respectively). The aPTT values at 240 and 480 minutes post-dose in the dabigatran groups were slightly greater than the pre-dose values. Dabigatran etexilate methanesulfonate prolonged aPTT in a dose-dependent manner. aPTT was the greatest at 120 minutes post-dose in all groups of dabigatran etexilate methanesulfonate, being approximately 1.8, 2.3 and 3.3-fold the pre-dose values (18.3 ± 0.13, 19.3 ± 0.64,

and 20.3 ± 0.44 seconds, respectively). aPTT was longer at 480 minutes post-dose than the pre-dose values.

(f) Anticoagulant action of various salts of dabigatran in rats (attached document 4.2.1.1-9)

Male and female CHBB:THOM rats (males aged 12 weeks and females aged 19 weeks, n = 6/sex/group) received oral dose of 70 mg/kg of dabigatran etexilate, 80.5 mg/kg of dabigatran etexilate methanesulfonate (equivalent to 70 mg/kg of dabigatran etexilate), or vehicle. The anticoagulation parameters (aPTT, thrombin time [TT], PT) were measured at 24 hours post-dose. Dabigatran etexilate affected the prolongation of the blood coagulation parameters significantly compared with dabigatran etexilate methanesulfonate in an equivalent amount.

3.(i).A.(1).3) Antithrombotic action in an animal model with thrombosis

(a) Rat venous thrombus model (attached documents 4.2.1.1-10 and 4.2.1.1-12)

Male CHBB:THOM rats (280-330 g, n = 4-6/group) received a single intravenous dose of dabigatran 0.01, 0.03, 0.05, or 0.1 mg/kg or vehicle. Thromboplastin followed 5 minutes after the test drug. The abdominal main artery was clamped after the thromboplastin dose and antithrombotic action was assessed based on the dry weight of the coagulation that formed in 10 minutes after the clamping. aPTT was measured pre-dose and at 5, 7, and 15 minutes post-dose of the test drug. The dry weight of the coagulation decreased dose dependently withthe dose of dabigatran and a dose of 0.033 mg/kg was required for a 50% reduction of the dry weight of coagulation (ED_{50}). Thrombus formation was completely blocked in the 0.1 mg/kg group. aPTT corresponding to the increase of dose (5 minutes post-dose of the test drug) and the dry weight of coagulation were inversely correlated.

Male CHBB:THOM rats (280-330 g, n = 6-10/group) received a single oral dose of dabigatran etexilate methanesulfonate 5, 10, 20, or 30 mg/kg, or vehicle. Thromboplastin followed at 0.5, 1, 2, 3, 5, or 7 (only after 20 and 30 mg/kg administration) hours post-dose of the test drug or at 1 hour post-dose of the vehicle. The abdominal main artery was clamped after thromboplastin administration to assess antithrombotic action and duration of action based on the dry weight of the coagulation that formed in 10 minutes after the clamping. Dabigatran etexilate methanesulfonate inhibited thrombus formation at 0.5 hour post-dose. The inhibition was complete at 0.5 hour post-dose in the 20 and 30 mg/kg groups. Duration of the inhibition of thrombus formation depended on the dose of dabigatran etexilate methanesulfonate, demonstrating significant inhibition until 2 hours post-dose in all groups and until 3 hours post-dose in the 10, 20, and 30 mg/kg groups compared with the vehicle group.

(b) Rabbit venous thrombus model (attached documents 4.2.1.1-11, 4.2.1.1-13)

The carotid arteries were removed in male NZW rabbits (2.8-3.2 kg, n = 4-10/group) and polycanol 0.5% was administered into the clamped removal region. Rapid intravenous infusion of dabigatran 0.03, 0.1, 0.3, or 0.5 mg/kg, or vehicle followed 2.5 minutes after polycanol administration. Another 2.5 minutes later (5 minutes after the polycanol administration), blood flow was restored and antithrombotic action was assessed based on the dry weight of the coagulation formed in 25 minutes from the blood flow restoration. aPTT was also measured pre-dose and at 2, 5, 15, and 30 minutes post-dose of the test drug. The dry weight of the

coagulation decreased depending on the dabigatran dose (ED_{50}, 0.066 mg/kg). Thrombus formation was almost completely inhibited in the 0.5 mg/kg group. aPTT corresponding to the increase of dose (at 2 minutes post-dose of the test drug) and the dry weight of coagulation were inversely correlated.

Male NZW rabbits (2.8-3.2 kg, n = 3-9/group) received a single oral dose of dabigatran etexilate methanesulfonate 1, 3, 5, 10, or 20 mg/kg. Their carotid arteries were removed under anesthesia at 2 hours post-dose and polycanol 0.5% was administered into the clamped removal region. Blood flow was restored 5 minutes after polycanol administration, and antithrombotic action was assessed based on the dry weight of the coagulation formed in 25 minutes from the blood flow restoration. The dry weight of the coagulation decreased dose dependently with the dose of dabigatran etexilate methanesulfonate and thrombus formation was almost completely inhibited in the 10 and 20 mg/kg groups.

Male NZW rabbits (2.8-3.2 kg, n = 4-9/group) received a single oral dose of dabigatran etexilate methanesulfonate 10 mg/kg or of vehicle. Their carotid arteries were removed under anesthesia at 1, 2, 3, 5, 7, or 24 hours post-dose of dabigatran etexilate methanesulfonate or at 2 hours post-dose of vehicle, and polycanol 0.5% was administered into the clamped removal region. Blood flow was restored 5 minutes after polycanol, and antithrombotic action and duration of action were assessed based on the dry weight of the coagulation formed in 25 minutes from the blood flow restoration. Antithrombotic action in the 10 mg/kg group was significantly larger compared with the vehicle group until 7 hours post-dose and the dry weight of coagulation was the smallest at 2 hours post-dose.

3.(i)A.(1).4) Bleeding effect

(a) Rat tail bleeding model (attached document 4.2.1.1-14)

Male CHBB:THOM rats (200 g, n = 3-11/group) intravenously received dabigatran 0.1, 0.3, 0.5, or 1 mg/kg or vehicle and time was measured from the tail cut pre-dose and at 15, 30, 45, 60, 90, and 120 minutes post-dose to the bleeding cessation. aPTT was also measured pre-dose, and at 15, 30, 60, and 120 minutes post-dose of the test drug. Bleeding time at 15 minutes post-dose was prolonged depending on dabigatran dose, revealing correlation with aPTT. Groups with longer bleeding time than the vehicle group at 15 minutes post-dose were found with doses ≥0.5 mg/kg, which is higher than the ED_{50} (0.033 mg/kg) for the antithrombotic action investigated in the rat venous thrombus model [see "3(i).A. (1).3).(a). Rat venous thrombus model"].

(b) Detoxification using a rat tail bleeding model (attached document 4.2.1.1-15)

Male CHBB:THOM rats (180-230 g, n = 7-13/group) received a rapid and intravenous dose of dabigatran 1 μmol/kg (approximately 0.5 mg/kg) or vehicle, followed by 25-minute continuous intravenous infusion of dabigatran 0.5 μmol/kg/hour (approximately 0.25 mg/kg/hour) or vehicle. Time was measured from the tail cut at 5 minutes pre-dose and at 25 minutes post-dose of the test drug to the bleeding cessation. aPTT was also measured at 5 minutes pre-dose and at 25 minutes post-dose of the test drug. Bleeding time and aPTT of the dabigatran group (n = 13) were 1455 ± 352 and 58 ± 8 seconds, respectively, and the parameters were significantly longer than those in the vehicle group (n = 11), which were 125 ± 8 and 7 ± 0.5 seconds, respectively. Furthermore, 5 minutes before the completion of 25-minute continuous intravenous infusion of

dabigatran or vehicle, Factor VIIa (eptacog alfa [activated, genetical recombination]) (0.1 or 0.5 mg/kg, n = 7-8/group), anti-inhibitor coagulant complex (freeze-dried human blood anti-inhibitor coagulant complex) (50 or 100 U/kg, n = 8/group) or vehicle were intravenously infused. Bleeding time of the concomitant use groups of dabigatran and Factor VIIa 0.1 or 0.5 mg/kg was reduced by 87% and 91%, respectively, compared with the dabigatran alone group, and aPTT of the concomitant use groups of dabigatran and Factor VIIa 0.1 or 0.5 mg/kg was shorter than the dabigatran alone group by approximately 50%. Bleeding time with the concomitant use of dabigatran and anti-inhibitor coagulant complex 50 or 100 U/kg was found shorter than with dabigatran alone by 90% and 88%, respectively, while aPTT with the concomitant use of dabigatran and anti-inhibitor coagulant complex 50 or 100 U/kg did not exhibit reduction compared with dabigatran alone.

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

3.(i).A.(2).1) Binding to receptors and ion channels (attached document 4.2.1.1-6)

Binding of dabigatran etexilate methanesulfonate and dabigatran to 80 types of receptors and ion channels was evaluated and dabigatran in up to 10 μM concentration did not inhibit the binding of specific agonists or antagonists to any receptor or ion channel. Dabigatran etexilate methanesulfonate inhibited the binding of specific agonists or antagonists to 17 types of receptors and ion channels, and the IC_{50} for them was ≥0.6 μM (0.67 μM [sodium ion channel] -12 μM [Muscarine M2 receptor]).

3.A.(2).2) Effect on cardiovascular and respiratory systems (attached documents 4.2.1.2-1 to 5)

In HEK293 cells in which human ether-a-go-go related gene (hERG) was expressed, dabigatran at up to 30 μM did not affect the voltage-dependent potassium current. Moreover, in isolated papillary muscles of guinea pigs, dabigatran at up to 10 μM did not affect the action potential duration and the cardiac contractility.

In male CHBB:THOM rats (approximately 500 g, n = 7-8/group), single oral dose of dabigatran etexilate methanesulfonate 30, 100, or 300 mg/kg did not affect the heart rate, systolic and diastolic blood pressure until 24 hours post-dose.

In male and female NZW rabbits (2-2.5 kg, n = 3/sex/group) under anesthesia, a single rising intravenous dose of dabigatran 0.1, 0.3, 1, 3 or 10 mg/kg did not affect the systolic blood pressure, heart rate, respiratory rate, breathing rate, and tidal volume at 1, 2, 5, 10, 15, and 30 minutes post-dose.

Male pigs under anesthesia (15-18.5 kg, n = 5-7/group) received a rising intravenous dose of dabigatran 0.3, 1, 3, 10, or 30 mg/kg or of vehicle. Dabigatran up to 3 mg/kg did not affect the heart rate, systolic and diastolic blood pressure, maximum left ventricular pressure (LVP-max), strength of left ventricular contraction (LV dP/dt-max), left ventricular end-diastolic pressure (EDP), femoral artery circulation (Q_{fem}), PQ interval, and QT interval at up to 2, 10, and 19 minutes post-dose. The systolic blood pressure and LV dp/dt-max in the 10 mg/kg group were higher than the vehicle group, with LVP-max and diastolic blood pressure rising significantly (at 2 minutes post-dose), and Q_{fem} decreased significantly compared with the vehicle group. Moreover, Q_{fem} in the 30 mg/kg group further decreased compared to that in the 10 mg/kg

group. The systolic blood pressure, diastolic blood pressure, LVp-max, LV dP/dt-max, and EDP rose significantly after dabigatran administration in the 30 mg/kg compared to the vehicle group. These parameters rose and then dropped to stay significantly lower than the vehicle group until the experiment completed. The PQ and QT intervals were not affected in any dabigatran groups.

3.(i).A.(2).3) Effect on central nervous system (general activity and locomotor activity) (attached documents 4.2.1.2-6 to 10)

Following single intravenous administration of dabigatran 3, 10, or 30 mg/kg or vehicle to male and female NMRI mice (aged 32-36 days, n = 5/sex/group), clinical signs of the animals were observed up to 24 hours post-dose. Significant decrease in grip strength was reported in the male mice of the 10 and 30 mg/kg groups compared with the vehicle group at 20 minutes post-dose.

Following single oral administration of dabigatran etexilate methanesulfonate 30, 100, 300, or 1000 mg/kg to male and female NMRI mice (aged 33-36 days, n = 5/sex/group), clinical signs of the animals were observed up to 24 hours post-dose. Four animals at 5 hours post-dose and 2 animals at 24 hours post-dose died or were euthanized in ≥100 mg/kg groups due to deterioration of clinical signs or bleeding complications. Decrease in grasp reflex and landing reflex was observed in ≥300 mg/kg groups at 45 minutes post-dose.

Single intravenous administration of dabigatran 3, 10, or 30 mg/kg did not affect the locomotor activity until at 22 hours post-dose in male and female Wistar rats (aged 60 days, n = 6/sex/group).

Single oral administration of dabigatran etexilate methanesulfonate 30, 100, or 300 mg/kg did not affect the locomotor activity until 90 minutes post-dose in male and female Wistar rats (aged 60 days, n = 4-6/sex/group).

Single oral administration of dabigatran etexilate methanesulfonate 30, 100, or 300 mg/kg did not affect the hexobarbital-induced sleeping time in male and female Wistar rats (aged 34-37 days, n = 4-5/sex/group).

3.(i).A.(2).4) Effect on gastrointestinal system (attached documents 4.2.1.2-11 to -17)

Following single intravenous administration of dabigatran 0.1, 0.3, or 1 mg/kg to male and female Wistar rats (130-160 g, n = 5/sex/group), the gastric emptying mildly deteriorated, which was not dose-dependent. Following single oral administration of dabigatran etexilate methanesulfonate 30, 100, or 300 mg/kg or vehicle to male and female Wistar rats (130-160 g, n = 5/sex/group) the gastric emptying decreased dose dependently with dabigatran etexilate methanesulfonate and was significantly lower in the 300 mg/kg group compared with the vehicle group.

Intravenous administration of dabigatran 0.1, 0.3, or 1 mg/kg did not affect the gastric secretion in male Wistar rats (130-160 g, n = 8/group). On the other hand, following intraduodenal administration of dabigatran etexilate methanesulfonate 10, 30, or 100 mg/kg or vehicle to male Wistar rats (130-160 g, n = 8/group), gastric secretion increased in the 10 mg/kg group compared with the vehicle group. Gastric secretion

decreased in line with the increase in the dose of dabigatran etexilate methanesulfonate, and was lower in the 100 mg/kg group compared with the vehicle group.

In male and female Wistar rats (130-160 g, n = 5/sex/group), intravenous administration of dabigatran 0.1, 0.3, or 1 mg/kg as well as oral administration of dabigatran etexilate methanesulfonate 30, 100, or 300 mg/kg did not affect the transport function of gastrointestinal tract for barium sulfate.

Dabigatran (10^{-9}-10^{-7} M) did not affect the resting tension as well as contraction induced by histamine, acetylcholine, serotonin and barium chloride of isolated guinea pig ileum samples.

3.(i).A.(2).5) Effects on urinary system (attached documents 4.2.1.2-18, 4.2.1.2-19)

Following single intravenous administration of dabigatran 0.3, 1, or 3 mg/kg or vehicle to ovariectomized female beagle dogs with perineal incision (10.8-15.3 kg, n = 8/group), the animals were measured for sodium excretion, chlorine excretion and potassium excretion into the urine from 2 hours pre-dose to 6 hours post-dose. The sodium and chlorine excretion into the urine decreased and urine potassium excretion significantly increased in the dabigatran 3 mg/kg group compared with the vehicle group.

In ovariectomized female beagle dogs with perineal incision (10.8-15.3 kg, n = 8/group), single oral administration of dabigatran etexilate methanesulfonate 1, 3, or 10 mg/kg did not affect the urine parameters (sodium excretion, chlorine excretion, potassium excretion into the urine) and serum parameters (creatinine, glucose, sodium quantity, potassium quantity) from 2 hours pre-dose to 6 hours post-dose.

3.(i).A.(2).6) Pharmacological effects of intermediate metabolites of dabigatran etexilate methanesulfonate (attached document 4.2.1.2-20)

[redacted] Inhibitory action against thrombin (IC_{50}, 20.7 nM) was weaker than that against Factor Xa (IC_{50}, 1.36 μM) in B. ED_{200} of B for aPTT was 0.37 μM (ED_{200}, 0.23 μM for dabigatran). D exhibited inhibitory action against thrombin (IC_{50}, 1.96 μM) but not against Factor Xa (IC_{50} >100 μM). aPTT was not evaluated for D.

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

3.(i).A.(3).1) Effects on central nervous system (attached document 4.2.1.3-1)

Following single oral administration of dabigatran etexilate methanesulfonate 30, 100, or 300 mg/kg orvehicle to male and female Han Wistar rats (aged 6-7 weeks, n = 4/sex/group), the animals were observed for general activity (modified Irwin test), body temperature, and locomotor activity pre-dose and at 2, 4, and 24 hours post-dose. The body temperature was significantly lower at 4 and 24 hours post-dose in the 300 mg/kg group compared with the vehicle group.

3.(i).(3).2) Effects on respiratory system (attached document 4.2.1.3-2)

Single oral administration of dabigatran etexilate methanesulfonate (equivalent to dabigatran etexilate 30, 100, and 300 mg/kg) to male Han Wistar rats (aged 6-7 weeks, n = 2-8/group) did not affect their respiratory rate, tidal volume and respiratory minute volume up to 8 hours post-dose.

3.(i).A.(3).3) Effects on cardiovascular system (attached documents 4.2.3.2-17, 4.2.3.2-18, 4.2.3.2-5)

Following repeated oral administration of dabigatran etexilate methanesulfonate 12, 36, or 200 mg/kg/day or vehicle to male and female rhesus monkeys (aged 3-6 years, n = 4-8/sex/group), electrocardiogram (ECG) (PR interval, QT interval, QRS interval), heart rate, and blood pressure of the animals were measured pre-dose and at 4, 13, 26 and 32 weeks post-dose, or pre-dose and at 13, 26, 39 and 52 weeks post-dose. No dose-dependent effects were observed.

Repeated oral administration of dabigatran etexilate methanesulfonate 17.3, 80.5, or 346 mg/kg to male and female CHBB:THOM rats (175.9-315.7 g, n = 10/sex/group) did not affect their heart rate and blood pressure.

3.(i).A.(4) Pharmacodynamic interaction

Not submitted

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

PMDA considers as follows:

Based on the therapeutic efficacy and pharmacological studies submitted in which inhibitory effects of dabigatran against thrombin are demonstrated and that suppression of thrombus formation has been confirmed in different animal thrombosis models, it has been concluded that antithrombotic action by dabigatran may be expected in humans. Moreover, while no secondary pharmacological effects that could cause clinical problems are expected from the non-clinical pharmacological studies, bleeding is definitely increased within the scope of the effective dose related to the major action of dabigatran etexilate. Based on these findings, the importance of evaluating the balance of the risk and benefit of dabigatran etexilate found in clinical studies is emphasized.

3(ii) Summary of pharmacokinetic studies

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

Pharmacokinetics of dabigatran was investigated after oral or intraduodenal administration of dabigatran etexilate methanesulfonate, or intravenous or intraduodenal administration of dabigatran to mice, rats, rabbits, and rhesus monkeys. Dabigatran concentrations in the sample were measured by HPLC-Tandem mass spectrometer (HPLC-MS/MS) and the determination range of dabigatran concentrations in the plasma sample was 4.00-400 ng/mL (100-500 ng/mL in some tests using monkeys). Considering that dabigatran and its acyl glucuronides have similar pharmacological activity, the pharmacokinetics of total dabigatran (dabigatran plus acyl glucuronides) was also evaluated. Radioactivity levels in samples of plasma, urine, and feces in the study using ^{14}C-labeled dabigatran etexilate methanesulfonate and ^{14}C-labeled dabigatran were determined by liquid scintillation counter.

Pharmacokinetic parameters are expressed as means unless otherwise noted.

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

3.(ii).A.(1).1) Single dose (attached documents 4.2.2.5-2, 4.2.2.5-4, 4.2.2.5-6, 4.2.2.5-7)

^{14}C-labeled dabigatran etexilate methanesulfonate 3.0 mg/kg was orally administered to male rats (n = 5). As a result, the maximum plasma concentration (C_{max}) of the total radioactivity and dabigatran was 305.4 ng eq/mL and 236.2 ng/mL, respectively; the time to reach the maximum blood concentration (t_{max}) was 0.5 hour for the both; the elimination half-life ($t_{1/2}$) was 1.65 and 1.12 hours, respectively; and the area under the blood concentration-time curve from 0 hour to infinity post-dose ($AUC_{0-\infty}$") was 569.7 ng eq h/mL and 464.6 ng h/mL, respectively. Following intravenous administration of dabigatran 3.0 mg/kg to male rats (n = 4), $AUC_{0-\infty}$ of plasma dabigatran was 4372 ng h/mL, the volume of distribution (V) was 0.63 L/kg, and the plasma clearance (CL) was 11.5 mL/min/kg. The bioavailability (BA) of dabigatran was 16.3% when converted to mol concentration.

Following oral administration of ^{14}C-labeled dabigatran etexilate methanesulfonate 17.3 mg/kg to female rabbits (n = 7) the C_{max} of total radioactivity and dabigatran in plasma was 1120 ng eq/mL and 226 ng/mL, respectively; t_{max} was 1.0 and 1.3 hours, respectively; $t_{1/2}$ was 6.32 and 2.70 hours, respectively; and $AUC_{0-\infty}$was 3950 ng eq h/mL and 910 ng h/mL, respectively. Following oral administration of 17.3 mg/kg of dabigatran etexilate methanesulfonate to female rabbits (n = 5), $AUC_{0-\infty}$ of dabigatran was 892 ng h/mL. On the other hand, following intravenous administration of ^{14}C-labeled dabigatran 0.3 mg/kg to female rabbits (n = 4), $AUC_{0-\infty}$ of dabigatran in plasma was 444 ng h/mL, V was 1.20 L/kg, and CL was 11.5 mL/min/kg. The BA of dabigatran converted to mol concentration was 5.4%.

Following oral administration of ^{14}C-labeled dabigatran etexilate methanesulfonate 2.7 mg/kg (as a dose of dabigatran etexilate) to male and female rhesus monkeys (n = 2/sex), pharmacokinetic parameters were measured. The C_{max} of dabigatran and total daibgatran in plasma was 54.8 and 151.8 ng/mL, respectively; t_{max} was 1.25 hours for the both; $t_{1/2}$ was 7.27 and 5.81 hours, respectively; and $AUC_{0-\infty}$ was 318.8 and 974.3 ng h/mL, respectively. The time course of total plasma radioactivity levels was similar to that of total dabigatran. Furthermore, following intravenous administration of ^{14}C-labeled dabigatran 0.3 mg/kg to male and female rhesus monkeys (n = 2/sex), the $AUC_{0-\infty}$ for total dabigatran and dabigatran in plasma was 1712 and 577.3 ng h/mL, respectively, while for dabigatran, V was 1.34 L/kg and CL was 8.9 mL/min/kg. The BA of total dabigatran converted to mol concentration was 7.7%.

After oral administration of ^{14}C-labeled dabigatran etexilate methanesulfonate and intravenous administration of ^{14}C-labeled dabigatran, the absorption rate of dabigatran etexilate methanesulfonate was 11% in mice, 21%-22% in rats, and <5% in rhesus monkeys as determined from the comparison of the cumulative urinary excretion rate of total radioactivity. Based on the comparison of the total radioactivity and the concentration of dabigatran following the administration of ^{14}C-labeled dabigatran etexilate methanesulfonate, the absorption rate of dabigatran etexilate methanesulfonate in rabbits was estimated to

be >5.4% of the BA.

3.(ii).A.(1).2) Repeated dose (attached documents 4.2.3.2-1 to -7, 4.2.3.2-9, 4.2.3.2-10, 4.2.3.2-13, 4.2.3.2-16 to -18, 4.2.3.2-22, 4.2.3.4.1-1, 4.2.3.4.1-2, 4.2.3.5.2-1 to -3, 4.2.3.5.3-2)

The repeat-dose pharmacokinetics of dabigatran was evaluated based on the 18 toxicokinetics studies with oral doses of dabigatran etexilate methanesulfonate (mice, 3 studies [dose, 30-300 mg/kg of dabigatran etexilate]; rats, 9 studies [10-300 mg/kg]; rabbits, 2 studies [15-200 mg/kg]; rhesus monkeys, 4 studies [12-500 mg/kg]) and 3 toxicokinetics studies with intravenous dabigatran dose (rats, 1 study [dabigatran 0.05-5 mg/kg]; rhesus monkeys, 2 studies [dabigatran 0.8-20 mg/kg]).

In the dose range evaluated, C_{max} and AUC of dabigatran increased generally in line with increasing dose. In the mice, rats and rhesus monkeys where gender related differences were evaluated, no consistent gender differences were found in any animal species. On the other hand, the coefficients of variation for C_{max} or AUC of plasma dabigatran after intravenous administration was ≤25 in rats and >25% and ≤50% in rhesus monkeys. The coefficients of variation for the C_{max} or AUC values after oral administration were higher than those for the intravenous administration in either animal species, and they were generally >40% and ≤80% or >80%, respectively. In 16 studies that evaluated the signs of accumulation or enzyme induction with repeated doses, 4 studies with oral administration of dabigatran etexilate methanesulfonate (mice, 2 studies; rats, 2 studies) found a tendency for reduced dabigatran exposure (C_{max}, AUC, etc.) with repeated doses.

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

3.(ii).A.(2).1) Single dose (attached document 4.2.2.3-3)

Tissue distribution of radioactivity following oral administration of ^{14}C-labeled dabigatran etexilate methanesulfonate 11.53 mg/kg to male albino rats (n = 3) was investigated by quantitative whole-body autoradiography. Radioactivity at 0.5 hour post-dose was extensively distributed in tissues and it peaked in the liver, with the stomach, upper gastrointestinal tract, and bladder excluded. Accumulation of radioactivity was found in the arterial wall, skin, and periosteum. Minimal radioactivity was detected in the brain. Tissue radioactivity was decreased at 2 hours post-dose in all tissues falling below the quantitation limit (64 ng eq/mL) at 24 hours post-dose. Following oral administration of ^{14}C-labeled dabigatran etexilate methanesulfonate 11.53 mg/kg to male pigmented rats (n = 2), radioactivity exhibited virtually similar tissue distribution to that of albino rats and no accumulation was found in the melanin-containing regions of the eyeball or skin.

Moreover, after single intravenous administration of ^{14}C-labeled dabigatran 5.0 mg/kg to male albino rats (n = 3) and male pigmented rats (n = 2), distribution and transition of radioactivity were similar to those following oral administration of ^{14}C-labeled dabigatran etexilate methanesulfonate.

3.(ii)A.(2).2) Plasma protein binding and distribution in blood cells (attached documents 4.2.2.3-2 to -4)

^{14}C-labeled dabigatran was added to the plasma of mice, rats, rabbits and rhesus monkeys (final concentration; mice, 100-10,000 ng/mL, other animal species, 50-5000 ng/mL). As a result, plasma protein

binding was 22%-39% and constant in all species regardless of the concentration evaluated.

Following single oral administration of ^{14}C-labeled dabigatran etexilate methanesulfonate 11.53 mg/kg or single intravenous administration of ^{14}C-labeled dabigatran 5 mg/kg to male albino rats (n = 3) and male pigmented rats (n =2), the blood cell/plasma concentration ratio of radioactivity (Cc/Cp) was 0.02 as a mean up to 2 hours post-dose but was 0.35 at 24 hours post-dose when the blood radioactivity concentration declined.

3.(ii).A.(2).3) Placental transfer (attached document 4.2.2.3-1)

Following single oral administration of ^{14}C-labeled dabigatran etexilate methanesulfonate 11.53 mg/kg to rats on gestation Day 15 to 19 (n = 2), the tissue radioactivity declined at 2 hours post-dose compared with that at 30 minutes post-dose in most tissues but increased in the epidermis and fetal tissue from 1428 and 17 ng eq/mL at 30 minutes post-dose to 2028 and 53 ng eq/mL at 2 hours post-dose, respectively. Radioactivity in the fetal tissue was lower compared with that in the blood and placental tissue of dams. Distribution and transfer of the tissue radioactivity following subcutaneous administration of ^{14}C-labeled dabigatran 5 mg/kg were similar to those with oral administration of dabigatran etexilate methanesulfonate.

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

3.(ii).A.(3).1) *in vivo* metabolism

(a) Metabolites in plasma（attached documents 4.2.2.4-2 to -7)

Following single oral administration of ^{14}C-labeled dabigatran etexilate methanesulfonate 14.5 mg/kg to male and female mice (n = 3/sex/time point), 7.24 mg/kg to male and female rats (n = 3/sex), and 72.4 mg/kg to male and female rhesus monkeys (male n = 1, female n = 2), dabigatran accounted for 91.3% and 100% of the total plasma radioactivity in mice (sampling point, 1 and 3 hours post-dose, respectively), 94.5% (0.5 hour post-dose) in male rats, 84.7% (0.5 hour post-dose) in female rats, and 43.3, 30.1, and 28.6% (2, 4, and 6 hours post-dose, respectively) in rhesus monkeys. Following intraduodenal administration of ^{14}C-labeled dabigatran etexilate methanesulfonate 72.4 mg/kg to a female rabbit (n = 1), dabigatran accounted for 52.0% of the total plasma radioactivity (2 hours and 4 hours post-dose combined). Other metabolites than dabigatran found in ≥5% of the total plasma radioactivity in different animal species were M579 in mice (maximum ratio, 5.4%), acyl glucuronide of dabigatran in female rats (5.2%), M630 (34.2%) and M602 (9.1%) in the rabbit, and acyl glucuronide of dabigatran in rhesus monkeys (71.4%).

Following single intravenous administration of ^{14}C-labeled dabigatran 4.72 mg/kg to male and female mice (n = 3 /sex/time point), male and female rats (n = 3/sex), female rabbit (n = 1), and male and female rhesus monkeys (n = 2/sex), dabigatran accounted for 93.7% and 90.3% of the total plasma radioactivity in mice (sampling points: 1 hour and 3 hours post-dose, respectively), 99.7% in male rats (0.5 hour post-dose), 100% in female rats (0.5 hour post-dose), 97.0% and 99.3% in a rabbit (2 and 4 hours post-dose, respectively), and 30.8%-40.6% in rhesus monkeys (2, 4, 6 hours post-dose). Metabolites other than dabigatran found in ≥5% of the total plasma radioactivity in different animal species were M579 in mice (9.7%) and acyl glucuronide of dabigatran in rhesus monkeys (69.2%).

Regarding mice and rats, no strain-related differences were found between the strains used in the metabolism studies (Crl, MMRI mice; Chbb, THOM rats) and the strains used in the toxicity studies (Crl, CD1 mice; Crl, WI [Han] rats) in the metabolites pattern in the plasma, urine, and bile.

(b) Urinary and fecal metabolites（attached documents 4.2.2.4-2 to -5)

Following single oral administration of ^{14}C-labeled dabigatran etexilate methanesulfonate14.5 mg/kg to male and female mice (n = 5/sex/time point), 7.24 mg/kg to male and female rats (n = 5/sex), 72.4 mg/kg to female rabbits (n = 2), and 72.4 mg/kg to male and female rhesus monkeys (male n = 1, female n = 2), the urinary excretion and fecal excretion rates of dabigatran were; 6.6% and 75.1% in mice (sampling point, 48 hours post-dose), respectively; 10.1% and 74.1% in male rats (24 hours post-dose),respectively; 6.4% and 76.8% (24 hours post-dose) in female rats, respectively; 2.3% and 59.3% (96 hours post-dose) in rabbits, respectively; and 1.2% and 69.9% (48 hours post-dose) in rhesus monkeys, respectively. Metabolites found in ≥5% of excretion rate other than dabigatran included the intermediate metabolite D (8.4%) in mice feces in the metabolism from dabigatran etexilate methanesulfonate to dabigatran, D in male rat feces (12.5%), D in female rat feces (8.3%), and another intermediate metabolite, B (11.8%) in rabbit feces in the metabolism from dabigatran etexilate methanesulfonate to dabigatran.

Following single intravenous administration of ^{14}C-labeled dabigatran 4.72 mg/kg to male and female mice (n = 3/sex/time point), male and female rats (n = 3/sex), female rabbit (n = 1), male and female rhesus monkeys (n = 2/sex), the urinary and fecal excretion rate of dabigatran were; 48.8% and 32.2% in mice (sampling point, 48 hours post-dose), respectively; 47.5% and 49.3% in male rats (24 hours post-dose), respectively; 48.1% and 39.7% in female rats (24 hours post-dose), respectively; 28.2% and 57.4% in a rabbit (72 hours post-dose), respectively; and 31.9% and 29.7% in rhesus monkeys (48 hours post-dose), respectively. Metabolites found in ≥5% of excretion rate other than dabigatran were acyl glucuronide of dabigatran and its urea condensate (20.3% combined) in the urine of rhesus monkeys.

(c) Metabolites in bile (attached documents 4.2.2.4-2 to -5)

Following single intraduodenal administration of ^{14}C-labeled dabigatran etexilate methanesulfonate 14.5 mg/kg to male and female mice (n = 3/sex/time point), 7.24 mg/kg to male and female rats (n = 3/sex), and 72.4 mg/kg to female rabbits (n = 2), the excretion rate of dabigatran into bile was 0.2% (sampling point: 6 hours post-dose) in mice, 10.3% (6 hours post-dose) in male rats, 6.1% (6 hours post-dose) in female rats, and 0.2% (4 hours post-dose) in rabbits. No metabolites other than dabigatran were found in a ≥5% excretion rate.

Following single intravenous administration of ^{14}C-labeled dabigatran 4.72 mg/kg to male and female mice (n = 3 /sex/time point), male and female rats (n = 3/sex), and female rabbits (n = 2), the excretion rate of dabigatran in bile was 10.6% (sampling point, 6 hours post-dose) in mice, 36.5% (6 hours post-dose) in male rats, 30.3% (6 hours post-dose) in female rats, and 16.8% (4 hours post-dose) in rabbits. No metabolites other than dabigatran were found in a ≥5% excretion rate.

(d) Metabolites in milk (attached document 4.2.2.5-3)

Following single oral administration of ^{14}C-labeled dabigatran etexilate methanesulfonate 11.5 mg/kg to rats on lactation day 11 or 12 (n = 5), the ratio of dabigatran to the radioactivity in milk at 1, 6, and 24 hours post-dose was 69.3%, 78.8%, and 100%, respectively. At 1 and 6 hours post-dose, M385 accounted for 30.7% and 21.2% of the radioactivity in milk, respectively. The total amount of M385 is estimated to be <0.03% of the administered dose based on the total yield in milk.

3.(ii).A.(3).2) *ex vivo* enzyme induction (attached document 4.2.2.4-9)

Following repeated oral administration of dabigatran etexilate methanesulfonate 3.46 or 115.3 mg/kg once daily for 4 days to male rats (n = 5/group), no significant increase of enzyme activity was exhibited in cytochrome P450 (CYP) 1A, 2B1/2, 3A, 2E1, and 4A1 of hepatic microsomes compared with the vehicle group.

3.(ii).A.(3).3) Pharmacological activity and chemical stability of acyl glucuronide of dabigatran (attached document 4.2.2.4-8)

From urine samples of rhesus monkeys that orally received dabigatran etexilate methanesulfonate, 1-*O*-acyl glucuronide of dabigatran and its positional isomers, 2-*O*-, 3-*O*-, and 4-*O*-acyl glucuronide, were isolated. After dabigatran and 1-*O*-, 2-*O*-, 3-*O*-, and 4-*O*-acyl glucuronide of dabigatran were added at a concentration of 1.76 μM* to the plasma, aPTT was prolonged to;112.9 to 129.7, 132.7 to 136.2, 149.9 to 153.4, 165.8 to 171.2, and 143.0 to 153.6 seconds, respectively, from 34.0 seconds in the negative control.

After 1-*O*-acyl glucuronide of dabigatran was incubated in a buffering solution with pH7.4 at 37ºC for up to 8 hours, 3 types of isomers (2-*O*-, 3-*O*-, 4-*O*-acyl glucuronides) and dabigatran, which is an aglycone, were formed. The apparent primary decomposition half-life of 1-*O*-acyl glucuronide of dabigatran was approximately 1.0 hour. It was demonstrated that 1-*O*-acyl glucuronide of dabigatran is subjected to non-enzymatic hydrolysis and intramolecular transfer reactions that are not mediated by esterase at the physiological pH.

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

3.(ii).A.(4).1) Urinary and fecal excretion (attached documents 4.2.2.4-6, 4.2.2.4-7, 4.2.2.5-1, 4.2.2.5-2, 4.2.2.5-4 to -7)

Following single oral administration of ^{14}C-labeled dabigatran etexilate methanesulfonate 3.46 mg/kg to male mice (n = 5), 3.0 mg/kg to male rats (n = 5), 17.3 mg/kg to female rabbits (n = 4), and 2.7 mg/kg to male and female rhesus monkeys (n = 2/sex), the cumulative urinary excretion of radioactivity (partly including the cage cleaning liquid) was 6.4%, 11.1%, 2.4%, and 3.4%, respectively, and the cumulative fecal excretion rate was 92.6%, 87.6%, 87.3%, and 89.8%, respectively (sampling point, 120 hours post-dose in

*Concentration of acyl glucuronide of dabigatran was determined from the UV absorption based on the assumption that the UV absorption coefficient of dabigatran was equivalent to those of 4 types of acyl glucuronide.

rhesus monkeys and 72 hours post-dose in other animal species). In mice and rats, ≥95% of the administered radioactivity was excreted by 48 and 24 hours post-dose.

Following single intravenous administration of ^{14}C-labeled dabigatran 4.72 mg/kg to male and female mice (n = 10/sex), 0.3 mg/kg to male rats (n = 5), 0.3 mg/kg to a male rhesus monkey (n = 1), and 0.3 mg/kg to a female rhesus monkey (n = 1), the cumulative urinary excretion rate of radioactivity (partly including the cage cleaning liquid) was 52.4%, 53.4%, 75.2%, and 78.8%, respectively, and the cumulative fecal excretion was 35.2%, 45.7%, 22.9%, and 21.8% , respectively (sampling point; 48, 72, 168, and 168 hours).

Between the strains of mice and rats used in the metabolic studies (Crl, MMRI mice; Chbb, THOM rats) and the strains used in the toxicity studies (Crl, CD1 mice; Crl, WI [Han] rats), no differences were found in the pattern of urinary and bile excretion.

3.(ii).A.(4).2) Excretion into bile and enterohepatic circulation (attached documents 4.2.2.4-5, 4.2.2.5-4, 4.2.2.5-5)

Following intraduodenal administration of ^{14}C-labeled dabigatran etexilate mathanesulfonate 14.5 mg/kg to male and female mice (n = 3/sex) and 3.0 mg/kg, to male rats (n = 5), the cumulative excretion rate of radioactivity into bile was 0.3% and 8.0%, respectively, (sampling point, 6 hours post-dose). Following intravenous and intraduodenal administration of ^{14}C-labeled dabigatran 3.0 mg/kg to male rats (n = 5), the cumulative excretion rate of radioactivity into bile was 35.6 % and 1.81%, respectively (sampling point, 6 hours post-dose).

