Report on the Deliberation Results

March 1, 2011

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

[Brand name]	Lixiana Tablets 15 mg and 30 mg
[Non-proprietary name]	Edoxaban Tosilate Hydrate (JAN*)
[Applicant]	Daiichi Sankyo Company, Limited
[Date of application]	March 29, 2010

[Results of deliberation]
In the meeting held on February 21, 2011, 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)*

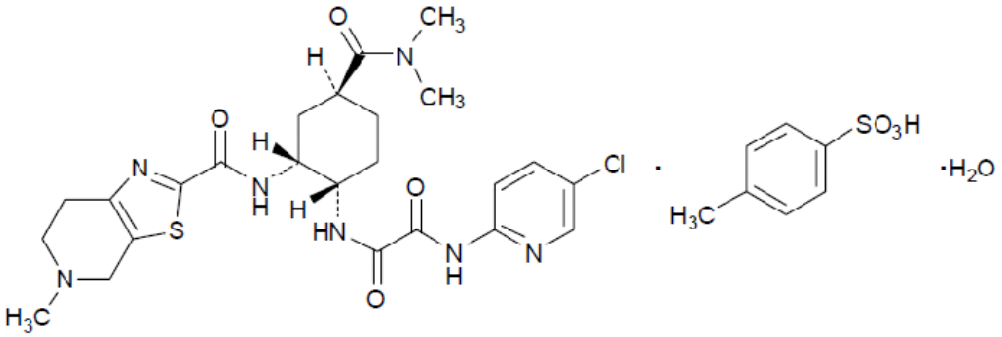
Review Report

February 9, 2011
Pharmaceuticals and Medical Devices Agency

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

[Brand name]	Lixiana Tablets 15 mg and 30 mg
[Non-proprietary name]	Edoxaban Tosilate Hydrate
[Name of applicant]	Daiichi Sankyo Company, Limited
[Date of application]	March 29, 2010
[Dosage form/Strength]	A film-coated tablet containing 15 mg or 30 mg of edoxaban
[Application classification]	Prescription drug (1) Drug with a new active ingredient

[Chemical structure]



Molecular formula: $C_{24}H_{30}ClN_7O_4S \cdot C_7H_8O_3S \cdot H_2O$
Molecular weight: 738.27
Chemical name:

N-(5-Chloropyridin-2-yl)-*N*′-[(1S,2R,4S)-4-(dimethylcarbamoyl)-2-(5-methyl-4,5,6,7-tetrahydro[1,3]thiazolo[5,4-c]pyridine-2-carboxamido)cyclohexyl] oxamide mono(4-methylbenzenesulfonate) monohydrate

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

Review Results

February 9, 2011

[Brand name]	Lixiana Tablets 15 mg and 30 mg
[Non-proprietary name]	Edoxaban Tosilate Hydrate
[Name of applicant]	Daiichi Sankyo Company, Limited
[Date of application]	March 29, 2010

[Results of review]

Based on the submitted data, it is concluded that the effect of the product to prevent venous thromboembolism in patients undergoing total knee replacement, total hip replacement, or hip fracture surgery, has been demonstrated and its safety is acceptable in view of the observed benefits. In the post-marketing surveillance, it is important to collect information on the occurrence of bleeding adverse events and information that allows assessment of the effects of factors such as age, surgical procedure, dose, and renal function on the occurrence of bleeding adverse events.

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

[Indication]	Prevention of venous thromboembolism in patients undergoing the following orthopedic surgery of the lower limbs: Total knee replacement, total hip replacement, and hip fracture surgery
[Dosage and administration]	The usual adult dosage is 30 mg of edoxaban administered orally once daily.

Review Report (1)

January 19, 2011

I. Product Submitted for Registration

[Brand name]	Lixiana Tablets 15 mg and 30 mg
[Non-proprietary name]	Edoxaban Tosilate Hydrate
[Name of applicant]	Daiichi Sankyo Company, Limited
[Date of application]	March 29, 2010
[Dosage form/Strength]	A film-coated tablet containing 15 mg or 30 mg of edoxaban
[Proposed indication]	Prevention of venous thromboembolism in patients undergoing the following orthopedic surgery of the lower limbs: Total knee replacement, total hip replacement, and hip fracture surgery
[Proposed dosage and administration]	The usual adult dosage is 30 mg of edoxaban administered orally once daily.
[Items warranting special mention]	None

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

The data submitted in this application and the applicant's response to the inquiries from the Pharmaceuticals and Medical Devices Agency (PMDA) are outlined below.

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

Edoxaban tosilate hydrate (hereinafter referred to as edoxaban) is an orally available inhibitor of activated blood coagulation factor X (factor Xa), discovered by Daiichi Sankyo Company, Limited. Edoxaban inhibits thrombus formation by selectively and reversibly inhibiting factor Xa, which plays an important role in the blood coagulation cascade.

In foreign countries, the clinical development of edoxaban was started in 20[redacted]. The development is underway so that the product will be approved for the following indications: "prevention of venous thromboembolism in patients undergoing orthopedic surgery of the lower limbs", "prevention of cerebral infarction and systemic embolism in atrial fibrillation", and "prevention of relapse of venous thromboembolism".

In Japan, the clinical development of edoxaban was started in 20[redacted], and the marketing application for edoxaban has currently been filed based on Japanese and foreign clinical study data. As of December 2010, edoxaban has not been approved in any countries including Japan.

2. Data relating to quality

2.A Summary of the submitted data

The products are film-coated tablets, each containing 20.2 or 40.4 mg of edoxaban tosilate hydrate (molecular formula of $C_{24}H_{30}ClN_7O_4S \cdot C_7H_8O_3S \cdot H_2O$, molecular weight of 738.27) (15 or 30 mg as edoxaban).

2.A.(1) Drug substance

2.A.(1).1) Characterization

a. Structure

The chemical structure of the drug substance has been elucidated by elementary analysis, ultraviolet spectrophotometry, infrared spectrophotometry (IR), hydrogen nuclear magnetic resonance spectroscopy (^{1}H-NMR), carbon nuclear magnetic resonance spectroscopy, mass spectrometry, and X-ray crystallography.

b. General properties

The determined general properties of the drug substance include description, crystallinity, solubility, hygroscopicity, optical rotation, melting point, thermal analysis, dissociation constant (pKa), partition coefficient, and crystalline polymorphism. Edoxaban tosilate hydrate is white to pale yellowish white powder. It is freely soluble in *N,N*-dimethylformamide and in dimethyl sulfoxide, soluble in methanol, slightly soluble in water, in acetonitrile, and in ethanol (99.5), very slightly soluble in acetone, and practically insoluble in 2-propanol and in ethyl acetate. It is not hygroscopic. The solubility was ≥4 mg/mL in acidic solutions (approximately pH ≤4.5), decreased with increasing pH, and was approximately 0.08 mg/mL in alkaline solutions (pH ≥8). Optical rotation ($[\alpha]_D^{20}$) was -93° (at approximately 1 mg/mL [redacted] solution). Melting point was approximately 249°C (with decomposition). Thermal analysis by [redacted] up to approximately [redacted]°C showed a mass decrease corresponding to [redacted] in edoxaban tosilate hydrate. pKa derived from [redacted] of [redacted] was 6.7. Partition coefficients were -0.91 in 1-octanol/Britton-Robinson buffer (pH 4.0) and 1.72 in 1-octanol/Britton-Robinson buffer (pH 8.0). As regards crystalline polymorphism, presence of 2 types of crystalline forms (form I and form II) was identified, but formation of form II was not confirmed under the conditions of the manufacturing process for the drug substance.

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

The drug substance is manufactured according to the following 4-step process.

Step 1: [redacted] is added to a mixture of [redacted] and [redacted], and the mixture is allowed to react to obtain [redacted].

Step 2: The reaction mixture containing [redacted] is cooled. [redacted], [redacted], [redacted] salt, and [redacted] are added and, after the addition of [redacted], the mixture is allowed to react. After adding [redacted] and [redacted], the mixture is cooled to allow precipitation of crystals. The crystals are filtered to obtain [redacted].

Step 3: [redacted] is mixed with [redacted], [redacted], and [redacted], and is allowed to dissolve. After the solution is filtered and cooled, [redacted] and [redacted] are added to the filtrate. After cooling, crystals of edoxaban tosilate hydrate that have precipitated are filtered out and powdered to obtain the drug substance.

Step 4: The drug substance is transferred into [redacted] polyethylene bags and filled in plastic drums.

Step [redacted] has been defined as the critical process and [redacted] has been defined as the critical intermediate. Control parameters and control values have been set for [redacted].

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

The proposed specifications for the drug substance include description (appearance, solubility), identification (IR), purity (heavy metals [color identification test], related substances [high performance liquid chromatography (HPLC)], enantiomers [HPLC], residual solvents [gas chromatography (GC)]), water content (Karl Fischer method), residue on ignition (mass measurement), particle size (laser diffraction method), and assay (HPLC).