After the bile was collected by up to 3 hours post-dose from the rats that received ^{14}C-labeled dabigatran 3.0 mg/kg intraduodenally and the bile was intraduodenally administered to other rats (n = 5), the cumulative excretion rate of radioactivity into bile up to 6 hours post-dose was approximately 0.4%.

3.(ii).A.(4).3) Excretion into milk (attached document 4.2.2.5-3)

Following oral administration of ^{14}C-labeled dabigatran etexilate methanesulfonate 11.5 mg/kg to rats (Crl, WI [HAM]) (n = 5) on lactation day 11 or 12, the plasma radioactivity at 1, 6 and 24 hours post-dose was 1160, 44.1, and 3.45 ng eq/g, respectively, and the radioactivity in milk was 132, 104 and 4.62 ng eq/g, respectively. Moreover, the total radioactivity secreted into milk up to 24 hours post-dose was 0.076% to 0.125% of the amount administered to dams.

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

As its pharmacokinetic characteristics when dabigatran etexilate that is a pro-drug is orally administered, low absorption in the gastrointestinal tract and large inter-individual variability of pharmacokinetics have been demonstrated. The applicant explains that the low solubility and the pro-drug being subjected to hydrolysis before systemically exposed are the reason for the low absorption of dabigatran etexilate. The comparison on the other hand, of dabigatran excretion into bile between intravenous administration and intraduodenal administration suggested that dabigatran is virtually not absorbed from the gastrointestinal

tract [see "3. (ii).A.(4).2) Excretion into bile and enterohepatic circulation"].

Based on the above, PMDA considers that the potential for clinical problems associated with the low absorption and large inter-individual variations of dabigatran etexilate required attention when evaluating its pharmacokinetics on humans despite the modest improvement of the solubility achieved in the development process of the formulation.

PMDA asked the applicant to explain the necessity for caution statements in the package insert taking into account the higher radioactivity in the fetal tissue at 2 hours post-dose than at 0.5 hour post-dose when pregnant rats orally received ^{14}C-labeled dabigatran etexilate mathanesulfonate, including the absence or presence and the extent of toxic findings in the fetus.

The applicant responded as follows:
The radioactivity in the fetal tissue was higher at 2 hours post-dose than at 0.5 hour post-dose. However, no toxicity on the embryo or fetus was detected in any of the studies of fertility and early embryonic development to implantation, embryo-fetal development and pre-natal and postnatal development. And all the findings observed in the embryo and fetus are considered to be caused by the maternal toxicity due to the anticoagulation action of dabigatran etexilate. Moreover, no teratogenic effects specific to the administration of dabigatran etexilate methanesulfonate were found in any species in the study regarding the embryo-fatal development conducted to evaluate the teratogenic effects of dabigatran etexilate methanesulfonate using rats and rabbits. No effects were found on the fertility or ability to conceive in the first filial (F_1) generation either. Decline in intrauterine survival rate was detected in the ≥70 mg/kg dabigatran etexilate methanesulfonate groups in the study using rats but the findings were ascribed to the maternal toxicity (vaginal bleeding) caused by the anticoagulation action of dabigatran particularly in the perinatal period.

Based on the above, while warning to pregnant women is considered unnecessary since no toxicity due to dabigatran etexilate methanesulfonate has been detected in the embryo and fetuses of rats, the placental transfer into the fetus of dabigatran etexilate observed in the animal experiments is to be stated in the package insert to provide information.

PMDA considers as follows:
While the explanation of the applicant is understandable that the embryo-fetus findings in the toxicological study were very likely caused by the maternal toxicity (vaginal bleeding) and the possibility for clinically relevant outcome is low, the transfer of dabigatran etexilate to the fetus was evaluated only up to 2 hours post-dose and decline of dabigatran etexilate level in the fetal tissue was not confirmed. Based on these facts, providing information on the fatal transfer of dabigatran etexilate is considered significant and therefore, the response of the applicant has been determined to be appropriate.

3.(iii) Summary of toxicological studies

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

Single-dose toxicity studies, repeated dose toxicity studies, genotoxicity studies, carcinogenicity studies, reproduction toxicity studies, and phototoxicity studies were performed as the toxicology study of dabigatran etexilate.

3.(iii).A.(1) Single-dose toxicity (attached documents 4.2.3.1-1, 4.2.3.1-2, 4.2.3.1-3, 4.2.3.1-4, 4.2.3.2-11, 4.2.3.2-12, 4.2.3.2-19)

Single dose toxicity was evaluated based on the results of the oral dose toxicity study (dabigatran etexilate methanesulfonate) and the intravenous dose toxicity study (dabigatran) using NMRI mice, Wistar rats, beagle dogs, or rhesus monkeys. The approximate lethal dose was determined to be >2000 mg/kg (oral dose) and >100 mg/kg (intravenous dose) in mice; >2000 mg/kg (oral dose) and 100 mg/kg (intravenous dose) in rats; >600 mg/kg (oral dose) and >20 mg/kg (intravenous dose) in dogs; and >600 mg/kg (oral dose) and >40mg/kg (intravenous dose) in monkeys. As post-dose symptoms, effects on the central nervous system (sedation, head shaking etc.) and effects on the respiratory function (dyspnoea etc.) were observed in mice and rats while dogs or monkeys exhibited abnormal , decreased weight gain, decreased food consumption, and bleeding in administration sites (intravenous infusion studies).

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

3.(iii).A.(2).1) Thirteen-week repeat oral dose toxicity studies in mice (attached document 4.2.3.2-2)

CD-1 mice (n = 10/sex/group) orally received dabigatran etexilate methanesulfonate 30, 100, or 300 mg/kg for 13 weeks. Based on the thymic inflammation observed in females in the 300 mg/kg/day group, the no observed adverse effect level (NOAEL) was determined to be 100 mg/kg/day.

3.(iii).A.(2).2) Four-week repeat oral dose toxicity studies in rats (attached document 4.2.3.2-5)

Wistar rats (n = 10/sex/group) orally received drug solution that had not undergone degradation 15, 70 and 300 mg/kg (as dabigatran etexilate methanesulfonate) and drug solution that had undergone forced degradation 300 mg/kg (as dabigatran etexilate methanesulfonate) for 4 weeks. Six rats in total, both males and females, died in the 300 mg/kg/day groups (drug solutions that had and had not undergone forced degradation) and the deaths were ascribed to cardiac tamponade or intra-abdominal haemorrhage except for the one caused by incorrect administration. Fibrillization of the thymus was detected in females in the 15 mg/kg/day group and in males and females in ≥70 mg/kg/day groups. Haemosiderin deposition, fibrillization, and recurrent bleeding in the thymus, spleen, and heart were detected in males and females in ≥70 mg/kg/day groups. Higher reticulocyte ratios were detected in males in ≥70 mg/kg/day groups. And prolonged PT in males and females, decreased body weight gain and decreased thymic weights in males were detected in 300 mg/kg/day groups (drug solutions that had or had not undergone forced degradation). By a 4-week washout, the changes above were recovered except for the lower thymic weights. For the recurrent bleeding in the thymus, spleen, and heart, studies conducted later (4.2.3.2.-6, 4.2.3.2-8) suggested that the flexibility of the probe used for oral dose was responsible in addition to the anticoagulation action of dabigatran etexilate methanesulfonate. Based on the above, the NOAEL was determined to be <15 mg/kg/day.

3.(iii).A.(2).3) Thirteen-week repeat oral dose toxicity studies in rats (attached document 4.2.3.2-6)

Following repeated oral administration of dabigatran etexilate methanesulfonate 30, 100, and 300 mg/kg as well as a mixture of dabigatran etexilate methanesulfonate added with 1% of its degradation product G 300 mg/kg to Wistar rats (n = 10/sex/group) for 13 weeks, 1 male in the 300 mg/kg/day (dabigatran etexilate methanesulfonate) group and 1 male and 1 female in the 300 mg/kg/day (containing G 1%) group died or were sacrificed. The causes of death or moribund states were determined to be unknown, incorrect administration, or the anticoagulation action of dabigatran etexilate methanesulfonate, respectively. Low spleen lymphocyte counts were observed in females in ≥100 mg/kg/day groups. Decreased locomotor activity, hunched position, piloerection, body temperature decreased, pallor, thoracodorsal cutaneous haemorrhage, thymus diseases (dark lesion, bleeding, eosinophilic crystal, inflammation, calcification, multinucleated giant cells), and hypercellularity of epithelium and vacuolation at the stomach border were observed in males and females in 300 mg/kg/day (without G content and with 1% G) groups. In addition, the gastric lesions were determined to be the changes caused by the local irritating property of the administered drug solution that exhibited acidity. The low spleen lymphocyte counts were determined to be unrelated to the administration of dabigatran etexilate methanesulfonate based on the lack of correlation with dose and the lack of other histopathological findings in the spleen. Based on the above, the NOAEL was determined to be 100 mg/kg/day.

3.(iii).A.(2).4) Twenty six-week repeat oral dose toxicity studies in rats (attached document 4.2.3.2-8, 4.2.3.2-9)

Following repeated oral administration of dabigatran etexilate methanesulfonate 10, 40, and 200 mg/kg to Wistar rats (n = 20/sex/group) for 26 weeks, 1 female in the 40 mg/kg/day group and 1 male in the 200 mg/kg/day group died. The causes of death were urinary tract infection (the female at 40 mg/kg/day) and unknown (the male at 200 mg/kg/day). Prolonged PT, haemosiderin deposition and fibrillization tendency in the spleen were detected in males and females in ≥10 mg/kg/day groups. Prolonged aPTT, high total bilirubin levels, haemosiderin deposition and fibrillization in the thymus were observed in males and females in the 200 mg/kg/day group. These findings were resolved or were recovering by a 6-week washout. The high total bilirubin levels were considered to be toxicologically irrelevant based on the absence of histopathological findings. Since the findings in the 10 and 40 mg/kg/day groups were mild and found in the control groups as well, the NOAEL was determined to be 40 mg/kg/day.

3.(iii).A.(2).5) Four-week repeat intravenous dose toxicity studies in rats (attached document 4.2.3.2-10)

Wistar rats (n = 10/sex/group) received repeated intravenous dabigatran 0.05, 0.5, or 5 mg/kg for 4 weeks. The NOAEL was determined to be 0.5 mg/kg/day based on the red urine, high blood fibrinogen levels, prolonged aPTT and TT, bleeding observed at administration sites, iliac lymph nodes, and the thymus observed in the 5 mg/kg/day group.

3.(iii).A.(2).6) Four-week repeat oral dose toxicity studies in rhesus monkeys (attached documents 4.2.3.2-15, 4.2.3.2-16)

Rhesus monkeys (n = 3/sex/group) received repeated oral dabigatran etexilate methanesulfonate 30, 100, or 300 mg/kg for 4 weeks. Prolonged PT and aPTT were detected in males and females in ≥30 mg/kg/day groups. Internal bleeding at blood sampling sites and changes in hematologic findings (low Hb, RBC, and Hct levels, high blood fibrinogen levels etc.) were observed in males and females in ≥100 mg/kg/day groups. Red colored stools, bleeding and polymorphonuclear infiltration at the urinary bladder serosal surface or the head subcutaneous tissue were observed in males in the 300 mg/kg/day group. By a 4-week washout, the findings above were recovered. The NOAEL was determined to be 30 mg/kg/day based on the above.

3.(iii).(2).7) Twenty six-week repeat oral dose toxicity studies in rhesus monkeys (attached documents 4.2.3.2-17)

Following repeated oral administration of dabigatran etexilate methanesulfonate 12, 36, or 200 mg/kg to rhesus monkeys (n = 4/sex/group) for 26 weeks, 1 female in the 200 mg/kg/day group was sacrificed because of serious anaemia. Prolonged PT and aPTT were observed in males and females in the 200 mg/kg/day group. Reduced body weight gain in males and reduced food consumption, bleeding (thymus, uterus, vagina and skin) in females were observed in the 200 mg/kg/day group. By a 6-week washout, the findings were recovered. The NOAEL was determined to be 36 mg/kg/day based on the above.

3.(iii).A.(2).8) Fifty two-week repeat oral dose toxicity studies in rhesus monkeys (attached document 4.2.3.2-18)

Following repeated oral administration of dabigatran etexilate methanesulfonate 12, 36, or 200 mg/kg to rhesus monkeys (n = 4/sex/group) for 52 weeks, 2 females in the 200 mg/kg/day group died and the cause was determined to be the dosing technique. In addition, 1 male in the 12 mg/kg/day group and 1 female in the 200 mg/kg/day group were sacrificed due to general deterioration of clinical conditions presumably caused by shigella infection. Prolonged TT or its tendency of it was observed in males and females in the 12 mg/kg/day. Prolonged PT and aPTT or their tendency of them in males and females were detected in ≥36 mg/kg/day groups. Bleeding or loss of blood caused by hematoma in males and females, and changes in hematologic findings (low Hb, RBC, Hct levels), retraction and atrophy of the thymus in males were observed in the 200 mg/kg/day group. By a 6-week washout, these findings were recovered. The NOAEL was determined to be 36 mg/kg/day based on the above.

3.(iii).A.(2).9) Four-week repeat intravenous dose toxicity studies in rhesus monkeys (attached documents 4.2.3.2-20, 4.2.3.2-21)

Rhesus monkeys (n = 3/sex/group) received repeated intravenous dose of dabigatran 0.8, 4, or 20 mg/kg for 4 weeks. Red swelling (oral periphery, anal, penis, vagina), internal bleeding, perivascular inflammation were observed in males and females, and changes in hematologic findings (low Hb, RBC, and Hct levels) were observed in females in the 20 mg/kg/day group. The NOAEL was determined to be 4.0 mg/kg/day based on the above.

3.(iii).A.(3) Genotoxicity

For the genotoxicity study, reverse mutation studies (4.2.3.3.1-4, 4.2.3.3.1-5, 4.2.3.3.1-6), mouse lymphoma tk assay (4.2.3.3.1-1, 4.2.3.3.1-2, 4.2.3.3.1-3), and human lymphocytes chromosomal aberration studies (4.2.3.3.1-14) as *in vitro*, and bone marrow micronucleus studies in rats (4.2.3.3.2-1, 4.2.3.3.2-2, 4.2.3.3.2-3) as *in vivo* studies were performed to evaluate the genotoxicity of dabigatran etexilate methanesulfonate and dabigatran. Based on the negative results in all the studies, it was determined that dabigatran etexilate methanesulfonate does not pose the risk of genetoxicity to humans.

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

3.(iii).A.(4).1) Carcinogenicity study in mice (attached document 4.2.3.4.1-1)

CD-1 mice (n = 54-63/sex/group) received repeated oral dabigatran etexilate methanesulfonate 30, 100, or 200 mg/kg for 102 to 104 weeks. With no increase observed in the frequency of neoplastic lesions by it, it was concluded that dabigatran etexilate methanesulfonate has no carcinogenicity. As non-neoplastic lesions, abnormal contents in the gastric intestinal tract and urinary bladder, necrosis hepatocellular, bleeding (alveolus, prostate gland, seminal vesicle), and expansion of uterine cavity and gland were detected.

3.(iii).A.(4).2) Carcinogenicity study in rats (attached document 4.2.3.4.1-2)

Wistar rats (n = 55-65/sex/group) received oral dabigatran etexilate methanesulfonate 30, 100, or 200 mg/kg for 104 weeks. Frequency of testicular cytoma in males in the 200 mg/kg/day group, and of ovarian granulosa cell tumor in females in ≥100 mg/kg/day groups increased. Since there were no significant differences from the control group and the increase in frequency was within the scope of the background control value, it was determined that they were not related to dabigatran etexilate methanesulfonate. Observed non-neoplastic lesions were; high mortality rates, pallor (internal organ and extremities), bleeding (nose, gastrointestinal tract, body cavity etc.), low RBC, Hct and Hb levels, prolonged PT and aPTT, high reticulocyte ratios, abnormal urinalysis values (RBC, Hb), prostatic findings (bleeding, inflammation, abscess, oedema, increase of pigment-phagocytic macrophage), ovarian cyst, increased pigment-phagocytic macrophage in the lungs, phagocytosis of lymphatic sinus erythrocytes or erythrocytes in lymph nodes, dermatitis, skin ulcers, thickening of the stomach border.

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

3.(iii).A.(5).1) Study on fertility and early embryonic development to implantation in rats (attached document 4.2.3.5.1-2)

Wistar rats (n = 24/sex/group) received oral dabigatran etexilate methanesulfonate15, 70, or 200 mg/kg from 29 days prior to mating and throughout the mating period in males, and from 15 days prior to mating to gestation day 6 in females. High preimplantation loss and low mean implantation numbers were seen in ≥70 mg/kg/day groups and decreased body weight gain, decreased food consumption, and a tendency for low corpora lutea numbers in males and females in the 200 mg/kg/day group were observed. The preimplantation loss and implantation numbers were within the scope of the background control values in the evaluation separately performed (4.2.3.5.1-1, 4.2.3.5.1-3) and were considered to be unrelated to dabigatran etexilate methanesulfonate. Based on the above, the NOAEL was determined to be 70 mg/kg/day for general toxicity

and 200 mg/kg/day for reproduction toxicity of parent animals.

3.(iii).A.(5).2) Study on embryo-fatal development of rats (attached document 4.2.3.5.2-1)

Following oral administration of dabigatran etexilate methanesulfonate15, 70, or 200 mg/kg to pregnant Wistar rats (n = 20-27/sex/group) from gestation day 7 to 16, 2 rats died in the 200 mg/kg/day group. Miscarriage was observed in 1 of the 2 animals. In dams, decreased body weight gain, decreased food consumption, tendency for higher numbers of resorption, and blood in the cornual area of the uterus were observed in ≥70 mg/kg/day groups. Higher numbers of resorption and blood in the vaginal opening were observed in the 200 mg/kg/day group. In fetuses on the other hand, bipartite ossification and malpositioning of sternebra, delayed ossification (occipital bone, cervical vertebral body, calcaneus, the 6th sternebra) were detected in ≥15 mg/kg/day groups, and lower fetal body weights, lower numbers of live fetuses, incomplete ossification of the occipital basilar apophysis, segmentation and branching of distant sternebra, separated body of the thoracic vertebra, and arcuate uterus were detected in the 200 mg/kg/day group. It was determined that findings in the fetuses in the 200 mg/kg/day group were caused by maternal toxicity and the delayed ossification was transient and of little toxicological significance. Based on the above, the NOAEL was determined to be 15 mg/kg/day for maternal general toxicity, 200 mg/kg/day for maternal reproduction toxicity, and 70 mg/kg/day for embryo-fatal development toxicity.

3.(iii).A.(5).3) Study regarding the embryo-fatal development of rabbits (attached document 4.2.3.5.2-3)

Following oral administration of dabigatran etexilate methanesulfonate 15, 70, or 200 mg/kg to pregnant Himalayan rabbits (n = 18-21/group) from gestation day 6 to 18, 1 rabbit in the 15 mg/kg/day group and 1 rabbit in the 70 mg/kg/day group died by incorrect dosing. No particular effects were noted in dams while in fetuses, fetal malformation (absent gallbladder, spina bifida, partially rudimentary brain, microglossia, lower appendicular skeletal muscle mass index associated with limb arthrosclerosis, cranial hernia, diaphragmatic thinning) in ≥15 mg/kg/day groups, and cerebral ventricle dilatation, hypoplastic gallbladder in the 200 mg/kg/day group were observed. The hypoplastic gallbladder and absent gallbladder were considered irrelevant to the effects of dabigatran etexilate methanesulfonate administered, based on the similar frequency detected in the study conducted to obtain the background value of the untreated control (4.2.3.5.2-4) using rabbits of the same strain. Other fetal malformations were determined to be unrelated to the administration of dabigatran etexilate methanesulfonate considering that they were solitary findings (spina bifida, partially rudimentary brain) or lacked dose-relationships (microglossia, lower appendicular skeletal muscle mass index associated with limb arthrosclerosis, cranial hernia, diaphragmatic thinning). The cerebral ventricle dilatation was determined to be irrelevant to the effect of dabigatran etexilate methanesulfonate because it emerged in a single animal of the litter. Based on the above, the NOAEL was determined to be 200 mg/kg/day for all of maternal general toxicity, reproduction toxicity, and embryo-fatal development toxicity.

3.(iii).A.(5).4) Study regarding prenatal and postnatal development of rats (attached document 4.2.3.5.3-2)

Following oral administration of dabigatran etexilate methanesulfonate 15, 30, or 70 mg/kg to Wistar rats (n = 21-29/group) from gestation day 6 to postnatal day 21, 1 rat in the 15 mg/kg/day group and 4 rats in the 70 mg/kg/day group died during pregnancy or delivery. The cause of the death during pregnancy was determined to be vaginal bleeding (1 in the 15 mg/kg/day group, and 1 in the 70 mg/kg/day group). In dams, intrauterine blood clot was observed in the 15 mg/kg/day group and 70 mg/kg/day group; spleen enlarged in ≥15 mg/kg/day groups; decreased body weight, decreased body weight gain in ≥30 mg/kg/day groups; and decreased food consumption in the 70 mg/kg/day group. In fetuses and babies (F_1), high postimplantation loss, high stillborn child numbers, low birth rates, and a tendency for low survival rates on day 4 after birth, and low weaning survival rate were noted in the 70 mg/kg/day group. Based on the above, the NOAEL was determined to be 30 mg/kg/day for maternal general toxicity, 70 mg/kg/day for maternal reproduction toxicity, and 70 mg/kg/day for F_1 animals.

3.(iii).A.(6) Phototoxicity (attached document 4.2.3.7-2)

An *in vitro* 3T3 NRU study was conducted with BALB/c 3T3 cells to expose dabigatran etexilate methanesulfonate to concentrations from 0.24 to 31.25 μg/mL under irradiation and non-irradiation of artificial sunlight. As a result, weak photoxicity was suggested in concentrations ≥15.63 μg/mL and the photoxicity ED_{50} value was determined to be 11.00 μg/mL.

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

Based on the *in vitro* 3T3 NRU study performed, dabigatran etexilate methanesulfonate is suggested to have phototoxicity, however, since the concentration range that exhibited phototoxicity was ≥15.63 μg/mL (ED_{50} value = 11.00 μg/mL), the applicant considered the photosafety of dabigatran etexilate is as follows:

Based on a presumably similar level of the maximum concentration in the plasma and skin suggested for dabigatran etexilate methanesulfonate by the systemic autoradiography results with rats, and its maximum plasma concentration of 291 ng/mL in humans, its maximum concentration in human skin is estimated as 291 ng/mL. This is approximately 1/50 the concentration that dabigatran etexilate methanesulfonate exhibits phototoxicity (15.63 mg/mL) and approximately 1/38 ED_{50}value (11.00 μg/mL). In clinical studies of dabigatran etexilate methanesulfonate on the other hand, the absence of clinical findings suggestive of phtotoxicity despite several years of administration to ≥950 subjects, warrants a conclusion that dabigatran etexilate methanesulfonate does not induce phototoxicity in humans.

PMDA asked the applicant to describe whether dabigatran has photoxicity or not since no photoxicity studies had been performed.

The applicant explained as follows:

The ultraviolet absorption spectrum is similar between dabigatran etexilate methanesulfonate and dabigatran both having the maximum absorption wavelength at ≥290 nm. The molar extinction/absorption coefficient was 6000 L/mol·cm for dabigatran etexilate methanesulfonate and 26,000 L/mol·cm for dabigatran. However,

dabigatran may have a cellular concentration lower than that of dabigatran etexilate methanesulfonate, taking into account: the lower membrane permeability that dabigatran demonstrated compared with dabigatran etexilate methanesulfonate in the membrane permeability study using Caco-2 cells; the extrapolability of the passive membrane permeability found in a cell strain to other strain under no involvement of active transport mechanism (Balimane PV, *et al*., *Arch Pharm Res.* 2007;30(4):507-518); and the absence of contribution of active uptake or active efflux to the transportation of dabigatran etexilate methanesulfonate or dabigatran in BALB/c 3T3 cells as suggested by the lack of P-glycoprotein (Pgp) expression in BALB/c 3T3 cells (Castro AF, *et al*., *Biochem Pharm.*1997;53:89-93). Therefore, it is inferred that dabigatran is not likely to pose stronger phototoxicity than dabigatran etexilate methanesulfonate.

PMDA accepted the response above but nonetheless considers that, because it is difficult to completely rule out the phototoxicity risk associated with dabigatran in clinical practice given the data submitted and because dabigatran etexilate methanesulfonate also exhibited weak phototoxicity, if phototoxicity related adverse events are reported during the post-marketing period, it is necessary to discuss on actions to be taken besides regarding this as a potential risk associated with dabigatran etexilate methanesulfonate. Clinical concerns other than phototoxicity may include bleeding associated with the pharmacological activity which will be adequately addressed by contraindicating patients with bleeding symptoms, patients with bleeding diathesis, and patients with hemostatic disorder in the package inserts together with adequate reminder regarding the risks in overdosage, to reduce safety concerns.

4. Clinical data

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

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

The solid oral formulations used in the studies included in the Clinical data section contain dabigatran etexilate methanesulfonate and the dose is expressed in terms of dabigatran etexilate.

4.(i).A.(1) Determination of concentration in biological samples

The dabigatran concentration in various samples was determined by HPLC-MS/MS, in which the lower limit of quantitation was 1.00 ng/mL for plasma, 1.00 ng/mL (2.0 or 20 ng/mL for some studies) for urine, and 0.100 ng/mL for dialysis samples. The plasma concentrations of dabigatran etexilate and its intermediate metabolites D and B, were measured by HPLC-MS/MS as was for dabigatran and the lower limit of quantitation was 1.00 ng/mL.

4.(i).A.(2) Bioequivalence (BE)

Various studies were performed in order to improve the solubility of dabigatran etexilate methanesulfonate in the course of development of the oral formulation and finally, a capsule formulation was selected filled by a content with a core of tartaric acid as its solubilizer. HPMC capsules have been used in major clinical studies conducted in Japan and foreign countries including the phase III multiregional clinical study, while gelatin capsules were used in a certain foreign clinical studies. The to-be-marketed formulation differs from

the HPMC capsule formulation used in the clinical studies in terms of the synthesis method of ingredients and the manufacturing process, but the formulations are identical.

4.(i).A.(2).1) BE of the formulation for clinical study and the to-be-marketed formulation (attached document 5.3.1.2.-11)

The formulation change standard between the 150 mg formulation used in the confirmatory trial and the 75 mg formulation (the to-be-marketed formulation) corresponds to the standard A referred to in "Guidelines for Bioequivalence Testing of Oral Drug Products with Different Strengths" (PFSB/ELD Notification No. 1124004 dated November 24, 2006). The dissolution defined in the specification satisfied the acceptance criteria for BE.

4.(i).A.(2).2) The relative BA of the HPMC capsule to the gelatin capsule (Study 1160.40, attached document 5.3.1.2-4, study period [redacted] to [redacted] 20[redacted]),

A crossover study was conducted in 12 foreign healthy adult male subjects. The 150 mg gelatin capsule was administered in the fasted state, followed by the 150 mg HPMC capsule in the fasted state, and then the 150 mg HPMC capsule after a meal (with a 14-day washout period between the treatment periods). Following single oral administration in the fasted state, the geometric mean ratio of C_{max} and $AUC_{0-\infty}$ of total dabigatran for the HPMS capsule versus the gelatin capsule was 94.6% and 91.0%, respectively.

4.(i).A.(2) Food effect (Study 1160.40, attached document 5.3.1.2-4, study period [redacted]to[redacted], 20[redacted])

Single oral dose of the 150 mg HPMC capsule was given to 12 foreign healthy adult male subjects in the fasted state and after a high-calorie, high-fat meal in a crossover fashion (with a 14-day washout period between the treatment periods). The median t_{max} of total dabigatran in the fasted state and after a high-calorie, high-fat meal was 2 and 4 hours, respectively; C_{max} was 93.1 ± 38.9 (mean ± standard deviation [SD]) and 93.9 ± 29.3 ng/mL, respectively; and $AUC_{0-\infty}$ was 687 ± 253 and 842 ± 259 ng·h/mL, respectively. The geometric mean ratios of C_{max} and $AUC_{0-\infty}$ for the fed administration to the fasted administration was 108.5% and 127.4%, respectively.

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

PMDA asked the applicant to explain the rationale for the omission of instructions for the timing of dosing relative to meals in the multiregional clinical study (Study 1160.26) that was to evaluate the relationship of efficacy and safety in the single dosing of the proposed product 110 mg and the proposed product 150 mg, although the AUC level of total dabigatran in fed administration was 27% higher than fasted administration found in Study 1160.40.

The applicant explained as follows:

While Study 1160.40 that evaluated the food effect using the HPMC capsule eventually saw an average 27% rise in $AUC_{0-\infty}$ after a meal, 1 subject exhibited an extremely low absorption in the fasted administration and reduced the mean value of the control group. No subjects demonstrated such low absorption in fed administration and the inter-individual variability was found smaller than in fasted administration (the

geometric coefficient of variation that indicates inter-individual variability was 51% in fasted administration and 32% in fed administration.). Since the difference between the two single dose, 110 mg and 150 mg, showed no discrepancies in efficacy and safety and since the trough and post-dose plasma concentrations of total dabiatran was dose-dependent, the degree of food effect is considered to have no clinical implications.

PMDA asked the applicant to provide the rationale for omitting instructions for the timing of dosing relative to meal in the administration of the proposed product, regarding the food effect when giving the proposed drug to Japanese patients.

The applicant responded as follows:
Study 1160.49 where 110 mg or 150 mg of dabigatran etexilate was administered twice daily to Japanese patients with non-valvular atrial fibrillation acquired information on whether meal was taken within 2 hours before the dosing prior to the blood sampling for pharmacokinetics. The plasma concentration of total dabigatran has been extracted in the time frame of 1 to 3 hours, 3 to 5 hours, and 10 to 16 hours post-dose from the data obtained in the study and has been tallied by the presence or absence of food intake after correcting the dose. While the plasma concentration at 1 to 3 hours post-dose in patients who took meal within 2 hours prior to administration was lower than those who did not take meal, the concentration rose in 3 to 5 hours and exceeded the concentration of the non-meal group eventually, suggesting delayed absorption by meal. The plasma concentration at 10 to 16 hours post-dose, which is the assumed time of the trough in twice daily dosing, was higher by 32% in the fed group. In order to assess whether the observed degree of food effect was related to the safety of dabigatran etexilate, the frequency of bleeding events and adverse events was evaluated by meal status prior to the administration of dabigatran etexilate (pre-dose rate of food intake). No consistent trends between the meal status and the frequency of bleeding or adverse events were found. Moreover, while no instructions on meal were defined related to dosing in Study 1160.26, dabigatran etexilate was not significantly inferior to warfarin, the control, in its safety excluding the frequency of symptoms related to dyspepsia, gastritis, and gastrointestinal haemorrhage. Based on the above, while the possibility cannot be ruled out for further assurance of safety by defining meal-related instructions in the administration of the proposed product, it is not necessary to restrict the administration to before or after a meal.

PMDA considers as follows:
Food effect on the pharmacokinetics of dabigatran etexilate was observed in the applicant's evaluation based on the obtained study results and when considering the high inter-individual variability of the plasma concentration of dabigatran, influence of the difference in the timing of dosing relative to meal cannot be ruled out on the efficacy and safety of the proposed product that requires a safer dose of 110 mg than the usual dose of 150mg. However, in Study 1160.62 where no meal-related instructions were defined, safety was not significantly inferior in the dabigatran etexilate group to the warfarin group that titrated the dose individually by monitoring the prothrombin time international normalized ratio (PT-INR). This indicates that omission of meal-related instructions has no major clinical implications in the dosage and administration defined in the study.

4.(ii) Summary of clinical pharmacology study

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

Results of *in vitro* studies using human biomaterials and of 48 clinical studies were submitted. Major results are shown below.

The formulation used is the HPMC capsule unless otherwise noted.

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

4.(ii).A.(1).1) Plasma protein binding and distribution in blood cells (attached documents 4.2.2.3-4, 5.3.1.1-3)

Human plasma added with ^{14}C-labeled dabigatran 50-5000 ng/mL (final concentration) was incubated. As a result, the plasma protein binding of ^{14}C-labeled dabigatran was constant regardless of the concentration.

Foreign healthy male adult subjects received a single oral dose of ^{14}C-labeled dabigatran etexilate methanesulfonate (200 mg as dabigatran etexilate) as solution or intravenous infusion of ^{14}C-labeled dabigatran 5 mg. As a result, the ratio of blood cell radioactivity to plasma radioactivity was 0.1 to 0.4 up to 8 hours post-dose in either administration.

4.(ii).A.(1).2) *In vitro* metabolism

(a) Metabolism of dabigatran etexilate methanesulfonate, dabigatran, and intermediate metabolite B, intermediate metabolite D (attached documents 4.2.2.6-1, 5.3.2.2-2)

Human liver microsomes were added with 100 μM of dabigatran etexilate methanesulfonate, dabigatran, or intermediate metabolite B or D and incubated at 37°C for 60 minutes (5 or 60 minutes for dabigatran etexilate methanesulfonate) in the presence or absence of nicotinamide adenine dinucleotide phosphate (NADPH). As a result, no dependency on NADPH was observed in the metabolism of any compound. Human liver microsomes pre-incubated in the presence of erythromycin (an irreversible inhibitor of NADPH and CYP3A) (1-100 μM) were added with 100 μM of ^{14}C-labeled dabigatran etexilate methanesulfonate, and then were incubated at 37°C for 30 minutes. As a result, no effects of erythromycin on the ester hydrolysis of dabigatran etexilate methanesulfonate or on the metabolites generation of dabigatran etexilate methanesulfonate were observed. Human CYP expression systems (CYP1A1, 1A2, 2A6, 2B6, 2C9-Arg, 2C19, 2D6-Val, 2E1, 3A4, 4A11) were added with 100 μM of ^{14}C-labeled dabigatran etexilate methanesulfonate and incubated for 60 minutes. Virtually no metabolism of dabigatran etexilate methanesulfonate was detected. In the presence of NADPH, human liver microsomes were added with different esterase inhibitors (paraoxon, bis-4-nitrophenylphosphate [BNPP], tetra-isopropylpyrophosphamide [*iso*-OMPA], phenylmethyl sulfonylfluoride [PMSF]) and dabigatran etexilate methanesulfonate or D, and incubated for 20 minutes. D generated by the metabolism of dabigatran etexilate methanesulfonate was 0.98% to 17.2% of the control group (no inhibitors added) and dabigatran generated by D was 10.0% to 14.1% of the control group (no inhibitors added). Moreover, human plasma was added with 10 mM of ethylenediaminetetraacetic acid

(esterase inhibitor) and 100 μM of dabigatran etexilate methanesulfonate, and incubated for 60 minutes. D generated by the metabolism of dabigatran etexilate methanesulfonate was 12.6% of the control group (no inhibitors added).

(b) Enzyme inhibition (attached document 5.3.2.2-1)

In human liver microsomes, dabigatran etexilate methanesulfonate, dabigatran, B, and D did not inhibit the activity of CYP 1A1/2, 2B6, 2C9, 2C19, 2D6, 2E1, 3A, or 4A11 at up to 10 μM. Dabigatran etexilate methanesulfonate at 100 μM, inhibited the activity of CYP2E1 and 3A4 by approximately 50%, and inhibited by up to 34% of the activity of other CYP forms. Of the inhibitory effects of dabigatran, B, and D at 100 μM on different CYP forms, the largest effect was detected in D against CYP1A2 (approximately 36% of the activity was inhibited).

(c) Enzyme induction (attached document 5.3.2.2-3)

Primary human hepatocytes were added with dabigatran etexilate methanesulfonate at 0.05, 0.1, 0.5, 1, 5, and 10 μM or with dabigatran at 0.1, 0.5, 1, 3, 10, and 30 μM (final concentration) and incubated for 3 days to evaluate enzyme activities of CYP1A2, 2B6, and 3A4. Enzyme activities induced by dabigatran etexilate methanesulfonate and dabigatran versus vehicle (0.08% DMSO) were 0.59- to 0.89-fold and 1.0- to 1.2-fold, respectively, in CYP1A2; 1.0- to 1.2-fold and 0.89- to 1.3-fold, respectively, in CYP2B6; and 0.85- to 0.96-fold and 0.87- to 0.97-fold, respectively, in CYP3A4. On the other hand, the enzyme activities induced by β-naphthoflavone, phenobarbital, and rifampicin (inducers of CYP1A2, 2B6, and 3A4) were 32-fold, 69-fold, and 32-fold that of the vehicle (0.08% DMSO), respectively.

(d) Glucuronic acid conjugation reaction of dabigatran (attached document 4.2.2.4-1)

Human liver, ileum, and jejunum microsomes were added with different concentrations of dabigatran (liver, 0.5-750 ng/mL; ileum, 10-1000 ng/mL; jejunum, 10-750 ng/mL) and incubated in the presence of UDP-glucuronic acid. As a result, the intrinsic clearance that indicates glucuronic acid conjugation reaction (V_{max}/K_m) was 0.462 to 4.083, 0.002 to 0.021, and 0.007 to 0.017 μL/mg/min, respectively.

Human UGT expression systems (UGT 1A1, 1A3, 1A4, 1A6, 1A7, 1A8, 1A9, 1A10, 2B4, 2B7, 2B15, 2B17) were added with dabigatran (150 or 750 μM) at pH 6.0 or 7.4 and incubated. As a result, glucuronic acid conjugation reaction was detected under any conditions in UGT1A9, 2B7, and 2B15 expression systems. The V_{max}/K_m of each conjugating enzyme was 0.004, 0.002, and 0.062 μL/mg/min, respectively, when dabigatran was added to UGT 1A9, 2B7, and 2B15 expression systems.

4.(ii).A.(1).3) *In vitro* Drug transporter study (attached document 4.2.2.2-1 to -3)

(a) Membrane permeability and Pgp transport

Involvement of the membrane permeability and drug transporter of ^{14}C-labeled dabigatran etexilate methanesulfonate and ^{14}C-labeled dabigatran was evaluated using Caco-2, the human colon carcinoma derived cells. Dabigatran etexilate methanesulfonate was transported from the basal side (B) to the apical side (A) with the apparent average permeation rate increased from 10×10^{-6} to 22×10^{-6} cm/s toward

absorption (A to B) and decreased from 62 × 10^{-6} to 8 × 10^{-6} cm/s toward secretion (B to A) with the increasing concentration (0.6-40 μM) of dabigatran etexilate methanesulfonate. B to A/A to B ratio of dabigatran etexilate methanesulfonate (2 μM) was 4.53, while in the presence of Pgp inhibitors, ciclosporin (12 μM), verapamil (200 μM), and zosquidar (5 μM), the ratio was 1.21, 1.39, and 0.83, respectively. In the presence of MK571 (25 μM), a multi-drug resistance associated protein (MRP) 2 inhibitor, the ratio was 3.15.