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

Stability tests shown in Table 1 were performed using pilot-scale lots.

Table 1. Storage conditions, packaging configuration, storage period, and attributes in stability tests of the drug substance

Test	Storage conditions	Packaging configuration	Storage period	Attributes
Long-term testing	25°C/60% RH	Polyethylene bag[redacted]/plastic drum	0, 3, 6, 9, 12, 18, 24, 36 months The test has been completed up to 18 months and is continuing.	Appearance Identification[a)b)c)] Related substances Enantiomers[c)] Stereoisomers[a)c)] Water content Microbial limits[a)b)d)] Particle size[a)] Assay [redacted][a)b)c)]
Accelerated testing	40°C/75% RH	Polyethylene bag[redacted]/plastic drum	0, 3, 6 months	
Stress testing (temperature, humidity)	[redacted]°C/[redacted]% RH	[redacted]	0, [redacted], [redacted] months	
	25°C/93% RH	Open petri dishes	0, [redacted], 2 months	
	40°C/75% RH	Open petri dishes	0, [redacted], 2 months	
Stress testing (temperature)	60°C	Glass bottles (tight)	0, [redacted], 2 months	
Stress testing (light)	[redacted] lx (D65 lamp) 25°C/60% RH	Open petri dishes	0, [redacted] million, 1.2 million lx·h[e)]	

a: The long-term testing was performed for 0, [redacted], [redacted], and 36 months.
b: The accelerated testing was performed for 0 and [redacted] months only.
c: The stress testing was performed only for 0 and [redacted] months or at 0 and [redacted] million lx·h.
d: Not performed in [redacted] testing.
e: At the total illuminance of 1.2 million lx·h, integrated near ultraviolet energy was ≥200 W·h/m^2

No change was observed over time in any of the studies. Therefore, the retest period of 30 months has been proposed for the drug substance when stored at room temperature, based on the "Guideline on Evaluation of Stability Data" (PFSB/ELD Notification No. 0603004 dated June 3, 2003). Long-term testing and accelerated testing using commercial scale lots will be performed.

2.A.(2) Reference standard or reference materials

The proposed specifications for the drug substance reference material include description (appearance), identification (IR, ^{1}H-NMR), purity (related substances [HPLC], enantiomers [HPLC], residual solvents [GC]), water content (Karl Fischer method), residue on ignition (mass measurement), and purity ([redacted]).

2.A.(3) Drug product

The development of the drug product was carried out based on the systematic "Quality by Design" (QbD) approach, in addition to the conventional empirical approach.

2.A.(3).1) Drug product and formulation

The product is film-coated tablets consisting of [redacted] and a coating layer. The [redacted] is composed of the drug substance, [redacted] (D-mannitol and partially pregelatinized starch), [redacted] (crospovidone), [redacted] (hydroxypropylcellulose), and [redacted] (magnesium stearate). The coating layer is composed of [redacted] (hypromellose, titanium oxide, talc, macrogol 6000), coloring agents (yellow iron sesquioxide [15-mg tablets], iron sesquioxide [30-mg tablets]) and [redacted] (carnauba wax, talc). Each of 30-mg tablets has a score line on one side.

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

The formulation of 15- and 30-mg tablets are [redacted] and [redacted].

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

The drug product is manufactured according to the following 6 process steps.

The first step (granulation process): [redacted] is added to purified water and dissolved by a stirrer to prepare the binding solution. [redacted], [redacted], [redacted], and [redacted] are mixed in [redacted]. After the mixing is complete, the binding solution is [redacted] and the mixture is granulated. After [redacted], the resultant material is dried to obtain granules. The dried granules are sized with a sizing machine to obtain sized granules.

The second step (mixing process): [redacted] is added to the sized granules and blended with [redacted] for tableting.

The third step (tableting process): The tableting granules are compressed using a tableting machine to obtain core tablets.

The fourth step (coating process):
15-mg tablets: [redacted], [redacted], [redacted], [redacted], and [redacted] are mixed in [redacted] to obtain dispersed powder for coating.

30-mg tablets: After [redacted] and [redacted] are mixed in [redacted], the mixture is [redacted] by [redacted] to obtain [redacted], [redacted], [redacted], [redacted], and [redacted] are mixed in [redacted] to obtain dispersed powder for coating.

Common to 15- and 30-mg tablets: The dispersed powder for coating is dissolved and dispersed in purified water to obtain the coating solution. The coating solution is sprayed on core tablets using a pan-coating machine. After drying, the mixed powder of carnauba wax and talc is sprayed to prepare the tablets.

The fifth step (inspection process): Tablets are inspected.

The sixth step (packaging process):
Press-Through-Pack (PTP) packaging: After a polypropylene (PP) film sheet is molded at high temperature using a PTP packaging machine, then the tablets are placed in there and heat-sealed with aluminum foil, and the sheet is cut to obtain PTP packages.

Plastic bottle packaging: Tablets are filled in high density polyethylene (HDPE) bottles, which are sealed with HDPE or PP caps to obtain plastic bottle packages.

The [redacted], [redacted], and [redacted] steps have been defined as critical process steps. In-process control

parameters and control values have been set in [redacted] process.

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

The proposed specifications for the drug product include description (appearance), identification (HPLC, ultraviolet-visible spectrophotometry [UV]), uniformity of dosage units (content uniformity), dissolution (paddle method, UV), and assay (HPLC). For [redacted], an alternative test or a real-time release test (RTRT) performed as [redacted] test are defined as follows as the release acceptance criteria for the drug product.

Description: To be controlled by an alternative test using the drug product [redacted] as the test sample.

Identification: To be controlled by near infrared spectrophotometry as an alternative test using the drug product [redacted] as the test sample.

Uniformity of dosage units: To be controlled as an RTRT by the design space to ensure the uniformity of the drug product, based on the combination of the following [redacted]: [redacted] measured by [redacted] test in [redacted], [redacted] measured by [redacted] test in [redacted], [redacted] measured by [redacted] test in [redacted], and [redacted] measured by [redacted] test in [redacted].

Dissolution: To be controlled as an RTRT by the design space to ensure the dissolution, based on the combination of the following [redacted]: [redacted] as the results of [redacted] test on [redacted], [redacted] measured by [redacted] test in [redacted], and [redacted] measured by [redacted] test in [redacted].

Assay: To be controlled as an RTRT by the design space to ensure the content of the active ingredient, based on the combination of the following [redacted]: [redacted]

If an alternative test or RTRT cannot be used as the release acceptance criteria, analytical tests are performed to judge the acceptability of the release based on the pre-determined acceptance criteria and the testing procedures.

2.A.(3).5) Stability of the drug product

Stability tests shown in Table 2 were performed using the pilot-scale lots.

Table 2. Storage conditions, packaging configuration, storage period, and attributes in stability tests of the drug product

Test	Storage conditions	Packaging configuration	Storage period	Attributes
Long-term testing	25°C/60% RH	PTP packaging Plastic bottle packaging	0, 3, 6, 9, 12, 18, 24, 36 months The test has been completed up to 12 months and is continuing.	Description Identification[a)] Uniformity of dosage units[b)] Dissolution Assay Related substances [redacted][c)] Stereoisomers[c)] [redacted] [redacted] Microbial limits[d)]
Accelerated testing	40°C/75% RH	PTP packaging Plastic bottle packaging	0, 3, 6 months	
Stress testing (temperature, humidity)	[redacted]°C/[redacted]% RH	[redacted]	0, [redacted], [redacted] months	
	[redacted]°C/[redacted]% RH	[redacted]	0, [redacted], [redacted] months	
	40°C/75% RH	Open petri dishes	0, [redacted], [redacted], 3 months	
Stress testing (temperature)	60°C	Glass bottle packaging	0, [redacted], 2 months	
Stress testing (light)	[redacted] lx (D65 lamp) 25°C/60% RH	Open petri dishes	0, [redacted] million, 1.2 million lx·h[e)]	

a: Performed only in [redacted] ([redacted] months or [redacted] lx·h) of the long-term testing, the accelerated testing, and the stress testing.
b: Performed only for [redacted] ([redacted] months) in the long-term testing and in the accelerated testing, not performed in [redacted] testing.
c: Performed every [redacted] years in the long-term testing, at [redacted] timepoints in the accelerated testing, and at [redacted] ([redacted] months) and only at [redacted] timepoints in the stress testing.
d: Performed every [redacted] years in the long-term testing, only at [redacted] ([redacted] months) and [redacted] timepoints in the accelerated testing, and not in the [redacted] testing.
e: At the total illuminance of 1.2 million lx·h, integrated near ultraviolet energy was ≥200 W·h/m^2

The long-term testing and the accelerated testing showed an increase in related substances in both packaging configurations, and a decrease in [redacted] and [redacted] in the PTP packaging. In the stress testing (temperature, humidity), no change was observed over time at [redacted]°C/[redacted]% RH, whereas an increase in related substances and a decrease in [redacted] and [redacted] were observed at 40°C/75% RH, and an increase in related substances, a decrease in [redacted], and a decrease in [redacted] and [redacted] were observed at [redacted]°C/[redacted]% RH. Increases in related substances were observed in the stress testing (temperature) and the stress testing (light).

The changes observed up to 12 months in the long-term testing and up to 6 months in the accelerated testing were within the acceptable range. Therefore, the shelf life of 24 months has been proposed for the drug product when stored at room temperature in a PTP or plastic bottle package, in accordance with the "Guideline on Evaluation of Stability Data." (PFSB/ELD Notification No. 0603004 dated June 3, 2003). Long-term testing and accelerated testing using commercial scale lots are planned.

2.B Outline of the review by PMDA

2.B.(1) Dissolution test

At the time of the regulatory submission, [redacted] was selected as the dissolution medium for the dissolution test in the specifications that is performed when application of RTRT is judged inappropriate. However, since the dissolution of the drug product in [redacted] is [redacted] than that in the dissolution medium of [redacted], it may not be possible to ensure the dissolution rate of [redacted]% in [redacted] minutes in [redacted], which is the acceptance criterion of RTRT for dissolution. Therefore, PMDA asked the applicant to explain whether or not it is necessary to change the specifications

for the dissolution by changing the dissolution medium of the dissolution test to [redacted].

The applicant responded as follows:
If [redacted] is used as the dissolution medium in the dissolution test, it may not be possible to ensure the dissolution rate of [redacted]% in [redacted] minutes in [redacted]. Therefore, [redacted] will be selected as the dissolution medium for the dissolution test and the specifications will be changed accordingly.

PMDA accepted the change in the specifications for the dissolution test and, based on the change in the dissolution medium of the dissolution test included in the specifications, asked the applicant to explain the change in the dissolution of the drug product over time when [redacted] buffer is used.

The applicant responded as follows:
Regarding the dissolution of the drug product, stability in [redacted] dissolution medium was evaluated in an additional test. Results of the accelerated testing up to 6 months and of the long-term testing up to 12 months showed that there was no change in the dissolution behavior compared with that at the start of the test. Therefore, the shelf life of the drug product will be proposed based on the results of the additional stability test [see Table 2 in "2.A.(3).5) Stability of the drug product"].

PMDA has concluded that there are no particular problems with determining the shelf life of the drug product based on the stability test performed using [redacted] as dissolution medium.

2.B.(2) Design space to ensure dissolution

Regarding the design space for ensuring the dissolution, the applicant explained as follows:
At the time of the regulatory submission, [redacted] had been determined as the factor affecting the dissolution, based on the [redacted] of the results from [redacted] to the commercial-scale production. After the submission, the concept of the control strategy on dissolution was changed from [redacted] to [redacted], and the dissolution-related risks were re-evaluated. As a result, a total of [redacted] factors, [redacted], were extracted as factors affecting dissolution. The subsequent systematic analysis of the above [redacted] factors based on the design of experiments provided an equation for calculating the dissolution rate that contains [redacted] as input variables. [redacted] was not included in the variables of the equation, which showed that [redacted] did not affect the dissolution within the range studied. With the above results taken into consideration, [redacted] were identified as factors that constitute the design space for ensuring the dissolution and then a design space for ensuring the dissolution was re-constructed.

Since the re-constructed design space for ensuring the dissolution of the drug product is configured based on the mathematical model, it is useful to ensure the performance of the model by confirming that the drug product with the appropriate dissolution rate is manufactured as expected. Therefore, PMDA considered that it was necessary to perform the dissolution test included in the specifications at release from the early post-marketing phase, and asked the applicant to confirm the performance of the equation for calculating the dissolution rate, by simultaneously carrying out the dissolution test on the commercial lots after approval, based on the production plan for the drug product as well.

The applicant responded as follows:
Regarding the equation for calculating the dissolution rate of the drug product, a maintenance

program will be established and the performance of the equation will be confirmed throughout the life cycle of the drug product according to the following schedule.

(1) According to the current production plan, [redacted] after 3 lots for process validation are manufactured. Therefore, the performance of the equation for calculating the dissolution rate will be confirmed by comparing the results of the calculation of dissolution rate with those of the actual dissolution test using the 3 process validation lots and the first commercial lot.

(2) If the confirmation work described in (1) above detects no discrepancy between both results, the equation for calculating the dissolution rate will be checked periodically by carrying out a similar comparison first after [redacted] months, and then every [redacted] months thereafter. The comparison will be carried out on [redacted] production lots if [redacted] at the specified timing.

PMDA considers as follows:
According to the explanation of the applicant, the re-constructed design space for ensuring the dissolution of the drug product has resulted from more exhaustive and systematic investigation of variables affecting dissolution compared with the design space used at the submission, and the relationship between each of the extracted variables and dissolution has been investigated appropriately. Therefore, the design space is defined based on a more thorough understanding of the process than at the submission. In addition, a maintenance program is established to ensure [redacted], and it is expected that the RTRT on the dissolution of the drug product will undergo appropriate maintenance, control, and improvement. Therefore, PMDA concluded that the re-constructed design space for ensuring the dissolution and the control strategy of dissolution are appropriate at the current moment.

2.B.(3) Design space to ensure the content of the active ingredient
The content of [redacted] based on RTRT tends to be lower than the actual observed value. Thus, in a certain lot, the RTRT-based value is [redacted]%, whereas the observed value was [redacted]%, which was close to the upper specification limit ([redacted]%). This result indicates the risk that, in lots with RTRT-based value close to the upper limit of the design space for ensuring the content, the actual content may exceed the upper specification limit. Therefore, PMDA required the applicant to narrow the range of the design space, such as using [redacted] as the design space for ensuring the content.

The applicant responded as follows:
Based on the opinion of PMDA, part of the design space will be narrowed to [redacted] so that lots with values that may exceed the upper limit of the specification are judged unacceptable by RTRT.

PMDA accepted the response of the applicant, taking into account that the re-established range of the design space for ensuring the content is appropriate for controlling the content based on RTRT.

Thus, PMDA has concluded that there is no particular problem with the quality of edoxaban, as determined by the submitted data and the control strategy using RTRT of the drug product that has been improved in the course of the review.

3. Non-clinical data
3.(i) Summary of pharmacology studies
3.(i).A Summary of the submitted data

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

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

a. Factor Xa inhibition (Attached document 4.2.1.1-1)

S-2222, a factor Xa-specific chromogenic substrate, and edoxaban tosilate hydrate (as edoxaban: 1, 2, 3 nM for human factor Xa; 4, 6, 8 nM for rat factor Xa; 0.5, 1, 1.5 nM for rabbit factor Xa; 1, 1.5, 2 nM for cynomolgus monkey factor Xa) were allowed to react with human, rat, rabbit, and cynomolgus monkey factor Xa. The inhibition constant (Ki) of edoxaban against factor Xa of each animal species was calculated from the absorbance of the chromophore released from the chromogenic substrate. Edoxaban competitively inhibited human, rat, rabbit, and cynomolgus monkey factor Xa, with Ki values of 0.561, 6.98, 0.457, and 0.715 nM, respectively.

b. Selective factor Xa inhibition (Attached document 4.2.1.1-1, 4.2.1.1-2)

Human thrombin, human factor IXa, human recombinant factor VIIa (rVIIa)/soluble tissue factor complex, human factor XIa, human trypsin, human chymotrypsin, human plasmin, human recombinant tissue plasminogen activator, or human activated protein C was allowed to react with the corresponding specific chromogenic substrate in the presence of edoxaban tosilate hydrate (as edoxaban: 10, 20, 30 μM for thrombin; 12.5, 25, 50 μM for factor IXa; 100, 150, 200 μM for other serine proteases). Ki of edoxaban against each serine protease was calculated from the absorbance of the chromophore released from the chromogenic substrate. Ki of edoxaban against thrombin and factor IXa were 6.00 and 41.7 μM, respectively, while Ki against other serine proteases was >100 μM.

c. Inhibition of prothrombinase complex (Attached document 4.2.1.1-3)

Prothrombinase complex (human factor Xa, human factor Va, phosphatidylcholine/phosphatidylserine liposome, $CaCl_2$) and edoxaban tosilate hydrate (0.4, 0.8, 1.2 nM as edoxaban) were allowed to react with S-2222. Ki of edoxaban against prothrombinase complex was calculated from the absorbance of the chromophore released from the chromogenic substrate. Separately, prothrombinase complex and edoxaban tosilate hydrate (2, 4, 6 nM as edoxaban) were allowed to react with prothrombin, and Ki of edoxaban against prothrombinase complex was calculated from the amount of thrombin produced. When S-2222 was used as the substrate, edoxaban competitively inhibited the prothrombinase activity of the prothrombinase complex, with Ki of 0.903 nM. When prothrombin was used as the substrate, edoxaban inhibited the prothrombinase activity in a noncompetitive/mixed manner with Ki of 2.98 nM.