The apparent mean permeation rate when dabigatran was added in 3 and 300 μM was 0.35×$10^{-6}$and 0.31 × 10^{-6} cm/s A to B, respectively, while 0.36 × 10^{-6} and 0.30 × 10^{-6} cm/s B to A, respectively. The B to A/A to B ratio on the other hand, was 1.09 and 0.95, respectively, demonstrating a low and directionless permeability, at a similar level to mannitol that is not affected by the presence of Pgp inhibitors.

The B to A/A to B ratio of dabigatran etexilate methanesulfonate (2 μM) and dabigatran (10 μM) in the Lewis lung carcinoma porcine proximal tubule cell line (LLC-PK1 cells) with human Pgp expressed in the cell which is, MDR1-expressing LLC-PK1 cells, was 7.33 and 1.35 times, respectively.

(b) Effects of Pgp inhibition and Pgp inhibitory effects of dabigatran etexilate

Inhibition of the dabigatran etexilate methanesulfonate transport by Pgp inhibitors was evaluated using Caco-2 cells. Transportation of dabigatran etexilate methanesulfonate was inhibited by amiodarone, clarithromycin, digoxin, itraconazole, quinidine, and ritonavir. The IC_{50} was >10 μM, 17.1, 74.5, 0.47, 33.4, and 13.2 μM, respectively.

Transcellular transport of digoxin was studied using MDR1-expressing LLC-PK1 cells in the presence or absence of dabigatran etexilate methanesulfonate (0.1-10 μM) or dabigatran (1-100 μM). Dabigatran etexilate methanesulfonate and dabigatran did not inhibit the directional transport of digoxin at up to the highest concentration investigated.

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

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

(a) Study 1160.28 (attached documents 5.3.3.3-4, 5.3.1.4-18, study period [redacted] to [redacted],20[redacted])

Table 1 shows the pharmacokinetic parameters of the plasma concentration of total dabigatran and dabigatran in Japanese healthy male adult subjects and Caucasian healthy male adult subjects with oral fasted administration of dabigatran etexilate 50 and 150 mg.

Table 1. Pharmacokinetic parameters of single and oral dose of dabigatran etexilate in Japanese and Caucasian healthy male adults
(Adapted from submitted data)

	Dose (mg)	N	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-tz} (ng·h/mL)	$AUC_{0-\infty}$ (ng·h/mL)	$t_{1/2}$ (h)
Total dabigatran							
Japanese	50	16	44.1 [70.5%]	2.00	328 [58.8%]	348 [55.4%]	8.07 [15.8%]
	150	15	123 [88.2%]	2.02	1010 [82.1%]	1050 [79.7%]	9.78 [14.2%]
Caucasian	50	16	38.8 [73.6%]	2.00	366 [64.8%]	389 [57.9%]	9.22 [13.4%]
	150	15	105 [96.0%]	2.00	988 [73.0%]	1030 [68.8%]	10.5 [21.8%]
Dabigatran							
Japanese	50	16	38.8 [70.7%]	2.00	270 [67.2%]	295 [59.0%]	7.59 [17.5%]
	150	15	102 [90.3%]	2.02	850 [82.7%]	880 [80.0%]	9.76 [14.2%]
Caucasian	50	16	34.9 [72.6%]	2.00	308 [72.4%]	334 [60.8%]	8.68 [23.8%]
	150	15	90.0 [95.5%]	2.00	850 [74.5%]	889 [70.2%]	10.5 [22.7%]

Other than t_{max}, geometric mean ratios [Geometric coefficient of variation], t_{max}, median
AUC_{0-tz}, the area under the plasma concentration-time curve from time 0 to the time of the last point with quantifiable concentration

The ratio of geometric mean AUC_{0-tz} for 1-*O*-, 2-*O*-, 3-*O*-, and 4-*O*- acyl glucuronides to total dabigatran was 5.51%, 4.16%, 3.53%, and 1.04%, respectively, in Japanese subjects, and 5.21%, 3.60%, 3.48% and 1.04%, respectively, in Caucasian subjects.

(b) Study 1160.1 (attached document 5.3.3.1-2, Study period [redacted] to [redacted], 19[redacted])

Following single oral administration of 10, 30, 100, 200, or 400 mg of dabigatran etexilate methanesulfonate to 40 foreign healthy male subjects (6 subjects for active drug, 10 subjects for placebo) as solutions in the fasted state, the median t_{max} for dabigatran ranged from 1.25 to 1.75 hours; C_{max} was 8.27, 21.5, 79.3, 126, and 243 ng/mL, respectively; and AUC_{0-12} was 40.0, 107, 375, 638, and 1240 ng·h/mL, respectively. The $t_{1/2}$ after administration of 100, 200, and 400 mg of dabigatran was 8.20, 9.83, and 10.4 hours, respectively.

(c) Study 1160.6 (attached document 5.3.1.1-3, study period [redacted] to [redacted], 20[redacted])

Following single intravenous administration of ^{14}C-labeled dabigatran 5 mg to 10 foreign healthy male adult subjects (5 subjects per group), the AUC_{0-tz} of total dabigatran was 524 ng·h/mL, the CL was 149 mL/min, and the steady-state V was 76.9L. After single fasted oral administration of ^{14}C-labeled dabigatran etexilate methanesulfonate as solutions equivalent to 200 mg of dabigatran etexilate, the AUC_{0-tz} was 1130 ng·h/mL and the absolute BA was 7.16%

4.(ii).A.(2).2) Multiple-dose study

(a) Study 1160.61 (attached document 5.3.3.3-9, Study period [redacted] to [redacted], 20[redacted])

Table 2 shows the pharmacokinetic parameters of plasma total dabigatran concentrations following multiple

oral administration of dabigatran etexilate 110 or 150 mg to Japanese and Caucasian healthy male adults in the fed state twice daily for 7 days.

Table 2. Pharmacokinetic parameters of total dabigatran after 110 or 150 mg of dabigatran etexilate administered twice daily for 7 days (adapted from the submitted data)

		110 mg of dabigatran etexilate twice daily		150 mg of dabigatran etexilate twice daily	
Day of measurement	Parameters	Japanese	Caucasian	Japanese	Caucasian
Day 1		N = 12	N = 12	N = 12	N = 12
	$AUC_{\tau,1}$[a] (ng·h/mL)	485 [19.6%]	392 [41.0 %]	623 [23.0 %]	696 [25.6 %]
	C_{max} (ng/mL)	94.4 [26.3 %]	68.6 [41.7 %]	116 [27.9 %]	118 [26.2 %]
	t_{max}(h)	4.00	3.00	4.00	3.00
Day 7		N = 11	N = 12	N = 12	N = 12
	$AUC_{\tau,ss}$ (ng·h/mL)	818 [18.8 %]	652 [44.4 %]	1,100 [19.1 %]	1,190 [26.0 %]
	$C_{max,ss}$ (ng/mL)	124 [25.5 %]	92.2 [47.3 %]	169 [26.3 %]	171 [26.1 %]
	$t_{max,ss}$(h)	4.00	3.00	4.00	4.00
	$t_{1/2,ss}$ (h)	10.7 [19.8 %]	13.7 [27.6 %]	11.8 [13.7 %]	12.4 [9.88 %]
	$R_{A,AUC,13}$[b]	1.71 [23.6 %]	1.66 [21.7 %]	1.77 [19.0 %]	1.72 [10.4 %]
	$R_{A,Cmax,13}$[c]	1.33 [31.0 %]	1.35 [28.2 %]	1.46 [23.1 %]	1.46 [14.8 %]

Other than $t_{max,}$ geometric mean ratios [geometric coefficient of variation]; $t_{max,}$ median
a. AUC after single dose
b. Cumulative rate of the dosing interval τ after the 13th dose indicated as comparison of AUC ratio after 13 doses and a single dose.
c. Cumulative rate of the dosing interval τ after the 13th dose indicated as a comparison of C_{max} after 13 doses and a single dose

4.(ii).A.(2).3) Evaluation of metabolism and pharmacokinetics in humans (Study 1160.6, attached document 5.3.3.1-1, study period [redacted] to [redacted], 20[redacted])

Following intravenous administration of ^{14}C-labeled dabigatran 5 mg to 5 foreign healthy male adult subjects, the ratio of dabigatran in the total plasma radioactivity was 99.3%, at 40 minutes, 98.0% at 2 hours, and 95.7% at 4 hours post-dose. Dabigatran was detected in 76.8% and 1.9% of the administered dose in urine and stool, respectively. Following single oral administration of ^{14}C-labeled dabigatran etexilate methanesulfonate as solution (equivalent to 200 mg of dabigatran etexilate) to 5 foreign healthy male adult subjects, only dabigatran was detected in the plasma at 2, 4, and 6 hours post-dose. Dabigatran was detected in 4.3% and 66.1% of the administered dose in urine and stool, respectively.

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

4.(ii).A.(3).1) Pharmacokinetics in Japanese patients with non-valvular atrial fibrillation (Study 1160.49, attached document 5.3.5.1-3, study period [redacted] 20[redacted] to [redacted] 20[redacted])

Following multiple oral administration of dabigatran etexilate 110 or 150 mg to Japanese patients with non-valvular atrial fibrillation twice daily for 12 weeks, the trough concentration of total dabigatran in plasma was 64.2 ± 43.2 (average ± SD) (41 patients) at Visit 3 (Day 4-10 of administration), 65.4 ± 39.7 (40 patients) at Visit 5 (Week 4 of administration), and 73.4 ± 42.2 ng/mL (39 patients) at Visit 7 (Week 12 of study) in

the 110 mg group of dabigatran etexilate; and 98.3 ± 76.1 (55 patients) at Visit 3, 92.8 ± 54.2 (50 patients) at Visit 5, and 90.2 ± 65.2 ng/mL (49 patients) at Visit 7 in the 150 mg group of dabigatran etexilate.

4.(ii).A.(3).2) Pharmacokinetics in foreign patients with non-rheumatic atrial fibrillation (Study 1160.20, attached document 5.3.5.1-1, study period [redacted] 20[redacted] to [redacted] 20[redacted])

Following multiple oral administration of dabigatran etexilate 50, 150 or 300 mg to foreign patients with non-rheumatic atrial fibrillation twice daily, the trough concentration of total dabigatran in plasma was 29.6 ± 17.7 (95 patients) at Visit 3 (Day 4-7 of administration), 30.0 ± 20.0 (91 patients) at Visit 5 (Week 4 of administration), and 30.2 ± 19.0 ng/mL (83 patients) at Visit 7 (Week 12 of study), in the 50 mg group of dabigatran etexilate; and 87.2 ± 59.3 (143 patients) at Visit 3, 95.1 ± 67.5 (140 patients) at Visit 5, and 92.7 ± 66.3 ng/mL (122 patients) at Visit 7 in the 150 mg group of dabigatran etexilate; and 185 ± 108 (136 patients) at Visit 3, 194 ± 118 (135 patients) at Visit 5, and 207 ± 129 ng/mL (121 patients) at Visit 7 in the 300 mg group of dabigatran etexilate.

4.(ii).A.(3).3) Pharmacokinetics in Japanese and Caucasian patients with non-valvular atrial fibrillation (Study 1160.26, attached document 5.3.5.1-4, study period [redacted] 20[redacted] to [redacted] 20[redacted])

Following multiple oral administration of dabigatran etexilate 110 or 150 mg to Japanese and Caucasian patients with non-valvular atrial fibrillation twice daily, the trough concentrations of total dabigatran in plasma in the steady-state (1 month post-randomization) were 81.2 ± 58.8 (4223 patients) and 114 ± 81.9 ng/mL (4218 patients), respectively, in the overall population; 64.5 ± 38.1 (96 patients) and 94.6 ± 49.0 ng/mL (103 patients), respectively, in the Japanese population. The plasma concentrations of total dabigatran in the steady-state at 2 hours post-dose were 153 ± 95.8 (4579 patients) and 213 ± 32 ng/mL (4598 patients), respectively, in the overall population; and 114 ± 66.4 (100 patients) and 177 ± 104 ng/mL (105 patients), respectively, in the Japanese population.

4.(ii).A.(3).4) Pharmacokinetic analysis in the patient population (attached document 5.3.5.3-2)

Pharmacokinetic analysis in the patient population was performed using 7931 plasma concentration data of 1965 patients in total. The data was obtained from Study 1160.19 on foreign patients who had undergone orthopedic surgery, Study 1160.20 (PETRO study) on foreign patients with non-rheumatic atrial fibrillation, and Study 1160.49 on Japanese patients with non-valvular atrial fibrillation. Dosage and administration, and the number of subjects administered in the 3 studies are as follows:

Study 1160.19: dabigatran etexilate (gelatin capsules) 50, 150, or 225 mg twice daily, as well as 300 mg once a day, 1435 patients, (blood sampling score, 4663 points)

Study 1160.20: dabigatran etexilate (gelatin capsules) 50, 150, or 300 mg twice daily, 427 patients (2603 points)

Study 1160.49: dabigatran etexilate 110 or 150 mg twice daily, 103 patients (665 points)

Distribution of major background factors of subjects included in the analysis was; age 68 (21-93) [median (range)], body weight 80 (43-155) kg, serum creatinine 0.87 (0.27-3.27) mg/dL, creatinine clearance (CL_{cr}) 88 (20-358) mL/min, glomerular filtration rate 70 (32-131) mL/min/1.73m^2; sex, male, 1005 female 960;

race, 1851 Caucasians, 107 Asians, 7 Blacks; indications, 1435 patients with deep vein thrombosis, 530 patients with atrial fibrillation (including 103 Japanese patients). Other than the factors above, hemoglobin level, history of smoking and drinking, presence or absence of left ventricular dysfunction, concomitant drugs (Pgp inhibitors, proton pump inhibitors [PPI], H_2 receptor antagonists etc.) were evaluated as covariates.

A 2-compartment model was selected with an absorption lag time and a primary absorption process as the basic model for the pharmacokinetics of total dabigatran. Inter-individual variability was incorporated in the apparent volume of distribution of the central compartment (V2/F) and the primary absorption rate constant (ka) in the proportional error model. The population mean of relative bioavailability (F) was fixed at 1 and inter-individual variability was incorporated in the proportional error model. For residual variability, a mixed model of proportional error and equal error was employed. The effects of CL_{cr} on the apparent clearance (CL/F) were incorporated into the model preferentially at the basic model stage to obtain a model with linear function up to CL_{cr} 120 mL/min and a constant CL/F at ≥120 mL/min.

Evaluation of covariates found significant effects in; CL_{cr}, age, sex, and indications as covariates on CL/F; body weight on V2/F; and presence or absence of concomitant use of PPI and concomitant use of Pgp inhibitors on F.

In patients with CL_{cr} ≥120 mL/min, CL/F was estimated to be 111 L/h while in patients <with 120 mL/min, a 0.64% reduction was estimated for CL/F of total dabigatran in line with every 1 mL/min decrease of CL_{cr}. CL/F was lower in women by 12.5% compared with men. CL/F decreased by 0.66% with 1 year aging from 68, the median age of the population included in the analysis. In patients with atrial fibrillation, CL/F was lower by 6.1% compared with patients who had orthopedic surgery. V2/F in a patient weighing 80 kg was estimated to be 728 L and the value increased by 1.10% in response to 1 kg increase. Concomitant use of Pgp inhibitors increased F by 15% but decreased PPI by 14.6%. Inter-individual variability related to V2/F, ka, and F was 26.1%, 95.3%, and 44.7%, respectively.

4.(ii).A.(4) Evaluation of intrinsic factors

4.(ii).A.(4).1) Pharmacokinetics in patients with renal impairment (Study 1160.23, attached document 5.3.3.3-6, study period [redacted] 20[redacted] to [redacted] 20[redacted])

Following oral administration of dabigatran etexilate 150 mg in the fasted state to foreign healthy adults (6 subjects) and subjects with mild (CL_{cr}, 50-80 mL/min, 6 patients), moderate (CL_{cr}, 30-50 mL/min, 6 patients), and severe ($CL_{cr.}$ <30 mL/min, 11 patients) renal impairment, the median t_{max} of total dabigatran was 2.00, 2.50, 2.00, and 2.00 hours, respectively; C_{max} was 85.3 ± 38.6 (mean ± SD), 109 ± 89.5, 138 ± 39.3, and 205 ± 126 ng/mL, respectively; $AUC_{0-\infty}$ was 901 ± 528, 1580 ± 1380, 2470 ± 263, and 6150 ± 3750 ng·h/mL, respectively; $t_{1/2}$ was 13.8 ± 4.02, 16.6 ± 8.71, 18.7 ± 3.20, and 27.5 ± 4.29 hours, respectively; and renal clearance was 62.9 ± 10.5, 42.0 ± 11.7, 25.6 ± 7.46, and 10.3 ± 5.47 mL/min, respectively. Following oral administration of dabigatran etexilate 50 mg in the fasted state to 6 patients under hemodialysis with end-stage renal disorder, the difference in plasma concentration of total dabigatran between the entrance and exit

sites of dialyzer at 0 to 0.5, 2, and 4 hours of dialysis and the drug concentration in the dialysis fluid demonstrated that 61% of total dabigatran in the circulating blood is eliminated by dialysis.

4.(ii).A.(4).2) Pharmacokinetics in patients with hepatic dysfunction (Study 1160.51, attached document 5.3.3.3-7, study period [redacted] to [redacted], 20[redacted])

Following oral administration of dabigatran etexilate 150 mg in the fasted state to foreign healthy adults (12 subjects) and subjects with mild hepatic dysfunction (Child Pugh Class B, 12 patients), the median t_{max} of total dabigatran was 2.00 hours in both groups; C_{max} was 107 ± 71.9 and 76.1 ± 71.2ng/mL, respectively; $AUC_{0-\infty}$ was 937 ± 649 and 922 ± 965 ng·h/mL, respectively; $t_{1/2}$ was 11.5 ± 1.70 and 11.8 ± 3.25 hours, respectively; and renal clearance was 65.2 ± 23.5 and 63.1 ± 24.0 mL/min, respectively. In the healthy adults, intermediate metabolite B and D were detected in up to a concentration of 1.42 and 1.51 ng/mL, respectively, and until 1.5 hours post-dose. In subjects with hepatic dysfunction, B exhibited its peak plasma concentration 2.67 ng/mL and was quantifiable until 2.00 hours post-dose while the peak plasma concentration of D was 28.6 ng/mL and D was quantifiable until 8.00 hours post-dose. AUC of dabigatran etexilate, D, and B was 26%, 8.5%, and 0.44%, respectively, of the AUC of total dabigatran in patients with hepatic dysfunction, while all were <0.4% in the healthy adults. Neither the protein binding of dabigatran nor the ratio of glucuronides AUC to total dabigatran AUC markedly differed between the healthy adults and subjects with hepatic dysfunction.

4.(ii).A.(4).3) Pharmacokinetics in the elderly (Study 1160.10, attached document 5.3.3.3-3, study period [redacted] 20[redacted] to [redacted] 20[redacted])

Following multiple oral administration of dabigatran etexilate 150 mg to 18 foreign healthy elderly (≥65) subjects (9 subjects per sex) twice daily in the fed state for 7 days, the C_{max} of total dabigatran was 256 and 255 ng/mL (mean), respectively, AUC_{τ} was 1770 and 1820 ng·h/mL in the male and female elders, respectively, at 4 days post-dose. C_{max} was 227 and 285 ng/mL, respectively, and AUCτ was 1670 and 1980 ng·h/mL, respectively, at 7 days post-dose.

4.(ii).A.(5) Drug interaction

4.(ii).A.(5).1) Pharmacokinetic interactions

(a) Pantoprazole (Study 1160.34, attached document 5.3.3.4-6, study period [redacted] to [redacted] 20[redacted])

Dabigatran etexilate 150 mg (gelatin capsules) was administered to 18 foreign healthy adult subjects in a crossover fashion (with a 14-day washout period), using the following 2 treatment regimens: On one regimen, subject received pantoprazole 40 mg twice daily on Day −2 and Day −1 and received pantoprazole at the same dose, followed 1 hour later by a single oral dose of dabigatran etexilate 150 mg in the fasted state on Day 1; and on the other regimen, administration of single oral dose of dabigatran etexilate 150 mg alone in the fasted state. The geometric mean for the $AUC_{0-\infty}$ and C_{max} of total dabigatran with and without concomitant pantoprazole were 71.5% (90% confidence interval [CI], 56.8-90.1) and 60.0% (45.7-78.8), respectively.

(b) Amiodarone (Study 1160.57, attached document 5.3.3.4-7, study period [redacted] to [redacted] 20[redacted])

An open group comparative study was conducted with 24 foreign healthy adult subjects (12 subjects per group) in 2 treatment groups: One group received 150 mg of dabigatran etexilate twice daily for 3 days from Day 1 to Day 3, followed by oral dose of dabigatran etexilate 150 mg and amiodarone 600 mg on Day 4; and the other group received a single dose of amiodarone 600 mg on Day 1. The geometric mean for the $AUC_{\tau,ss}$ and $C_{max,ss}$ of total dabigatran with and without concomitant amiodarone were 158% (90% CI, 128-195) and 150% (117-190), respectively. On the other hand, the geometric mean for the $AUC_{0-\infty}$ and C_{max} of amiodarone with and without concomitant dabigatran were 110% (83.8-145) and 112% (82.3 to 153), respectively.

(c) Atorvastatin (Study 1160.58, attached document 5.3.3.4-8, study period [redacted] to [redacted] 20[redacted])

A three period, cross-over study was conducted in 24 foreign healthy adult subjects using the following 3 treatment regimens (with a washout ≥6 days): On the first regimen, dabigatran etexilate 150 mg was administered twice daily (in the fasted state in the morning and in the fed state in the evening) for 3 days from Day 1 to Day 3, followed by a single dose on Day 4 in the morning; and on the second regimen, the first regimen was accompanied with 80 mg of concomitant oral dose of atorvastatin for 4 days only in the morning from Day 1 to Day 4 in the fasted state; or on the third regimen, 80 mg atorvastatin alone was orally administered for 4 days from Day 1 to Day 4 in the morning in the fasted state. The geometric mean for the $AUC_{\tau,ss}$ and $C_{max,ss}$ of total dabigatran with and without concomitant atorvastatin were 82.1% (90% CI, 72.6-92.9) and 80.0% (70.1-91.4), respectively. The geometric mean for the $AUC_{\tau,ss}$ and $C_{max,ss}$ of atorvastatin with and without concomitant dabigatran etexilate were 118% (105-132) and 106% (89.8-125), respectively.

(d) Verapamil (Study 1160.74, attached document 5.3.3.4-10, study period [redacted] to [redacted] 20[redacted])

Drug interaction in the concomitant use of single or multiple dose of verapamil with dabigatran etexilate was studied in foreign healthy adults with different dosing time relations and different formulations of verapamil (immediate release tablets [IR tablet] or extended release tablets [ER tablet]). Single dose of verapamil was administered in a cross-over fashion (with a washout ≥4 days), while multiple dose of verapamil was in a fixed dosing order. Table 3 shows the results.

Table 3. Effect of verapamil on the pharmacokinetic parameters of total dabigatran by treatment regimen (adapted from the submitted data)

	Dosage and administration of verapamil	Dosage and administration of Dabigatran etexilate methanesulfonate	n	Geometric mean ratio [a][%] (90% CI)	
				$AUC_{0-\infty}$	C_{max}
1	120 mg (IR) single oral dose	150 mg of single oral dose followed by verapamil dose 1 hour later	20	243 (191-308)	279 (215-362)
2	120 mg (IR) single oral dose	150 mg of single oral dose and verapamil dose at the same time	20	208 (164-264)	229 (176-297)
3	240 mg (ER) single oral dose	150 mg of single oral dose and verapamil dose at the same time	20	171 (134-217)	191 (147-248)
4	120 mg (IR) multiple oral dose twice daily for 3 days (Day 1-Day 3)	150 mg single oral dose followed by morning verapamil dose 1 hour later on Day 4	20	154 (119-199)	163 (122-217)
5	In addition to 4, 120 mg (IR) multiple oral dose twice daily from Day 6 to Day 7.	150 mg single oral dose 2 hours prior to Day 8 morning verapamil dose	20	118 (91-152)	112 (84-149)
6	In addition to 5, 120 mg (IR) multiple oral dose 4/day from Day 10 to 11	150 mg single oral dose followed by morningverapamil dose 1 hour later on Day 12	19	139 (107-181)	134, (100-180)

a:The total dabigatran $AUC_{0-\infty}$ or C_{max} with concomitant drug/the total dabigatran $AUC_{0-\infty}$ or C_{max} without concomitant drug

(e) Quinidine (Study 1160.90, attached document 5.3.3.4-15, study period [redacted] to [redacted] 20[redacted])

A two period, cross-over study was conducted in 32 foreign healthy adults using the following 2 treatment regimens: On Regimen A, 200 mg of quinidine was administered every 2 hours 5 times in total, followed by a 6-day washout, and then by oral dose of dabigatran etexilate 150 mg twice daily for 2 days, then 1 morning dose on Day 3, and 3 hours later, start oral dose of quinidine 200 mg every 2 hours 5 times in total, then with an oral dose of dabigatran etexilate 150 mg 1 hour later; and on Regimen B, 150 mg of oral dabigatran etexilate was administered twice daily for 3 days (6 days washout period for subjects on Regimen A $\rightarrow$ B, $\geq$2 days washout period for subjects on Regimen B $\rightarrow$ A). The geometric mean for the $AUC_{\tau,ss}$ and $C_{max,ss}$ of total dabigatran increased by approximately 53% and 56%, respectively, compared with dabigatran etexilate alone. Concomitant use of quinidine did not prolong $t_{1/2}$ but delayed t_{max} for 2 hours. The geometric mean for the $C_{max,ss}$ of dabigatran etexilate, D, and B increased by 38.7%, 42.5%, and 48.4%, respectively, compared with dabigatran etexilate alone. At the final dabigatran etexilate dose 1 hour after the 5th quinidine dose, no differences were found in the AUC_{0-tz} and C_{max} of quinidine and 3-OH-quinidine from those with quinidine alone.

(f) Clarithromycin (Study 1160.82, attached document 5.3.3.4-13, study period [redacted] to [redacted] 20[redacted])

A study with fixed sequences was conducted in 20 foreign healthy adult subjects. Single oral administration of dabigatran etexilate 150 mg in the fasted state (Control period 1), after a $\geq$5 days washout period, was followed by clarithromycin 500 mg twice daily for 4 days, with a single dabigatran etexilate 150 mg 1 hour after the initial dose (Study period 1). Then, 4 days of 500 mg clarithromycin twice daily was further followed by another clarithromycin for 1 day on Day 5 (Control period 2) and then by clarithromycin 500 mg in the morning on the next day with subsequent single dose of dabigatran etexilate 150 mg 1 hour later (Study period 2). In the administration of dabigatran etexilate following the initial dose of clarithromycin 1 hour later (Study period 1), the geometric mean for the $AUC_{0-\infty}$ and C_{max} of dabigatran decreased by approximately

10% and 13%, respectively, compared with the administration of dabigatran etexilate alone (Control period 1). In the concomitant use of clarithromycin in multiple dose (Study period 2), the geometric mean for the $AUC_{0-\infty}$ and C_{max} of total dabigatran increased by approximately 19% and 15%, respectively, compared with the administration of dabigatran etexilate alone. On the other hand, concomitant use of dabigatran etexilate did not affect the $AUC_{\tau,ss}$ and $C_{max,ss}$ of clarithromycin.

(g) Rifampicin (Study 1160.100, attached document 5.3.3.4-16, study period [redacted] to [redacted] 20[redacted])

Dabigatran etexilate 150 mg was orally administered to 24 foreign healthy adult subjects. Following oral dose of dabigatran etexilate 150 mg once in the morning in the fasted state on Day 1, rifampicin was orally administered once daily in the evening (8:00 pm) for 7 days from Day 2 to Day 8. Then, oral dose of dabigatran etexilate 150 mg followed, once in the morning in the fasted state, on Day 9, Day 16, and Day 23. As a result, the geometric mean for the $AUC_{0-\infty}$ and C_{max} of total dabigatran on Day 9 decreased to 33% and 34%, respectively, of those on Day 1, and the urinary excretion rate decreased to 33% of the result on Day 1. On the other hand, no effects of rifampicin were observed in the $t_{1/2}$ and renal clearance of total dabigatran and the ratio of dabigatran in total dabigatran. The geometric mean for the $AUC_{0-\infty}$ of total dabigatran on Day 16 and Day 23 were 82% and 85%, respectively, of the result prior to rifampicin administartion.

(h) Ketoconazole (Study 1160.101, attached document 5.3.3.4-17, study period [redacted] to [redacted] 20[redacted])

Dabigatran etexilate 150 mg was orally administered to 24 foreign healthy adult subjects. Following oral administration of dabigatran etexilate 150 mg once after breakfast on Day 1 (Period 1), and after a 6-day washout from Day 2 to Day 7, dabigatran etexilate 150 mg and ketoconazole 400 mg were orally administered once after breakfast on Day 8. Then, oral dose of ketoconazole 400 mg once after breakfast on Day 9 (Period 2), oral dose of ketoconazole 400 mg once daily after breakfast from Day 10 to Day 16, and oral dose of dabigatran etexilate 150 mg once after breakfast on Day 15 (Period 3) followed. As a result, the geometric mean for the $AUC_{0-\infty}$ and C_{max} of total dabigatran was 2.38-fold and 2.35-fold dabigatran etexilate alone (Day 1), respectively, in the concomitant use of single ketoconazole and single dabigatran etexilate (Day 8), and 2.53-fold and 2.49-fold, respectively, after the multiple dose of ketoconazole (Day 15).

Other than mentioned above, studies were conducted with diclofenac sodium and digoxin for their drug interaction with dabigatran etexilate but virtually no effects on the pharmacokinetic parameters (AUC and C_{max}) of total dabigatran and the concomitant drugs were observed depending on their presence or absence.

4.(ii).A.(5).2) Pharmacodynamic interactions

(a) Enoxaparin (Study 1160.78, attached document 5.3.3.4-12, study period [redacted] to [redacted] 20[redacted])

A two period cross-over study was conducted in 23 foreign healthy adult subjects using 2 regimens (with a washout period ≥5 days). One regimen administered dabigatran etexilate 220 mg once in the morning on Day 1 in the fasted state and the other regimen subcutaneously administered enoxaparin 40 mg once daily in the morning for 3 days from Day -3 to Day -1, followed by oral dose of dabigatran etexilate 220 mg in the fasted state once in the morning on Day 1. As a result, the geometric mean for the $AUC_{0-\infty}$ and C_{max} of total

dabigatran after the prior administration of enoxaparin was 84% and 86%, respectively, of those with dabigatran etexilate alone. The area under the curve of the effect of the activities by Factor Xa plus Factor IIa when dabigatran etexilate was administered after the prior enoxaparin ($AUEC_{0-48}$) and the maximum ratio to the baseline (values in the screening) (ER_{max}) were 164% and 115%, respectively, of the results obtained by administrating dabigatran etexilate alone.

(b) Clopidogrel (Study 1160.83, attached document 5.3.3.4-14, study period [redacted] to [redacted] 20[redacted])

A three period cross-over study was conducted in 24 foreign healthy adult subjects using the following 3 regimens (a 14-day washout): Regimen A, multiple dose of dabigatran etexilate 150 mg twice daily for 2 days followed by a single dose of clopidogrel 150 mg on Day 3; Regimen B, a single dose of clopidogrel 300 mg followed by multiple dose of clopidogrel 75 mg once daily for 4 days; and Regimen C, a single dose of clopidogrel 300 mg, followed by multiple dose of clopidogrel 75 mg once daily for 4 days with multiple dose of dabigatran etexilate 150 mg twice daily for 2 days starting on Day 3, followed by a single dose of dabigatran etexilate 150 mg on Day 5. No effects of the concomitant use of dabigatran etexilate and clopidogrel were observed on the pharmacokinetic parameters ($AUC_{0-tz,ss}$, $C_{max,ss}$, t_{max} etc.) of total dabigatran and clopidogrel as well as the pharmacodynamic indices related to the activity of dabigatran (aPTT, ECT, TT) or clopidogrel (ADP-induced platelet aggregation).

After single administration of clopidogrel 600 mg to 12 foreign healthy adult subjects, followed by a 14-day washout, and then by oral dose of dabigatran etexilate 150 mg twice daily for 4 days (once daily only in the morning on Day 4) with concomitant clopidogrel 600 mg in the morning on Day 4, the $AUC_{\tau,ss}$ and $C_{max,ss}$ of total dabigatran with concomitant clopidogrel were higher by 32% and 43%, respectively, than with dabigatran etexilate alone.Prolonged coagulation markers (aPTT, ECT, TT) and approximately 36% increase in the $AUEC_{\tau,ss}$ of ECT, which was the most affected, were observed.

4.(ii).A. (6) Pharmacodynamic evaluation

4.(ii).A.(6).1） Single oral dose in foreign healthy adults (Study 1160.1, attached document 5.3.3.1-2, study period [redacted] to [redacted] 19[redacted])

Following oral administration of dabigatran etexilate methanesulfonate 10, 30, 100, 200, or 400 mg to 30 (6 subjects per group) foreign healthy adults as solution in the fasted state, aPTT prolongation and PT-INR effect - time course were parallel to the time course of the plasma total dabigatran and plasma dabigatran concentrations. The maximum effect was expressed at the same time point with the C_{max} of total dabigatran and dabigatran. The maximum aPTT prolongation at ≥100 mg was 1.5 to 2.4 times. The mean aPTT prolongation at 8 hours post-dose was 1.24-fold in the 100 and 200 mg group, and 1.51-fold in the 400 mg group.

4.(ii).A.(6).2) Multiple oral dose in Japanese and Caucasian healthy adults (Study 1160.61, attached document 5.3.3.3-9, study period [redacted] to [redacted] 20[redacted])

Table 4 shows the pharmacodynamic parameters after multiple oral dose of dabigatran etexilate 110 or 150

mg to Japanese and Caucasian healthy male adults twice daily for 7 days in the fed state.

Table 4. Pharmacodynamic parameters following multiple oral dose of dabigatran etexilate 110 or 150 mg to Japanese and foreign healthy adults twice daily for 7 days (adapted from submitted data)

Dosage and administration	dabigatran etexilate 110 mg twice daily		dabigatran etexilate 150 mg twice daily	
Subjects	Japanese (N = 11)	Caucasian (N = 12)	Japanese (N = 12)	Caucasian (N = 12)
aPTT[a]	1.83 ± 0.144	1.85 ± 0.222	1.97 ± 0.185	1.94 ± 0.315
ECT[a]	2.22 ± 0.295	2.05 ± 0.305	2.69 ± 0.377	2.62 ± 0.404

a: ratio of the pharmacodynamic parameters on Day 7 of the multiple dose to baseline (mean ± SD)

4.(ii).A.(7) Effect on the QTc interval (Study 1160.54, attached document 5.3.4.1-1, study period [redacted] to [redacted] 20[redacted])

A randomized, double-blind, four period cross-over study was conducted (with a washout period ≥4-days) in 40 foreign healthy adult subjects (20 subjects per sex). Single oral administration of dabigatran etexilate 150, 600 mg, or placebo was followed by a single oral dose of moxifloxacin 400 mg (positive control). Following oral administration of dabigatran etexilate 150 or 600 mg, the median t_{max} of total dabigatran was 2.0 and 3.0 hours, respectively, while the geometric mean (range) for the C_{max} was 87.8 (17.4-281) and 383 (146-769) ng/mL, respectively.

Changes from baseline in the mean QTcI (corrected QT interval) of dabigatran etexilate 150, 600 mg, or placebo near the t_{max} of dabigatran (1.5-3 hour post-dose) was -6.59 to -3.53 (upper limit of the 90% CI, -2.39 to 0.67), -6.64 to -3.90 (-2.43 to 0.21) and -5.54 to -2.23 (-1.34 to 1.89) ms, respectively. The QTcI 1.5 to 3.0 hours after moxifloxacin was prolonged by 9.4 ms from baseline and by 14.2 ms from placebo.

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

4.(ii).B.(1) Pharmacokinetic differences between Japanese and non-Japanese populations

Based on the comprehensive meta-analysis using the Phase I and Phase II studies in healthy adults, patients who had received lower limb orthopedic surgery, and patients with non-valvular atrial fibrillation, the applicant concluded that the pharmacokinetics after dabigatran etexilate administration were similar to each other between Japanese and Caucasian subjects. However, while Study 1160.29 demonstrated higher total dabigatran exposure to Japanese than to Caucasian subjects in healthy adults, the comparison of the plasma total dabigatran concentration between the overall study population and the Japanese subgroup in Study 1160.26 revealed lower values in the Japanese subgroup than the overall population in patients with non-valvular atrial fibrillation. Considering these results, PMDA asked the applicant to explain the causes of such differences and to separately explain the pharmacokinetic differences between Japanese and non-Japanese patients with non-valvular atrial fibrillation rather than a “comprehensive meta-analysis”.

The applicant explained as follows:

Based on the 14 Phase I studies conducted in Japanese and non-Japanese healthy adults, it is considered that there are no significant pharmacokinetic differences between Japanese and Caucasian healthy adults. In the

studies, the geometric mean for the $AUC_{\tau,ss}$ of dabigatran etexilate 110 or 150 mg twice daily was higher in Japanese than in Caucasians by 25% and 33%, respectively. However, the difference between the median turned out smaller, which were 6% and 21%, respectively, and in the 10th to 90th percentile range of individual data, the data range of Japanese subjects was virtually included in the range of Caucasian subjects. On the other hand, in the comparison of pharmacokinetics in patients with non-valvular atrial fibrillation, no differences in trough concentration were observed between Japanese and Caucasians in Phase II study regarding the plasma total dabigatran concentration. While Study 1160.26 found the trough concentration ($C_{pre,ss}$) in Japanese patients lower than the overall study population by approximately 11%, with the concentration at 2 hours post-dose ($C_{2,ss}$) lower by approximately 19%, the data range of Japanese patients was within the data range of overall study population at the 10th and 90th percentile, leading to a conclusion that there are no significant pharmacokinetic differences between Japanese and non-Japanese patients either (see Figure 1.).