3.(i).A.(1).2) Anticoagulant effect (Attached document 4.2.1.1-1)

Prothrombin time (PT) was measured by adding edoxaban tosilate hydrate (0.05, 0.1, 0.2, 0.4, 0.8, 1.6 μM as edoxaban) to human, rat, rabbit, and cynomolgus monkey plasma. Edoxaban prolonged PT in humans, rats, rabbits, and cynomolgus monkeys, with the concentration required for 2-fold prolongation in coagulation time (CT2) being 0.256, 0.647, 0.149, and 0.320 μM, respectively. In addition, activated partial thromboplastin time (APTT) and thrombin time (TT) were measured by adding edoxaban tosilate hydrate (as edoxaban: 0.125, 0.25, 0.5, 1 μM for APTT; 2, 4, 8, 16 μM for TT) to human plasma. Edoxaban prolonged both APTT and TT, with CT2 for APTT and TT being 0.508 and 4.95 μM, respectively.

3.(i).A.(1).3) Inhibition of factor Xa derived from mutant blood coagulation factor X (Attached document 4.2.1.1-4)

Wild type human recombinant blood coagulation factor X (wild type factor X) and mutant human recombinant blood coagulation factor with amino acid substitution Ala 112 Thr or Gly 152 Arg (Ala 112 Thr mutant factor X or Gly 152 Arg mutant factor X) were activated by factor X-activating enzyme derived from snake venom (RVV-X). As a result, Ki of edoxaban was 0.89 nM against wild type factor Xa, 0.85 nM against Ala 112 Thr mutant factor Xa, and 1.1 nM

against Gly 152 Arg mutant factor Xa. In a separate experiment, wild type factor X, Ala 112 Thr mutant factor X, or Gly 152 Arg mutant factor X was added to human plasma devoid of blood coagulation factor X, together with edoxaban tosilate hydrate (0.01, 0.03, 0.1, 0.3, 1 μM as edoxaban). As a result, edoxaban prolonged PT and APTT; CT2 of edoxaban for PT was 0.12, 0.12, and 0.11 μM, respectively, and CT2 of edoxaban for APTT was 0.50, 0.45, and 0.46 μM, respectively.

3.(i).A.(1).4) Pharmacological activity of metabolite D21-2393

a. Factor Xa inhibition (Attached document 4.2.1.1-5)

S-2222 was allowed to react with human factor Xa, or rat factor Xa in the presence of D21-2393, a metabolite of edoxaban tosilate hydrate (carboxylate produced by hydrolysis of *N,N*-dimethylcarbamoyl group of edoxaban), (1, 2, 3 nM for human factor Xa; 4, 8, 12 nM for rat factor Xa) or the vehicle. Ki of D21-2393 against human and rat factor Xa was calculated from change in absorbance. D21-2393 competitively inhibited human and rat factor Xa, with Ki of 0.767 nM and 6.88 nM, respectively.

b. Anticoagulant effect (Attached document 4.2.1.1-5)

PT and APTT in human and rat plasma were measured by adding D21-2393 (0.0625, 0.125, 0.25, 0.5 μM for human PT; 0.188, 0.375, 0.75, 1.5 μM for human APTT; 0.25, 0.5, 1, 2 μM for rat PT; 0.75, 1.5, 3, 6 μM for rat APTT) or the vehicle to human or rat plasma. D21-2393 prolonged PT and APTT in human and rat plasma; CT2 of D21-2393 for PT was 0.258 μM in human plasma and 0.898 μM in rat plasma, and CT2 of D21-2393 for APTT was 0.811 μM in human plasma and 3.63 μM in rat plasma.

3.(i).A.(1).5) Antithrombotic effect in rat thrombosis model

a. Rat venous thrombosis model (Attached document 4.2.1.1-6)

Edoxaban tosilate hydrate (0.1, 0.5, 2.5 mg/kg as edoxaban) or the vehicle was administered orally in a single dose to male Wistar rats (10 weeks old, n = 8) and, at 30 minutes after administration, a platinum needle was placed into the vena cava in the abdomen. At 60 minutes after the placement of the platinum needle (90 minutes after administration), the weight of the thrombus adhering to the platinum needle was measured. The thrombus weight decreased in an edoxaban dose-dependent manner and the weight in the edoxaban 2.5 mg/kg group was significantly lower compared with the vehicle group. In the plasma collected at 90 minutes after administration, suppression of human factor Xa activity was observed in the edoxaban 0.5 and 2.5 mg/kg groups, but PT prolongation was not observed in either of the edoxaban groups. In the edoxaban 2.5 mg/kg group, plasma edoxaban concentrations at 30 and 90 minutes after administration were 188 and 106 ng/mL, respectively.

b. Rat phlebothrombosis model (Attached document 4.2.1.1-7)

Edoxaban tosilate hydrate (0.5, 2.5, 12.5 mg/kg as edoxaban) or the vehicle was administered orally in a single dose to male Wistar rats (10 weeks old, n = 8) and, at 30 minutes after administration, hypotonic saline (0.225%) was administered intravenously for 2 minutes at a rate of 5 mL/kg/min. After administration of hypotonic saline, the inferior vena cava was ligated below the left renal vein and, after 10 minutes, the inferior vena cava was further ligated at the site 1.5 cm below the site of the first ligation. At 60 minutes after the second ligation (102 minutes after administration), the weight of the thrombus at the ligated site was measured. The thrombus weight decreased in an edoxaban dose-dependent manner and the weight was significantly lower in all edoxaban groups compared with the vehicle group. In the plasma collected at 29 minutes after administration, suppression of human factor Xa activity was observed in the edoxaban 2.5 and 12.5 mg/kg groups, and PT prolongation was observed in the edoxaban 12.5 mg/kg group. Plasma edoxaban concentrations at 29 minutes after administration in the edoxaban 0.5, 2.5, and 12.5 mg/kg groups were 20.5, 194, and 449 ng/mL, respectively.

c. Rat arteriovenous shunt model (Attached document 4.2.1.1-8)

Edoxaban tosilate hydrate (0.5, 2.5, 12.5 mg/kg as edoxaban) or the vehicle was administered orally in a single dose to male Wistar rats (10 weeks old, n = 6) and, at 13 minutes after administration, an arteriovenous shunt was made between the carotid artery and the jugular vein using a polyethylene catheter with an inserted copper wire. From 30 minutes after administration, blood was circulated through the shunt for 12 minutes, after which the shunt was removed, and the amount of protein in the thrombus generated within the shunt was measured. The amount of protein in the thrombus decreased in an edoxaban dose-dependent manner, the amount was significantly lower in the edoxaban 2.5 and 12.5 mg/kg groups compared with the vehicle group. In the plasma collected at 42 minutes after administration, suppression of human factor Xa activity was observed in the edoxaban 2.5 and 12.5 mg/kg groups, and prolongation of PT was observed in the edoxaban 12.5 mg/kg group. Plasma edoxaban concentration at 42 minutes after administration in the edoxaban 2.5 and 12.5 mg/kg groups was 172 and 396 ng/mL, respectively.

d. Rat disseminated intravascular coagulation model (Attached document 4.2.1.1-9)

Edoxaban tosilate hydrate (0.1, 0.5, 2.5 mg/kg as edoxaban) or the vehicle was administered orally in a single dose to male Wistar rats (11 weeks old, n = 6) and, at 30 minutes after administration, Thromboplastin C Plus (2.48 U/kg) was administered intravenously into the femoral vein for 1 minute. Platelet count and fibrinogen concentration at 41 minutes after administration increased in an edoxaban dose-dependent manner, both platelet count and fibrinogen concentration were significantly higher in all edoxaban groups compared with the vehicle group. Thrombin-antithrombin III complex (TAT) concentration decreased in an edoxaban dose-dependent manner, being significantly lower in all edoxaban groups compared with the vehicle group. In plasma collected at 41 minutes after administration, suppression of human factor Xa activity was observed in the edoxaban 0.5 and 2.5 mg/kg groups. Plasma edoxaban concentration at 41 minutes after administration was below the lower quantitation limit (5 ng/mL) in the edoxaban 0.1 mg/kg group, 16.2 ng/mL in the 0.5 mg/kg group, and 163 ng/mL in the 2.5 mg/kg group.

3.(i).A.(1).6) Antithrombotic effect of edoxaban and drugs in the same therapeutic class (Attached document 4.2.1.1-10)

Edoxaban tosilate hydrate (0.30, 1.0, 3.0 mg/kg as edoxaban) or the vehicle was administered orally, or enoxaparin sodium (enoxaparin, 100, 300, 1000 IU/kg) or the vehicle was administered subcutaneously, in a single dose to male Wistar rats (10 weeks old, n = 8). At 30 minutes after administration, a platinum needle was placed into the inferior vena cava, and at 60 minutes after placing the platinum needle (90 minutes after administration), the amount of protein in the thrombus adhering to the needle was measured. The amount of protein in the thrombus decreased in an edoxaban or enoxaparin dose-dependent manner. The dose required to prevent thrombus formation by 50% (ED_{50}) was 1.9 mg/kg for edoxaban and 500 IU/kg for enoxaparin. In the plasma collected at 27 minutes after administration, PT was significantly longer in the edoxaban 3.0 mg/kg group compared with the vehicle group, while APTT was not affected. In animals receiving enoxaparin, APTT at ≥300 IU/kg and PT in the 1000 IU/kg group were significantly longer compared with the vehicle group.

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

3.(i).A.(2).1) Effect on platelet aggregation (Attached document 4.2.1.2-1)

Edoxaban tosilate hydrate (0.01, 1, 100 μM as edoxaban) or the vehicle was added to human platelet-rich plasma in the presence of collagen, U46619, or ADP. Separately, edoxaban tosilate hydrate (0.1, 1, 10 μM as edoxaban) or the vehicle was added to washed human platelet suspension in the presence of thrombin. Using both systems, the effect of edoxaban to prevent platelet aggregation induced by each stimulus was investigated. IC_{50} of edoxaban against

platelet aggregation induced by collagen, U46619, ADP, and thrombin was >100, >100, >100, and 2.90 μM, respectively.

3.(i).A.(2).2) Effect on bleeding time (Attached document 4.2.1.2-2)

Edoxaban tosilate hydrate (3.0, 10, 20 mg/kg as edoxaban) or the vehicle was administered orally, or enoxaparin (800, 1600, 3200 IU/kg) or the vehicle was administered subcutaneously, in a single dose to male Wistar rats (10 weeks old, n = 8). At 30 minutes after administration, the caudal artery was cut and the time of bleeding from the cut end was measured (if bleeding did not stop within 30 minutes, the bleeding time was regarded as 30 minutes). Bleeding time was significantly longer in the edoxaban 10 and 20 mg/kg groups and enoxaparin 3200 IU/kg group compared with the respective vehicle group; bleeding time in the edoxaban and enoxaparin groups was prolonged up to 1.72 and 6.52 times, respectively, as that in the vehicle group. At 27 minutes after administration, PT was prolonged in an edoxaban and enoxaparin dose-dependent manner, and APTT was prolonged in an enoxaparin dose-dependent manner.

3.(i).A.(2).3) Suppression of anticoagulant activity of edoxaban by rVIIa (Attached document 4.2.1.2-3)

After edoxaban tosilate hydrate (0, 150, 450 ng/mL as edoxaban) and rVIIa (0, 5, 50, 500 ng/mL) were added to human plasma, the mixture was allowed to react in the presence of Thromboplastin C Plus (0.25 U/mL). PT was significantly longer in edoxaban alone groups compared with the vehicle group, but significantly shorter in edoxaban + rVIIa groups compared with the edoxaban alone groups.

3.(i).A.(2).4) Suppression of anticoagulant activity of edoxaban by anti-inhibitor coagulant complex, blood coagulation factor IX complex, and rVIIa (Attached document 4.2.1.2-4)

After edoxaban tosilate hydrate (0, 150, 300 ng/mL as edoxaban) was added to human plasma together with anti-inhibitor coagulant complex (0, 0.15, 0.5, 1.5 U/mL), blood coagulation factor IX complex (0, 0.15, 0.5, 1.5 U/mL), or rVIIa (0, 100, 300, 1000 ng/mL), the mixture was allowed to react in the presence of HemosIL PT-fibrinogen HS PLUS. PT was significantly longer in edoxaban alone group compared with the vehicle group, but significantly shorter in groups treated with edoxaban in combination with anti-inhibitor coagulant complex, blood coagulation factor IX complex, or rVIIa, compared with edoxaban alone groups.

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

3.(i).A.(3).1) Central nervous system

a. Mice (Attached document 4.2.1.3-1)

Edoxaban tosilate hydrate (20, 60, 200 mg/kg as edoxaban) or the vehicle was administered orally in a single dose to male ddY mice (4-5 weeks old, n = 3-10), and animals were monitored for general symptoms and behavior from 30 minutes to 6 hours after administration. As a result, loss of huddling was observed in the 20 mg/kg group and abnormal phonation was observed in one third of animals in the 200 mg/kg group. Edoxaban did not affect either the locomotor activity during the period of 60 minutes from 1 hour post-dose or motor coordination at 1 hour after administration.

Edoxaban tosilate hydrate (20, 60, 200 mg/kg as edoxaban) or the vehicle was administered orally in a single dose to male ddY mice (4-5 weeks old, n = 10) and, at 1 hour after administration, electric pulses were applied via an auricular electrode and the seizure threshold current (current at which tonic extension occurred) was measured. Edoxaban did not affect the seizure threshold current in electric shock-induced convulsions. Using male ddY mice (4-5 weeks old, n = 10), the time of occurrence of each phase of pentylenetetrazole (PTZ)-induced convulsions, i.e., myoclonic jerk (fine clonic convulsions of face, forelimbs, etc.), clonic

convulsions (systemic clonic convulsions), tonic flexion (tonic convulsions characterized by hind limb flexion), and tonic extension (tonic convulsions characterized by hind limb extension) was measured. Edoxaban had no effect on the threshold dose for any of the PTZ-induced convulsions.

b. Cynomolgus monkeys (Attached document 4.2.1.3-2)

Edoxaban tosilate hydrate (20, 60, 200 mg/kg as edoxaban) or the vehicle was administered orally in a single dose to male and female cynomolgus monkeys (4 years old, n = 2 for males and females each, cross-over design with a 6-day interval between each dose, fasted for approximately 18 hours before administration). Edoxaban had no effect on general symptoms or behavior up to 24 hours after administration or locomotor activity or body temperature up to 8 hours after administration.

3.(i).A.(3).2 Cardiovascular system

a. *In vitro* studies

i) hERG test (Attached document 4.2.1.3-3)

Edoxaban up to 20 μg/mL had no effect on hERG K^+ channel current in human embryonic kidney 293 (HEK293) cell line engineered to express human ether-a-go-go related gene (hERG).

ii) Guinea pig right ventricular papillary muscles (Attached document 4.2.1.3-4)

Edoxaban tosilate hydrate (6, 20 μg/mL as edoxaban), E-4031 (class III antiarrhythmic agent, positive control; 0.1 μM) or the vehicle was added to right ventricular papillary muscle preparations (n = 4) of male Hartley guinea pigs (4-6 weeks old), and cardiac action potential induced by electric stimuli (rectangular wave with 1 Hz frequency, 1 msec duration, and voltage approximately 1.3-1.5 times the contraction threshold) was recorded. Edoxaban (6, 20 μg/mL) did not have any significant effect on any of cardiac action potential parameters (resting membrane potential, action potential amplitude, overshoot, action potential duration at 20% repolarization [APD_{20}], APD_{50}, APD_{90}, maximum upstroke velocity). In contrast, E-4031 significantly prolonged APD_{20}, APD_{50}, APD_{90} (15.5, 35.0, and 35.0%, respectively)

b. *In vivo* studies

i) Cynomolgus monkeys (Attached document 4.2.1.3-2)

Edoxaban tosilate hydrate (20, 60, 200 mg/kg as edoxaban) or the vehicle was administered orally in a single dose to male and female cynomolgus monkeys (4 years old, n = 2/sex/dose, cross-over design with a 6-day interval between each dose, fasted for approximately 18 hours before administration). Edoxaban up to 200 mg/kg had no effect on systolic, diastolic, or mean blood pressure, heart rate, electrocardiographic parameters (PR interval, QRS width, QT interval, QTci) during the period from 15 minutes to 8 hours after administration, or on plasma histamine level at 1 and 4 hours after administration.

3.(i).A.(3).3 Respiratory system (Attached document 4.2.1.3-2)

Edoxaban tosilate hydrate (20, 60, 200 mg/kg as edoxaban) or the vehicle was administered orally in a single dose to male and female cynomolgus monkeys (4 years old, n = 2/sex/dose, cross-over design with a 6-day interval between each dose, fasted for approximately 18 hours before administration). Edoxaban up to 200 mg/kg had no effect on respiratory rate, blood pH, blood gases (pO_2, pCO_2), or haemoglobin oxygen saturation at 1, 2, 4, and 8 hours after administration.