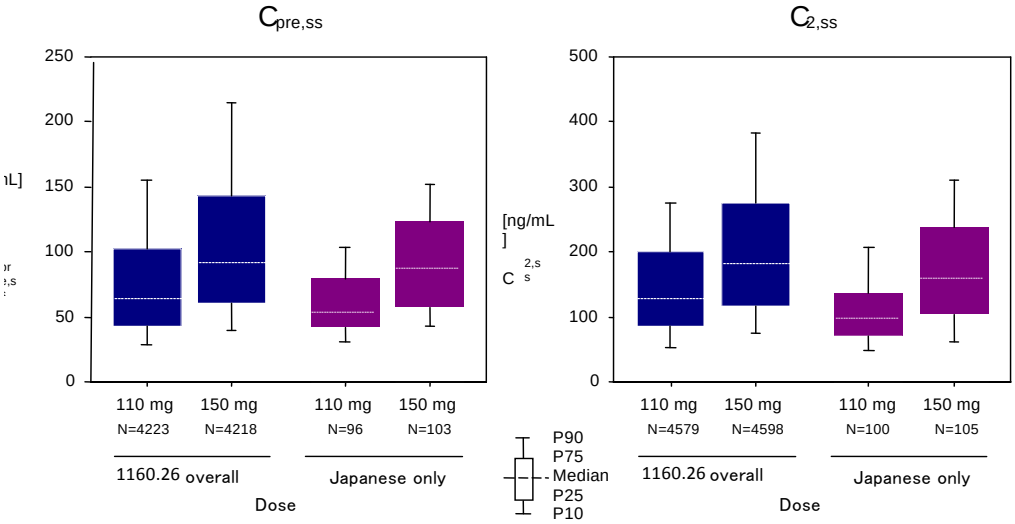


Figure 1. Trough and 2 hours post-dose plasma total dabigatran concentration in the steady state in Study 1160.26 (adapted from submitted data)

PMDA considers as follows:

Although the inter-individual variability of the plasma concentration of dabigatran etexilate is large, the pharmacokinetic differences observed between Japanese and non-Japanese populations was not to become much problem by setting up identical dosage between both population in interpreting the results obtained in Study 1160.26.

4.(ii).B.(2) Relation between exposure and reaction in dabigatran etexilate

The applicant explained the relation between the exposure of dabigatran etexilate, and its efficacy and safety as follows:

In Study 1160.26, no clear differences were observed depending on the occurrence or no occurrence of stroke and systemic embolism in either the trough concentration in plasma and plasma concentration at 2 hours post-dose of total dabigatran, or the aPTT at each time point. This indicates that minor differences in the plasma concentration of dabigatran etexilate did not affect its efficacy significantly. On the other hand, the

aggregated data by the dosage of dabigatran etexilate demonstrated a clearly lower incidence of efficacy related events in the 150 mg group than in the 110 mg group, and this indicates that dosage was more related to efficacy.

In Study 1160.26, the trough concentration of total dabigatran in plasma was the most applicable indicator to predict bleeding events among the trough concentration in plasma, plasma concentration at 2 hours post-dose of total dabigatran, and the aPTT at each time point. Based on an evaluation of the influence on the relation between the plasma trough concentration and the bleeding risk by age, renal function, or concomitant drugs and other factors that affect the exposure of total dabigatran, it was predicted that a certain degree of variation due to such factors would not affect the bleeding risk significantly. However, when more than one factors coincide with each other, for example, in the elderly with deteriorated renal function who concomitantly used aspirin (ASA) for example, altered relation between the increased exposure and bleeding risk could significantly increase the bleeding risk.

PMDA asked the applicant to explain the reason for concluding that the dosage was more related to efficacy than exposure, taking into consideration the inter-individual variability of 74% to 82% in the trough concentration and 2 hours post-dose concentration of dabigatran observed in Study 1160.26 [see "4.(ii).A.(3).3 Pharmacokinetics in Japanese and Caucasian patients with non-valvular atrial fibrillation"]

The applicant explained as follows:
Since the inter-individual variability of the plasma concentration was large after oral dabigatran etexilate dose but small after the intravenous dose of dabigatran (coefficient of geometric variation, 17.9%), it was considered that the inter-individual variability was mainly caused by the difference in absorption. Reflecting the large inter-individual variability, Study 1160.26 demonstrated differences of exposure in accordance with the differences in dosage when comparing the 10th percentile, geometric mean, and the 90th percentile of concentration between dosage groups while distribution of individual concentration data overlapped between the 110 mg group and 150 mg group of dabigatran etexilate. Reduction in the occurrence of stroke is expected with the increase in exposure when considering the action mechanism of dabigatran etexilate. However in Study 1160.26, while increase in exposure of dabigatran etexilate was observed by aging and deterioration of renal function, frequency of stroke rose in line with aging and in line with the decrease of CL_{cr}. In the elderly or patients with deteriorated renal functions, exposure of dabigatran etexilate will increase but at the same time, frequency of stroke will likely increase too because it is a risk factor for stroke at the same time. Patients were randomized in Study 1160.26 leaving no inter-group difference in the distribution of age or renal functions and higher efficacy was confirmed in the 150 mg group compared with the 110 mg group.

Based on the above data, it was discussed that dosage had been better related to efficacy than exposure.

PMDA considers as follows:
Based on the applicant's explanation, it is possible to consider that the efficacy of dabigatran etexilate may not increase correspondingly with the amount of dabigatran exposure depending on the patients' background

factors. This makes it difficult to explain how it will affect the efficacy, if dose of dabigatran etexilate is reduced for safety or to reduce the risk of bleeding events particularly in patients with background factors that could increase exposure. On the other hand, dose reduction for risk avoidance should be accepted, given the explanation by the applicant that bleeding risk will increase in patients with background factors that could increase exposure, and therefore, the relationship between exposures and bleeding risk may be different in the presence of multiple background factors that increases exposure. The validity of the dosage and administration will continuously be evaluated in the clinical section [see "4.(iii).B.(3) Dosage and administration"]

4.(ii).B.(3) Drug interaction mediated by Pgp

4.(ii). B.(3).1) Interaction between dabigatran etexilate and verapamil

PMDA asked the applicant to discuss on necessary alert regarding concomitant use of dabigatran etexilate with verapamil, considering that; increase in the total dabigatran exposure in the concomitant use of dabigatran etexilate with verapamil may be similar to that in the concomitant use with ketoconazole that is contraindicated for concomitant use in the package insert (draft) depending on the relation of timing between the proposed product and verapamil; concomitant use of the proposed product with verapamil is expected in Japanese patients with non-valvular atrial fibrillation; and the proposed product requires reduction in view of the exposure of dabigatran etexilate or the bleeding risk in the patient.

The applicant, given the results of Study 1160.74, explained that alert would be provided in the package insert (draft) to take the proposed product ≥2 hours prior to verapamil for 3 days from the start of verapamil when the proposed product is used concomitantly with verapamil.

PMDA asked the applicant to explain the rationale of the proposed alert to specify ≥2 hours prior to verapamil administration when dosing the proposed product as well as the rationale of specifying 3 days as the duration.

The applicant responded as follows:

It is considered that the interaction between dabigatran etexilate and verapamil demonstrated in Study 1160.74 was caused by the inhibition of Pgp in the gastrointestinal tract and the reduction in the interaction by multiple dose could possibly be caused by the induction of Pgp by verapamil (Lemma GL *et al. Clin Pharmacol Ther.* 2006;79:218-230, Collet A *et al. Biochem Pharmacol.* 2004;68:783-790). By dosing dabigatran etexilate prior to verapamil, most of the absorption process of dabigatran etexilate should complete without being affected by verapamil in the gastrointestinal tract.

According to the results of Study 1160.74, the half-life of verapamil was 5.21 hours, and the half-life of norverapamil, a metabolite, was 7.15 hours. Based on the absence of significant differences in the plasma concentration of verapamil and norverapamil between immediately before and 12 hours after the morning dose on Day 3 of verapamil multiple dose, the pharmacokinetics of verapamil is considered to reach the steady-state within 3 days when administered twice daily. The alert mentioned earlier has been defined given the decreased effect on the exposure of dabigatran etexilate in the steady-state of verapamil than in single-

dose administration, and the demonstrated reduction of the effect on the exposure of dabigatran etexilate by dosing dabigatran etexilate 2 hours prior to verapamil as well. Concomitant use of verapamil in the steady-state is cautioned in the package insert (draft) considering the 50% to 60% increase of dabigatran etexilate exposure.

PMDA considers as follows:
While the mechanism is unknown for the reduction of interaction with dabigatran etexilate caused by multiple dose of verapamil, the alert based on the data from Study 1160.74 regarding the interaction between verapamil and dabigatran etexilate may avoid significant rise of dabigatran etexilate in the plasma concentration as detected in the single concomitant use of verapamil and dabigatran etexilate. The final decision on whether establishing an alert for the concomitant use of dabigatran etexilate and verapamil is appropriate or not, will be based on the result of the expert discussion.The appropriateness of the alert for the concomitant use of dabigatran etexilate and verapamil will be finally determined considering the results in the expert discussion.

4.(ii).B.(3).2) Interactions between dabigatran etexilate and other Pgp inhibitors
The applicant explained that they found in an *in vitro* evaluation that the possibility is low for concomitant use with ciclosporin A, itraconazole, or nelfinavir (all with minor Pgp inhibitory effect) to exceed the amount of exposure detected in the study with verapamil or ketoconazole. It has been also described that, the gastrointestinal concentration of the inhibitor when dabigatran etexilate is absorbed, is a critical factor on the degree of effect from Pgp inhibitors on the plasma total dabigatran concentration. Based on these facts, PMDA asked the applicant to consider the gastrointestinal concentration of representative Pgp inhibitors and explain again if concomitant use with these Pgp inhibitors really has smaller effect on the plasma total dabigatran concentration than the concomitant use with ketoconazole.

The applicant explained as follows:
IC_{50} in the membrane transport inhibition of dabigatran etexilate by the Pgp inhibitors obtained from *In vitro* studies was compared with gastrointestinal concentrations of the Pgp inhibitors determined from literature reports. The gastrointestinal concentration of ketoconazole orally administered in 400 mg is estimated to be 3011 μM, an equivalent to 891 times the *in vitro* IC_{50} value. It is assumed that the gastrointestinal Pgp is completely inhibited in the concomitant use with ketoconazole, although the timing of dose, dissolution from the drug product, solubility, and loss from the gastrointestinal tract are taken into account. In view of these, the increase rate (AUC up to 2.53 times) of dabigatran etexilate BA under this circumstance is considered to represent a complete inhibition of gastrointestinal Pgp. Therefore, the possibility that the concomitant use with other strong Pgp inhibitors should not produce larger influence than the concomitant use with ketoconazole is considered to be extremely low.

PMDA asked the applicant to assess the necessity for contraindicating nelfinavir for concomitant use which has higher ratio of estimated gastrointestinal concentration and IC_{50}value than ketoconazole and itraconazole contraindicated for concomitant use, or saquinavir and ritonavir for which possibility for complete inhibition

of gastrointestinal Pgp cannot be ruled out although they are associated with lower ratio of estimated gastrointestinal concentration and IC_{50}value than ketoconazole and itraconazole. These matters were asked to be discussed by taking into account information on alerts in other countries and safety measures the applicant proposes.

The applicant explained as follows:
While the estimated gastrointestinal concentrations for various Pgp inhibitors are based on the assumption that the drug administered has been entirely dissolved, nelfinavir, saquinavir, and ritonavir are of low solubility into water and their actual gastrointestinal concentrations may possibly be lower than the values estimated this time. Since no interaction studies have been conducted for these 3 drugs and the proposed product, the degree of rise in the blood concentration of dabigatran etexilate is unknown in concomitant use of them in humans. No examples of concomitant use with these drugs have been reported in the multiregional clinical studies either in the overall study population or in the Japanese subgroup. Consequently, no conclusion could be reached concerning to the effects of concomitant use on bleeding events. Considering these circumstances, the proposed package insert (draft) in the European and the US applications alerts for concomitant use with nelfinavir, saquinavir, and ritonavir as well as other Pgp inhibitors except for ketoconazole.

Based on the above, the package insert in Japan (draft) contraindicates ketoconazole (except for topical administration) and itraconazole for concomitant use, and calls for attention on Pgp inhibitors including nelfinavir, irritonavir, and saquinavir for concomitant use that may increase bleeding event risk by rising the blood concentration of dabigatran etexilate. Interaction with these drugs will be verified in the specified use-results survey intended in the basic plans such as post-marketing surveillance (PMS) and further caution will be discussed such as revision of the interaction section in the instructions for use as needed.

PMDA accepted the explanation of the applicant as the above.

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 45 studies (2 Japanese Phase I and 1 Phase II studies, 39 foreign Phase I and 2 Phase II studies, 1 multiregional clinical study conducted in Japan and overseas) were submitted. The results from 1 Japanese and 8 foreign clinical studies were submitted as reference data [see "4.(i). Summary of biopharmaceutic studies and associated analytical methods" and "4.(ii). Summary of clinical pharmacology study" for BE and pharmacokinetics.] The results from the main studies are summarized below.

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

4.(iii).A.(1).1) Single oral dose study (Study 1160.28, attached document 5.3.3.3-4, study period [redacted] to [redacted] 20[redacted])

A double-blind study was conducted in 40 Japanese and Caucasian healthy adult male subjects (20 Japanese

subjects, 20 Caucasian subjects) at 1 study site in the UK. The subjects received single oral dose of dabigatran etexilate 50, 150, or350 mg or placebo in an escalation regimen in the fasted state (fasting ≥10 hours) (a ≥13-day washout). However, the study was terminated at the completion of the 150 mg dose period and 350 mg dose was not carried out.

An adverse event was observed in 1 Japanese subject at 50 mg dose (influenza).

No clinically relevant variations were observed in clinical laboratory tests, vital signs, and ECG.

4.(iii).A.(1).2) Single and multiple oral dose studies (Study 1160.29, attached document 5.3.3.3-5, study period, [redacted] 20[redacted] to [redacted] 20[redacted])

An open-label study was conducted in 42 Japanese and Caucasian healthy adult male subjects (21 Japanese subjects, 21 Caucasian subjects) at 1 study site in France. The subjects received a single oral dose of dabigatran etexilate 150, 220, or 300 mg after breakfast, followed by a 5-day washout and then the same oral dosage for 7 days (150 mg once daily after breakfast, 220 mg once daily after breakfast, and 150 mg twice daily after breakfast and dinner).

Adverse events in Japanese subjects were found in; 1 subject (headache) in 150 mg single dose, 5 subjects (stomachache, 1 subject; bloating, 5 subjects) in 220 mg multiple dose, 1 subject (haematuria) in 300 mg single dose, 1 subject (abdominal pain upper) in 300 mg multiple dose, while in Caucasian subjects were found in; 1 subject (epistaxis) in 150 mg multiple dose, 1 subject (rash) in 220 mg multiple dose, and 2 subjects (rhinitis) in 300 mg multiple dose.

Regarding the clinical laboratory tests, haematuria was found in 1 Japanese subject post single 300 mg dose and shift to the multiple dose phase was halted. No abnormal findings or abnormal variations were observed in vital signs and ECG.

4.(iii).A.(1).3) Multiple oral dose study (Study 1160.61, attached document 5.3.3.3-9, study period [redacted] to [redacted] 20[redacted])

An open-label study was conducted in 48 Japanese and Caucasian healthy adult male subjects (24 Japanese subjects, 24 Caucasian subjects) at 1 study site in Japan. The subjects received multiple oral dose of dabigatran etexilate 110 or 150 mg twice daily after breakfast and dinner for 7 days.

Adverse events were found in Japanese subjects alone, in 2 subjects (nausea, periodontitis, 1 subject each) in the 110 mg group and in 2 subjects (abdominal pain, gingival bleeding, 1 subject each) in the 150 mg group with 1 subject discontinued due to the development of an adverse event.

No clinically relevant variations were observed in clinical laboratory tests, vital signs, and ECG..

4.(iii).A.(1).4) High single oral dose study (Study 1160.60, attached document 5.3.3.1-4, study period [redacted] 20[redacted])

A double-blind study was conducted in 10 foreign healthy adult male subjects at 1 study site in Germany. The subjects received a single oral dose of dabigatran etexilate 600, 750, or 900 mg, or placebo in the fasted state (≥10-hour fasting). The study was discontinued at the completion of the 600 mg period. The 750 mg and 900 mg doses were never administered.

Adverse events were observed in 2 subjects (nausea, puncture site phlebitis, 1 subject each) at 600 mg.
No clinically relevant variations were observed in clinical laboratory tests, vital signs, and ECG.

4.(iii).A.(1).5) Multiple oral dose study in the elderly (Study 1160.10, attached document 5.3.3.3-3, study period [redacted] to [redacted], 20[redacted])

An open-label study was conducted in 36 foreign healthy elderly subjects aged ≥65 (male 18, female 18) at 1 study site in Germany. The subjects received multiple oral dose of dabigatran etexilate 150 mg twice daily after breakfast and dinner for 7 days (dabigatran etexilate alone group), or multiple oral dose of pantoprazole 40 mg twice daily after breakfast and dinner for 2 days, followed by multiple oral dose of dabigatran etexilate 150 mg and multiple oral dose of pantoprazole 40 mg twice daily after breakfast and dinner for 7 days (concomitant pantoprazole group).

Adverse events were found in 5 subjects in the dabigatran etexilate alone group (haematoma, 2 subjects; bloating, faeces soft, back pain, phlebitis, 1 subject each) and in 3 subjects in the concomitant pantoprazole group (faeces soft, 2 subjects; haematoma, gingival bleeding, bloating, 1 subject each).

No clinically relevant variations were observed in clinical laboratory tests, vital signs, and ECG.

4.(iii).A.(1).6) Single-dose study in patients with decreased renal function (Study 1160.23, attached document 5.3.3.3-6, study period [redacted] 20[redacted] to [redacted] 20[redacted])

An open-label study was conducted to orally administer a single dose of dabigatran etexilate 50 (end-stage renal disorders group) or 150 mg (other groups) in 35 foreign subjects with no renal disorders or with varying degrees of renal disorders (control group [CL_{cr}, >80 mL/min], 6 subjects; mild renal disorders group [50< CL_{cr}, ≤80 mL/min], 6 patients; moderate renal disorders group [30< CL_{cr}, ≤50 mL/min], 6 patients; severe renal disorders group [CL_{cr} ≤30 mL/min], 11 patients; end-stage renal disorders group [uremia that requires dialysis],6 patients) in the fasted state (a ≥10-hour fasting) at 1 study site in Germany.

Adverse events were noted in 2 patients during screening (headache, infusion site swelling, 1 patient each), 6 patients from 1day pre-dose to 4-5 days post-dose (headache, 2 patients; diarrhoea, dyspepsia, bloating, post procedural bleeding, 1 patient each), and 5 patients at 4 to 5 days post-dose and after (sleep disorder, dizziness, headache, tremor, joint swelling, 1 patient each).

No clinically relevant variations were observed in clinical laboratory tests, vital signs, and ECG.

4.(iii)A.(1).7) Single-dose study in patients with decreased hepatic function (Study 1160.51, attached document 5.3.3.3-7, study period [redacted] to [redacted] 20[redacted])

An open-label study was conducted in 12 foreign subjects with no hepatic disorder and 12 subjects with moderate liver disorder at 1 study site in Germany. The subjects received single oral administration of dabigatran etexilate 150 mg in the fasted state (a ≥10-hour fasting).

Adverse events were noted in 4 subjects during screening (speech disorder/hypoacusis/dysphagia, psoriasis, ear discomfort, nasal congestion, 1 subject each), 4 patients under treatment by dabigatran etexilate (headache, 2 subjects; back pain, erythema, 1 subject each), and 1 subject post-treatment (hypoglycemia, 1 subject).

No clinically relevant variations were observed in clinical laboratory tests, vital signs, and ECG.

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

4.(iii).A.(2).1) Foreign Phase II study (Study 1160.20, attached document 5.3.5.1-1, study period [redacted] 20[redacted] to [redacted] 20[redacted])

A parallel comparative group study was conducted in patients with paroxysmal, persistent, or permanent(chronic), non-rheumatic atrial fibrillation having ≥1 risk factors for stroke at 55 sites in total located in Denmark, Netherlands, Sweden, and the US in order to evaluate safety and efficacy of dabigatran etexilate used with or without concomitant ASA. The details are as follows:

Target number of subjects, 476 in total; concomitant use of dabigatran etexilate 50 mg twice daily and ASA 0 mg once daily (dabigatran etexilate 50 mg bid + ASA 0 mg qd group), dabigatran etexilate 50 mg bid + ASA 81 mg qd group, and dabigatran etexilate 50 mg bid + ASA 325 mg qd group, 34 subjects each; dabigatran etexilate 150 mg bid + ASA 0 mg qd group, dabigatran etexilate 150 mg bid + ASA 81 mg qd group, dabigatran etexilate 150 mg bid + ASA 325 mg qd group, dabigatran etexilate 300 mg bid + ASA 0 mg qd group, dabigatran etexilate 300 mg bid + ASA 81 mg qd group, and dabigatran etexilate 300 mg bid + ASA 325 mg qd group, 51 subjects each; 68 subjects in warfarin group.). In this study, a 3 × 3 factorial trial design was adopted with the 3 doses of dabigatran etexilate (50, 150, or 300 mg bid) and the 3 doses of ASA (0, 81, or 325 mg qd) as factors. There were 10 dose groups in total with a warfarin group added as a control. Dosage and administration were defined as 50, 150, or 300 mg of dabigatran etexilate twice daily (after breakfast and dinner) with 0, 81, or 325 mg of concomitant ASA once daily (after breakfast) to orally administer for 12 weeks, or warfarin once daily (morning or evening) to orally administer for 12 weeks with a target PT-INR ≥2.0 and ≤3.0. Doses were blinded for dabigatran etexilate but not for ASA and warfarin. It was decided that reduction of dabigatran etexilate (from twice daily to once a day [morning or evening]) would be considered if aPTT has been prolonged post-dose by ≥2.5 times the facility criteria with a baseline CL_{cr} ≤50 mL/min.

Major inclusion criteria were; patients with diagnosis of non-rheumatic atrial fibrillation (paroxysmal, persisetnt, permanent) based on the ECG findings within the past 6 months; with ≥1 risk factors of stroke

(hypertension requiring treatment by antihypertensive [systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg], history of diabetes mellitus [type 1 or type 2], or symptomatic cardiac failure or left ventricular failures [ejection fraction <40%], or ischaemic stroke or transient ischaemic attack, age >75, history of coronary artery disease*), ≥8weeks of treatment with warfarin or other vitamin K antagonists prior to inclusion, and a PT-INR within the therapeutic range (2.0-3.0) at Visit 1 (7-4 days pre-dose). In this study, the country where the study has been conducted was used as a factor to randomly stratify patients.

The study enrolled 593 patients. 502 of them were randomized into investigative product groups and all of the randomized patients received the investigational product. The group details of randomization were; dabigatran etexilate 50 mg bid + ASA 0 mg qd group, 58 patients; dabigatran etexilate 50 mg bid + ASA 81 mg qd group, 20 patients; dabigatran etexilate 50 mg bid + ASA 325 mg qd group, 27 patients; dabigatran etexilate 150 mg bid + ASA 0 mg qd group, 99 patients; dabigatran etexilate 150 mg bid + ASA 81 mg qd group, 34 patients; dabigatran etexilate 150 mg bid + ASA 325 mg qd group, 33 patients; dabigatran etexilate 300 mg bid + ASA 0 mg qd group, 98 patients; dabigatran etexilate 300 mg bid + ASA 81 mg qd group, 33 patients; dabigatran etexilate 300 mg bid + ASA 325 mg qd group, 30 patients; and warfarin group, 70 patients. The randomized 502 patients that had received the investigational product at least once were defined as subjects of the safety and efficacy analysis. 493 of the 502 patients (103 patients in the dabigatran etexilate 50 mg group, 162 patients in the dabigatran etexilate 150 mg group, 158 patients in the dabigatran etexilate 300 mg group, 70 patients in the warfarin group) excluding subjects of grave deviation from the protocol were defined as subjects of the analysis regarding pharmacodynamic parameters. Of the 502 patients that received the investigational product, 38 patients were discontinued (5 patients in the dabigatran etexilate 50 mg group, 11 patients in the dabigatran etexilate 150 mg group, 20 patients in the dabigatran etexilate 300 mg group, 2 patients in warfarin group) mostly due to “onset of adverse events”.

In this study, due to the bleeding frequently observed in the dabigatran etexilate 300 mg bid with concomitant ASA group, the safety data monitoring committee recommended termination of ASA concomitant with 300 mg bid of dabigatran etexilate and concomitant ASA dose with dabigatran etexilate 300 mg bid was terminated on September 1, 2004. Termination of ASA dose based on the recommendation of the safety data monitoring committee or adverse events occurred with 50 mg, 150 mg, and 300 mg of dabigatran etexilate in 1, 4, and 8 patients, respectively.

CL_{cr} ≤50 mL/min was found in 55 patients (13 patients in the dabigatran etexilate 50 mg group, 17 patients in the dabigatran etexilate150 mg group, 18 patients in the dabigatran etexilate 300 mg group, 7 patients in the warfarin group) and dabigatran etexilate was reduced from twice daily to once daily for 12 of the 55 patients under dabigatran etexilate (1 patient in the 50 mg group, 5 patients in the 150 mg group, 6 patients in the 300 mg group). Then, 1 patient in the dabigatran etexilate 50 mg group after reduction was returned to twice daily.

*History of coronary disease was originally defined as a criterion that must be met when the study was designed but was changed to one of risk factors for the purpose of accelerating inclusion on [redacted], 20[redacted].

The ratio of retention time within the target scope of PT-INR (2.0-3.0) tothe treatment duration was 57.2% on average in the 70 patients in the warfarin group.

For thromboembolic events (the efficacy endpoint), 4 patients in dabigatran etexilate 50 mg group were reported (systemic embolism, 1 patient in the dabigatran etexilate 50 mg bid + ASA 0 mg qd group; ischaemic stroke and acute coronary syndrome, 1 patient each in the dabigatran etexilate 50 mg bid + ASA 81 mg qd group; angina pectoris, 1 patient in the dabigatran etexilate 50 mg bid + ASA 325 mg qd group). The evaluation by the Steering Committee of the study on the other hand did not consider the acute coronary syndrome and angina pectoris as thromboembolic events but did for the systemic embolism and ischaemic stroke.

For bleeding events (the safety endpoint), major bleeding was observed in 1 patient in dabigatran etexilate 300 mg bid + ASA 81 mg qd group (gastrointestinal haemorrhage/gastric ulcer) and 3 patients in dabigatran etexilate 300 mg bid + ASA 325 mg qd group (rectal haemorrhage, lower gastrointestinal haemorrhage, gastrointestinal haemorrhage, 1 patient each). The mean CL_{cr} with the 4 patients was all >50 mL/min, and their aPTT during the treatment by dabigatran etexilate was not longer than other patients in the 300 mg group.

Major bleeding or clinically relevant bleeding in the dabigatran etexilate 50 mg group, were reported in; 0 of 59 (0%) patients without concomitant ASA, 1 of 21 (4.8%) patients with 81 mg concomitant ASA, 1 of 27 (3.7%) patients with concomitant ASA 325 mg, 2 of 107 (1.9%) patients in total. In the dabigatran etexilate 150 mg group, they were reported in; 9 of 101 patients (8.9%) without concomitant ASA, 2 of 36 (5.6%) patients with 81 mg concomitant ASA, and 2 of 33 (6.1%) patients with 325 mg concomitant ASA, 13 of 170 (7.6%) patients in total. In the dabigatran etexilate 300 mg group, they were reported in; 6 of 105 (5.7%) patients without concomitant ASA, 5 of 34 (14.7%) patients with 81 mg concomitant ASA, and 6 of 30 (20.0%) patients with 325 mg of concomitant ASA, 17 of 169 (10.1%) patients in total. In the warfarin group, they were reported in 4 of 70 (5.7%) patients.

Occurrence of any bleeding event (of major bleeding, clinically relevant bleeding, or other minor bleeding) in the dabigatran etexilate 50 mg group was reported in; 2 of 59 (3.4%) patients without concomitant ASA, 2 of 21 (9.5%) patients with 81 mg concomitant ASA, and 3 of 27 (11.1%) patients with 325 mg concomitant ASA, 7 of 107 (6.5%) patients in total. In the dabigatran etexilate 150 mg group, bleeding events were reported in; 15 of 101 patients (14.9%) without concomitant ASA, 8 of 36 (22.2%) patients with 81 mg concomitant ASA, and 7 of 33 (21.2%) patients with 325 mg concomitant ASA, 30 of 170 (17.6%) patients in total. In the dabigatran etexilate 300 mg group, they were reported in; 14 of 105 (13.3%) patients without concomitant ASA, 11 of 34 (32.4%) patients with 81 mg concomitant ASA, and 14 of 30 (46.7%) patients with 325 mg of concomitant ASA, 39 of 169 (23.1%) patients in total. In the warfarin group, 12 of 70 (17.1%) patients reported bleeding events

The breakdown of major bleeding events (occurring in >8 patients in the overall study population, or in >1.7% incidence) are; contusion in 17 patients (1 patient without concomitant ASA, 2 patients with 325 mg concomitant ASA in the dabigatran etexilate 150 mg group; 3 patients without concomitant ASA, 2 patients with 81 mg concomitant ASA, 3 patients with 325 mg concomitant ASA in the dabigatran etexilate 300 mg group; 6 patients in warfarin group), epistaxis in 16 patients (1 patient without concomitant ASA, 1 patient with 325 mg concomitant ASA in the dabigatran etexilate 150 mg group; 4 patients without concomitant ASA, 2 patients with 81 mg concomitant ASA, 2 patients with 325 mg concomitant ASA in the dabigatran etexilate 300 mg group; 5 patients in warfarin group), haematoma in 9 patients (1 patient without concomitant ASA in the dabigatran etexilate 50 mg group; 2 patients without concomitant ASA, 1 patient with 81 mg concomitant ASA, 1 patient with 325 mg concomitant ASA in the dabigatran etexilate 150 mg group; 1 patient without concomitant ASA, 1 patient with 81 mg concomitant ASA, 2 patients with 325 mg concomitant ASA in the dabigatran etexilate 300 mg group), haematuria in 9 patients (5 patients without concomitant ASA, 2 patients with 81 mg concomitant ASA in the dabigatran etexilate 150 mg group; 2 patients without concomitant ASA in the dabigatran etexilate 300 mg group).

Incidence of adverse events was 58% (62 of 107 patients), 65% (170 of 111 patients), 67% (114 of 169 patients), in the dabigatran etexilate 50 mg group, 150 mg group, 300 mg group, respectively, and 50% (35 of 70 patients) in warfarin group. Adverse events that occurred in >3% of overall study population included dizziness in 6.0% (30 of 502 patients), fatigue in 4.8% (24 of 502 patients), diarrhoea in 4.2% (21 of 502 patients), dyspepsia in 4.2% (21 of 502 patients), contusion in 3.8% (19 of 502 patients) headache in 3.6% (18 of 502 patients), nausea in 3.2% (16 of 502 patients), epistaxis in 3.2% (16 of 502 patients) generally being mild.

Adverse events that led to discontinuation were found in; 4.7% (5 of 107 patients), 5.3% (9 of 170 patients), 8.9% (15 of 169 patients) in the dabigatran etexilate 50 mg group, 150 mg group, and 300 mg group, respectively. No adverse events were found that led to discontinuation in warfarin group. Adverse events that led to discontinuation mainly included gastrointestinal disorders in 17 patients (abdominal pain upper, nausea, gastrointestinal haemorrhage, dyspepsia each occurring in ≥2 patients), renal and urinary disorders in 5 patients (including 3 patients of haematuria), and bleeding in 11 patients.

No deaths were reported during the study period but 1 patient for whom the investigational product was terminated 55 days after the start of treatment due to abdominal pain, queasy and vomiting died 40 days after the termination. Dabigatran etexilate 300 mg was administered once daily with concomitant ASA 81 mg to the patient. It was determined that the death was neither related to the investigational product nor to the bleeding complications.

Incidence of serious adverse events (including death) was 7.5% (8 of 107 patients), 9.4% (16 of 170 patients), 6.5% (11 of 169 patients) and 2.9% (2 of 70 patients) in the dabigatran etexilate 50, 150, or 300 mg groupas well as in warfarin group, respectively. Serious adverse events in these groups including post-treatment were found in 9, 17, 13, and 3 patients, respectively, and frequently observed System Organ Classes (SOC) of

adverse events were cardiac disorders (14 patients) and gastrointestinal disorders (9 patients). Nine serious adverse events were determined to have a causal relationship with the investigational product.

Patients with clinically significant hematocrit reduction detected post-dose accounted for 7.5% (8 of 107 patients), 13.1% (22 of 168 patients), and 14.3% (24 of 168 patients) in the dabigatran etexilate 50 mg group, 150 mg group, and 300 mg group, respectively, and 7.1% (5 of 70 patients) in warfarin group.

Patients with clinically significant hemoglobin reduction detected post-dose accounted for 1.9% (2 of 105 patients), 4.8% (8 of 166 patients), and 9.9% (16 of 161 patients) in the dabigatran etexilate 50 mg group, 150 mg group, and 300 mg group, respectively, and 4.3% (3 of 70 patients) in warfarin group. Patients with clinically meaningful reduction detected in the dabigatran etexilate 300 mg group accounted for 6.7% (7 of 105 patients) without concomitant ASA, 11.8% (4 of 34 patients) with concomitant ASA 81 mg, and 16.7% (5 of 30 patients) with concomitant ASA 325 mg.

Increase of transaminase (aspartate aminotransferase [AST] or alanine aminotransferase [ALT]) that exceeded 3 times the upper limit of normal (ULN) was observed in 0.9% (4 of 432 patients) of dabigatran etexilate group and 0% of warfarin group. No patients met Hy's Law criteria (increase of transaminase greater than 3 times ULN with an increase of bilirubin greater than 1.5 to 2 times ULN). In 1 patient who died of cardiac failure congestive, transaminase increased to exceed 3 times ULN followed by an increase of bilirubin to 1.45 mg/dL. An autopsy confirmed hepatic congestion alone. In another case, transaminase increased following ALP increase due to obstructive pancreatitis. The patient was hospitalized because of intestinal ischemia and then died. Causal relationship between the investigational product and adverse events was ruled out in both patients.

Patients with a high level of cellular blood components detected in urine accounted for 5.5% (3 of 55 patients) and 4.8% (2 of 42 patients) in the dabigatran etexilate 50 mg group without or with concomitant ASA, respectively; 10.0% (10 of 100 patients) and 5.0% (3 of 60 patients) in the dabigatran etexilate 150 mg group without or with concomitant ASA, respectively; 9.6% (10 of 104 patients) and 11.7% (7 of 60 patients) in the dabigatran etexilate 300 mg group without or with concomitant ASA, respectively; and 3.2% (2 of 62 patients) in warfarin group.

Any abnormal findings compared with the baseline values detected in 12-lead ECG after the administration of the investigational product with no clinically meaningful variations observed in vital signs (blood pressure, heart rate) were reported as adverse events.

aPTT was 32.8 seconds at baseline measured 4 to 7 days after warfarin, the previous treatment, was terminated (Visit 2) and after dabigatran etexilate methanesulfonate was administered 50, 150, or 300 mg twice daily, the mean trough aPTT was prolonged to 38.9, 48.6, and 58.6 seconds, respectively, which corresponds to 1.19 (in the 50 mg group), 1.48 (in the 150 mg group), and 1.79 (in the 300 mg group) times baseline values (aPTT ratio), respectively. aPTT exhibited a non-linear increase in line with the elevation of

plasma total dabigatran level and a model that combined Emax model and a linear model described the relationship between aPTT and the plasma level.

ECT was 32.4 seconds at baseline measured 4 to 7 days after warfarin, the previous treatment, was terminated (Visit 2) and following administration of dabigatran etexilate methanesulfonate 50, 150, or 300 mg twice daily, the mean trough ECT was prolonged to 42.4, 65.5, and 102 seconds, respectively, which corresponds to 1.31 (in the 50 mg group), 2.02 (in the 150 mg group), and 3.15 (in the 300 mg group) times baseline values (ECT ratio), respectively. The relationship between ECT and plasma total dabigatran level could be described in a linear model.

Ratio of the elevation from baseline of D dimer, a degradation product of fibrin that may be used as an indicator for hypercoagulation and thrombogenesis was 17%, 9%, and 1% in the 50 mg, 150 mg, and 300 mg dose twice daily group, respectively.

Based on the results of the study, the applicant discussed as follows:
Based on the frequency of bleeding and results of aPTT and D dimer, dabigatran etexilate 150 mg twice daily was assumed to be a safe and adequately effective dose, and this dosage and administration was decided to be verified in Phase III study. Dabigatran etexilate 50 mg twice daily appeared inferior to warfarin (the control group) that controlled INR within 2.0 to 3.0 in view of reducing the risk of stroke. Therefore, a possibility was considered that a dosage of dabigatran etexilate effective enough and safer than warfarin could exist between 50 mg twice daily and 150 mg twice daily.

4.(iii).A.(2). 2) Foreign long-term extension study (Study 1160.42, attached document 5.3.5.1-2, study period [redacted] 20[redacted] to [redacted] 20[redacted])

An open-label study was conducted in order to evaluate the long-term safety and efficacy in the long-term administration of dabigatran etexilate alone or with concomitant ASA. Non-rheumatic atrial fibrillation patients with ≥1 stroke risk factors received dabigatran etexilate 150 mg once daily, 150 mg twice daily, 300 mg once daily, or 300 mg twice daily in a total of 50 sites located in Denmark, Netherlands, Sweden, and the U.S. Concomitant use of ASA was accepted depending on the doctor's discretion. Two years of treatment duration was originally intended but it was changed to 4 years on [redacted], 20[redacted], and then to 5 to 7 years on [redacted], 20[redacted]. Later, considering the increasing data from Study 1160.26, this study was completed in [redacted] 20[redacted].

Major inclusion criteria were patients who received dabigatran etexilate in Study 1160.20 and completed the study without termination of the treatment, and if assigned to dabigatran etexilate 50 mg twice daily group, patients who did not show excessive bleeding tendency through out the study were chosen.

Of 432 patients treated with dabigatran etexilate in Study 1160.20 (105 patients in the dabigatran etexilate 50 mg twice daily group [50 mg bid group], 166 patients in the 150 mg twice daily group [150 mg bid group], 161 patients in the 300 mg twice daily group [300 mg bid group]), 396 patients who completed Study 1160.20

were eligible for the current study but 35 of these patients did not participate. Consequently, 361 patients (98 patients in the dabigatran etexilate 150 mg once daily group [150 mg qd group], 89 patients in the 150 mg bid group, 50 patients in the 300 mg once daily group [300 mg qd group], 124 patients in the 300 mg bid group) were included in the current study and 208 patients completed the treatment of the study.

A total of 432 patients treated with dabigatran etexilate in Study 1160.20 were included in the safety and efficacy analysis. In the evaluation of dosage and administration, 361 patients treated with the investigational product in Study 1160.42 were separately included in the analysis.

Since dosage and administration has been changed during this study, many patients received dabigatran etexilate in plural administrations and dosages. The number of patients exposed per dosage and administration were; 1 patient with 50 mg qd, 105 patients with 50 mg bid, 102 patients with 150 mg qd, 356 patients with 150 mg bid, 90 patients with 300 mg qd, and 161 patients with 300 mg bid.

More than half of the patients who participated in Study 1160.42 received dabigatran etexilate for more than 4 years (1500-1700 days).