3.(i).A.(3).4 Kidney (Attached document 4.2.1.3-5)

Edoxaban tosilate hydrate (0, 60, 200 mg/kg as edoxaban) or the vehicle was administered orally in a single dose to male CD (SD) IGS rats (6 weeks old, n = 8). Edoxaban up to 200 mg/kg had no effect on the urinary excretion of electrolytes (Na^+, K^+, Cl^-) or urine output up

to 5 hours after administration.

3.(i).A.(4) Pharmacodynamic drug-drug interactions
No data submitted.

3.(i).B Outline of the review by PMDA
PMDA considers as follows:
The submitted pharmacology data demonstrate that edoxaban inhibits factor Xa and prevents thrombus formation in various animal models of thrombosis. Therefore, PMDA has concluded that edoxaban is expected to prevent thromboembolism in humans. Results of the nonclinical studies suggest that the risk of bleeding due to the pharmacological action of edoxaban is unlikely to be markedly enhanced compared with approved drugs. Nevertheless, since bleeding is enhanced by edoxaban within effective doses, it is important to evaluate the balance of risks and benefits based on the results of clinical studies.

3.(ii) Summary of pharmacokinetic studies
3.(ii).A Summary of the submitted data
After ^{14}C-labeled edoxaban tosilate hydrate was administered to animals or added to *in vitro* study systems, radioactivity in plasma, tissues, and body waste samples was measured by liquid scintillation counting (LSC), and radioactivity distributed throughout the body was measured by whole-body autoradio-luminography.

Plasma concentrations of edoxaban and its metabolites D21-3231 and D21-2393 in rats, cynomolgus monkeys, rabbits, and mice were measured by validated liquid chromatography-tandem mass spectrometry (LC-MS/MS). Plasma concentrations in rats, rabbits, and mice were measured after sodium fluoride was added to plasma samples to prevent the degradation of analytes. The quantitation range of edoxaban was approximately 5 to 3000 ng/mL.

3.(ii).A.(1) Absorption
3.(ii).A.(1).1) Single dose (Attached document 4.2.2.2-1 to 3, 4.2.2.2-5)
Edoxaban tosilate hydrate (0.3, 1, 3, 10 mg/kg as edoxaban) was administered orally in a single dose to male rats (n = 4). As a result, the maximum plasma edoxaban concentration (C_{max}) and the area under the plasma concentration-time curve up to 24 hours after administration ($AUC_{0\text{-}24h}$) increased in an almost dose-proportional manner. ^{14}C-labeled edoxaban tosilate hydrate (3 mg/kg as edoxaban) was administered orally in a single dose to male rats (n = 3). As a result, plasma radioactivity concentration reached the maximum level at 0.67 hours after administration and then decreased biphasically. Blood radioactivity concentration reached the maximum level at 0.5 hours after administration, showing changes over time roughly parallel to those of plasma radioactivity concentration.

Edoxaban tosilate hydrate (0.3, 1 mg/kg as edoxaban) was administered intravenously in a single dose to male rats (n = 4). As a result, the elimination half-life ($t_{1/2}$) of edoxaban was 0.694 and 1.32 hours. Total body clearance (CL) was 1.97 and 1.86 L/h/kg, respectively, and the volume of distribution at steady state (V_{ss}) was 1.60 and 2.14 L/kg, respectively. Following a single oral dose of edoxaban (0.3, 1 mg/kg) in rats, the absolute bioavailability (BA) of edoxaban was 40.6% and 38.9%, respectively.

Edoxaban tosilate hydrate (0.3, 1, 3, 10 mg/kg as edoxaban) was administered orally in a single dose to male cynomolgus monkeys (n = 4). As a result, the plasma edoxaban level reached C_{max} at 1.13 to 3.25 hours after administration, and both C_{max} and $AUC_{0\text{-}24h}$ increased with dose, but less than in proportion to dose. Edoxaban tosilate hydrate (0.3, 1 mg/kg as edoxaban) was

administered intravenously in a single dose to male cynomolgus monkeys (n = 4). As a result, $t_{1/2}$ of edoxaban was 1.50 and 2.22 hours, respectively. CL was 0.432 and 0.462 L/h/kg, respectively, and V_{ss} was 0.833 and 0.988 L/kg, respectively. Following a single oral dose of edoxaban (0.3, 1 mg/kg) in cynomolgus monkeys, BA was 53.6% and 55.6%, respectively.

^{14}C-labeled edoxaban tosilate hydrate (1 mg/kg as edoxaban) was administered orally in a single dose to male cynomolgus monkeys (n = 3). As a result, plasma radioactivity concentration reached the maximum level at 2.3 hours after administration, and $t_{1/2}$ in the terminal phase was 5.3 days.

3.(ii).A.(1).2) Repeated dose
(Attached document data 4.2.2.2-4, 4.2.3.7.5-8, 4.2.3.2-2, 4.2.3.2-3, 4.2.3.2-6)

^{14}C-labeled edoxaban tosilate hydrate (3 mg/kg/day as edoxaban) was administered orally to male rats (n = 3) for 14 days. As a result, no significant difference was observed in C_{max} and $AUC_{0\text{-}24h}$ of plasma radioactivity between Day 1 and Day 14.

Edoxaban tosilate hydrate (54 mg/kg/day as edoxaban) was administered orally to male and female rats (n = 5/sex/dose, n = 4/sex/dose for data marked with *) for 14 days. The pharmacokinetic parameters in males and females were as follows: C_{max} of edoxaban was 1140 and 2600 ng/mL, respectively, on Day 1, and 1240 and 1960* ng/mL, respectively, on Day 14; and $AUC_{0\text{-}24h}$ of edoxaban was 4020 and 8170 ng·h/mL, respectively, on Day 1, and 4260 and 7590* ng·h/mL, respectively, on Day 14, showing no accumulation with repeated administration.

Edoxaban tosilate hydrate (6, 12, 18, 20, 60, 200 mg/kg/day as edoxaban) was administered orally to male and female rats each (n =3/sex/dose) for 28 days. As a result, plasma edoxaban concentration increased with increasing dose, but C_{max} and $AUC_{0\text{-}24h}$ of edoxaban increased less than in proportion to dose. C_{max} and $AUC_{0\text{-}24h}$ were higher in females than in males in ≥60 mg/kg/day, and tended to increase with repeated administration.

Edoxaban (10, 30, 100 mg/kg/day) was administered orally to male and female cynomolgus monkeys (n = 4/sex/dose, n = 2/sex/dose for data marked with **) for 28 days. As a result, C_{max} of edoxaban was 397, 722, and 1630 ng/mL, respectively, in males and 457, 688, and 1646 ng/mL, respectively, in females on Day 1; and 358, 495, and 701 ng/mL, respectively, in males and 328, 553, and 691** ng/mL, respectively, in females on Day 27. $AUC_{0\text{-}24h}$ of edoxaban was 4061, 10,051, and 21,206 ng·h/mL, respectively, in males and 4187, 6860, and 23,365 ng·h/mL, respectively, in females on Day 1; and 3273, 5963, and 11,307 ng·h/mL, respectively, in males and 3269, 6213, and 10,229** ng·h/mL, respectively, in females on Day 27. Thus, edoxaban did not accumulate with repeated administration.

3.(ii).A.(2) Distribution
3.(ii).A.(2).1) Tissue distribution (Attached document 4.2.2.3-1 to 3, 4.2.2.2-5)

^{14}C-labeled edoxaban tosilate hydrate (3 mg/kg as edoxaban) was administered orally in a single dose to male albino rats (n = 1 per timepoint). Whole-body autoradiography at 1 hour after administration showed the highest radioactivity concentration in the gastrointestinal content and in the bladder urine, followed by intestinal tract, kidney, liver, preputial gland, Harderian gland, pituitary gland, and nasal cavity, in this order. At 24 hours after administration, tissue radioactivity had decreased markedly, with the highest radioactivity being observed in the intestinal content.

^{14}C-labeled edoxaban tosilate hydrate (3 mg/kg as edoxaban) was administered orally in a single dose to male albino rats (n = 3 per timepoint). Measurement of radioactivity concentration in isolated tissues showed that the highest level was reached at 8 hours after administration in the

large intestine and at 1 hour after administration in other tissues. The peak radioactivity concentrations in the small intestine, stomach, bladder, kidney, and liver were as high as 6 to 24 times that in the plasma, whereas the peak radioactivity concentrations in the cerebrum and in the cerebellum were 0.05 times that in the plasma. Tissue radioactivity concentration decreased roughly in parallel with plasma radioactivity concentration. At 168 hours after administration, the radioactivity concentration in the cerebellum was 5.8% of the maximum level in the same tissue, the radioactivity concentrations in the cerebrum, white adipose tissue, thyroid gland, brown adipose tissue, skin, testis, and eyeball were ≤2.4% of the maximum level in the respective tissues, and the radioactivity concentrations in other tissues were ≤0.6% of the maximum level in the respective tissue.

^{14}C-labeled edoxaban tosilate hydrate (3 mg/kg as edoxaban) was administered orally in a single dose to pigmented male rats (n = 1 per timepoint). The peak radioactivity concentration was reached at 1 hour after administration in all tissues except the eyeball, with the highest radioactivity being observed in the kidney. The peak radioactivity level in the eyeball was reached at 96 hours after administration, and the level was higher than that in the kidney. The radioactivity concentration in the eyeball decreased only gradually from 96 hours after administration ($t_{1/2}$ of approximately 260 hours), and was higher compared with the blood and other tissues even at 336 hours after administration. These results suggested the affinity of edoxaban or its metabolite(s) to melanin-containing tissues.

^{14}C-labeled edoxaban tosilate hydrate (1 mg/kg as edoxaban) was administered orally in a single dose to male cynomolgus monkeys (n = 3). The radioactivity level at 336 hours after administration was the highest in the eyeball, which was followed by the skin. The radioactivity levels in the liver, kidney, lung, heart, etc., were higher than that in the blood.

3.(ii).A.(2).2) Placental transfer (Attached document 4.2.2.3-4)

^{14}C-labeled edoxaban tosilate hydrate (3 mg/kg as edoxaban) was administered orally in a single dose to rats on Gestation Day 13 (n = 3 per timepoint). The radioactivity level at 0.5 hours after administration was higher in the placenta, and lower in the fetuses and the yolk sac fluid, compared with the level in the plasma of dams. ^{14}C-labeled edoxaban tosilate hydrate (3 mg/kg as edoxaban) was administered orally in a single dose to rats on Gestation Day 18 (n = 3 per timepoint). At 0.5 hours after administration, the radioactivity concentration was higher in the placenta, and lower in each tissue of fetuses (liver, kidney, heart, lung, blood, brain) and in the amniotic fluid of dams, compared with the level in the plasma of dams. At 24 hours after administration, the radioactivity level had decreased in the whole body, but the radioactivity level was higher in the placenta, uterus, and ovary of dams and in the liver, kidney, lung, and heart of fetuses, compared with the level in the plasma of dams. Radioactivity further decreased in the whole body at 48 hours after administration

3.(ii).A.(2).3) Plasma protein binding rate and distribution in blood cells (Attached document 4.2.2.3-5, 4.2.2.3-6)

Plasma protein binding rates of ^{14}C-labeled edoxaban tosilate hydrate (final concentration of 0.2-5 μg/mL as edoxaban) were 31.6% to 34.5% in rats, 44.9% to 46.4% in dogs, 48.0% to 50.2% in cynomolgus monkeys, and 54.3% to 56.6% in humans.

When ^{14}C-labeled edoxaban tosilate hydrate (final concentration of 0.2-5 μg/mL as edoxaban) was added to blood, the distribution rate of the radioactivity in blood cells was 56.3% to 57.8% in rats, 52.3% to 55.4% in dogs, 38.0% to 38.2% in cynomolgus monkeys, and 45.7% to 47.4% in humans.

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

3.(ii).A.(3).1 Rats (Attached document 4.2.2.2-3, 4.2.2.4-1, 4.2.2.4-2, 4.2.2.4-4, 4.2.2.5-1)

^{14}C-labeled edoxaban tosilate hydrate (3 mg/kg as edoxaban) was administered orally in a single dose to male rats (n = 3). At 1 and 4 hours after administration, the unchanged compound accounted for 50.9% and 52.7%, respectively, of the plasma radioactivity, and D21-3231 (de-chloropyridinylaminated form generated by the hydrolysis of edoxaban) accounted 32.4% and 26.7%, respectively. Since edoxaban is unstable in rat plasma, part of D21-3231 detected in rat plasma was considered to be generated by the hydrolysis of edoxaban after plasma sample collection.

In rat urine samples collected up to 24 hours after administration, the unchanged compound accounted for 70.7% of the radioactivity, D21-3231 accounted for 19.7%, and D21-1402 (*N*-demethylated form generated by *N*-demethylation at position 5 of tetrahydrothiazolopyridine ring of edoxaban) accounted for 1.4%.

In rat feces samples collected up to 24 hours after administration, the unchanged compound accounted for 69.7% of the radioactivity, D21-3231 accounted for 5.8%, and D21-1402 accounted for 3.9%.

In rat bile samples collected up to 24 hours after administration, the unchanged compound accounted for 35.5% of the radioactivity, while D21-3231, D103-2684 (*N*-oxide form at position 5 of tetrahydrothiazolopyridine ring of edoxaban), D21-1402, and D21-2135 (*N*-demethylated form generated by demethylation of *N,N*-dimethylcarbamoyl group of edoxaban) accounted for 17.5%, 5.4%, 6.8%, and 1.3%, respectively, of the radioactivity.

In the rat liver at 1 and 4 hours after administration, the unchanged compound accounted for 63.3% and 55.5%, respectively, of the radioactivity. D21-3231 accounted for 4.5% and 8.2%, respectively, and D21-1402 accounted for 11.1% and 11.5%, respectively.

In the rat kidney at 1 and 4 hours after administration, the unchanged compound accounted for 71.8% and 56.4%, respectively, of the radioactivity, D21-3231 accounted for 12.8% and 15.0%, respectively, and D21-1402 accounted for 2.6% and 3.6%, respectively.

In the rat metabolic study, the total radioactivity excreted up to 24 hours after administration was 25.3% in urine, 64.0% in feces, and 23.1% in bile. The unchanged form in urine, feces, and bile accounted for 17.9%, 44.6%, and 8.3%, respectively, of the total dose administered.

3.(ii).A.(3).2 Cynomolgus monkeys (Attached document 4.2.2.2-5, 4.2.2.4-1, 4.2.2.4-3, 4.2.2.4-4)

^{14}C-labeled edoxaban tosilate hydrate (1 mg/kg as edoxaban) was administered orally in a single dose to male cynomolgus monkeys (n = 3). At 2 and 4 hours after administration, the unchanged compound accounted for 60.7% and 56.0%, respectively, of plasma radioactivity, whereas metabolites (D21-3231, D103-2684, D21-1402) accounted for 3.1% to 5.0% at 2 hours after administration and 3.0% to 5.4% at 4 hours after administration.

In the urine samples collected from 0 to 8 hours, and from 8 to 48 hours, after administration, the unchanged compound accounted for 52.7% and 58.5%, respectively, of the radioactivity. Metabolites (D21-3231, D103-2684, D21-1402, D21-2135) accounted for 1.0% to 5.5% of the radioactivity from 0 to 8 hours after administration, and 1.7% to 5.6% from 8 to 48 hours after administration.

In feces samples collected from 0 to 24 hours, and from 24 to 72 hours, after administration, the

unchanged compound accounted for 34.6% and 27.8%, respectively, of the radioactivity. Metabolites (D21-3231, D21-1402, D21-2135) accounted for 4.7% to 12.1% of the fecal radioactivity from 0 to 24 hours after administration and 4.0% to 13.5% of the radioactivity from 24 to 72 hours after administration.

In cynomolgus monkeys, the total radioactivity excreted into urine from 0 to 8 hours and from 8 to 48 hours after administration was 30.6% and 11.2%, respectively, of the dose administered, and the radioactivity of the unchanged compound accounted for 16.6% and 6.6%, respectively, of the dose administered. The total radioactivity excreted into feces from 0 to 24 hours and from 24 to 72 hours after administration was 18.0% and 25.7%, respectively, of the dose administered, and the radioactivity of the unchanged compound accounted for 6.0% and 7.5%, respectively of the dose administered.

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

3.(ii).A.(4).1) Excretion into feces and urine (Attached document 4.2.2.5-1, 4.2.2.2.-5)

^{14}C-labeled edoxaban tosilate hydrate (3 mg/kg as edoxaban) was administered orally in a single dose to male rats (n = 3). As a result, 72.5% of the administered radioactivity was excreted into feces, 24.8% into urine, and 0.3% into expired air, by 168 hours after administration.

^{14}C-labeled edoxaban tosilate hydrate (1 mg/kg as edoxaban) was administered orally in a single dose to male cynomolgus monkeys (n = 3). As a result, 51.0% of the administered radioactivity was excreted into feces and 42.0% into urine by 336 hours after administration.

3.(ii).A.(4).2) Excretion into bile (Attached document 4.2.2.5-2, 4.2.2.5-3)

^{14}C-labeled edoxaban tosilate hydrate (3 mg/kg as edoxaban) was administered orally in a single dose to male rats (n = 3) intubated with a bile duct cannula. As a result, 24.9%, 35.0%, and 24.4% of the administered radioactivity was excreted into bile, urine, and feces, respectively, by 48 hours after administration.