The annual event rate (number of events per 100 patient-year [Studies 1160.20 and 1160.24 combined]) of the composite endpoint, which is the primary endpoint for efficacy, (stroke [fatal or non-fatal], transient ischaemic attack, systemic embolism, myocardial infarction [fatal or non-fatal], other serious cardiac events, death) was 0.0% in the 50 mg qd group, 17.0% in the 50 mg bid group, 5.0% in the 150 mg qd group, 5.7% in the 150 mg bid group, 4.5% in the 300 mg qd group, and 2.4% in the 300 mg bid group.

Regarding safety, the annual event rate (number of events per 100 patient-year [Study 1160.20 and 1160.42 combined]) of any bleeding events (of major bleeding, clinically relevant bleeding, or other minor bleeding) was 15.8% (0% in the 50 mg qd group, 25.5% in the 50 mg bid group, 21.5% in the 150 mg qd group, 14.7% in the 150 mg bid group, 14.9% in the 300 mg qd group, 58.5% in the 300 mg bid group) of the entire population. The annual event rate for major bleeding was 2.9% of the entire population (0% in the 50 mg qd group, 0% in the 50 mg bid group, 6.6% in the 150 mg qd group, 3.1% in the 150 mg bid group, 0.8% in the 300 mg qd group, 7.3% in the 300 mg bid group).

When subjects were stratified by with or without concomitant ASA, the annual event rate for any bleeding events in the entire population was 32.4% with concomitant ASA and 13.2% without concomitant ASA. The annual event rate of any bleeding events in the 150 mg bid group, in the300 mg qd group, and in the 300 mg bid group was 26.9%, 23.9%, and 135% with concomitant ASA, respectively, and 13.1%, 13.1%, and 39.8% without concomitant ASA, respectively. The annual event rate of major bleeding in the overall population was 5.3% with concomitant ASA and 2.2% without concomitant ASA. The annual event rate for major bleeding in the 150 mg bid group, 300 mg qd group, and 300 mg bid group with and without concomitant ASA was 6.4%, 0%, 20.8% and 2.3%, 1.1%, 3.2%, respectively.

Major bleeding was observed in 4 patients in the 150 mg qd group, 26 patients in the 150 mg bid group, 2 patients in the 300 mg qd group, and 6 patients in the 300 mg bid group, 36 patients in total. The breakdown was as follows; 14 major bleedings was classified as gastrointestinal disorders in SOC (4 patients with melaena; 1 patient each with duodenal ulcer haemorrhage, faeces discoloured, gastric haemorrhage, gastric ulcer, gastritis haemorrhagic, gastrointestinal haemorrhage, gingival bleeding, haematemesis, large intestinal haemorrhage, lower gastrointestinal haemorrhage, rectal haemorrhage), 7 classified as nervous system disorder in SOC (3 patients with cerebral haemorrhage; 2 patients with haemorrhagic stroke; 1 patient each with haematomyelia, haemorrhage intracranial), 4 classified as vascular disorders in SOC (2 patients with aortic aneurysm rupture; 1 patient each with aortic aneurysm, aortic dissection, bleeding), 4 classified as injury, poisoning and procedural complications in SOC (2 patients with post-procedural haemorrhage; 1 patient each with contusion, subdural haematoma), 3 patients classified as eye disorders in SOC (eye haemorrhage, 2 patients; retinal haemorrhage, 1 patient), 3 classified as investigations in SOC (2 patients with haemoglobin decreased; 1 patient with occult blood), 3 classified as respiratory, thoracic and mediastinal disorders in SOC (3 patients with epistaxis), 2 classified as blood and lymphatic system disorders in SOC (2 patients with anaemia), and 1 classified as neoplasms benign, malignant and unspecified (including cysts and polyps) in SOC (1 patient with colon cancer). In 6 patients among them (5 patients with 150 mg bid, 1 patient with 300 mg qd) the major bleeding (3 patients with cerebral haemorrhage; 1 patient each with gastrointestinal haemorrhage, aortic aneurysm rupture, aortic dissection) was fatal.

Major bleeding or clinically relevant bleeding occurred in 103 patients. Frequently observed SOCs were gastrointestinal disorders at 8.6%, renal and urinary disorders at 5.1%, respiratory, thoracic and mediastinal disorders at 4.4%. In gastrointestinal disorders, rectal haemorrhage at 3.5%, gastrointestinal haemorrhage at 1.2%, melaena at 0.9%, haemorrhoidal haemorrhage at 0.7%, and gingival bleeding at 0.5% were of high incidence. Haematuria at 5.1% and epistaxis at 3.7% in renal and urinary disorders, and in respiratory, thoracic and mediastinal disorders, respectively, were of high incidence.

The total number of bleeding events occurred in the patients was 198. Frequently observed SOCs were gastrointestinal disorders at 14.6%, respiratory, thoracic and mediastinal disorders at 11.8%, injury, poisoning and procedural complications at 11.8%, and vascular disorders at 10.0%. In gastrointestinal disorders, rectal haemorrhage at 5.3%, gingival bleeding at 2.5%, haemorrhoidal haemorrhage at 1.6%, haematochezia at 1.4%, melaena at 1.2% were of high incidence. In SOC other than gastrointestinal disorders, epistaxis occurring at 10.6%, haematuria at 8.3%, hematoma at 7.9%, and contusion at 6.0% were frequent. Basically in all SOC, incidence of bleeding events rose in response to the increase of dose and length of exposure duration of the investigational product.

Bleeding events led to termination of investigational product in 34 of 432 patients (7.9%).

The rate of adverse events was 0% in the 50 mg qd group, 57.1% in the 50 mg bid group, 69.6% in the 150 mg qd group, 89.0% in the 150 mg bid group, 95.6% in the 300 mg qd group, and 80.7% in the 300 mg bid group. Adverse events of high incidence by SOC were; gastrointestinal disorders (56%, 242 patients),

infections and infestations (50%, 216 patients), general disorders and administration site conditions (44.9%, 194 patients), nervous system disorders (42.4%, 183 patients), musculoskeletal and connective tissue disorders (39.8%, 172 patients), respiratory, thoracic and mediastinal disorders (38.4%, 166 patients), cardiac disorders (38.0%, 164 patients), and vascular disorders (31.3%, 135 patients). Nausea (10.2%), dyspepsia (9.5%), diarrhoea (9.0%), constipation (7.4%), abdominal pain upper (6.9%) were frequent in gastrointestinal disorders while in nervous system disorders, dizziness (17.4%) and headache (9.7%) were of high incidence.

Twenty eight patients died during the treatment with the investigational product. Moreover, 5 patients died during the follow-up period and 1 patient after the study. Five of these patients (3 patients with cerebral haemorrhage, 1 patient with gastrointestinal haemorrhage, 1 patient with cardiogenic shock/cardiac arrest) were determined to have a causal relationship with the investigational product. Aortic aneurysm rupture, ischaemic stroke, and aortic dissection were noted as other fatal bleeding events. The patient with aortic dissection was the one observed with cardiogenic shock/cardiac arrest mentioned earlier. Most of other causes of death were complication of infection and patients' cardiac disease.

Serious adverse events occurred in 222 of 432 patients (51.4%). SOCs of the serious adverse events noted in high frequency were; cardiac disorders (22.5%), infections and infestations (10.2%), nervous system disorders (10.0%), and gastrointestinal disorders (9.7%). Serious adverse events noted in high (≥1%) frequency include; cardiac failure (5.3%), atrial fibrillation (3.9%), bradycardia (2.1%), cardiac failure congestive (1.9%), myocardial infarction (1.9%), angina unstable (1.6%), angina pectoris (1.6%) in cardiac disorders; pneumonia (4.4%) in infections and infestations; syncope (2.5%), dizziness (1.9%), and ischaemic stroke (1.6%) in nervous system disorders; and inguinal hernia (1.9%), gastrointestinal haemorrhage (1.4%), etc., in gastrointestinal disorders. Frequency of serious adverse events was increased dose dependently with dabigatran etexilate as a whole.

The investigational product was discontinued due to adverse events in 135 of 432 patients (31.3%). SOCs of the adverse events that were noted in high frequency and led to discontinuation were gastrointestinal disorders (7.2%), cardiac disorders (6.3%), and nervous system disorders (4.9%).

The investigational product was discontinued due to outcome events (including adverse events that caused deaths) of the efficacy endpoint in 48 of 432 patients (11.1%). Outcome events of high incidence (occurring in ≥3 [0.7%] patients in total) were ischaemic stroke (1.2%), cardiac arrest (0.9%), cardiac failure (0.9%), myocardial infarction (0.7%), cerebrovascular accident (0.7%), cerebral haemorrhage (0.7%), peripheral embolism (0.7%), and sudden death (0.7%).

In the patients with abnormal liver function test results noted during Study 1160.20 and Study 1160.42, > 3-fold ULN increase in transaminase (AST or ALT) was observed in 1.5% in all dosages and all administrations combined. AST or ALT >3-fold ULN accompanied with bilirubin >1.2-fold ULN was observed in 5 patients. AST or ALT >3-fold ULN accompanied with bilirubin >2-fold ULN was found only in 3 patients. Hepatic

enzyme was recovered to normal range in all patients excluding those with pancreatic carcinoma/liver metastasis. The investigational product was discontinued in 5 patients due to increase in liver function test results. Decrease in hemoglobin, hematocrit, and erythrocytes count that were presumably related to the bleeding events were observed. As other abnormal clinical test results, variation in electrolyte (increase or decrease of sodium and phosphate, increase of potassium and calcium), increase or decrease in glucose, increase in creatinine/blood urea nitrogen, uric acid, triglycerides, and cholesterol were noted.

There were no clinically meaningful findings in vital signs or ECG.

Based on the results of the study, the applicant discussed as follows:
The incidence of stroke and other embolism was ≥5%/year in the dabigatran etexilate 150 mg once daily group and the 50 mg twice daily group, which was higher than <1.5%/year in the 300 mg and the 150 mg twice daily groups. On the other hand, in the 300 mg twice daily group, the incidence of bleeding was 58.5%/year, and the rate of major bleeding was ≥ 7%/year, which were the highest. Based on the above results, it was suggested that 150 mg twice daily would best balance efficacy and safety as dosage and administration. Since efficacy was insufficient in the 150 mg once daily group, it was decided that 110 mg twice daily would be evaluated in Study 1160.26 as a candidate for the dosage and administration effective with a lower bleeding risk.

4.(iii).A.(2).3) Japanese Phase II study (Study 1160.49, attached document 5.3.5.1-3, study period [redacted] 20[redacted] to [redacted] 20[redacted])

An open-label study was conducted in Japanese patients with non-valvular atrial fibrillation who had ≥1 thromboembolism risk factors at 25 study sites in total in Japan to compare the safety and pharmacodynamics (blood coagulation parameters) of dabigatran etexilate with warfarin. The subjects received dabigatran etexilate 110 or 150 mg twice daily (in the morning and evening) or warfarin once daily (in the morning or evening) so as to keep PT-INR at 2.0 to 3.0 (PT-INR at 1.6-2.6 for patients aged ≥70) for 12 weeks (target number of patients, 50 patients per group, 150 patients in total)

Major inclusion criteria were; diagnosis of non-valvular atrial fibrillation (paroxysmal, persistent, permanent) based on the findings of ≥2 ECGs, with a ≥1 week interval between them, within 1 year prior to the confirmation of consent, together with ≥1 of the risk factors of thromboembolism (hypertension [systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg], currently receiving treatment by antihypertensive, diabetes mellitus [type I or type II], left cardiac failure [symptomatic cardiac failure congestive or a left ventricular ejection fraction (LVEF) <40%], history of ischaemic stroke or transient ischaemic attack; age ≥75, history of coronary artery disease). Patients diagnosed with valvular disease (mitral valve stenosis, high degree of cardiac valve disease for example) by echocardiography or those who had undergone heart valve prosthesis or heart valve surgery were excluded.

The study enrolled 211 patients, of whom 174 patients were randomized into investigational product groups (53 in the dabigatran etexilate 110 mg group, 59 in the dabigatran etexilate 150 mg group, 62 in the warfarin

group). Seven patients in the dabigatran etexilate 110 mg group with confirmed violation of "history of clinically relevant hepatic disease" and "absence of ECG indicating atrial fibrillation findings" in the exclusion criteria turned out prior to the administration of the investigational product, and 1 patient in the 150 mg group stopped coming to the hospital and was unable to get in contact prior to the administration of the investigational product were excluded. The investigational product was administered to remaining 166 patients (46 in dabigatran etexilate 110 mg group, 58 in dabigatran etexilate 150 mg group, and 62 in warfarin group). A total of 166 patients who had received the investigational product at least once were included in the analysis for safety and efficacy. Of 166 patients treated with the investigational product, discontinuation was identified in 19 patients (5 in the dabigatran etexilate 110 mg group, 9 in the dabigatran etexilate 150 mg group, 5 in the warfarin group) and their major reason was "occurrence of adverse events" (4 in the dabigatran etexilate 110 mg group, 8 in the dabigatran etexilate 150 mg group, 4 in the warfarin group).

In the warfarin group patients, the rate of PT-INR within the therapeutic range as measured in the site was 47.5 % prior to, and 74.6% at 12 weeks after the start of, the investigational product.

Thromboembolism events as an efficacy endpoint occurred in 0 of 46 patients in the dabigatran etexilate 110 mg group, 0 of 58 patients in the dabigatran etexilate 150 mg group, and 1 of 62 patients (1.6%) in the warfarin group. Ischaemic stroke occurred in the patient of the warfarin group. The subject concomitantly used ASA and was assigned to develop"haemorrhagic cerebral infarction" in terms of adverse event since the person's cerebral infarction was complicated with haemorrhagic variations. Ischaemic stroke occurred during pre-treatment screening in 1 patient in the dabigatran etexilate 110 mg group and in 1 patient in the dabigatran etexilate 150 mg group during follow-up period at 10 days post-treatment.

Regarding bleeding events as the safety endpoint, major bleeding events occurred in 0 of 46 patients in the dabigatran etexilate 110 mg group, 1 of 58 patients (1.7%, prostatic haemorrhage) in the dabigatran etexilate 150 mg group, 2 of 62 patients (3.2%, 1 patient with haemorrhagic cerebral infarction; 1 patient with left fundal haemorrhage due to age-related macular degeneration,) in the warfarin group. Of these, the prostatic haemorrhage was caused by the injury in the prostatic artery by the manual procedure of cystoscopy. The haemorrhagic cerebral infarction was a complication of cerebral infarction with later haemorrhagic changes. The 3 patients with major bleeding all concomitantly used ASA. Major bleeding or clinically relevant bleeding occurred in 2 of 46 patients (4.3%) in the dabigatran etexilate 110 mg group, 5 of 58 patients (8.6%) in the dabigatran etexilate 150 mg group, and 7 of 62 patients (11.3%) in the warfarin group. Any bleeding events (of major bleeding, clinically relevant bleeding, or other minor bleeding) occurred in 10 of 46 patients (21.7%) in the dabigatran etexilate 110 mg group, 20 of 58 patients (34.5%) in the dabigatran etexilate 150 mg group, and 15 of 62 patients (24.2%) in the warfarin group. The number of patients with major bleeding or clinically relevant bleeding when subjects were stratified by with or without concomitant ASA were; 1 of 10 patients (10.0%) with concomitant ASA, 1 of 36 patients (2.8%) without concomitant ASA in the dabigatran etexilate 110 mg group; 4 of 13 patients (30.8%) with concomitant ASA, 1 of 45 patients (2.2%) without concomitant ASA in the dabigatran etexilate 150 mg group; and 5 of 23 patients (21.7%) with concomitant ASA, 2 of 39 patients (5.1%) without concomitant ASA in the warfarin group. The number of

patients with any bleeding event when subjects were stratified by with or without concomitant ASA was; 2 of 10 patients (20.0%) with concomitant ASA, 8 of 36 patients (22.2%) without concomitant ASA in the dabigatran etexilate 110 mg group; 5 of 13 patients (38.5%) with concomitant ASA, 15 of 45 patients (33.3%) without concomitant ASA in the dabigatran etexilate 150 mg group; and 10 of 23 patients (43.5%) with concomitant ASA, 5 of 39 patients (12.8%) without concomitant ASA in the warfarin group.

Major adverse events (with ≥3% incidence in any one of the treatment groups) were listed in Table 5.

Table 5. Major adverse events (incidence ≥3% in any one of the treatment group) (adapted from submitted data)

System Organ Class Preferred terminology	Dabigatran etexilate 110 mg bid group N (%)	Dabigatran etexilate 140 mg bid group N (%)	Warfarin group N (%)
Patients subjected to safety evaluation	46	58	62
Patients with adverse events	29 (63.0)	49 (84.5)	41 (66.1)
Infections and infestations	10 (21.7)	14 (24.1)	13 (21.0)
Nasopharyngitis	5 (10.9)	10 (17.2)	8 (12.9)
Chronic sinusitis	2 (4.3)	0	0
Blood and lymphatic system disorders	1 (2.2)	3 (5.2)	0
Coagulopathy	0	2 (3.4)	0
Metabolic and nutrition disorders	1 (2.2)	2 (3.4)	2 (3.2)
Diabetes mellitus	1 (2.2)	2 (3.4)	0
Psychiatric disorders	1 (2.2)	3 (5.2)	1 (1.6)
Insomnia	1 (2.2)	3 (5.2)	0
Nervous system disorder	2 (4.3)	5 (8.6)	6 (9.7)
Headache	0	2 (3.4)	2 (3.2)
Eye disorders	1 (2.2)	5 (8.6)	6 (9.7)
Conjunctival haemorrhage	0	2 (3.4)	1 (1.6)
Cardiac disorders	1 (2.2)	4 (6.9)	0
Cardiac failure	0	2 (3.4)	0
Vascular disorders	1 (2.2)	4 (6.9)	1 (1.6)
Hypertension	1 (2.2)	2 (3.4)	0
Respiratory, thoracic and mediastinal disorders	8 (17.4)	10 (17.2)	7 (11.3)
Epistaxis	2 (4.3)	5 (8.6)	3 (4.8)
Gastrointestinal disorders	10 (21.7)	23 (39.7)	9 (14.5)
Diarrhoea	1 (2.2)	4 (6.9)	2 (3.2)
Symptoms related todyspepsia[a)]	3 (6.5)	8 (13.8)	1 (1.6)
Abdominal pain upper	0	3 (5.2)	0
Dyspepsia	2 (4.3)	1 (1.7)	0
Abdominal discomfort	0	2 (3.4)	0
Stomach discomfort	1 (2.2)	2 (3.4)	0
Gastritis	0	0	1 (1.6)
Constipation	2 (4.3)	2 (3.4)	3 (4.8)
Gingival bleeding	2 (4.3)	2 (3.4)	3 (4.8)
Stomatitis	2 (4.3)	0	0
Haemorrhoidal haemorrhage	1 (2.2)	2 (3.4)	0
Skin and subcutaneous tissue disorders	2 (4.3)	11 (19.0)	6 (9.7)
Haemorrhage subcutaneous	1 (2.2)	7 (12.1)	3 (4.8)
Pruritus	0	2 (3.4)	1 (1.6)
Rash	0	2 (3.4)	0
Acne	0	0	2 (3.2)
Musculoskeletal and connective tissue disorders	3 (6.5)	5 (8.6)	5 (8.1)
Arthralgia	0	1 (1.7)	2 (3.2)
Renal and urinary disorders	2 (4.3)	2 (3.4)	2 (3.2)
Haematuria	2 (4.3)	2 (3.4)	1 (1.6)
General disorders & administration site conditions	1 (2.2)	4 (6.9)	3 (4.8)
Oedema peripheral	0	0	2 (3.2)
Injury, poisoning and procedural complications	3 (6.5)	4 (6.9)	7 (11.3)
Excoriation	0	0	2 (3.2)

a) Symptoms related to dyspepsia: in order to avoid underestimating the effects on the gastrointestinal system, 5 events of abdominal pain upper, dyspepsia, abdominal discomfort, gastric discomfort, and gastritis were collectively tallied up.

Adverse events that led to discontinuation of treatment were observed in; 3 of 46 patients (6.5%) in the dabigatran etexilate 110 mg group, 8 of 58 patients (13.8%) in the dabigatran etexilate 150 mg group, and 4

of 62 patients (6.5%) in the warfarin group. The breakdown is; coagulopathy (2 patients [both PT-INR elevation], dabigatran etexilate 150 mg group); dizziness, pharyngolaryngeal discomfort, abdominal distension, dyspepsia, nausea vomiting (1 patient each in the dabigatran etexilate 110 mg group); haematuria (1 patient in the dabigatran etexilate 110 mg group, 1 patient in the dabigatran etexilate 150 mg group); third degree atrioventricular block, cardiac arrest, cardiac failure, abdominal discomfort, oesophagitis, rectal haemorrhage, renal impairment prostatic haemorrhage, blood bilirubin increased (1 patient each in the dabigatran etexilate 150 mg group); haemorrhagic cerebral infarction, white matter lesion, macular degeneration, retinal haemorrhage, femur fracture (1 patient each in the warfarin group).

Serious adverse events were observed in; 6 patients in the dabigatran etexilate 150 mg group (1 patient with pneumonia, 1 patient with prostate cancer, 1 patient with atrioventricular block third degree/cardiac arrest/cardiac failure, 1 patient with cardiac failure congestive, 1 patient with muscle fatigue, 1 patient with prostatic haemorrhage), 5 patients in the warfarin group (1 patient with asthma/femur fracture/pneumonia, 1 patient with dizziness, 1 patient with haemorrhagic cerebral infarction, 1 patient with toothache, 1 patient with pharyngeal injury). These serious adverse events were all determined to have no causal relationship to the investigational product except for 1 patient with haemorrhagic cerebral infarction with warfarin.

Regarding ALT, AST, ALP, and total bilirubin that are clinical laboratory tests for hepatic function, no patients were found with >2-fold ULN in any treatment group. In urinary tests, the number of patients found with urinary occult blood - or ± pre-dose, and ≥ + 1 post-dose was 1 of 46 patients (2.2%) in the dabigatran etexilate 110 mg group, 7 of 57 patients (12.3%) in the dabigatran etexilate 150 mg group, and 7 of 60 patients (11.7%) in the warfarin group. In occult blood tests, the number of patients found negative pre-dose and positive post-dose was 3 of 42 patients (7.1%), 7 of 50 patients (14.0%), and 4 of 59 patients (6.8%), respectively.

Based on the results of the study, the applicant discussed as follows:
As pharmacodynamic reaction, the relationship between aPTT and plasma total dabigatran level, and ECT and plasma total dabigatran level could be described by the model structured in the foreign Study 1160.20 suggesting that there was no difference between Japanese and foreign patients in anticoagulation action under the same dosage in the subjects.

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

4.(iii).A.(4).1) Phase III multiregional clinical study (Study 1160.26, attached document 5.3.5.1-4, study period [redacted] 20[redacted] to [redacted] 20[redacted])

An open-label, parallel-group, comparative, multiregional clinical study that involved 44 countries including Japan was conducted in 951 sites in total (treatment duration, 12-36 months [12-23 months in Japan]) to verify the non-inferiority of dabigatran etexilate 110 and 150 mg twice daily to warfarin with dose titrated to the therapeutic range (target PT-INR 2.0-3.0, or 2.0-2.6 for Japanese patients aged ≥70) in patients with non-valvular atrial fibrillation including Japanese patients. Dosage of dabigatran etexilate was blinded in this study. Outcome events and major bleeding, which are the primary endpoint and the secondary endpoint,

respectively, were reviewed and verified by the independent event monitoring committee under the blind condition. The target number of patients was originally 15,000 (5000 per group) but enrollment progressed quicker than expected. Earlier completion of enrollment was predicted and there were concerns that the number of events to evaluate the primary endpoint may end up fewer than planned. Therefore, the number of patients was changed to 18,000 (6000 per group) on [redacted], 20[redacted].

The inclusion criteria specified patients with atrial fibrillation who had ≥1 risk factors of stroke listed from (a) to (e) below:
(a) history of stroke, transient ischaemic attack, or systemic embolism, (b) LVEF <40% within the past 6 months from the time of giving consent (based on echocardiograph, RI, or vascular imaging using a contrast media [angiogram]), (c) symptomatic cardiac failure confirmed to be ≥NYHA II within the past 6 months from the time of giving consent, (d) aged ≥75 at the time of giving consent, (e) aged ≥65 at the time of obtaining consent with any of the following disease; diabetes mellitus under treatment (insulin, oral hypoglycaemic agent, or diet), coronary artery disease (history of myocardial infarction, those detected by an exercise test, those detected by myocardial perfusion scintigraphy, history of coronary artery bypass graft [CABG] operation or percutaneous coronary intervention [PCI], or stenosis ≥75% detected by coronary angiography), or hypertension that requires medication. On [redacted], 20[redacted], randomization was defined for an even distribution of patients who had or had not undergone an anticoagulant therapy (lifetime treatment duration of vitamin K antagonist exceeding or within 2 months respectively) among groups.

In this study, an interim analysis was planned to carry out when the number of primary endpoint events reached 50% and 75% of the predicted number of patients (450) to decide on early termination for efficacy or non-efficacy termination. The first interim analysis was carried out by the independent safety data monitoring committee on [redacted], 20[redacted] then the second interim analysis on [redacted], 20[redacted]. The termination criteria were not met in either occasion. *

(a) Overall study results
Of 20,377 patients enrolled, 2264 patients were not assigned, due to unqualification, consent withdrawn and other reasons. 18,113 patients were randomized (6015 patients in the dabigatran etexilate 110 mg group, 6076 patients in the dabigatran etexilate 150 mg group, and 6022 patients in the warfarin group). The randomized 18,113 patients were included in the efficacy analysis set and 18,042 patients that had been treated with the investigational product (5984 patients, 6059 patients, 5999 patients, respectively) were included in the safety analysis set. The main reasons for discontinuation of the investigational product in 3822 patients (1338 patients, 1400 patients, 1084 patients, respectively) were patients' reluctance to take the investigational product in 1292 patients (427 patients, 460 patients, 405 patients, respectively), or outcome

*Criteria of early termination for efficacy, when the boundaries of less than - 4 × standard error ($P < 0.00003$) at 50% and less than - 3 × standard error ($P < 0.00135$) at 75% chosen for the log hazard ratio of any dabigatran etexilate group versus the warfarin group are exceeded in successive interim analysis held with a ≥3-month interval.
When there is a criteria of non-efficacy termination, extremely small probability at individual time points that non-inferiority of dabigatran etexilate to warfarin would be demonstrated at the completion of the clinical study (the conditional power to detect calculated based on the data observed under an alternative hypothesis, level of significance 0.00125 for each comparison at one side)

events in 678 patients (260 patients, 249 patients, 178 patients, respectively). The median total exposure duration of the investigational product in 3 treatment groups (dabigatran etexilate 110 mg group, dabigatran etexilate 150 mg group, and warfarin group) was 1.82 years, 1.78 years, and 1.88 years, respectively, and the patient-year was 10,229.2, 10,252.9, 10,661.2, respectively.

Demographic and other baseline characteristics were similar among treatment groups. Mean age of subjects was 71.5 years and male subjects accounted for 63.6%. Racially, 70.0% of the subjects was Caucasian, 15.9% Asian, 1.0% black, and others were 13.2%. Mean body weight was 82.6 kg. The median CL_{cr} was 68.4 mL/min, and the ratio of patients ≥80 mL/min, ≥50 mL/min and <80 mL/min, ≥30 mL/min and <50 mL/min, and <30 mL/min was 31.2%, 45.8%, 18.5%, and 0.4%, respectively. The mean systolic and diastolic blood pressures were 131.0 and 77.0 mmHg, respectively. In atrial fibrillation, persistent, paroxysmal, permanent patients accounted for 32.0%, 32.8%, and 35.2%, respectively. At randomization, patients with no history of using vitamin k antagonists (including those with ≤2 month use) accounted for 50.4%. The ratio of patients wearing a pacemaker or implantable defibrillator was 10.7% and 2.2%, respectively. Previously, 27.6% of patients had received electrical cardioversion and 2.1% of patients had received atrioventricular nodal ablation.

The ratio of subjects who had 1, 2, and 3 risk factors was 31.1%, 33.1%, and 32.8%, respectively. Three percent of subjects had no risk factors for stroke (considered as deviation patients from the protocol). The mean $CHADS_2$ score at baseline was 2.1 (median, 2.0) in all 3 treatment groups. Approximately one third of the entire subjects had $CHADS_2$ score ≥3.

In approximately 88% of subjects, thrombolytic agents were used (oral coagulant, 62.3%; ASA, 39.5%; clopidogrel, 5.6% etc.) while antihypertensive agents were used in 80.1% of patients. In approximately 90% of patients, beta-blockers, Ca antagonists, digoxin, and other drugs commonly used in patients with atrial fibrillation were used. Proton pump inhibitors were also used in 14.2% of patients. Types and frequency of concomitant drugs at baseline and during the treatment with the investigational product were similar among the 3 treatment groups. During the treatment period by the investigational product, ASA was used ≥ once concomitantly in 39.7% of the patients and in 20.5% of patients throughout the treatment period. Clopidogrel was used concomitantly ≥ once in 7.4% of patients and throughout the treatment period in 2.4% of patients. Throughout the treatment period with the investigational product, ASA plus clopidogrel were concomitantly used in 1.2% of patients. Proton pump inhibitors were concomitantly used (≥ once) in 23.5% of patients and the rate of concomitant use in the 2 dose groups of dabigatran etexilate was higher (24.6% in the dabigatran etexilate 110 mg group, 24.7% in the dabigatran etexilate 150 mg group) than warfarin group (21.1%). The rate of concomitant use (≥ once) of amiodarone, verapamil, diltiazem, and quinidine was 14.9%, 7.2%, 11.8%, and 0.7%, respectively.

The ratio of mean PT-INR time in therapeutic range (TTR) (2.0-3.0) in the warfarin group increased throughout the treatment period. The ratio of overall mean PT-INR TTR during the treatment with the investigational product was 64.2% (median, 67.1%). The ratio of time with < PT-INR 2 monotonically

decreased during the study period while the ratio of time with > PT-INR 3 was virtually consistent between 13.0% and 13.6% from 6 months post-randomization to the completion of study.

The ratio of overall mean PT-INR TTR in patients with history of vitamin k antagonist use was 66.9% (median, 69.2%), and 61.6% in patients without such history (median, 64.6%). Throughout the study period, the ratio of mean PT-INR TTR was constantly higher in patients with history of vitamin k antagonist use than in patients without such history or with history of ≤2 month use.

i) Efficacy

The annual event rates are listed in Table 6 for "occurrence of any stroke (including haemorrhagic strokes) or systemic embolism" (the primary endpoint) as well as "occurrence of any stroke (including haemorrhagic strokes), systemic embolism, or any death events" and " occurrence of any stroke (including haemorrhagic strokes), systemic embolism, pulmonary embolism, acute myocardial infarction, or vascular death (including haemorrhagic death)" (the secondary endpoints). Regarding the primary endpoints, the hazard ratio for the dabigatran etexilate 110 mg group versus the warfarin group calculated based on Cox regression model was 0.91 (95% CI, 0.75-1.12), and the hazard ratio for the dabigatran etexilate 150 mg group versus the warfarin group was 0.66 (95% CI, 0.53-0.82) demonstrating the non-inferiority of both dabigatran etexilate 110 mg group and dabigatran etexilate 150 mg group to warfarin group (non-inferiority acceptance limit was 1.46, Hochberg multiple comparison).

Kaplan-Meier curve for the initial occurrence of the primary endpoint was as in Figure 2.

Table 6. Frequency and annual event rate of strokes/systemic embolism, stroke/systemic embolism/all death events, stroke/systemic embolism/pulmonary embolism/acute myocardial infarction/vascular death (overall, randomized) (adapted from submitted data)

	Drug 110 mg group (N = 6,015)	Drug 150 mg group (N = 6,076)	Warfarin group (N = 6,022)
Patient-year	11,900	12,039	11,797
Stroke/systemic embolism	182 (1.53)	133 (1.10)	198 (1.68)
Stroke/systemic embolism/all death events	575 (4.83)	518 (4.30)	609 (5.16)
Stroke/systemic embolism/pulmonary embolism/acute myocardial infarction/ vascular death	493 (4.14)	433 (3.60)	496 (4.20)
Stroke	171 (1.44)	121 (1.01)	184 (1.56)
Ischaemic stroke	152 (1.28)	102 (0.85)	132 (1.12)
Haemorrhagic stroke	14 (0.12)	12 (0.10)	45 (0.38)
Unknown	7 (0.06)	9 (07)	10 (0.08)
Systemic embolism	14 (0.12)	13 (0.11)	19 (0.16)
All death events	445 (3.74)	437 (3.63)	486 (4.12)
Pulmonary embolism	14 (0.12)	18 (0.15)	11 (0.09)
Acute myocardial infarction	86 (0.72)	89 (0.74)	63 (0.53)
Vascular death	288 (2.42)	273 (2.27)	316 (2.68)

n (annual event rate %)
For each patient with event occurrence, the composite endpoint and each endpoint were individually tallied up.
Patient-year = all randomized patients (study completion day - randomization day + 1) combined/365.25
Annual event rate (%) = (number of patients with events/patient-year) × 100

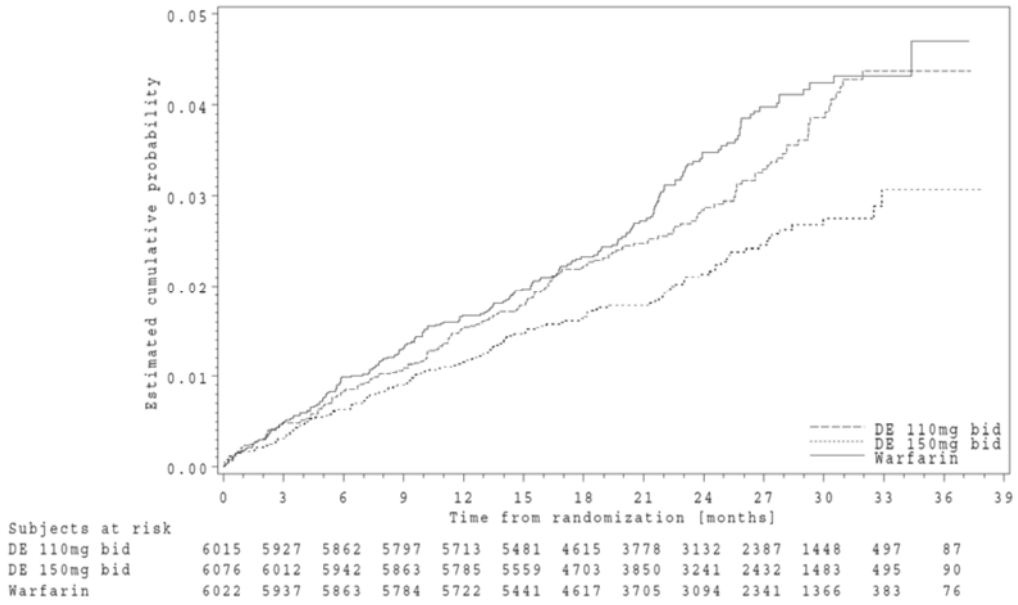


Figure 2. Kaplan-Meier curve for occurrence of initial stroke/systemic embolism (adapted from submitted data)

The annual event rate of stroke/systemic embolism in patients with no history of vitamin k antagonists was 1.57%, 1.07%, and 1.67% for dabigatran etexilate 110 mg, 150 mg, and warfarin, respectively, and in patients with history of vitamin k antagonists, 1.49%, 1.14%, and 1.69%, respectively.

The annual event rate for stroke/systemic embolism by concomitant antiplatelet medication used during the study period was higher in patients with concomitant antiplatelet medication (ASA, clopidogrel, ASA plus clopidogrel) than patients in any treatment group without them.

ii) Safety

The incidence of adverse events was 78.6%, 78.3%, and 75.9% with dabigatran etexilate 110 mg group, dabigatran etexilate 150 mg group, and with warfarin group, respectively. Adverse events with an incidence rateof ≥3% in any one of the group are listed in Table 7.

Table 7. Adverse events (incidence ≥3% in any one of the group): Safety analysis population

System Organ Class (SOC)/ Preferred Term (PT) （MedDRA version 12.0）	Dabigatran etexilate 110 mg group N (%)	Dabigatran etexilate 150 mg group N (%)	Warfarin group N (%)
Patients	5984 (100.0)	6059 (100.0)	5999 (100.0)
Patients with adverse events	4706 (78.6)	4745 (78.3)	4551 (75.9)
Infections and infestations	1822 (30.4)	1855 (30.6)	1975 (32.9)
Nasopharyngitis	314 (5.2)	309 (5.1)	327 (5.5)
Urinary tract infection	242 (4.0)	253 (4.2)	315 (5.3)
Upper respiratory tract infection	266 (4.4)	261 (4.3)	297 (5.0)
Bronchitis	261 (4.4)	277 (4.6)	284 (4.7)
Pneumonia	226 (3.8)	221 (3.6)	235 (3.9)
Blood and lymphatic system disorders	293 (4.9)	306 (5.1)	277 (4.6)
Anaemia	181 (3.0)	207 (3.4)	164 (2.7)
Metabolism and nutrition disorder	624 (10.4)	649 (10.7)	683 (11.4)
Mental disorder	350 (5.8)	339 (5.6)	321 (5.4)
Nervous system disorder	1211 (20.2)	1247 (20.6)	1247 (20.8)
Dizziness	457 (7.6)	458 (7.6)	555 (9.3)
Headache	252 (4.2)	236 (3.9)	243 (4.1)
Eye disorders	425 (7.1)	394 (6.5)	452 (7.5)
Cardiac disorders	1139 (19.0)	1113 (18.4)	1223 (20.4)
Atrial fibrillation	303 (5.1)	313 (5.2)	326 (5.4)
Cardiac failure congestive	197 (3.3)	187 (3.1)	210 (3.5)
Cardiac failure	169 (2.8)	171 (2.8)	201 (3.4)
Vascular disorders	680 (11.4)	642 (10.6)	712 (11.9)
Hypertension	252 (4.2)	234 (3.9)	266 (4.4)
Respiratory, thoracic and mediastinal disorders	1242 (20.8)	1319 (21.8)	1345 (22.4)
Dyspnoea	497 (8.3)	525 (8.7)	550 (9.2)
Cough	319 (5.3)	310 (5.1)	345 (5.8)
Epistaxis	109 (1.8)	127 (2.1)	178 (3.0)
Gastrointestinal disorders	2073 (34.6)	2088 (34.5)	1442 (24.0)
Diarrhoea	355 (5.9)	367 (6.1)	327 (5.5)
Dyspepsia	367 (6.1)	345 (5.7)	83 (1.4)
Nausea	245 (4.1)	259 (4.3)	208 (3.5)
Constipation	187 (3.1)	177 (2.9)	167 (2.8)
Abdominal pain upper	178 (3.0)	170 (2.8)	80 (1.3)
Musculoskeletal and connective tissue disorders	1311 (21.9)	1341 (22.1)	1365 (22.8)
Arthralgia	249 (4.2)	313 (5.2)	328 (5.5)
Back pain	295 (4.9)	289 (4.8)	331 (5.5)
Pain in extremity	226 (3.8)	228 (3.8)	212 (3.5)
General disorder & administration site conditions	1373 (22.9)	1451 (23.9)	1402 (23.4)
Oedema peripheral	446 (7.5)	442 (7.3)	453 (7.6)
Fatigue	370 (6.2)	367 (6.1)	353 (5.9)
Chest pain	288 (4.8)	355 (5.9)	342 (5.7)
Injury, poisoning and procedural complication	821 (13.7)	872 (14.4)	979 (16.3)
Fall	183 (3.1)	178 (2.9)	234 (3.9)
Contusion	149 (2.5)	152 (2.5)	197 (3.3)

Frequency and annual event rate of major and other bleeding events are shown in Table 8. Regarding the incidence of major bleeding, the hazard ratio for dabigatran etexilate 110 mg group versus warfarin group was 0.79, significantly lower (P = 0.0021), as calculated based on Cox regression model. The hazard ratio

for dabigatran etexilate 150 mg versus warfarin was 0.93, demonstrating no significant differences in incidence of major bleeding between dabigatran etexilate 150 mg and warfarin (P = 0.3218) groups.

Table 8. Frequency and annual event rate of major bleeding and other bleedings (overall population, randomized) (adapted from submitted data)

	Dabigatran etexilate 110 mg group (N = 6015)	Dabigatran etexilate 150 mg group (N = 6076)	Warfarin group (N = 6022)
Patient-year	11,900	12,039	11,797
Major bleeding Life threatening major bleeding Other major bleeding	318 (2.67) 143 (1.20) 196 (1.65)	375 (3.11) 175 (1.45) 226 (1.88)	396 (3.36) 210 (1.78) 208 (1.76)
Haemorrhage intracranial[1)]	25 (0.21)	36 (0.30)	85 (0.72)
Minor bleeding[2)]	1566 (13.16)	1787 (14.84)	1930 (16.36)
All bleeding[2)] events	1749 (14.70)	1990 (16.53)	2152 (18.24)

n (annual event rate %)
Tallied up initial bleeding events only excluding recurrent ones.
1) Haemorrhage intracranial, haemorrhagic stroke, subdural or subarachnoid haemorrhage reviewed and confirmed in the independent event monitoring committee
2) Events reported by the investigator, not reviewed by the independent event monitoring committee.
Patient-year = all randomized patients (study completion day - randomization day + 1) combined/365.25
Annual event rate (%) = (number of patients with events/patient-year) × 100

The ratio of patients who exhibited ALT or AST >5-fold ULN (5×ULN) and ≤10×ULN, or ALT or AST >×3ULN associated with bilirubin >2×ULN for dabigatran etexilate 110 and 150 mg groups, as well as warfarin group was 0.7%, 0.8%, and 0.9%, respectively. The ratio of patients who revealed the highest increase of hepatic function test values (ALT or AST >20×ULN, or ALT or AST >3×ULN accompanied with bilirubin >2×ULN) within the criteria was 0.2%, 0.3%, and 0.5%, respectively.

(b) Results in Japanese subgroup

The study was conducted in 49 sites in Japan from [redacted] 20[redacted] to [redacted] 20[redacted] (Target number of Japanese patients, 300 patients [100 patients per group]). A total of 346 Japanese patients were enrolled, and 20 patients were unqualified and excluded from the assignment. 326 patients were randomized (107 to dabigatran etexilate 110 mg group, 111 to dabigatran etexilate 150 mg group, and 108 to warfarin group). Among them, 324 patients (106, 110, and 108, respectively) were treated with the investigational product and 317 patients (97.8%) completed the study. The median of the total exposure duration for the investigational product in the 3 treatment groups (dabigatran etexilate 110 mg, dabigatran etexilate 150 mg, warfarin) was 1.33, 1.32, and 1.33 years, respectively, which were 126.1, 134.7, and 147.1 patient-years, respectively.

i) Efficacy

The annual event rates are listed in Table 9. for "occurrence of any stroke (including haemorrhagic strokes) or systemic embolism" (the primary endpoint) as well as "occurrence of any stroke (including haemorrhagic strokes), systemic embolism, or any death event" and "occurrence of any stroke (including haemorrhagic strokes), systemic embolism, pulmonary embolism, acute myocardial infarction, or vascular death (including haemorrhagic death)" (the secondary endpoint). Regarding the incidence of stroke or systemic embolism in the Japanese subgroup, the hazard ratio of dabigatran etexilate 110 mg and 150 mg groups versus warfarin

group was 0.52 and 0.25, respectively.

Table 9. Frequency and annual event rate of strokes/systemic embolism, stroke/systemic embolism/all death events, stroke/systemic embolism/pulmonary embolism/acute myocardial infarction/vascular death (Japanese, randomized population) (adapted from submitted data)

	Dabigatran etexilate 110 mg group (N = 107)	Dabigatran etexilate 150 mg group (N = 111)	Warfarin group (N = 108)
Patient-year	145	150	151
Stroke/systemic embolism	2 (1.38)	1 (0.67)	4 (2.65)
Stroke/systemic embolism/all death events	2 (1.38)	3 (2.00)	5 (3.31)
Stroke/systemic embolism/pulmonary embolism/acute myocardial infarction/vascular death	2 (1.38)	2 (1.33)	5 (3.31)
Stroke	2 (1.38)	1 (0.67)	3 (1.99)
Ischaemic stroke	2 (1.38)	0 (0.00)	2 (1.33)
Haemorrhagic stroke	0 (0.00)	1 (0.67)	1 (0.66)
Systemic embolism	0 (0.00)	0 (0.00)	2 (1.33)
All death events	1 (0.69)	2 (1.33)	4 (2.65)
Pulmonary embolism	0 (0.00)	0 (0.00)	0 (0.00)
Acute myocardial infarction	0 (0.00)	0 (0.00)	0 (0.00)
Vascular death	1 (0.69)	1 (0.67)	4 (2.65)

n (annual event rate %)
For each patient with event occurrence, the composite endpoint and each endpoint were individually tallied up.
Patient-year = all randomized patients (study completion day - randomization day + 1) combined/365.25
Annual event rate (%) = (number of patients with events/patient-year) × 100

ii) Safety

Adverse events observed in ≥3% in any one of the group were as in Table 10.

Table 10. Adverse events with incidence ≥3% in any one of the group (Japanese subgroup) (adapted from submitted data)

System Organ Class (SOC)/Preferred Term (PT) (MedDRA version 12.0)	Dabigatran etexilate 110 mg group N（%）	Dabigatran etexilate 150 mg group N (%)	Warfarin group N (%)
Patients	106 (100.0)	110 (100.0)	108 (100.0)
Patients with adverse events	102 (96.2)	103 (93.6)	101 (93.5)
Infections and infestations	63 (59.4)	70 (63.6)	60 (55.6)
Nasopharyngitis	48 (45.3)	56 (50.9)	53 (49.1)
Bronchitis	5 (4.7)	5 (4.5)	1 (0.9)
Upper respiratory tract infection	0 (0.0)	5 (4.5)	1 (0.9)
Pneumonia	4 (3.8)	1 (0.9)	3 (2.8)
Herpes zoster	0 (0.0)	4 (3.6)	3 (2.8)
Metabolism and nutrition disorders	7 (6.6)	14 (12.7)	14 (13.0)
Diabetes mellitus	2 (1.9)	3 (2.7)	4 (3.7)
Gout	0 (0.0)	2 (1.8)	4 (3.7)
Nervous system disorder	19 (17.9)	19 (17.3)	26 (24.1)
Headache	6 (5.7)	5 (4.5)	8 (7.4)
Dizziness	4 (3.8)	4 (3.6)	5 (4.6)
Hypoaesthesia	3 (2.8)	1 (0.9)	5 (4.6)
Eye disorders	12 (11.3)	12 (10.9)	16 (14.8)
Cataract	4 (3.8)	5 (4.5)	7 (6.5)
Ear and labyrinth disorders	6 (5.7)	7 (6.4)	7 (6.5)
Vertigo	4 (3.8)	3 (2.7)	1 (0.9)
Cardiac disorders	16 (15.1)	9 (8.2)	5 (4.6)
Cardiac failure	5 (4.7)	1 (0.9)	1 (0.9)
Cardiac failure congestive	4 (3.8)	0 (0.0)	0 (0.0)
Vascular disorders	13 (12.3)	8 (7.3)	11 (10.2)
Hypertension	8 (7.5)	4 (3.6)	7 (6.5)
Respiratory, thoracic and mediastinal disorders	17 (16.0)	28 (25.5)	18 (16.7)
Oropharyngeal pain	2 (1.9)	5 (4.5)	1 (0.9)
Rhinitis allergic	0 (0.0)	5 (4.5)	0 (0.0)
Cough	4 (3.8)	4 (3.6)	3 (2.8)
Gastrointestinal disorders	55 (51.9)	69 (62.7)	43 (39.8)
Diarrhoea	3 (2.8)	15 (13.6)	6 (5.6)
Dyspepsia	10 (9.4)	14 (12.7)	2 (1.9)
Abdominal pain upper	6 (5.7)	10 (9.1)	2 (1.9)
Constipation	5 (4.7)	4 (3.6)	9 (8.3)
Periodontitis	5 (4.7)	2 (1.8)	9 (8.3)
Reflux esophagitis	6 (5.7)	1 (0.9)	1 (0.9)
Vomiting	2 (1.9)	6 (5.5)	5 (4.6)
Colonic polyp	5 (4.7)	3 (2.7)	4 (3.7)
Gastritis	5 (4.7)	5 (4.5)	5 (4.6)
Nausea	5 (4.7)	5 (4.5)	2 (1.9)
Dental caries	1 (0.9)	5 (4.5)	4 (3.7)
Epigastric discomfort	4 (3.8)	4 (3.6)	1 (0.9)
Gastritis atrophic	4 (3.8)	4 (3.6)	0 (0.0)
Gingivitis	4 (3.8)	3 (2.7)	4 (3.7)
Abdominal discomfort	3 (2.8)	4 (3.6)	4 (3.7)
Abdominal pain	1 (0.9)	4 (3.6)	2 (1.9)
Toothache	2 (1.9)	4 (3.6)	1 (0.9)
Hepatobiliary disorders	6 (5.7)	3 (2.7)	6 (5.6)
Hepatic function abnormal	4 (3.8)	0 (0.0)	2 (1.9)
Skin and subcutaneous tissue disorders	25 (23.6)	24 (21.8)	23 (21.3)
Eczema	7 (6.6)	6 (5.5)	10 (9.3)
Rash	3 (2.8)	6 (5.5)	2 (1.9)
Dry skin	0 (0.0)	4 (3.6)	1 (0.9)
Musculoskeletal and connective tissue disorders	27 (25.5)	44 (40.0)	26 (24.1)
Back pain	11 (10.4)	19 (17.3)	14 (13.0)
Arthralgia	6 (5.7)	10 (9.1)	7 (6.5)
Pain in extremity	5 (4.7)	4 (3.6)	3 (2.8)
Reproductive system and breast disorders	4 (3.8)	5 (4.5)	4 (3.7)
Benign prostatic hyperplasia	0 (0.0)	4 (3.6)	1 (0.9)

General disorders & administration site conditions	14 (13.2)	28 (25.5)	15 (13.9)
Chest pain	5 (4.7)	8 (7.3)	3 (2.8)
Oedema peripheral	5 (4.7)	4 (3.6)	6 (5.6)
Injury, poisoning and procedural complication	23 (21.7)	26 (23.6)	19 (17.6)
Contusion	5 (4.7)	9 (8.2)	3 (2.8)
Falls	4 (3.8)	5 (4.5)	3 (2.8)

Safety analysis population, all patients treated with the investigational product ≥ once
The ratio was calculated by dividing with the total number of patients in each treatment group.

The frequency and annual event rate for major bleeding and other bleeding events are shown in Table 11. Regarding the incidence of major bleeding events in the Japanese subgroup, the hazard ratio for the dabigatran etexilate 110 and 150 mg groups versus the warfarin group was 1.68 and 1.02, respectively. The hazard ratio of the dabigatran etexilate 110 mg and dabigatran etexilate 150 mg groups versus the warfarin group of any bleeding events were 0.79 and 1.06, respectively.

Table 11: Frequency and annual event rate of major bleeding and other bleeding events (Japanese, randomized) (adapted from submitted data)

	Dabigatran etexilate 110 mg group (N = 107)	Dabigatran etexilate 150 mg group (N = 111)	Warfarin group (N = 108)
Patient-year	145	150	108
Major bleeding Life threatening major bleeding Other major bleedings	8 (5.53) 1 (0.69) 7 (4.84)	5 (3.33) 3 (2.00) 2 (1.33)	5 (3.31) 2 (1.33) 3 (1.99)
Haemorrhage intracranial [1)]	1 (0.69)	1 (0.67)	1 (66)
Minor bleeding[2)]	35 (24.19)	50 (33.26)	50 (33.14)
All bleeding events[2)]	40 (27.64)	52 (34.59)	51 (33.81)

N (annual event rate %)
Tallied up initial bleedings only excluding any recurrent ones.
1) Haemorrhage intracranial, haemorrhagic stroke, subdural or subarachnoid haemorrhage reviewed and confirmed in the independent event monitoring committee
2) Events reported by the investigator, not reviewed by the independent event monitoring committee.
Patient-year = all randomized patients (study completion day - randomization day + 1) combined/365.25
Annual event incidence (%) = (number of patients with events/patient-year) × 100

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

4.(iii).B.(1) Clinical positioning of dabigatran etexilate

PMDA asked the applicant to describe the clinical positioning of the proposed product in the anticoagulant therapy to reduce the risk of cerebral embolism in patients with atrial fibrillation, including the advantages and disadvantages compared with conventional drugs.

The applicant responded as follows:

In the representative guidelines in Japan such as "Guidelines for Pharmacotherapy of Atrial Fibrillation, (JCS 2008)"(*Circulation Journal*. 2008;72(Suppl IV):1581-1638), "Guidelines for the management of cardiac diseases complicated with cerebrovascular disease, chronic kidney disease, or peripheral vascular disease. (JCS 2008)(*Circulation Journal*.2008;72(supple IV):1465-1544), and "Japanese Guidelines for the Management of Stroke 2009;Tokyo: Kyowa-kikaku; 2010), warfarin therapy with titration by PT-INR is positioned to be a therapy to recommend or eligible for consideration as an antithrombotic therapy to prevent

stroke in patients with non-valvular atrial fibrillation associated with the risks of stroke. Antiplatelet therapy such as ASA is not recommended in the guidelines, just positioned to be eligible for consideration when warfarin treatment is contraindicated.

The anticoagulant therapy with warfarin is the only antithrombotic therapy in Japan that has been established as standard to reduce the risk of stroke in patients with non-valvular atrial fibrillation. The therapy has a narrow therapeutic range and requires titration by regular monitoring of blood coagulation. Its interaction with various drugs and foods containing vitamin k is also a concern. In Study 1160.26, non-inferiority of dabigatran etexilate 110 mg and 150 mg twice daily to warfarin was demonstrated regarding the reduction effect on annual events incidence for stroke or systemic embolism that was the primary endpoint. The risk of major bleeding from dosing dabigatran etexilate 150 mg twice daily was similar to warfarin and the risks of symptomatic haemorrhage intracranial and fatal bleeding were significantly lower than warfarin. Furthermore, the risk of receiving dabigatran etexilate 110 mg twice daily for major bleeding, haemorrhage intracranial, and fatal bleeding was significantly lower than with warfarin. In addition, dabigatran etexilate has advantages compared with warfarin such as; treatment available with fixed dose and administration, no titration by regular PT-INR monitoring required, no diet restriction required such as vitamin K, and reduced drug interactions that could cause problems, rapid attainment of maximum plasma level post-dose compared with existing drugs, and a shorter half-life facilitating rapid onset and dissipation of effects. On the other hand, disadvantages in dabigatran etexilate include lack of neutralizers specific for the coagulation effects of dabigatran etexilate and possible higher risks for gastrointestinal haemorrhage compared with conventional drugs.

Considering these advantages and disadvantages compared with conventional drugs, dabigatran etexilate is to be used as a new standard drug or first choice drug. It is to be used in patients to whom existing drugs have not been used due to associated problems such as, patients for whom regular blood coagulation tests cannot be implemented for whom interactions with concomitant drugs would pose problems. The lack of neutralizers such as vitamin K for existing drugs, should not cause significant problems when considering the rapid dissipation of effects of dabigatran etexilate.

PMDA concluded as follows regarding the clinical positioning of dabigatran etexilate:
Currently, regular PT-INR monitoring and dose titration are required against the increase of bleeding risk in warfarin that is recommended to use as the standard therapy to reduce the risk of stroke in patients with non-valvular atrial fibrillation. Interaction with many drugs and foods has been of concern. In the results of the overall population of Study 1160.26 regarding efficacy, non-inferiority to warfarin, the control drug, was verified and safety that is considered clinically acceptable was demonstrated based on the comparison with the control group to indicate a similar risk for major bleeding to, or lower risk for haemorrhage intracranial and fatal bleeding than warfarin. Given the characteristics of warfarin and dabigatran etexilate as described by the applicant, dabigatran etexilate may possibly become an alternative anticoagulant drug for the reduction of the risk of stroke in patients with non-valvular atrial fibrillation. On the other hand, due to the concern over the considerably limited evaluation of efficacy and safety of dabigatran etexilate in Japanese

patients as the result of the extremely small number of Japanese patients included in the study, study results raising concern over the risk of gastrointestinal haemorrhage higher than warfarin, and drug interactions and food effects although they are lower than warfarin, careful consideration will be required in selecting drugs appropriate to individual patients taking into account the characteristics of warfarin and dabigatran etexilate, or patients' background when considering treatment with anticoagulant drug to Japanese patients with non-valvular atrial fibrillation.

4.(iii).B.(2) Efficacy of dabigatran etexilate

4.(iii).B.(2).1) Design of Study 1160.26

The applicant explained as follows regarding the measure to reduce bias that could arise when evaluating the outcome in Study 1160.26 that adopted the design of Prospective Randomized Open with Blinded outcome Evaluation (PROBE):

To reduce the bias that arises in the assessment in an open-labeled design, measures and procedure were formulated as: (a) Major bleeding events which is critical for the evaluation of primary and secondary endpoints of efficacy, and safety evaluation, shall be assessed and confirmed individually in a blinded design by ≥2 event evaluators who belong to the independent event monitoring committee that is independent of the study sponsor, (b) Management of the data set subjected to evaluation by the independent event monitoring committee shall be left to a research organization independent of the study sponsor, and information that identifies the treatment group shall be masked, (c) Results of analysis of individual treatment groups under study shall not be disclosed to the study sponsor and to anyone involved in the conduct of the study, (d) Management and supervision of the evaluation shall be performed by the independent safety data monitoring committee that is independent of the study sponsor, and (e) The observation, types and results of the test that formed the basis of the decision in the evaluation of study sites regarding each outcome event and major bleeding, shall be collected in the form defined in the case report form, together with the source material or diagnostic imaging reports. Furthermore, in order to reduce bias in the report by the investigators, measures and procedures were formulated as: (a) Clinically significant outcomes that are supported objectively shall be used, (b) The dose of dabigatran etexilate shall be blinded, (c) Reasons for hospitalization of all inpatients shall be investigated and classified, (d) Questions regarding stroke and bleeding shall be asked to the patient at each visit, (e) Reports on transient ischaemic attacks that may possibly be classified as strokes shall be confirmed by the independent event monitoring committee in a blinded design, (f) Reports on adverse events suggesting strokes or bleedings shall be confirmed by an independent research organization in charge of data management, (g) Variations in hemoglobin level in the clinical laboratory tests shall be investigated if there is a possibility of being classified as major bleeding, (h) Reports on anaemia that could be concerned as an event shall be evaluated by an independent research organization in charge of data management. Based on these, it is concluded that regarding the evaluation data set, masking the information on the treatment group and patient's identity and evaluating based on objective and integrated data was able to eliminate the bias permitted to the evaluator which is the biggest potential problem associated with PROBE method, and the adoption of PROBE method for evaluation of the outcome events of the primary and secondary endpoints and major bleeding as in the study was appropriate.

PMDA considers the design of Study 1160.26 as follows:
While the possibility may not be ruled out that it led a situation likely to permit bias in the management of subjects and safety and efficacy evaluation by the investigator, the adoption of PROBE method in Study 1160.26 that started 20[redacted] was unavoidable since warfarin, the control drug of the study, was to be titrated by monitoring PT-INR of individual patients. In addition, in Study 1160.26, while it must be said that the influence of the design of PROBE method on the study outcome is unknown, the different measures to objectively evaluate any stroke (including haemorrhagic events) or onset of systemic embolism, bleeding events (major and minor bleeding) selected as the primary endpoint for efficacy and the safety endpoint are considered to be effective in order to reduce bias. It is concluded that evaluation for efficacy and safety of dabigatran etexilate may be feasible to some extent based on the study results focused on objective indicators.

4.(iii).B.(2).2) Safety and efficacy of dabigatran etexilate in Study 1160.26
The applicant explained the rationale for the non-inferiority margin established as follows regarding the objective of Study 1160.26 to verify the non-inferiority of dabigatran etexilate (110 mg or 150 mg, twice daily) to warfarin in the reduction of risk for stroke and systemic embolism:
The non-inferiority margin of 1.46 in Study 1160.26 was established as the margin for the hazard ratio to assure ≥50% efficacy of warfarin based on the 62% relative risk reduction of warfarin treatment group versus placebo group for stroke (95% CI, 48%-72%, respectively) obtained through meta analysis of 6 past placebo controlled studies in patients with non-valvular atrial fibrillation conducted previously.

Further, the applicant described the safety and efficacy of dabigatran etexilate demonstrated in Study 1160.26 as follows:
In Study 1160.26 in patients with non-valvular atrial fibrillation who had ≥1 stroke risk factor, non-inferiority of dabigatran etexilate 150 mg twice daily as well as dabigatran etexilate 110 mg twice daily was demonstrated versus warfarin regarding the risk reduction of stroke and systemic embolism. An intergroup comparison of the onset of each event conducted as secondary evaluation found that dabigatran etexilate 150 mg twice daily reduced the risk of stroke and systemic embolism compared with warfarin, and both dabigatran etexilate 150 and 110 mg twice daily reduced the risk of haemorrhagic stroke compared with warfarin. Risk for major bleeding was similar to, and risk for haemorrhage intracranial and fatal bleeding was significantly lower than warfarin in the dabigatran etexilate 150 mg twice daily grouup. Risk for major bleeding, haemorrhage intracranial, and fatal bleeding was significantly lower than warfarin in the dabigatran etexilate 110 mg twice daily group. On the other hand, dabigatran etexilate groupwas higher in the incidence of gastrointestinal haemorrhage. Particularly in major bleeding in the gastrointestinal tract, dabigatran etexilate 150 mg twice daily group had significantly higher incidence rate than warfarin group. With dabigatran etexilate groups, while incidence of gastrointestinal haemorrhage was higher than warfarin group, the number of major bleeding and all bleeding events was smaller than that of the warfarin group and the risks for haemorrhagic stroke and haemorrhage intracranial were lower than warfarin group. These led to an overall conclusion that benefits of dabigatran etexilate were not significantly compromised compared with warfarin in light of bleeding risk. Regarding the net clinical benefit (stroke, systemic embolism, pulmonary embolism, myocardial infarction, all death events, and major bleeding), the composite endpoint established

as an indicator to evaluate risks and benefits combined, the hazard ratio versus warfarin group was 0.93 and 0.91, respectively, in dabigatran etexilate 110 mg twice daily group and dabigatran etexilate 150 mg twice daily group, suggesting the benefits of dabigatran etexilate versus warfarin.

In conclusion, dabigatran etexilate is a drug with well balanced benefits and risks for the risk reduction of stroke and systemic embolism in patients with atrial fibrillation. It was thought preferable to use the two doses of dabigatran etexilate appropriately depending on the risk of bleeding.

PMDA considers as follows regarding the safety and efficacy of dabigatran etexilate as demonstrated in Study 1160.26.
The non-inferiority margin established in Study 1160.26 is acceptable for the purpose of confirming the drug efficacy of dabigatran etexilate but in order to evaluate its clinical usability, a comprehensive comparison of efficacy and safety performance with a control drug is nonetheless required. It is concluded that clinical usability at least equivalent to warfarin has been demonstrated in the overall study for dabigatran etexilate by its non-inferiority to warfarin (at 110 mg and 150 mg twice daily) for the reduction of the risk for stroke and systemic embolism and by its risk reduction for clinically significant conditions such as haemorrhage intracranial, any bleeding events, and death as demonstrated and suggested respectively in the outcomes of Study 1160.26. In addition, while the higher incidence of gastrointestinal bleeding in dabigatran etexilate group than in warfarin group requires consideration and attention should be paid to patients associated with high risk of gastrointestinal haemorrhage, for example, by avoiding dabigatran etexilate however significance of the availability of dabigatran etexilate into clinical practice has been considered to be demonstrated based on the assumption that measures mentioned earlier will be taken appropriately.

4.(iii).B.(2).3) Outcomes in Japanese patients in Study 1160.26
PMDA pointed out differences in the intrinsic and extrinsic ethnic factors between Japanese subjects and non-Japanese subjects and asked the applicant to explain the rationale of the conclusion that it was appropriate to collectively evaluate the Japanese and non-Japanese subgroups in Study 1160.26 and to extrapolate the overall study outcomes into Japanese patients.

The applicant responded as follows.
Regarding the differences in the intrinsic ethnic factors, sex, age, and body weight of the intrinsic ethnic factors related to the characteristics of the patient population as mentioned in ICH E5 guidelines were compared between the overall study population and Japanese subgroup of Study 1160.26. As the result of comparison of characteristics of the overall study population and the Japanese subgroup, the mean age was 71.5 and 71.2 years, respectively, while males accounted for 63.6% and 76.7%, respectively, indicating no significant differences. For the body weight, the mean weight was 64.5 kg in the Japanese subgroup suggesting a trend for lighter weights compared with 82.6 kg in the overall study population. As for the body weight, Study 1160.26 showed that the trough level and the level 2 hours post-dose were elevated by 21% and 6%, respectively, in patients weighing <50 kg to patients weighing ≥50 kg. Within Japanese patients, the trough level in patients weighing <50 kg was virtually similar (lower by 2%) to that in patients weighing

≥50 kg and the 2 hours post-dose level was higher by 11%. In a pharmacodynamic analysis of the study population based on studies in Japanese and non-Japanese patients, effects of body weight on pharmacodynamics was small, estimatingV2/F to increase by 1.10% per 1 kg weight increase. In conclusion, it can be considered that body weight is not a factor that is able to significantly affect pharmacodynamics. Next, the degree of renal impairment was compared considering that the efficacy and safety of dabigatran etexilate may be affected by renal impairment. The ratio of patients with severe (CL_{cr} <30 mL/min) and moderate (CL_{cr} ≥30mL/min and <50 mL/min) renal impairment was 0.4% and 18.5%, respectively, in the overall study population and 0.3% and 21.8%, respectively, in the Japanese subgroup demonstrating no significant differences.

Differences in the extrinsic ethnic factors were evaluated according to "Disease definition/Diagnostic", "Medical practice and therapeutic approach (prophylaxis)", "Methodology/Endpoints", and "Drug compliance" listed in ICH E5 guideline. Regarding "Disease definition/Diagnostic", the guidelines for pharmacotherapy of atrial fibrillation that is the representative guideline for treatment method in Japan and the guideline for management of patients with atrial fibrillation, which is the representative foreign guideline from ACC/AHA/ESC (*Circulation.*2006;114:700-752.). They both define atrial fibrillation as a frequent arrhythmia characterized by uncoordinated atrial activation with consequent lack of rhythmical contraction for the atrium to send blood to the ventricles. ECG recording during an attack is indispensable due to the difficulty in differentiation of the frequent premature atrial contraction and atrial fibrillation based on the patient's subjective symptoms alone. It was considered that the definition and diagnosis of atrial fibrillation were not different between Japanese patients and non-Japanese patients. Regarding "Medical practice and therapeutic approach", the "Guidelines for pharmacotherapy of atrial fibrillation" which is the representative guideline for treatment method in Japan, and the representative foreign guideline from ACC/AHA/ESC (*Circulation.* 2006;114:700-752.) for management of patients with atrial fibrillation, both recommend stratification of the risk for stroke etc. to select a proper anticoagulation therapy. This indicated that there were no significant differences in the antithrombotic therapy between Japanese patients and non-Japanese patients. However, the optimal range for antithrombotic therapy with warfarin is specified as PT-INR 1.6 to 2.6 in Japan for the elderly aged ≥70 based on several prospective studies. In conclusion, it is considered that there is no difference in medical practice and therapeutic approach (prophylaxis) between Japanese patients and non-Japanese patients, except for the optimal therapeutic range of warfarin specified from PT-INR 1.6 to 2.6 in Japan for the elderly aged ≥70. Regarding "Methodology/Endpoints", Study 1160.26 adopted the design of PROBE and outcome events of the primary and secondary endpoints as well as major bleeding were reviewed and confirmed by the independent event monitoring committee in a blinded study. As for the methodology, it was concluded that the methodology did not affect the evaluation of therapeutic effect of dabigatran etexilate given that the independent event monitoring committee during Study 1160.26 collectively reviewed and confirmed the events specified as endpoints, using identical definitions for the diseases and events specified as endpoints or otherwise clear definitions both in and out of Japan. For "Drug compliance", in Study 1160.26, drug compliance was calculated and confirmed as the rate of actual number of dose taken versus the planned number of dose for the patients assigned to dabigatran etexilate or determined for the patients assigned to warfarin based on the PT-INR control state (ratio of time while the

PT-INR under warfarin stayed within the target range of 2.0 to 3.0). The ratio of patients receiving dabigatran etexilate with drug compliance ≤50%, and ≥80% but ≤120 % was 1.4% (164 of 11,506 patients) and 95.1% (10,938 of 11,506 patients), respectively, in the overall study and 1.4% (3 of 214 patients) and 94.9% (203 of 214 patients) in the Japanese subgroup, respectively, demonstrating no significant differences. As so far described, as the result of evaluating sensitivity to intrinsic ethnic factors and extrinsic ethnic factors, it has been concluded that efficacy and safety of dabigatran etexilate is insensitive to ethnic factors and therapeutic effect of dabigatran etexilate may be assessed by collective evaluation of the outcomes of Study 1160.26 from the Japanese subgroup and other population. It has been also concluded that the overall performance of the study may be extrapolated into the Japanese subgroup to assess the therapeutic effects of dabigatran etexilate.

PMDA considers the explanation by the applicant reasonable that while targets of control over warfarin differ between Japanese patients and non-Japanese patients, there are no significant differences in the extrinsic ethnic factors including treatment policies and treatment selection regarding anticoagulation therapy in non-valvular atrial fibrillation. In addition, given the presumed absence of clinically relevant differences between Japanese and non-Japanese patients in the anticoagulation action or pharmacokinetics of dabigatran etexilate based on the applicant's claim concerning to the intrinsic ethnic factors, it has been concluded that conducting Study 1160.26 as a multiregional study involving Japan was appropriate and collective evaluation of outcomes from the Japanese subgroup and from non-Japanese groups is feasible.

The applicant explained the outcomes in Japanese subgroup of Study 1160.26 as follows:
The hazard ratio with dabigatran etexilate 110 mg twice daily and dabigatran etexilate 150 mg twice daily groups for stroke and systemic embolism incidence versus warfarin group in the Japanese subgroup was 0.52 and 0.25, respectively. Based on the feasibility of patient enrollment in the Japanese subgroup of Study 1160.26, the target number of patients was set up at 300 (100 patients per group), and the hazard ratio was set up at <3.5 as an indicator to assume that the incidence of thromboembolism events are similar between dabigatran etexilate group and warfarin group. The results of this study were within the scope of this indicator. The number of patients with major bleeding events in dabigatran etexilate 110 mg group and 150 mg group as well as in warfarin group in the Japanese subgroup was 8 of 145, 5 of 150, and 5 of 151 patients, respectively, with an annual event rate for major bleeding at 5.53%, 3.33%, and 3.31%, respectively. The number of patients with any bleeding event was 40 of 107, 52 of 111, and 51 of 108 patients, respectively, with an annual event rate of 27.64%, 34.59%, and 33.81%, respectively. In conclusion, there were no significant inconsistencies between the Japanese subgroup and the overall study population regarding the tendency of result in the frequency of stroke and systemic embolism, as well as bleeding events (major bleeding and any bleeding event) which are the primary endpoints in the Japanese subgroup. No significant inconsistencies in the incidence of adverse events were observed either, between the overall study population and the Japanese subgroup.

PMDA considers as follows:
It is actually extremely difficult to assess the similarity in outcomes between the overall study population

and the Japanese subgroup in Study 1160.26 due to the extremely small target number of patients in the Japanese subgroup specified based on the enrollment feasibility as claimed by the applicant. An evaluation within the scope of available data found the outcomes of the composite endpoint, which is the primary endpoint for efficacy, within the range of the criteria preset as a guide to assume a similar level of outcomes between dabigatran etexilate group and warfarin group. No major inconsistencies were observed either in the outcomes of the components of the composite endpoint, bleeding events, the secondary endpoints, and adverse events between the overall study population and the Japanese subgroup. Regarding bleeding events, while the incidence of major bleeding and any bleeding events in the overall population of the study was lower in dabigatran etexilate group than in warfarin group, dabigatran etexilate and warfarin were the same in major bleeding in the Japanese subgroup, both with 5 patients, and dabigatran etexilate 150 mg twice daily group was slightly higher in any bleeding events. Regarding the issue, while possibility could not be ruled out for an influence from the difference in the target value of warfarin control between Japan and other countries, the control drug as mentioned earlier, and the necessity was suggested to consider the difference when evaluating the risk and benefit balance of dabigatran etexilate in Japan, it was presumed that clinically acceptable outcomes were obtained. In conclusion, it is considered that efficacy and safety of dabigatran etexilate in similar degree to the study outcomes observed in the overall population should be hoped for in Japanese patients despite the limited discussion on the Japanese subgroup in a small number of patients. However, since data on the efficacy and safety of dabigatran etexilate either in 150 mg or in 110 mg twice daily in Japanese patients is extremely limited, collecting post-marketing information on Japanese patients is highly important.

4.(iii).B.(3) Dosage and administration

4.(iii).B.(3).1) Usual dose and reduced dose

PMDA asked the applicant to explain the reason for its conclusion that the dose of dabigatran etexilate 110 and 150 mg twice daily adopted in the overall population in Study 1160.26 was appropriate for Japanese patients as well, taking into account the design and outcomes of Study 1160.49 in Japan.

The applicant responded as follows.

Study 1160.49 in Japan aimed at not only confirming safety when the dose of Study 1160.26 was administered to Japanese patient but also exploring doses through the oral administration of dabigatran etexilate 110 or 150 mg twice daily for 12 weeks, based on the incidence of bleeding events as one of the safety observations as well as pharmacodynamic parameters. In Study 1160.49, additional dose groups to explore, <220 mg/day of dabigatran etexilate for example, would be ethically difficult because of the negative perception for the preventive effect in dabigatran etexilate 150 mg/day on thromboembolism based on the outcomes from foreign clinical studies at the time of devising the study. As a guide for safety evaluation, warfarin was specified for the control group titrated to a target PT-INR 2.0 to 3.0 (PT-INR 1.6-2.6 for those aged ≥70). Later, an annual event rate of 5.0% to 8.5% for stroke or systemic embolism in foreign Study 1160.42, a long-term extension study for up to 5 years with dabigatran etexilate 100 to 150 mg/day was confirmed by the safety data monitoring committee, which was similar to the incident associated with no treatment. This led to the adoption of dabigatran etexilate 110 or 150 mg twice daily in Study 1160.49

in Japan to explore dosage and administration of dabigatran etexilate in Japanese patients based on the incidence rate of bleeding events and pharmacodynamic parameters with warfarin as control. Consequently, a thromboembolic event occurred in 1 of 62 (1.6%) patients as ischaemic stroke in warfarin group alone. Major bleeding was found in 1 of 58 patients (1.7%) in the 150 mg group and in 2 of 62 patients (3.2%) in the warfarin group. Major bleeding and clinically relevant minor bleeding showed increase of onset in line with the dosage of dabigatran etexilate but the incidence in the 110 and 150 mg groups were both lower than in the warfarin group. However, when compared with warfarin, the incidence of any bleeding event was higher in dabigatran etexilate 150 mg group than warfarin group. Also in the pharmacodynamics outcomes, it was confirmed that aPTT and ECT were both prolonged in line with the increase of dabigatran etexilate dose. In addition, when comparing the trough ECT of the steady state between the two 150 mg twice daily groups in Study 1160.49 in Japan and in Study 1160.20 outside Japan, which enables direct comparison, the trough plasma level of both studies was virtually consistent with each other. Moreover, the post-dose trough plasma level with 110 mg twice daily as evaluated in 1160.49 study, fell on the straight line of the dose-level correlation model that was interpolated from the dosage evaluated in Study 1160.20, leading to a conclusion that there were no differences in the exposure obtained between the 2 studies. This suggested that there were no differences in anticoagulation action between Japanese and foreign patients with the target disease by an equivalent dosage, permitting estimation of dose-response. Based on the above, it has been concluded that the bleeding event incidence and the results of pharmacodynamic parameters in Study 1160.49 in Japanese patients were similar to Study 1160.20 in non-Japanese patients, and 150 mg twice daily of dabigatran etexilate was determined to be an appropriate dose for Japanese patients.

The applicant established the final dosage and administration for Japanese patients based on the safety and efficacy outcomes in Study 1160.26 as follows: Study 1160.26 as a whole verified the non-inferiority to warfarin group in the annual event rate of stroke and systemic embolism as the primary endpoints for efficacy of both the dabigatran etexilate 110 and 150 mg groups. On the other hand regarding bleeding that required utmost attention among safety endpoints, the annual event rate of major bleeding, minor bleeding, and any bleeding events in the 2 dabigatran etexilate dose groups was lower than the warfarin group in the entire study (18,113 patients). The annual event rate for major bleeding with dabigatran etexilate 110 and 150 mg, as well as with warfarin was 2.67%, 3.11%, and 3.36%, respectively.

The hazard ratio of the dabigatran etexilate 110 mg group for major bleeding versus the warfarin group was 0.79, which was significantly lower ($P = 0.0021$). On the other hand, the hazard ratio of the dabigatran etexilate 150 mg group for major bleeding versus the warfarin group was 0.93, demonstrating no significant difference in incidence between groups ($P = 0.3218$). Other data show that the incidence of haemorrhagic stroke, life-threatening bleeding, and haemorrhage intracranial in both dabigatran etexilate 110 and 150 mg groups was significantly lower compared with the warfarin group.

The annual event rate for major bleeding in the Japanese subgroup in Study 1160.26 (326 patients) was the lowest in the warfarin group and the highest in the dabigatran etexilate 110 mg group. The annual event rate of any bleeding events was slightly higher in the dabigatran etexilate 150 mg group than the warfarin group,

which was presumably brought about by the high ratio of the time when INR control was <2.0 in patients aged ≥ 70 with atrial fibrillation in the Japanese subgroup. While evaluation of the similarity between the overall study population and the Japanese subgroup in study outcomes was associated with difficulty partly due to the small number of patients in the latter included in Study 1160.26, incidence of bleeding events in the Japanese subgroup was within the clinically acceptable range in any group within the data obtained. This finding was determined reasonably consistent with the study as a whole and 150 mg twice daily was established as the usual dose and 110 mg twice daily as the reduced dose for Japanese patients based on the outcomes of the overall study.

PMDA considers as follows:
The difficulty in dose-finding in Japanese patients is understandable given the low event rate of thromboembolism in non-valvular atrial fibrillation and the absence of surrogate endpoints that are able to properly evaluate the efficacy of dabigatran etexilate. Moreover, since the dose range that would be effective and safe had been narrowed down already based on the foreign study outcomes obtained previously, Study 1160.49 in Japan was not able to go beyond confirming safety of Japanese patients at the dosage set in the multiregional Phrase III clinical study and to conduct rigorous dose-finding study. Acknowledging the event rate for bleeding and outcomes of pharmacodynamic parameters in Study 1160.49 in Japan, participation of Japanese patients in Study 1160.26 that adopted 150 mg and 110 mg both twice daily was not of a major problem. However, given the background so far described, Study 1160.26 should preferably have included an ample number of Japanese subjects that could have allowed discussion of the appropriateness of dosage and administration in Japanese subject based on the outcomes of the study. It is hard to consider that adequate consideration was actually given to the dosage for Japanese patients given the extremely small number of Japanese subjects included in the study. Particularly for the bleeding events in Study 1160.26, while incidence of major bleeding and any bleeding event was lower in dabigatran etexilate group than in warfarin group, major bleeding occurred in 5 patients each in the dabigatran etexilate group and in warfarin group in the overall study population in the Japanese subgroup while slightly higher incidence was seen in dabigatran etexilate 150 mg twice daily group for any bleeding event. This suggests that a dose <150 mg twice daily could turn out to be better balanced between risk and benefit in Japanese patients with higher bleeding risks, considering the background that the epidemiologically demonstrated possibility for fewer embolism in Japanese than in Caucasians while focusing more on safety. As for the specific value of reduced dose, 110 mg twice daily should be appropriate as a dosage and administration that expects at least similar efficacy to warfarin based on the results of Study 1160.26 as a whole. As so far described, since clinical usability also can be expected by dabigatran etexilate 110 mg and 150 mg twice daily to Japanese patients with non-valvular atrial fibrillation, the usual dose established as 150 mg twice daily for Japanese is considered appropriate, while future data collection on the efficacy, safety, and reason of choosing each dose is essential. Moreover, since the efficacy is similar to warfarin while is likely to be lower than that of dabigatran etexilate 150 mg twice daily, and its safety is higher than that of 150 mg twice daily as suggested in Study 1160.26, dabigatran etexilate 110 mg twice daily is appropriate for the reduced dosage and administration in patients with backgrounds where excessive pharmacological action and subsequent bleeding are concerned when the usual dose of dabigatran etexilate is administered.

The dosage and administration of dabigatran etexilate will be discussed further considering the results in the expert discussion.

4.(iii).B.(3).2) Patients for reduced dose

PMDA considers:

Unlike warfarin, there is no monitoring indicator available in clinical practice that reflects its drug efficacy for dabigatran etexilate. When administration of dabigatran etexilate is considered, adequate understanding of the bleeding risk factors in individual patients and appropriate decision on the necessity for reduction to 110 mg twice daily should be indispensable. Therefore, alerts in the package insert should be important on the situations where reduction to 110 mg twice daily would be appropriate including those where bleeding risks are potentially higher.

Based on the above, PMDA asked the applicant to explain the ground for listing age ≥75, concomitant use with Pgp inhibitors, and history of gastrointestinal haemorrhage as higher risks of bleedingin patients, as well as the reason for its conclusion that 110 mg twice daily is appropriate for the reduced dosage.

The applicant explained as follows:

The reason for listing age ≥75, concomitant use with Pgp inhibitors, and history of gastrointestinal haemorrhage as higher risks for bleeding in patients is as follows:

The frequency of bleeding in Study 1160.26 was stratified by age ≥75 and <75 to find out that the annual event rate of major bleeding or any bleeding event was higher in patients aged ≥75 in either dabigatran etexilate group or in the warfarin group. As the result of analysis of the time until major bleeding occurred using Cox regression model (a model using age, CL_{cr} [mL/min] at baseline, sex, with or without concomitant ASA as covariates and incorporating interaction terms of treatment groups and each covariate), the hazard ratio of dabigatran etexilate group versus warfarin group demonstrated a tendency for elevation with aging, exceeding 1 at age >85 in the dabigatran etexilate 110 mg group and at age >75 in the 150 mg group. With these findings, it was considered that patients aged ≥75 should be defined as those of high risk of bleeding and 110 mg twice daily should be preferable in them based on the obtained results demonstrating lower risk of bleeding in the dabigatran etexilate 110 mg group than in the 150 mg group in patients ≥75.

The relationship between the plasma trough level of total dabigatran and the incidence of major bleeding and any bleeding event in Study 1160.26 was analyzed by logistic regression. As a result, it was estimated that the 2.5-fold increase of exposure as detected with single concomitant dose of ketoconazole or verapamil would elevate the risk of major bleeding approximately 2.1-fold. And it was presumed that the 1.6-fold increase of exposure as detected with multiple concomitant doses of quinidine, amiodarone, and verapamil would increase the risk of major bleeding approximately 1.48-fold compared with the trough level at dabigatran etexilate 150 mg twice daily. Based on the above, it was considered that reduction of potential risk for bleeding was necessary when Pgp inhibitors are to be used concomitantly. The 110 mg twice daily dose was considered preferable for patients with concomitant Pgp inhibitors based on the generally lower

bleeding risk in the dabigatran etexilate 110 mg group than in the 150 mg group found in the entire Study 1160.26.

In Study 1160.26, gastrointestinal major bleeding, life-threatening gastrointestinal bleeding, and all gastrointestinal bleeding event occurred in higher frequencies in dabigatran etexilate group than in warfarin group. Other results found were; higher risk of gastrointestinal haemorrhage in patients with history of gastrointestinal haemorrhage; or 2 to 3-fold increase of frequency for gastrointestinal haemorrhage in patients with adverse events with symptoms related to gastritis (gastritis, gastrooesophageal reflux disease, oesophagitis, gastritis erosive, gastric haemorrhage, haemorrhagic gastritis, haemorrhagic erosive gastritis) regardless of the treatment group; and higher annual event rates of major bleeding in patients with concomitant PPI or H_2 receptor antagonists. Consequently, it was considered that 110 mg twice daily should be preferable, based on the lower risk of gastrointestinal haemorrhage in dabigatran etexilate 110 mg group than in 150 mg group, in patients with history of gastrointestinal haemorrhage defined as high risk for bleeding events.

Regarding the bleeding risk in Japanese patients, incidence of bleeding was considered in Study 1160.26 and 1160.49 in Japan in patients aged ≥75, with concomitant Pgp inhibitors, with concomitant PPI or H_2 receptor antagonists (no data collected on history of gastrointestinal haemorrhage).

The frequency of major bleeding with dabigatran etexilate in Study 1160.26 was higher in patients aged ≥75 than those aged <75, and in patients with concomitant Pgp inhibitors than patients without them in both of the 2 doses of dabigatran etexilate. While no consistency between doses of dabigatran etexilate was observed, the frequency in the 150 mg group was higher in patients with concomitant PPI or H_2 receptor antagonists than in patients without them. When comparison was made for the occurrence of bleeding between patients with and without concomitant Pgp inhibitors or concomitant PPI or H_2 receptor antagonists in the dabigatran etexilate 110 mg and 150 mg groups, the risk of bleeding was lower in patients without concomitant drugs. Major bleeding with dabigatran etexilate occurred in 1 patient alone at 150 mg in Study 1160.49 in Japan who was aged <75 and used Pgp inhibitor and H_2 receptor antagonist concomitantly.

Based on the findings so far described that; frequency of bleeding and adverse events was generally higher with patients aged ≥75, using concomitant P-glycoprotein inhibitor, PPI or H_2 receptor inhibitor in Japanese patients as well as in Study 1160.26; frequency of bleeding at dabigatran etexilate 110 mg group was lower than at 150 mg group; there was no major differences in incidence of adverse events among treatment groups except for the serious adverse events in Study 1160.49 in Japan; occurrence of stroke or systemic embolism in 110 mg group was not increased compared with 150 mg group, 110 mg twice daily would be considered preferable for patients aged ≥75, with concomitant Pgp inhibitors, or with history of gastrointestinal haemorrhage in Japanese patients as well.

PMDA considers as follows:
While there are generally no major problems in cautioning about the elderly, concomitant use with Pgp

inhibitors, and history of gastrointestinal haemorrhage as the background of higher bleeding risk, the fact that 2.0 to 2.6 was defined as target PT-INR should be considered when interpreting the study outcomes of the elderly. It was so defined to satisfy the target PT-INR (1.6-2.6) recommended in the "Guidelines for Pharmacotherapy of Atrial Fibrillation, (JCS 2008)" as well as the target PT-INR (2.0-3.0) defined in the protocol of the entire study so as to assure safety in the elderly aged ≥70 assigned to warfarin treatment in the Japanese subgroup in Study 1160.26, and to permit comparison with local treatment standards for proper evaluation of drug efficacy in the multiregional clinical study (Study 1160.26). While the applicant cited the higher ratio of time of PT-INR <2.0 in age ≥70 in warfarin group in the Japanese subgroup as the reason for the lowest annual event rate of major bleeding found in warfarin group in the Japanese subgroup, the control state of PT-INR is likely to reflect the clinical practice in Japan. Considering that statistics (Gordon T *Public Health Rep.*1957;72:543-53.) by the US National Institute oh Health [NIH]) also epidemiologically demonstrated the possibility for fewer embolism in Japanese than in Caucasian subjects, bleeding risk tolerable in clinical practice should be discussed based on the risk with warfarin for reference, with caution and a priority on safety as required for those aged ≥70, including dose reduction.

In patients with concomitant Pgp inhibitors, it is appropriate to consider reduction to 110 mg twice daily focused on safety since it is presumed that increase of exposure causes elevated risk of bleeding based on the result of stratifying the frequency of bleeding in Study 1160.26. The stratification with or without concomitant use for individual Pgp inhibitors found that the event rate of bleeding tended to be higher in patients with concomitant use than in those without (CTD2.7.4 Table 2.1.1.1.1.33). This applies to verapamil particularly, given the frequent use of it for concomitant use. For concomitant use of dabigatran etexilate with verapamil, caution is required to when to dose [see “4.(ii)B.(3).1) Interaction between dabigatran etexilate and verapamil”]. Also, the annual event rate of major bleeding and any bleeding event was also higher in patients with concomitant PPI (≥ once) and H_2 receptor antagonists (≥ once) compared with those without them in any treatment group. However, when the annual event rate in dabigatran etexilate group was compared with that in warfarin group, with or without concomitant use of these drugs, the annual event rate with dabigatran etexilate was lower in virtually all occasions. Regarding history of gastrointestinal haemorrhage, gastrointestinal disorders or gastrointestinal haemorrhage were observed in Study 1160.26 more in dabigatran etexilate group than in warfarin group. Therefore, in Japanese patients, it is appropriate to consider reduction to 110 mg twice daily focused on safety due to a larger number of events of gastrointestinal haemorrhage expected in high risk patients for gastrointestinal haemorrhage including those treated with PPI or H_2 receptor antagonists, and there are still unknown mechanism in the development of gastrointestinal disorders or gastrointestinal haemorrhage caused by dabigatran etexilate.

Based on the findings so far described, caution statement in the package insert for the elderly, concomitant Pgp inhibitors, and history of gastrointestinal haemorrhage as high risk of bleeding to consider reduction to 110 mg dabigatran etexilate twice daily should be appropriate but the details of the patients subjected to reduction as high risk of bleeding and content of the caution will be further discussed taking into account the results in the expert discussion.

4.(iii).B.(3).3) Dose reduction in patients with renal impairment

PMDA asked the applicant to explain the rationale for the dose of dabigatran etexilate 110 mg twice daily to patients with moderate renal impairment (CL_{cr} 30-50 mL/min).

The applicant responded as follows:

In Study 1160.26, the annual event rate of stroke and systemic embolism in patients with moderate renal impairment (CL_{cr} 30-50mL/min) was 2.36% in dabigatran etexilate 110 mg group, 1.23% in dabigatran etexilate 150 mg group, and 2.36% in warfarin group, higher than in patients with mild renal impairment (CL_{cr} >50 mL/min) in either treatment group but it was thought that reduction to dabigatran etexilate 110 mg twice daily would not do any harm in efficacy compared with warfarin. On the other hand, regarding the incidence of bleeding events specified as an indicator for safety, the annual event rate of major bleeding was higher in patients with moderate renal impairment than those with CL_{cr} >50 mL/min in either treatment group in Study 1160.26 as a whole. The annual event rate of major bleeding in patients with moderate renal impairment was 5.42% in dabigatran etexilate 110 mg group, 5.08% in dabigatran etexilate 150 mg group, and 5.28% in warfarin group. The annual event rate of any bleeding was 19.17% in dabigatran etexilate 110 mg group, 20.83% in dabigatran etexilate 150 mg group, and 19.60% in warfarin group. On the other hand, the number of patients with moderate renal impairment was 71 in the Japanese subgroup of Study 1160.26 and the annual event rate of major bleeding was 11.96% in dabigatran etexilate 110 mg group, 0% in dabigatran etexilate 150 mg group, and 7.68% in warfarin group. The annual event rate of any bleeding was 39.87% in dabigatran etexilate 110 mg group, 32.61% in dabigatran etexilate 150 mg group, and 40.94% in warfarin group. Based on the above, the rate of bleeding events in patients with moderate renal disorders did not demonstrate any clear differences between treatment groups of dabigatran etexilate but the analysis of the pharmacokinetics of the patient population indicated that deterioration in renal function would elevate the plasma dabigatran etexilate level, which would elevate the bleeding risk. As the result of these efficacy and safety findings, based on the inference drawn from the pharmacokinetic model, it has been concluded that considering reduction to dabigatran etexilate 110 mg twice daily would be appropriate to assure safety in patients with moderate renal impairment (CL_{cr} 30-50 mL/min).

PMDA considers as follows:

While the higher annual event rate of stroke and systemic embolism in dabigatran etexilate 110 mg group than in 150 mg group in patients with moderate renal disorders in Study 1160.26 indicates the possibility for reduced efficacy by dose reduction, when considering the similar rates in dabigatran etexilate 110 mg group and in warfarin group, efficacy may be expected with the reduced dose. In addition, while patients with moderate renal disorders revealed no clear differences in the occurrence of bleeding events depending on the treatment group, their incidence of bleeding events was higher than those with CL_{cr} >50 mL/min in any group, and based on the potential elevation of plasma dabigatran etexilate level in patients with moderate renal impairment (CL_{cr} 30-50 mL/mi) given that exposure of dabigatran etexilate increases in line with deterioration of renal function, it was concluded that considering dose reduction to dabigatran etexilate 110 mg twice daily for patients with moderate renal impairment (CL_{cr} 30-50 mL/min) would be appropriate. It was also concluded that the response of the applicant was appropriate to contraindicate the administration to

patients with severe renal impairment (CL_{cr} <30 mL/min) that had been excluded from Study 1160.26. However, given that no evaluation with sufficient number of patients has been performed regarding Japanese patients, post-marketing data collection should be necessary focused on the safety and efficacy in Japanese patients with renal impairment.

4.(iii).B.(3).4) Necessity for dose titration based on the body weight

PMDA asked the applicant to explain the necessity for dose titration in patients with low body weight since it is estimated that Japanese patients are generally lower weighted than foreign patients.

The applicant explained as follows:

In Study 1160.26, the ratio of patients per body weight category at baseline in the overall study population and the Japanese subgroup was 2.1% and 8.3%, respectively, in <50 kg patients, and 0.2% and 1.2%, respectively, in patients <40 kg, showing more low-weighted patients included in the Japanese subgroup than in the overall study population. The annual event rate of stroke and systemic embolism by body weight at baseline (<50 kg, ≥50 kg and <100 kg, ≥100 kg) was higher in lower-weighted patients and the tendency was particularly obvious in warfarin group. No consistent trends were observed with dabigatran etexilate in the Japanese subgroup. Likewise, the annual event rate of major bleeding by body weight at baseline revealed a tendency for higher annual event rates in lower weighted patients (<50 kg) than in higher weighted patients (≥ 50 kg) in the entire study, but no consistent tendencies were observed when ≥50 kg and <100 kg, and ≥100 kg were compared. No consistent tendencies were observed in the Japanese subgroup either. Regarding all bleeding events, consistent tendencies were observed neither in the overall study population nor in the Japanese subgroup. Considering the results of analysis of the subgroup described above, no dose titration by body weight should be necessary.

PMDA concluded as follows:

While Study 1160.26 as a whole demonstrated slightly higher tendencies in annual event rate of stroke and systemic embolism as well as major bleeding, in patients weighing <50 kg with dabigatran etexilate, the difference was small and similar tendencies were also detected in warfarin group titrated with PT-INR. The ratio of light-weighted patients was higher in the Japanese subgroup than in the overall study population in Study 1160.26 but no clear effects of body weight were detected in the subgroup in annual event rate of stroke and systemic embolism, major bleeding, and any bleeding event with dabigatran etexilate. Based on the above findings, uniform dose titration of dabigatran etexilate in lower weighted Japanese patients with atrial fibrillation should not be necessary.

Given the above discussion, PMDA, as suggested by the applicant, considers dabigatran etexilate 150 mg twice daily and 110 mg twice daily to be acceptable as usual dosage and administration for the former, and for the latter, as dosage and administration for patients with a background where risk of bleeding is concerned with dabigatran etexilate 150 mg twice daily, such as those with concomitant Pgp inhibitors and with history of gastrointestinal haemorrhage. PMDA would like to discuss further taking into account the results of the expert discussion.

4.(iii).B.(4) Indication and target patients of dabigatran etexilate

PMDA asked the applicant to clarify by providing reasons why patients with atrial fibrillation were considered to be included in the target patients of dabigatran etexilate in addition to those with non-valvular atrial fibrillation.

The applicant responded as follows.

Atrial fibrillation is etiologically classified into rheumatic (or valvular) atrial fibrillation, non-valvular atrial fibrillation, and lone atrial fibrillation. Non-valvular atrial fibrillation is defined as atrial fibrillation without history of rheumatic mitral valve disease, artificial valve or repair of mitral valve in "Guidelines for management of anticoagulant and antiplatelet therapy in cardiovascular disease (JCS 2009)".

From these etiological classes, most patients included in Study 1160.26 were presumably those with non-valvular atrial fibrillation because of the exclusion criteria employed as "patients who have undergone heart valve prosthesis that requires anticoagulation therapy, or those with hemodynamically relevant cardiac valve diseases that will require surgical intervention during the study period". However, since it is impossible to rigorously identify individual onset factors, there could have been inclusions of patients who developed atrial fibrillation caused by valvular disease and later developed a complication that was a risk factor to induce new onset of non-valvular atrial fibrillation. Moreover, while 97.0% of 18,113 subjects had risk factors of stroke in Study 1160.26, patients who had no risk factors of stroke and did not meet the inclusion criteria were also included in dabigatran etexilate 110 mg and 150 mg, and warfarin treatment groups in 181 of 6015 patients (3.0%), 198 of 6076 patients (3.3%), and 168 of 6022 patients (2.8%), respectively, and these patients might include those with lone atrial fibrillation that developed without distinct underlying diseases.

Since these etiologically different types of atrial fibrillation share the same onset mechanism of thromboembolism and there is no pathological difference, there are no major differences in antithrombotic treatment either. Anticoagulation therapy or antiplatelet therapy depending on the embolism risk is needed.

In "Guidelines for management of anticoagulant and antiplatelet therapy in cardiovascular disease (JCS 2009)", history of cerebral infarction, transient ischaemic attack or systemic embolism, mitral valvular stenosis, and artificial valve (mechanical valve) are mentioned as high risks of the embolism that requires warfarin therapy. In line with the accumulation of risks, age ≥75, hypertension, cardiac failure or left ventricular contraction contraction decreased (LVEF ≤35% or fractional shortening ≤25%), diabetes mellitus, are mentioned as moderate risks that require warfarin therapy. Cardiomyopathy, age 65 to 74, female gender, coronary artery disease, or thyrotoxicosis are mentioned as risks for which warfarin therapy may as well be considered. To mitral valvular stenosis and mechanical valve replacement patients, basically anticoagulation therapy is specified even if not complicated with atrial fibrillation.

As so far described, when considering atrial fibrillation not in light of the etiology of atrial fibrillation but as a risk factor of thromboembolism, limiting the target patients of dabigatran etexilate to those with non-

valvular atrial fibrillation would deprive part of patients with valvular atrial fibrillation and those with lone atrial fibrillation of treatment opportunities. Moreover, warfarin antithrombotic therapy employed as control is indicated for these atrial fibrillations in the treatment guidelines and dabigatran etexilate achieved results not inferior to warfarin overall in efficacy and safety. Therefore, on the assumption that patients with atrial fibrillation other than non-valvular atrial fibrillation would be included, the proposed indication specified "Reduction of risks of stroke and systemic embolism in patients with atrial fibrillation".

PMDA considers as follows:
The "Guidelines for the diagnosis and treatment of cardiovascular diseases (Joint research team report 2008)" seeks anticoagulation therapy or antiplatelet therapy according to the risk of embolism for atrial fibrillation but lists mitral valve stenosis and artificial valve (mechanical valve) as high risks of embolism. The guideline recommends PT-INR target 2.0 to 3.0 regardless of age for patients who particularly need the strong anticoagulation action of these. However, "patients with heart valve prosthesis or those with hemodynamically relevant valvular diseases that will require surgical intervention during the study period" were defined as exclusion criteria in Study 1160.26 and no clinical outcomes available to evaluate the safety and efficacy of dabigatran etexilate. Considering the absence of rationale at present to expect adequate efficacy achieved by dabigatran etexilate in "patients with heart valve prosthesis that requires anticoagulation therapy, or those with hemodynamically relevant valvular diseases that will require surgical intervention during the study period", dabigatran etexilate may not be aggressively recommended. Based on the above, "patients who have undergone heart valve prosthesis that requires anticoagulation therapy, or those with hemodynamically relevant valvular diseases that will require surgical intervention during the study period" should not be considered appropriate subjects of dabigatran etexilate and it should be proper to describe the indication of dabigatran etexilate as "Reducing the risk of stroke and systemic embolism in non-valvular atrial fibrillation" excluding such patients and patients with rheumatic mitral disease. Moreover, lone atrial fibrillation is considered one of good indications of dabigatran etexilate. Since the guidelines define non-valvular atrial fibrillation as atrial fibrillation without history of rheumatic mitral disease, artificial valve, and repair of mitral valve, lone atrial fibrillation should be included in the range of non-valvular atrial fibrillation. Details of the atrial fibrillation patients for whom treatment by dabigatran etexilate is appropriate as well as definition of indications for it will be further evaluated with the results of the expert discussion also taken into account, including the appropriateness of administration of dabigatran etexilate to "patients with heart valve prosthesis or those with hemodynamically relevant valvular diseases that will require surgical intervention during the study period".

PMDA asked the applicant to clarify if patients with atrial fibrillation already under warfarin treatment and well controlled with blood coagulation monitoring are considered also as subjects for the treatment with the proposed product.

The applicant responded as follows.
In order to assess the safety and efficacy of dabigatran etexilate in atrial fibrillation patients already under warfarin treatment and successful control with blood coagulation monitoring, frequency and annual event

rate of stroke and systemic embolism, as well as bleeding were evaluated in patients with history of vitamin k antagonists and successful PT-INR control prior to the inclusion in Study 1160.26. Regarding the switching from warfarin, it was agreed that the investigational product would start with PT-INR <2.0. The annual event rate with dabigatran etexilate 110 and 150 mg, and warfarin groups was 1.45%, 1.01%, and 1.58% for stroke and systemic embolism, respectively; 2.95%, 2.91%, and 3.55% for major bleeding, respectively; and 15.45%, 16.80%, and 17.85% for any bleeding events, respectively, demonstrating efficacy and safety with the two doses of dabigatran etexilate both no worse than with warfarin.

As described so far, it was considered that advantages of dabigatran etexilate should be expected also in atrial fibrillation patients already under warfarin treatment and successful control with blood coagulation monitoring and it was considered appropriate to include atrial fibrillation patients already under warfarin treatment and successful control with blood coagulation monitoring as its target.

PMDA concluded as follows:
Patients of poor PT-INR control under warfarin are considered appropriate as subjects of dabigatran etexilate. In administering warfarin, long-term, continued blood monitoring and titration will be critical even with patients already under successful control. Considering the demonstrated safety and efficacy of dabigatran etexilate no worse than warfarin in patients under successful control by warfarin, switching may be considered for patients under successful control besides poor controlled patients and the clinical implication of such switching will be significant given the frequent drug interactions associated with warfarin. In addition, regarding the bridging therapy in a major surgery that requires suspension of the anticoagulant, by concomitant intravenous or subcutaneous injection of heparin that has a short half-life before and after the surgery recommended in "Guidelines for management of anticoagulant and antiplatelet therapy in cardiovascular disease (JCS 2009)", dabigatran etexilate with a half-life shorter than warfarin and rapid onset and dissipation of effects will be able to eliminate the necessity for such bridging therapy to perform surgery [see"4.(iii).B.(5).5 Pre-surgery washout and switching to other anticoagulants"]. As so far described, dabigatran etexilate may include switching from warfarin in patients already under warfarin as its indication in the clinical practice. It should be feasible if adequate consideration is given to the bleeding risk, etc., based on the subjects' background and to appropriateness of switching to dabigatran etexilate, despite its disadvantages of difficulty in proper selection or titration of dosage depending on the situation. The difficulty includes the decision on the appropriateness of dose reduction in patients for whom it is impossible to monitor drug efficacy and higher bleeding risk as later described is predicted.

4.(iii).B.(5) Safety

4.(iii).B.(5).1) Risk of bleeding

The applicant explained as follows regarding the occurrence of bleeding adverse events by dabigatran etexilate:
In Study 1160.26, the hazard ratio of major bleeding in dabigatran etexilate 110 mg group versus warfarin group was 0.79, which was significantly lower (P = 0.0021). On the other hand, the hazard ratio of major bleeding with dabigatran etexilate 150 mg group versus warfarin group was 0.93 revealing no significant

differences of incidence between the two (P = 0.3218). The risks of life-threatening bleeding, haemorrhagic stroke, and haemorrhage intracranial with dabigatran etexilate 110 mg group and 150 mg group were all significantly lower than warfarin (P <0.05).

The annual event rate of major bleeding in dabigatran etexilate 110 mg and 150 mg groups, as well as in warfarin group in the Japanese subgroup was 5.53%, 3.33%, and 3.31%, respectively, and the hazard ratio with dabigatran etexilate 110 mg twice daily group and dabigatran etexilate 150 mg twice daily group was 1.68 and 1.02, respectively, versus warfarin group. It was considered that these results suggested no different tendencies from the overall study or other study regions.

The annual event rate of gastrointestinal major bleeding was higher in dabigatran etexilate groups than with warfarin group in the overall study but no clear tendencies were identified in the Japanese subgroup. The tendency of rising risk of bleeding with concomitant ASA was observed in the overall study and likewise in the Japanese subgroup.

PMDA considers as follows:
While higher risk of bleeding is generally expected with higher effects in reducing thromboembolism in anticoagulation therapy, Study 1160.26 suggested that risks of haemorrhage intracranial, any bleeding events, and death were all lower in dabigatran etexilate (110 mg or 150 mg twice daily) groups than in warfarin group. Lower risks of haemorrhagic stroke and haemorrhage intracranial, both highly valued in medical care, are also suggested with the use of dabigatran etexilate than with warfarin. Based on these facts, the availability of dabigatran etexilate in clinical practice should be higly significant. The tendency of bleeding risk in the Japanese subgroup was not lower in than dabigatran etexilate group than in the warfarin group, but the degree of bleeding risk in dabigatran etexilate, when compared with warfarin, is uncertain since the number of Japanese patients included was extremely small. Based on these, it is considered at present that the risk of bleeding in dabigatran etexilate is within clinically acceptable range given the outcomes observed in the overall population of Study 1160.26 that generally can be expected in Japanese population as well, as described above. Post-marketing data collection is nonetheless required including the information concerning the appropriateness of the two doses of dabigatran etexilate [see “4.(iii).B.(2).3) Outcomes in Japanese patients in Study 1160.26”]

Since verapamil and diltiazem are used for tachycardiac atrial fibrillation for rate control more often in Japan compared with Europe and the US, a possible role of the interaction and subsequent increase of exposure of dabigatran etexilate to elevate the risk of bleeding cannot be ruled out and adequate caution in the package insert is considered necessary to address the risk. Details of the caution will be further considered taking into account the results of the expert discussion as well.

4.(iii).B.(5).2) Risk of bleeding with concomitant thrombolytic agents
PMDA asked the applicant to explain the increase of risk for bleeding and assurance of safety when the proposed product is used concomitantly with other thrombolytic agents.

The applicant responded as follows.
In the Japanese subgroup in Study 1160.26, among the thrombolytic agents used ≥ once during the study period, ASA (33.4%), oral anticoagulants (29.1%), and injection anticoagulants (8.9%) were frequently used. No patients used 2 agents of ASA and clopidogrel concomitantly with dabigatran etexilate during the study period.

The annual event rate of major bleeding elevated by concomitant ASA (≥ once) in dabigatran etexilate 110 mg group and 150 mg group, as well as with warfarin group (patients with ASA, 7.88%, 7.18%, 7.17%, respectively; without, 4.26%, 1.06%, 1.83%, respectively) and the annual event rate of any bleeding events also elevated (patients with ASA, 29.55%, 37.69%, 40.64%, respectively; without ASA, 26.61%, 32.77%, 31.19%, respectively).

The annual event rate of major bleeding in dabigatran etexilate 110 mg group and 150 mg group, and in warfarin group was 6.60%, 1.63%, and 9.16%, respectively, in patients with concomitant oral anticoagulants (≥ one time), and 4.75%, 4.49%, and 2.86%, respectively, in patients without them. No marked influence by the concomitant use was detected. The annual event rate of any bleeding events was 26.41%, 40.83%, and 36.63%, respectively, in patients with concomitant oral anticoagulants (≥ one time), and 28.52%, 30.31%, and 33.59%, respectively, in patients without them. No marked influence by the concomitant use was detected.

With dabigatran etexilate 110 mg group and 150 mg group as well as with warfarin group, the annual event rate of major bleeding increased by the concomitant injection of anticoagulants (≥ one time) (patients with concomitant injection, 18.32%, 25.61%, 8.54%, respectively; patients without, 4.48%, 0.74%, 2.87%), as well as of any bleeding events (patients with concomitant injection, 45.81%, 57.62%, 34.15%, respectively; patients without, 26.16%, 31.92%, 33.78%, respectively).

As so far described, among the thrombolytic agents used in the Japanese subgroup during the study period, concomitant use of ASA and injection anticoagulants elevated the annual event rate of bleeding events, and based on this, the sections for important basic precautions (2), (3) and the section for interactions in the package insert (draft) caution for the concomitant use with these agents associated with possible elevation of bleeding events by concomitant use with the proposed product. In addition, since the annual event rate of any bleeding events in the concomitant use with dabigatran etexilate 110 mg twice daily is lower than with dabigatran etexilate 150 mg twice daily, one way to solve this concomitant issue may be to reduce the dose of dabigatran etexilate to 110 mg twice daily. However, it was concluded that concomitant use with these agents would be recommended only to patients for whom administration of the proposed product is appropriate considering the therapeutic benefit and safety, given the absence of consistent tendencies of risk reduction by dabigatran etexilate 110 mg twice daily compared to 150 mg twice daily in concomitant use with these agents in the form of annual event rate of major bleeding, as well as the risk for elevation of the event rate for thromboembolism by the reduction of the proposed product that cannot be ruled out.

PMDA concluded as follows:
In patients with atrial fibrillation complicated with ischaemic heart disease, permanent administration of ASA and administration of clopidogrel for at least 12months are recommended, suggesting a possibility for concomitant use of 3 agents including dabigatran etexilate. In addition, experience of concomitant use in Japan is very limited because of the restriction in Study 1160.26 of concomitant use to patients complicated with angina unstable, effort angina stable, and myocardial infarction (non-acute) that warfarin would not help as substitute as perceived in Japan, or to atrial fibrillation patients who had revascularization procedure such as percutaneous coronary intervention (PCI) or coronary artery bypass. Consequently, evidence has not been established for the effect of combination therapy while clearly associated with elevated risk of bleedingwhen drugs are administered alone. Therefore, risks and benefits of individual patients should be considered before deciding such use. Data regarding the evaluation of bleeding risk from concomitant use of other thrombolytic agents in Japanese patients also need to be continuously collected post-marketing.

4.(iii).B.(5).3) Risk of gastrointestinal disorders
PMDA asked the applicant to explain the cause of more gastrointestinal disorders (34.6% in dabigatran etexilate 110 mg group, 34.5% in dabigatran etexilate 150 mg group, 24.0% in warfarin group) or gastrointestinal haemorrhage (9.3% in dabigatran etexilate 110 mg group, 10.5% in dabigatran etexilate 150 mg group, 7.1% in warfarin group) observed in dabigatran etexilate group than in warfarin group in Study 1160.26, appropriate measures to avoid the incidence of gastrointestinal disorders or gastrointestinal haemorrhage as well as specific procedure to address the occurrence of such adverse events including suspension or reduction of the drug.

The applicant responded as follows.
At present, the cause is unknown for more gastrointestinal disorders or gastrointestinal haemorrhage observed with dabigatran etexilate than with warfarin in Study 1160.26. While in dabigatran etexilate group in Study 1160.26, the risk of any gastrointestinal haemorrhage slightly increased in patients who had dyspepsia, with warfarin, the risk was 2-fold in patients who had dyspepsia of those who did not. During the period of Study 1160.26, patients having dyspepsia were instructed to take the drug with a large volume of water or with meal and improvement of the condition with such measure was reported but no systematic evaluation has been performed. PPI was used to alleviate dyspeptic symptoms.

In patients who had gastritis and related adverse events (gastrooesophageal reflux, oesophagitis) in Study 1160.26, the risk of major gastrointestinal haemorrhage increased to 3.8 to 4.3-fold, and to 4.9-fold of those who did not, in dabigatran etexilate group and in warfarin group, receptively. Similarly, the risk of any gastrointestinal haemorrhage increased to 2.2 to 2.6-fold and to 3.4-fold in dabigatran etexilate group and in warfarin group, respectively. The risk of gastrointestinal haemorrhage presumably rises in patients having gastritis-like symptoms as in the above, but it has not been identified whether this is by a specific mechanism or by the influence related to dabigatran etexilate or tartaric acid, the additive. Detailed data analysis regarding dyspepsia is planned in RE-LYABLE test (a long-term extension study that enrolls participants in

Study 1160.26 but no Japanese patients enrolled) and gastrointestinal disorders and gastrointestinal haemorrhage will be the priority investifation subject in the post-marketing surveillance plans in Japan as well.

In addition, revision of the important basic precaution (1) of the package insert (draft) is requested in order to alert these adverse events, from "When you use the proposed product, acknowledge the risk of bleeding and carefully observe the patient. Take appropriate measures including suspension for any abnormalities detected such as bleeding." to "When you use the proposed product, acknowledge the risk of bleeding and carefully observe the patient for signs of bleeding or anaemia. Take appropriate measures including suspension for any abnormalities detected such as bleeding. Bleeding under treatment with the proposed product may occur at any sites. Be alert to abnormal decrease in hemoglobin, hematocrit, or blood pressure. Given the frequent gastrointestinal bleeding associated particularly, be careful for haematemesis, haematochezia, abdominal pain, and abdominal distension and suspend treatment when they are detected."

PMDA concluded as follows:
Frequency of gastrointestinal haemorrhage was higher in dabigatran etexilate group than in warfarin group in the overall study population of Study 1160.26, and the number of major gastrointestinal haemorrhage occurred in dabigatran etexilate 110 mg group and 150 mg group, and in warfarin group was in 3, 1, and 1 patient, respectively, in the Japanese subgroup. Since the onset of gastrointestinal haemorrhage may require suspension of anticoagulant for certain amount of time, at present warfarin should be remembered as a choice besides the reduction to dabigatran etexilate 110 mg twice daily based on the increased risk of embolism in patients with history of gastrointestinal haemorrhage. In patients with no history of bleeding but with history of upper gastrointestinal ulcer, caution is required to decide between dabigatran etexilate and warfarin. The high risk of gastrointestinal haemorrhage in patients with gastritis requires appropriate measures including suspension of treatment at the onset of the symptom but the decision should be careful and the bleeding risk including gastrointestinal heamorrhage and benefits of risk reduction of stroke should be taken into account. Continued data collection in post-marketing surveillance with an emphasis on gastrointestinal disorders and gastrointestinal haemorrhage should be important and careful tracking of the progress after approval is necessary. Appropriateness of dabigatran etexilate treatment in patients with history of gastrointestinal haemorrhage, and upper gastrointestinal tract ulcer, as well as the details of the alert in the package insert will be discussed further taking into consideration of the results of the expert discussion.

4.(iii)B.(5).4) Risk of myocardial infarction

The risk of acute myocardial infarction with dabigatran etexilate was further studied, considering the tendency for higher occurrence of myocardial infarction in dabigatran etexilate group than in warfarin group in Study 1160.26 where onset of myocardial infarction was observed in 86 of 6015 patients in dabigatran etexilate 110 mg group, 89 of 6076 patients in dabigatran etexilate 150 mg group, and 63 of 6022 patients in warfarin group during the study period.

The applicant explained the occurrence of myocardial infarction in Study 1160.26 as follows:

In order to detect any inter-group imbalance in the patients' background related to myocardial infarction, complication with coronary diseases, complication with cardiac failure, history of myocardial infarction, concomitant use of ASA at baseline, demographic characteristics (age, sex, BMI) were selected and studied, but found no such imbalance. In addition, incidence of myocardial infarction was analyzed using Cox regression model with these as covariates to find no effects of covariates on the hazard ratio of dabigatran etexilate 110 mg and 150 mg groups versus the warfarin group. Furthermore, no myocardial infarction occurred in the Japanese subgroup. In order to evaluate the inter-group difference in the risk of coronary artery disease other than myocardial infarction, all the reported events related to ischaemic pathology of the coronary artery were searched by using the Medical Dictionary for Regulatory Activities (MedDRA). The frequency was compared between adverse events related to ischaemic coronary diseases excluding myocardial infarction, identified as events from the entire patients who received the proposed product. The frequency of adverse events was 2.6% (157 of 5984 patients) in dabigatran etexilate 110 mg group, 2.4% (143 of 6059 patients) in dabigatran etexilate 150 mg group, and 2.8% (165 of 5999 patients) in warfarin group, demonstrating no imbalance between each group in the incidence of symptoms derived from ischaemic coronary artery diseases. The inter-group differences did not significantly alter when myocardial infarction was included.

PMDA asked the applicant to explain the presence or absence of variation of risk factors of coronary artery before and after the administration and then, the possible influence of dabigatran etexilate on the risk factors.

The applicant responded that no aggravating tendency was found in dabigatran etexilate groups by comparing variations in risk factors which are casual blood glucose, total cholesterol, triglyceride, creatinine, systolic blood pressure, and diastolic blood pressure before and after dabigatran etexilate and warfarin administration.

PMDA concluded as follows on the risk of myocardial infarction by dabigatran etexilate:
The cause is still unknown for the higher incidence of myocardial infarction in dabigatran etexilate 150 mg group than in warfarin group in the entire Study 1160.26. In addition, the analysis was performed with an extremely low frequency and therefore at present, the possibility for increased risk of myocardial infarction by dabigatran etexilate remains unknown. As so far described, while post-marketing data collection should be appropriate on the risk of myocardial infarction by dabigatran etexilate, necessity for alert on the package insert will be examined considering the results of the expert discussion.

4.(iii).B.(5).5) Pre-surgery washout and switching with other anticoagulants
PMDA asked the applicant to explain the necessity for washout of the proposed product in patients undergoing surgery and an appropriate washout period.

The applicant responded as follows:
Different Japanese guidelines consider continued oral administration of warfarin to be preferable in dental procedure and minor surgery (tooth extraction etc.) where bleeding is easily handled, if postoperative

bleeding is easily addressed likewise with body surface surgery, considering the significant thromboembolism occurring in an approximately 1% frequency when warfarin is suspended for such procedure. In the perioperative period of a major surgery, a so-called bridging therapy with heparin is recommended that suspends warfarin 3 to 5 days prior to surgery and switches to heparin to adjust aPTT to 1.5 to 2.5-fold of normal control value and then suspend heparin 4 to 6 hours prior surgery or neutralize it with protamine sulfate immediately prior to surgery.

Regarding dabigatran etexilate, interaction between the plasma pharmacokinetics of dabigatran, an active metabolite, and its anticoagulation action has been confirmed from pharmacodynamic evaluations using blood coagulation parameters. Following oral administration of dabigatran etexilate to healthy adults in the fasted state, the plasma total dabigatran level peaked at 0.5 to 2 hours post-dose and the terminal half-life was 9.41 and 10.1 hours on average in young males and females, respectively. This suggests that the onset and dissipation of anticoagulation action of dabigatran etexilate is more rapid than those of warfarin. Moreover, since dabigatran is mainly eliminated through the kidney, pharmacokinetics of dabigatran etexilate is affected by renal impairment. It has been confirmed that following oral administration of dabigatran etexilate to patients with mild (CL_{cr} 50-80 mL/min), moderate (CL_{cr} 30-50 mL/min) and severe (CL_{cr} <30 mL/min) renal impairment, the geometric mean of terminal half-life of total dabigatran is prolonged to 15.3, 18.4, and 27.2 hours, respectively.

Based on the above, considering that washout of dabigatran etexilate is necessary in patients undergoing surgery, rules for pre-surgery washout were defined in the dabigatran etexilate groups in Study 1160.26 depending on the degree of renal impairment and bleeding risk related to surgery as; a 2 to 3-days, 4-days, and 5-days pre-surgery washout in patients with high bleeding risk[*] correspoinding to mild, moderate, and severe renal impairment, respectively; and a 24-hour (2 doses), minimum 2-day, or 2 to 5-day pre-surgery washout for those with standard bleeding risk, corresponding to the mild, moderate, and severe renal impairment, respectively. Under the provision for patients with standard bleeding risk, the plasma total dabigatran concentration is expected to decrease to approximately 25% of the steady state or under.

The overall temporary suspension of dabigatran etexilate due to surgery or treatment procedure was shorter than that required with warfarin. Moreover, switching of anticoagulation therapy before and after these procedure (with subcutaneous low-molecular-weight heparin or unfractionated heparin) was less frequent in dabigatran etexilate group than in warfarin group. With dabigatran etexilate, the amount of time required from suspension to the procedure was ≤2 days in approximately 30% of patients, >2 days and ≤5 days in approximately 21%, and >5 days in approximately 8% of patients. With warfarin, the amount of time required from suspension to the procedure was ≤2 days in 6.4%, > 2 days and ≤5 days in 26.2%, and >5 days in approximately 25% of patients. In order to assess the efficacy and safety of dabigatran etexilate with washout carried out according to the rule, the frequency of stroke and systemic embolism, as well as bleeding

[*]Other important factors that decide the haemorrhagic risk related to surgery include the age of patients, complications (e.g. serious heart disease, respiratory disease, and hepatic disease) and concomitant antiplatelet drugs.

occurring 7 days prior to and 30 days after a treatment such as non-elective surgery, was studied in patients who suspended anticoagulation therapy including dabigatran etexilate and warfarin, the control drug, in Study 1160.26. The frequency of stroke and systemic embolism in dabigatran etexilate 110 mg group and 150 mg group as well as in warfarin group was 1.2% (2 of 167 patients), 0.5% (1 of 196 patients), and 1.9% (3 of 162 patients), respectively, for 7 days prior to, and 3.0% (5 of 167 patients), 0.5% (1 of 196 patients), and 3.1% (5 of 162 patients), respectively, for 30 days after the treatment. The comparison of frequency of major bleeding resulted in 10.2% (17 of 167 patients), 6.6% (13 of 196 patients), and 9.3% (15 of 162 patients), respectively, for 7 days prior to, and in 10.2% (17 of 167 patients), 13.3% (26 of 196 patients), and 14.8% (24 of 162 patients), respectively, for 30 days after the operation. The comparison of minor bleeding resulted in 6.0% (10 of 167 patients), 6.1% (12 of 196 patients), and 6.8% (11 of 162 patients) for 7 days prior to, and 12.0% (20 of 167 patients), 10.2% (20 of 196 patients) and 14.2% (23 of 162 patients) for 30 days after the surgery.

As so far described, based on the absence of major differences observed in the efficacy and safety results between patients in dabigatran etexilate group and in warfarin group associated with the washout as defined in Study 1160.26, pre and postoperative washout durations will be defined according to the above mentioned provision as well as resumption of dabigatran etexilate administration when normal hemostasis is restored. They will be described on the package insert (draft).

PMDA considers as follows:
In clinical practice, duration of a preoperative washout of an anticoagulant is considered based on the risk of bleeding and embolism with individual patients prior to the surgery. In Study 1160.26, it was provided that 24 hours prior to operation is sufficient for dabigatran etexilate to conduct a surgery that requires a washout of an anticoagulant if with normal bleeding risk, normal or mildly impaired renal function. Based on the similar degrees of efficacy and safety demonstrated in dabigatran etexilate group and in warfarin group in a study under the provision, the provision may serve as an indicator for the timing of washout in clinical practice. For warfarin, a so-called bridging therapy with heparin is required that suspends warfarin 3 to 5 days prior to operation and suspends heparin 4 to 6 hours prior to operation or neutralizes it with protamine sulfate immediately prior to surgery. Dabigatran etexilate should have an advantage of no requirement for such bridging therapy. However, sufficient assessment has not been performed of the timing of washout in patients with higher risks of bleeding, and post-marketing data collection should be required. Provision for washout will be considered based on the results of the expert discussion.

Regarding the switching to other anticoagulants (injection agents) or from other coagulants (injection agents) to the proposed drug, the applicant explains that they are defined in the package insert (draft) in the US and Europe to set a 12-hour interval preceding the switch to other anticoagulants (injection agents) after the dose of the proposed drug , and switching from other anticoagulants (injection agents) to the proposed drug should precede by 2 hours before the next injection planned or be carried out when continuous intravenous injection (e.g., unfractionated heparin) is suspended. On the other hand, the applicant has no experience with Japanese patients and therefore, it is necessary to continue post-marketing data collection.

4.(iii).B.(5).6) Coagulation markers

PMDA asked the applicant to produce the ground for the specification in the description included in the important basic precaution of the package insert (draft) stating that "aPTT (activated partial thromboplastin time) may be useful as an indicator for excessive anticoagulation action in bleeding patients. aPTT >80 seconds indicates a high risk of bleeding." and explain on specific measure in clinical practice (in what situation aPTT is measured, how the measured aPTT is reflected in the administration of the proposed product).

The applicant explained as follows:

Interaction between aPTT and plasma level of dabigatran etexilate is not linear. Its sensitivity to concentration declines in the high concentration region of dabigatran etexilate but nonetheless aPTT is a coagulation marker widely used in clinical practice and is considered useful as an indicator for excessive anticoagulation action. Excessive exposure of dabigatran etexilate or excessive prolongation of aPTT may indicate a bleeding risk exceeding that with warfarin.

In Study 1160.26, the trough aPTT in patients who did not exhibit major bleeding was 72.2 seconds in the 90th percentile, demonstrating difference in the risk of major bleeding when stratified with a trough aPTT value of 80 seconds as the threshold. The trough aPTT in the 90th percentile was 76.4 seconds in patients with dabigatran etexilate 150 mg in Study 1160.26 and patients with >80 seconds accounted for <10% of the overall population. Study 1160.20, for patients (non-Japanese) with atrial fibrillation, defined to reduce administration of dabigatran etexilate when the trough aPTT after dabigatran etexilate dose exceeded 2.5-fold ULN at the study sites in patients with glomerular filtration rate (GFR) ≤50 mL/min predicted to have higher exposure (the baseline aPTT was 33.9 seconds in this study, and 2.5 times of this amounted to approximately 85 seconds). However, no major bleeding occurred in 12 of 502 patients subjected to reduction according to the criteria of aPTT prolongation. In addition, in patients with GFR ≤50 mL/min, minor bleeding or clinically relevant bleeding occurred in 7 patients, but none of them was among the patients subjected to reduction based on prolonged aPTT criteria. Based on the results of foreign studies 1160.20 and 1160.26, trough aPTT ≥80 seconds was considered to be an indicator to detect excessive exposure of dabigatran etexilate.

While Study 1160.26 indicated that no regular monitoring of the plasma level or anticoagulation action of dabigatran etexilate is necessary, nonetheless measuring aPTT should be useful in considering suspension of dabigatran etexilate when excessive exposure of it is suspected (for example, overdosage, acute renal failure, concomitant use of Pgp inhibitors which is contraindicated, major bleeding). When measuring aPTT to determine if dabigatran etexilate is the cause of major bleeding occurring in a patient treated with it, the trough aPTT would be preferable for this purpose if possible. Measuring aPTT is also considered useful when seeking measures, such as delaying the surgery, to avoid the risk of major bleeding or clinically relevant bleeding if a patient on dabigatran etexilate is undergoing surgery. In a major surgery, etc., that requires completely restored blood coagulation function, it is recommended to confirm a prior ≥24-hour washout of

dabigatran etexilate and aPTT reduced to the vicinity of ULN in starting the surgery.

Reduction to dabigatran etexilate 110 mg is recommended when the trough aPTT in the steady state exceeds 80 seconds in patients on dabigatran etexilate 150 mg, considering a balance between the benefit of preventive effects for stroke and the risk of bleeding. If the trough aPTT measured on and after Day 4 from the reduction to 110 mg exceeds 80 seconds, it is recommended to make a decision on the appropriateness to continue treatment based on the risk and benefit balance.

PMDA considers as follows:
The aPTT test is widely used and may assess the approximate strength of anticoagulation therapy with dabigatran etexilate in daily clinical practice. However, the dose titration method based on aPTT that the applicant advocates lacks robust rationale. aPTT cannot be determined to be useful as an indicator for the efficacy and safety of dabigatran etexilate while its potential is not ruled out to assist judgment on whether anticoagulation action is excessive or not. Consequently, while associated with a short half-life, the inability to accurately monitor the blood coagulation function should be pointed out as its disadvantage versus warfarin. Furthermore, measures for bleeding that requires treatment need to be disseminated through the package insert, etc. Significance of aPTT measurements will be determined based on the results in the expert discussion.

4.(iii).B.(6) Post-marketing surveillance
The applicant explained its current plan for the post-marketing surveillance as follows:
The mean exposure time of the drug in the Japanese subgroup in Study 1160.26 was 15.11 months and there were 326 Japanese patients (218 patients on dabigatran). Considering the long-term use predicted with the proposed product, a specified use-results survey is intended in order to evaluate its safety and efficacy in the long-term use (follow-up period, 2 years; planned number of subjects, 3000). On the other hand, as the result of an evaluation conducted according to ICHE2E on the safety of dabigatran etexilate, bleeding is listed as the important identified risks; hepatic toxicity, an event identified in other antithrombin drug (ximelagatran) as the important potential risk; and children, the elderly, patients with renal impairment, patients with impaired liver functions, pregnant women as the important missing information; and amiodarone, quinidine, verapamil, clarithromycin, ketoconazole, rifampicin, clopidogrel, and aspirin as identified or potential interactions. Among the above, bleeding will be investigated as priority investigation item in the specified use-results survey, while voluntary reports will be collected and information on patients in the survey will be evaluated for other issues

PMDA feels the necessity for adequate data collection on the safety and efficacy of dabigatran etexilate in the post-marketing surveillance given the extremely small number of Japanese patients included in Study 1160.26. Particularly, evaluations of dabigatran etexilate are considered important for: the safety including bleeding risks in patients using concomitant antiplatelet drugs, who are aged, or with renal impairment; the safety regarding gastrointestinal disorders and gastrointestinal haemorrhage; the effects by concomitant drugs (including verapamil); and the relationship between dosage and safety. Data collection on the incidence

of myocardial infarction is also considered necessary. Details of the post-marketing surveillance will be further investigated considering the results of the expert discussion.

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

Reported in Review report (2)

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

Reported in Review report (2)

IV. Overall Evaluation

Based on the submitted data, it is concluded that the efficacy of dabigatran etexilate in patients with non-valvular atrial fibrillation to reduce the risk of stroke and systemic embolism has been demonstrated and its safety is acceptable in view of its observed benefits.

Considering that dose titration with regular monitoring of blood coagulation is not required and interaction with other drugs or foods is reduced compared to conventional treatments, availability of dabigatran etexilate in clinical practice as a drug that may become a standard or first choice in addition to warfarin is considered beneficial despite the concern over gastrointestinal disorders and gastrointestinal haemorrhage. Further investigation is necessary for detailed definition of the indications of dabigatran etexilate such as exclusion of patients with valvular diseases or artificial valve. Moreover, safety in patients with gastrointestinal disorders and gastrointestinal haemorrhage, or in elderly patients, or in patients with renal disorders needs to be evaluated in the post-marketing surveillance.

The proposed product may be approved, if it can be concluded that there are no particular problems based on the results of the expert discussion.

Review report (2)

November 16, 2010

I. Product Submitted for Registration

[Brand name]	Pradaxa Capsules 75 mg Pradaxa Capsules 110 mg (The proposed Japanese brand name will be changed.)
[Non-proprietary name]	Dabigatran Etexilate Methanesulfonate
[Name of applicant]	Nippon Boehringer Ingelheim Co., Ltd.
[Date of Application]	March 4, 2010

II. Content of the Review

The outline of the Expert Discussion and the subsequent review by the Pharmaceuticals and Medical Devices Agency (PMDA) is described in the following sections.

The expert advisers 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 dabigatran etexilate

The conclusion of PMDA that dabigatran etexilate may become one alternative of anticoagulants for reduction of the risk of stroke in patients with non-valvular atrial fibrillation based on the following discussion was supported by the expert advisers:

Considering the results of the multiregional phase III study (Study 1160.26) performed in patients with non-valvular atrial fibrillation, the efficacy of dabigatran etexilate 110 mg and 150 mg twice daily to reduce the risk of stroke and systemic embolism was demonstrated as non-inferior to warfarin currently recommended as the standard therapy to reduce the risk of ischaemic stroke in patients with non-valvular atrial fibrillation. Dabigatran etexilate's clinically acceptable safety was also demonstrated in its risk of symptomatic haemorrhage intracranial and fatal bleeding lower than warfarin. In addition, dabigatran etexilate, unlike warfarin, is expected to offer advantages such as treatment can be continued without particular dose titration and adjustment of administration once started, clinically relevant interaction of drugs is reduced, and no diet is required such as vitamin k. Since the evaluation of efficacy and safety of dabigatran etexilate in Japanese patients is considerably limited and the study outcome over the risk of gastrointestinal haemorrhage was higher than warfarin, PMDA concluded that when considering treatment with anticoagulant drug to Japanese patients with non-valvular atrial fibrillation, careful consideration will be required in selecting drugs appropriate to individual patients taking into account the characteristics of warfarin and dabigatran etexilate, or the patients' background. Some experts voiced that this conclusion is reasonable, while there were opinions that given the short half-life of dabigatran etexilate with a requirement for 2 doses a day, the use of

warfarin should be considered when unstable effect can be predicted due to poor compliance. Finally, the conclusion by PMDA was supported by the expert advisors.

2. Evaluation of Study 1160.26

(1) Design of Study 1160.26

The following PMDA's conclusion was supported by the expert advisers:

The adoption of PROBE method in Study 1160.26 (started in 20[redacted]) was unavoidable since warfarin (the control drug of the study) should be titrated by monitoring PT-INR of individual patients. Considering the various measures taken to reduce bias and the evaluation conducted with focus on objective indicators, evaluation for efficacy and safety of dabigatran etexilate may be feasible to some extent.

(2) Efficacy and safety of dabigatran etexilate and results in Japanese patients in Study 1160.26

The following PMDA's conclusions were supported by the expert advisers:

While targets of PT-INR control over warfarin actually differ between Japanese patients and non-Japanese patients, there should be no clinically relevant differences in anticoagulation action or pharmacokinetics of dabigatran etexilate if the dosage and administration defined in Study 1160.26 is used. Therefore, collective evaluation of outcomes from the Japanese subgroup and from non-Japanese groups in Study 1160.26 is feasible. And at least in the study as a whole, similar or higher degree of clinical usability of dabigatran etexilate versus warfarin has been demonstrated in Study 1160.26 given the non-inferiority of dabigatran etexilate 150 mg and 110 mg twice daily to warfarin regarding the risk reduction for stroke and systemic embolism as well as the lower risks than with warfarin suggested for clinically emphasized haemorrhage intracranial, any bleeding event, and death. In addition, the following PMDA's conclusion was discussed:

While it is extremely difficult to evaluate the similarity of results in Study 1160.26 between the overall study population and Japanese subgroup due to the extremely small number of Japanese patients included in the study, it is considered that there is no significant inconsistency in the results of the composite endpoint as the primary endpoint for efficacy as well as the results of each element of the composite endpoints, bleeding events, secondary endpoints, and adverse events. As a result, it is concluded that efficacy and safety of dabigatran etexilate observed in the overall study population should be expected in Japanese as well. The expert advisors voiced their concerns and opinions as follows but eventually supported the PMDA'S conclusion considering that such concerns and opinions did not deny the conclusion itself:

The adequacy of the efficacy and safety evaluation of dabigatran etexilate in Japanese is a concern given the significantly small ratio of Japanese patients in the multiregional clinical study; to evaluate the similarity of results between the overall study population and a subgroup with such small number of patients might not be reasonable in the first place; and it is critical to confirm the efficacy and safety of dabigatran etexilate in Japanese patients based on the post-marketing data and the post-marketing surveillance should include sufficient number of patients.

3. Dosage and administration

(1) Usual dose and reduced dose

PMDA's conclusion was discussed as follows:

PMDA concluded that the participation of Japanese patients in Study 1160.26 that adopted 150 mg and 110 mg both twice daily was not of a major problem given the incidence of bleeding events and pharmacodynamic parameters in Japanese Study 1160.49. Based on the results of the entire Study 1160.26, the usual dose of 150 mg twice daily and the reduced dose of 110 mg twice daily for patients whose background raises a concern over bleeding with the usual dose, has been determined by PMDA and the appropriateness of this conlusion has been discussed. Expert advisors supported the appropriateness of the participation of Japanese patients in Study 1160.26 and the usual dose of dabigatran etexilate. There were opinions that the rationale of selecting the dose 110 mg twice daily was insufficient, since it is in the scope of the dosage and administration but had never been evaluated prior to 1160.26. There were also opinions stating that since it is not known exactly how 110 mg twice daily was selected, although an equivalent efficacy to warfarin was obtained with this dose, it was reasonable to provide information on 110 mg twice daily as an option for reduction in the precautions rather than in the dosage and administration. However, there were opinions stating that the PMDA conclusion is reasonable, and that it should be stipulated in the dosage and administration that 110 mg twice daily is the only alternative of reduction considering the availability of a drug product for 75 mg. The PMDA's conclusion was eventually supported by the expert advisors.

Based on the above, PMDA has concluded that it is appropriate to define the dosage and administration as follows:
Dosage and administration

The usual adult dosage is 150 mg (two 75 mg capsules) of Dabigatran Etexilate administered orally twice daily. The dose should be reduced to 110 mg of Dabigatran Etexilate (one 110 mg capsule) twice daily as needed.

(2) Subjects for reduced dose
PMDA's conclusion was discussed that subjects applicable for the reduction of the proposed product are (a) the elderly aged ≥70, (b) patients with moderate renal disorders (CL_{cr} 30-50 mL/min), (c) patients using Pgp inhibitors concomitantly, (d) patients with history of gastrointestinal haemorrhage, and an alert should be included in the package insert about them.

Regarding (a), PMDA concluded that it is appropriate to reduce dabigatran etexilate for the elderly from the usual dose and considering that the target PT-INR of 2.0 to 2.6 was selected for patients assigned to warfarin group and aged ≥70, unlike those <70, in the Japanese subgroup in Study 1160.26, careful selection of dosage including reduction is required for those aged ≥70 rather than ≥75 as the applicant proposed to prioritize on safety. Expert advisors eventually supported the conclusion after they expressed their opinions such as; the rationale is insufficient to set up a cut-off value unique to Japanese, but PMDA explained that careful selection of the dose including reduction is required for patients aged ≥70, focusing on safety when considering that the cut-off value for the elderly in the present clinical practice of Japan is reflected in the target PT-INR for Japanese in clinical studies. An expert advisor suggested that careful dosing of dabigatran

etexilate including its reduction is necessary in the elderly ≥70 when considering the present clinical practice in Japan.

Regarding (b), PMDA's conclusion was supported by the expert advisors that it is appropriate to consider reduction to 110 mg twice daily of dabigatran etexilate in patients with moderate renal impairment based on the higher incidence of bleeding events than those with > CL_{cr} 50 mL/min in any treatment group while no marked inter-group differences in the development of bleeding events within patients with moderate renal disorders (CL_{cr} 30-50 mL/min)were noted, and considering that the exposure of dabigatran etexilate increases with the deterioration of renal function.

Regarding (c), PMDA's conclusion that careful dosing including the reduction to 110 mg twice daily of dabigatran etexilate is required focusing on safety of patients with concomitant Pgp inhibitors, when considering the higher incidence of bleeding events in patients with Pgp inhibitors than those without and that the risk for bleeding presumably increases by the increase of exposure of dabigatran etexilate during the concomitant use of Pgp, was supported with an opinion from an expert advisor that attention should be paid to the interaction of them in patients with atrial fibrillation for whom sometimes concomitant use of verapamil or amiodarone is unavoidable. As for verapamil that is associated with frequent use in patients with atrial fibrillation, PMDA's conclusion that it may be concomitantly used with dabigatran etexilate if used accordingly with the administration described by the applicant was supported by the expert advisors.

Regarding (d), expert advisors expressed their opinions such as; PMDA's opinion is appropriate that reduction to 110 mg twice daily of dabigatran etexilate should be considered to patients with history of gastrointestinal haemorrhage, focusing on their safety, given the larger number of gastrointestinal disorders or gastrointestinal haemorrhage found with dabigatran etexilate group than with warfarin group in Study 1160.26 and still onset mechanism of gastrointestinal disorders and gastrointestinal haemorrhage by dabigatran etexilate is unknown; if the inhibited absorption of PPI may decrease action of dabigatran etexilate, it should also be alerted. PMDA explained that data collection in the post-marketing surveillance is necessary on the possible influence associated with concomitant use with PPI or H_2 receptor antagonists that are expected to be frequently used with dabigatran etexilate, although no sufficient ground warranting an alert has been obtained in clinical studies at present regarding the efficacy and safety in the concomitant use with them. Expert advisors eventually supported this PMDA's conclusion

PMDA asked the applicant to define the precautions related to the dosage and administration based on the discussion above as "In patients with moderate renal disorders (CL_{cr} 30-50 mL/min) or with a concomitant P-glycoprotein inhibitor, reduction to 110 mg twice daily of proposed product should be considered because the blood concentration of the proposed product may rise. Also, in patients aged ≥70 or those considered having a higher risk of bleeding such as history of gastrointestinal haemorrhage, reduction of proposed product to 110 mg twice daily should be considered."

The applicant responded that it would carry the above alert in the package insert and PMDA considered the

response appropriate.

4. Indication

PMDA's following conclusion has been discussed: "patients with valve prosthesis that requires anticoagulation therapy, or those with hemodynamically relevant valvular diseases that will require surgical intervention during the study period" may not be considered appropriate subjects to administer dabigatran etexilate at present and it is appropriate to define the indication of dabigatran etexilate as "reducing the risk of stroke and systemic embolism in non-valvular atrial fibrillation" including lone atrial fibrillation with such patients and patients with rheumatic mitral disease excluded. The conclusion was reached by the following consideration: the Study 1160.26 that verified the efficacy and safety of dabigatran etexilate was performed on patients with non-valvular atrial fibrillation and that "Guidelines for the diagnosis and treatment of cardiovascular diseases (Joint research team report 2008)" seeks anticoagulation therapy or antiplatelet therapy for atrial fibrillation that responds to the risk of embolism and recommends PT-INR target 2.0 to 3.0 regardless of age for patients with higher risk for embolism such as those with mitral valve stenosis and artificial valve (mechanical valve) who particularly need the strong anticoagulation action, unlike those with non-valvular atrial fibrillation. An expert advisor expressed an opinion that "patients with atrial fibrillation" is desirable as the indication of dabigatran etexilate so as not to deprive treatment opportunities from patients with higher risk for thromboembolism such as those with valvular atrial fibrillation. Another opinion followed that PMDA's conclusion is appropriate based on the clinical studies submitted. PMDA explained that patient populations which the balance of risk and benefit of dabigatran etexilate has not been clarified should be eliminated from the indication of dabigatran etexilate considering the subjects of the clinical studies. Expert advisors eventually supported the PMDA's conclusion. There was an opinion that "ischaemic stroke" should be more desirable than "stroke" which is not appropriate since haemorrhagic stroke is included in it because dabigatran etexilate is inherently not a drug to prevent cerebral haemorrhage. Furthermore, PMDA's conclusion was supported by the expert advisors that switching may be considered as an application of dabigatran etexilate in clinical practice for patients already under warfarin and successful control of PT-INR along with the poorly controlled patients with warfarin if adequate consideration is given to the appropriateness of dabigatran etexilate.

Based on the discussion above, PMDA concluded that it is appropriate to define the indication as follows:

Indication

Reducing the risk of ischaemic stroke and systemic embolism in patients with non-valvular atrial fibrillation

5. Safety

(1) Bleeding risk

PMDA's conclusions listed below and alerts in the package insert (draft) to reduce the bleeding risk of dabigatran etexilate were discussed:

PMDA concludes as follows: the bleeding risk that accompanies the risk reduction for thromboembolism with dabigatran etexilate is within the clinically tolerable range based on the comparison with the warfarin group in Study 1160.26; bleeding risk apparently increases with concomitant antiplatelet drugs than when

drugs are administered alone and appropriateness of concomitant use should be decided considering the risk and benefit for individual patient and the potential for the increase of bleeding risk in the concomitant use with antiplatelet drugs needs to be adequately communicated in the package insert; the instruction adopted in Study 1160.26, in which efficacy and safety similar to warfarin was demonstrated, stating that surgery may be performed with a 24-hour prior washout of dabigatran etexilate if the renal function is normal or mildly impaired and the bleeding risk is normal, may be used as a guide in clinical practice for the timing of washout; the dose titration method based on aPTT that the applicant advocates as an indicator to reduce bleeding risk by dabigatran etexilate lacks a robust rationale and cannot be considered as a useful indicator for the safety of dabigatran etexilate. Expert advisors generally supported these PMDA's conclusions with opinions expressed as follows. The bleeding risk in the post-PCI 3-drug concomitant use of 2 anti-platelet drugs and warfarin in patients with ischaemic heart disease complicated with atrial fibrillation has been at issue in clinical practice and rise of bleeding risk is also predicted with dabigatran etexilate in the concomitant use with 2 antiplatelet drugs. While reduction to 110 mg twice daily should be considered in such use, high risk of thromboembolism is also predicted in patients under antiplatelet drugs. Dosage and administration for individual patients therefore, should be left to the doctor's decision and safety should be evaluated sufficiently in the post-marketing surveillance rather than uniform dose titration. There was another opinion stating that the package insert should clarify that aPTT is rather a reference data than a useful indicator of efficacy of dabigatran etexilate. Another opinion stated that administration up to the day before surgery or substitution with heparin should be recommended for dabigatran etexilate due to its short half-life and the onset of embolism by a few days of suspension more concerned than with warfarin.

PMDA, based on the discussion above, concluded that the alert is appropriate which the applicant suggested for concomitant use with antiplatelet drugs in the important basic precautions. PMDA requested an alert in the important basic precautions for the suspension of dabigatran etexilate at surgery and related measures that states, "In patients undergoing surgery or invasive procedure, administration of the proposed product should be suspended temporarily corresponding to the increase of associated bleeding risk. Suspension should be 24 hours prior to surgery or invasive procedure if possible. When undergoing a major surgery that requires complete hemostatic function or the patients has high risk of bleeding, suspension ≥2 days prior to surgery should be considered as well as an alternative therapy (heparin, etc.). After the surgery, hemostasis should be confirmed before resuming the drug product.", and for aPTT, "aPTT (activated partial thromboplastin time) may become an indicator for excessive anticoagulation action in bleeding patients. Trough aPTT >80 seconds was often associated with major bleeding in the Phase III multiregional study that included Japanese patients".

The applicant replied that it would describe the alert of aPTT as the above and "In patients undergoing surgery or invasive procedure, administration of the proposed product should be suspended temporarily corresponding to the increase of associated bleeding risk. Suspension should be 24 hours prior to surgery or invasive procedure when possible. When undergoing a major surgery that requires complete hemostatic function or the patients has high risk of bleeding, suspension ≥ 2 days prior to surgery should be considered as well as an alternative therapy (heparin etc.) similarly to the conventional anticoagulation therapy. After

the surgery, hemostasis should be confirmed before resuming the proposed product." for an alternative therapy when the proposed product has been suspended, considering the lack of data.

PMDA considered the applicant's response to be appropriate.

(2) Risk of gastrointestinal disorders

The followingconclusions of PMDA were supported by expert advisors:

At present, an alternative to select warfarin should be remembered as well as the reduction to 110 mg twice daily of the proposed product in patients with history of gastrointestinal haemorrhage, due to the higher frequency of gastrointestinal haemorrhage in dabigatran etexilate group than in warfarin group in Study 1160.26, and appropriate measures including suspension need to be taken in patients who had symptoms related to gastritis at the onset of the symptom because of the higher event rates for gastrointestinal haemorrhage.

PMDA concluded that it is appropriate to specify the patients with history of gastrointestinal haemorrhage or upper abdominal ulcer for careful administration based on the discussion above.

(3) Risk of myocardial infarction

The following conclusion of PMDA was supported by expert advisors:

The cause is unknown for the higher incidence of myocardial infarction in dabigatran etexilate 150 mg group than in warfarin group in the overall Study 1160.26 and at present, the possibility of increase in incidence risk for myocardial infarction with dabigatran etexilate is still not clear enough to warrant specific alerts. Post-marketing data collection on the occurrence of myocardial infarction is important.

6. Post-marketing surveillance

The applicant submitted its plan to conduct a post-marketing specified use-results survey (2 years of follow-up, planned number of subjects 3000) focused on "bleeding" as priority investigation item in order to evaluate the safety and efficacy of the proposed product in the long-term use while examining the data on the safety and interaction between concomitant drugs in special populations such as the elderly, patients with renal impairment, and patients with impaired liver functions. PMDA understands the necessity for adequate data collection on the safety and efficacy of dabigatran etexilate in the post-marketing surveillance given the extremely small number of Japanese patients included in Study 1160.26. PMDA also considers the necessity of the post-marketing surveillance which will enable the following evaluation: the safety including bleeding risks, particularly in patients using concomitant antiplatelet drugs, aged, or with renal impairment; the safety regarding gastrointestinal disorders and gastrointestinal haemorrhage; the effects by concomitant drugs; the relation between dosage and safety. PMDA also considered data collection on the incidence of myocardial infarction necessary. Expert advisors expressed opinions that the conclusion by PMDA is appropriate, and that a post-marketing clinical study in a non-randomized prospective cohort design should likely collect more useful data if conducted as substitute for the post-marketing surveillance when considering the extremely small number of Japanese. However, there was an opinion in response to this that a survey with a sufficient

number of subjects should be conducted first to investigate the issues PMDA pointed out, and PMDA's conclusion was supported after all.

PMDA, based on the discussion so far, asked the applicant to re-examine its post-marketing surveillance plan involving possible increase of the number of subjects to allow : evaluation of safety of dabigatran etexilate including the risk of bleeding in patients with concomitant antiplatelet drugs, the elderly, or patients with renal impairment; evaluation of safety related to gastrointestinal disorders and gastrointestinal haemorrhage; evaluation of influence by concomitant drugs; data collection on the background and safety of patients on the reduced dose of proposed product 110 mg twice daily; evaluation of relationship between dosage and safety; enabling evaluation of influence from drugs listed for "precautions for concomitant use" or those likely to be used concomitantly with the proposed product (including PPI, H_2 receptor antagonists); enabling data collection on the measures to handle the washout period of the proposed product as well as the onset of thromboembolism associated with washout in patients undergoing surgery or various invasive procedures., or data collection regarding the occurrence of myocardial infarction

The applicant submitted the outline of a post-marketing surveillance plan (draft) with around 5000 patients to investigate to allow adequate evaluation of the findings by PMDA, and of background factors that presumably affect the onset of stroke and systemic embolism as the efficacy endpoints of the proposed product.

PMDA considered the outline of the post-marketing surveillance plan (draft) presented by the applicant to be appropriate and accepted the applicant's response while indicating further, detailed review required.

7. Others

Regarding the PMDA's conclusion that contraindicating the proposed product in patients with severe renal impairment is appropriate, the expert advisor commented as follows:

Contraindicating in patients with severe renal impairment is appropriate but not unambiguously so considering that Study 1160.23 has demonstrated that dabigatran etexilate is eliminated by dialysis. PMDA asked the applicant to clarify if it considers dialysis as a contraindication to the drug, and the applicant responded that it assumes that patients with severe renal impairment include dialysis patients and it will include an alert in the contraindication section that reads "Patients with severe renal disorders (cleatinine clearance <30 mL/min) including dialysis patients ". PMDA considered it appropriate to unambiguously indicate that dialysis patients are included in the contraindication and accepted the response of the applicant. Although dabigatran etexilate is eliminated by dialysis, it has been shown that the geometric mean of half-life is 32.3 hours in patients with terminal renal impairment when administered dabigatran etexilate at the start of 4 hours of dialysis, longer than the corresponding values in patients with mild, moderate, and severe renal impairment which are 15.3, 18.4, and 27.2 hours, respectively.

The expert advisor suggested that potential increase of the risk for embolism should be precautioned considering the short half-life of dabigatran etexilate and poor compliance or missed doses associated with

the proposed drug that requires intake twice daily. PMDA requested to include statement of measures to take, in case of missed dose, in the package insert to alert overdosing, as well as possible increase of the risk for embolism in such occasion. The applicant responded that instructions would be unambiguously stated to take one dose as quickly as possible on the same day due to the possibility for increased risk of embolism events in case of missed dose, and to wait for ≥6 hours before the time for next dose to avoid the risk of elevation of the blood concentration of the proposed product as well as not to take 2 doses at a time in case of missed dose. PMDA considered the applicant response to be appropriate.

The expert advisor suggested that measures were necessary to prevent mix-up of drugs considering the unusual relationship between the specification and dosage of dabigatran etexilate that is defined to take two 75 mg low content capsules for the usual dose of 150 mg or one 110 mg high content capsule for the reduced dose of 110 mg. PMDA instructed the applicant to devise measures to reduce the risk of medical malpractice.

The applicant responded that packaging such as PTP sheets would be made distinguishable for 75 mg and 110 mg capsules as a measure to reduce the risk of medical malpractice such as mix-up of formulations or drugs at intake and a caution statement with pictures of drug products would be prepared for healthcare professionals and patients to instruct to take two 75 mg capsules for 150 mg at a time twice daily, and one 110 mg capsule for 110 mg at a time twice daily.

PMDA considered the policy the applicant suggested for measures to reduce the risk of medical malpractices generally appropriate.

8. Specification of drug substance

PMDA asked the applicant to integrate the specifications of the drug substances manufactured with manufacturing method A and manufacturing method B into one common specification. The applicant responded that they would be integrated into the specification for the drug substance manufactured by the method A.

PMDA considered the response from the applicant appropriate.

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, there were no particular problems. Thus, 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 on-site inspection was conducted in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the new drug application (5.3.5.1-3, 5.3.5.1-4).

As a result, the following findings were noted at some trial sites: inconsistencies of description between the source document and the case report form (adverse events undocumented, misdescription of findings), some source document (electrocardiographic chart) not stored, protocol deviations (some laboratory tests not performed, assignment before qualification), and inclusion of subjects meeting the exclusion criteria defined in the protocol (subjects with ALP or CL_{cr} value deviation). The sponsor's failure was also found out in some cases to take adequate measures for the inconsistencies between the source document and case report forms but, PMDA concluded that there should be no problem with conducting a regulatory review based on the submitted application documents.

IV. Overall evaluation

Based on the above review, PMDA has concluded that the proposed product 75 mg and 110 mg may be approved after specifying the indication and the dosage and administration as shown below.

It is appropriate to establish the re-examination period for the proposed product 75 mg and 110 mg is 8 years, neither the drug substance nor the drug product is classified as a poisonous drug or a powerful drug, and the proposed product is not classified as a biological product or a specified biological product.

[Indication]	Reduction in the risk of ischaemic stroke and systemic embolism in patients with non-valvular atrial fibrillation
[Dosage and administration]	The usual adult dosage is 150 mg (two 75 mg capsules) of Dabigatran Etexilate administered orally twice daily. The dose should be reduced to 110 mg of Dabigatran Etexilate (one 110 mg capsule) twice daily as needed.