^{14}C-labeled edoxaban tosilate hydrate (3 mg/kg as edoxaban) was administered orally in a single dose to male rats (n = 3) intubated with a bile duct cannula, and bile samples collected up to 8 hours after administration were administered intraduodenally to another set of male rats (n = 3). As a result, 11.2%, 13.2%, and 55.7% of the administered radioactivity was excreted into bile, urine, and feces, respectively, by 48 hours after administration, which suggested that edoxaban and metabolites excreted into the bile were re-absorbed.

3.(ii).A.(4).3) Secretion in milk (Attached document 4.2.2.5-4)

^{14}C-labeled edoxaban tosilate hydrate (3 mg/kg as edoxaban) was administered orally in a single dose to lactating female rats (n = 3) on day 9 postpartum. The radioactivity concentration in milk was 894.20 ng eq./mL at 1 hour after administration, then decreased over time. The radioactivity concentration in milk at 48 hours after administration was 53.54 ng eq./mL. The radioactivity concentration in the plasma of dams was 321.26 ng eq./mL at 1 hour after administration, then decreased over time. The radioactivity concentration in milk was higher than that in the plasma at all timepoints of sample collection.

3.(ii).A.(5) Other pharmacokinetic studies (Attached document 4.2.2.7-1, 4.2.2.7-2)

^{14}C-labeled edoxaban tosilate hydrate (1 mg/kg as edoxaban) was administered intravenously in a single dose to multidrug resistance gene (*mdr1a/1b*)-knockout (KO) mice and to wild type (WT) mice (n = 3 per timepoint). At 0.5 and 1 hour after administration, the tissue/plasma concentration (T/P) ratio of edoxaban in the brain of KO mice was approximately 18 and 11 times, respectively, as that in WT mice. In the liver and kidney, no marked difference was observed in T/P ratio between KO mice and WT mice.

^{14}C-labeled edoxaban tosilate hydrate (1 mg/kg as edoxaban) was administered intravenously in a single dose to *mdr1a/1b* KO mice and to WT mice (n = 1 per timepoint), and tissue distribution of the radioactivity was quantified by whole-body autoradio-luminography. Results showed that the tissue/blood concentration (T/B) ratio in the cerebrum, cerebellum, and adrenals in KO mice at 0.5 hours after administration were 6.0, 3.8, and 1.8 times, respectively, as that in WT mice. In contrast, the T/B ratio in the liver and the kidney in KO mice were 0.83 and 1.3 times, respectively as that in WT mice, showing no marked difference.

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

PMDA asked the applicant to consider the necessity of providing a caution or information about the high residual level of edoxaban in the eyeball of pigmented rats and cynomolgus monkeys.

The applicant explained as follows:
Since edoxaban shows photoabsorption in ultraviolet-visible light region (wavelength of 290-700 nm), 2 types of *in vitro* photosafety studies were performed. In the photo-cytotoxicity test using BALB/3T3 cells and the photo-chromosomal aberration test using CHL cells, edoxaban did not enhance the cytotoxicity or induce photo-chromosomal aberration [see "3.(iii).A.(6).2) Photosafety study"]. In the 4-, 13-, and 52-week repeated dose toxicity studies in cynomolgus monkeys, no abnormality was observed in ophthalmological or ocular histological examination in any of the animals studied [see "3.(iii).A.(2).4) Four-week repeated oral dose toxicity study in cynomolgus monkeys, 5) Thirteen-week repeated oral dose toxicity study in cynomolgus monkeys, 6) Fifty two-week repeated oral dose toxicity study with 13-week recovery in cynomolgus monkeys"]. Furthermore, in the 39-week repeated oral dose study on ocular function in cynomolgus monkeys, no findings related to edoxaban administration were observed in ophthalmological examination, intraocular pressure test, electroretinogram, or ocular necropsy [see "3.(iii).A.(6).3) Ocular function test"]. No Japanese and foreign clinical studies on edoxaban were specifically focused on ocular safety. Therefore, among adverse events reported in each clinical study, those classified as eye disorders in System Organ Class were investigated. Retinal disorder is considered to be the adverse event that may be attributed to the melanin affinity of edoxaban. Except diabetic retinopathy in patients who have diabetes mellitus as an underlying disease, 2 adverse events that are directly indicative of retinal disorder were observed in Japanese and foreign clinical studies in patients with non-valvular atrial fibrillation (NVAF), but their causal relationship with edoxaban was ruled out by the investigator. Vision blurred and diplopia, albeit not directly suggestive of retinal disorder, are known to accompany retinal disorder. Vision blurred was observed in 1 subject in the phase III study in Japanese patients undergoing total hip replacement (THR) (Japanese THR phase III study) and in 2 subjects in Japanese and foreign clinical studies in NVAF patients, and diplopia was observed in 1 subject in the Japanese THR phase III study. In all 3 subjects who had vision blurred, the symptom disappeared without any treatment or after treatment with antibacterial eye-drops, and the causal relationship of the vision blurred with edoxaban was ruled out by the investigator. A causal relationship to diplopia observed in 1 subject could not be ruled out by the investigator, but the symptom was mild in severity and improved by drug therapy. Thus, clinical studies of edoxaban conducted in Japan and in foreign countries did not show any results that strongly suggested the possibility of the occurrence of retinal disorder attributed to the melanin affinity of edoxaban. Based on these results, the applicant considers that it is unnecessary to provide any special caution or information on the residual edoxaban in the eyeball.

PMDA considered as follows:
Edoxaban is used for only a limited time period until the risk of developing venous thromboembolism (VTE) is reduced after orthopedic surgeries of the lower limbs. In addition, taking account of the results of the nonclinical and clinical studies, it is unlikely that residual edoxaban in the eyeball observed in animals would pose any safety problems in human patients.

Based on the above, PMDA accepted the applicant's explanation that there is no need to provide caution or information at the current moment.

3.(iii) Summary of toxicology studies

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

Toxicity studies of edoxaban conducted include single-dose toxicity studies, repeated-dose toxicity studies, genotoxicity studies, reproductive and developmental toxicity studies, toxicity studies on metabolites, photosafety studies, and ocular function studies.

3.(iii).A.(1) Single-dose toxicity studies (Attached document 4.2.3.1-1, 4.2.3.1-3)

Single oral dose toxicity studies were conducted in male and female SD rats and in female cynomolgus monkeys. The approximate lethal dose was determined to be >2000 mg/kg in both male and female rats and >400 mg/kg in female cynomolgus monkeys. Edoxaban-related changes observed were PT and APTT prolongation and decreased factor Xa activity in cynomolgus monkeys at ≥200 mg/kg and decreased platelet count in the 400 mg/kg group.

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

3.(iii).A.(2).1) Four-week repeated oral dose toxicity study in rats (Attached document 4.2.3.2-2)

Edoxaban tosilate hydrate (20, 60, 200 mg/kg/day as edoxaban) or the vehicle was administered orally to male and female SD rats (n = 10/sex/dose) for 4 weeks. Bleeding and inflammation of the pancreas were observed in males at ≥20 mg/kg/day, pneumonic foci containing hemoglobin crystals were observed in males at ≥60 mg/kg/day and in females of the 200 mg/kg/day group, and thymic bleeding containing hemoglobin crystals was observed in females of the 200 mg/kg/day group. Based on the above, the no observed adverse effect level (NOAEL) was determined to be <20 mg/kg/day in males and 60 mg/kg/day in females.

3.(iii).A.(2).2) Four-week repeated oral dose toxicity study in rats (Additional study) (Attached document 4.2.3.2-3)

Edoxaban tosilate hydrate (6, 12, 18 mg/kg/day as edoxaban) or the vehicle was administered orally to male SD rats (n = 10) for 4 weeks. As a result, no changes related to edoxaban were observed. Based on the above, the NOAEL was determined to be 18 mg/kg/day.

3.(iii).A.(2).3) Twenty six-week repeated oral dose toxicity study with 4-week recovery in rats (Attached document 4.2.3.2-4)

Edoxaban tosilate hydrate (6, 18, 54 mg/kg/day as edoxaban) or the vehicle was administered orally to male and female SD rats (n = 10/sex/dose) for 26 weeks. One male in the vehicle group and 1 female in the 54 mg/kg/day group died on Day 101 and Day 163 of administration, respectively. The deaths were supposedly caused by error in administration. There were no other edoxaban-related changes, and the NOAEL was determined to be 54 mg/kg/day in both males and females.

3.(iii).A.(2).4) Four-week repeated oral dose toxicity study in cynomolgus monkeys (Attached document 4.2.3.2-6)

Edoxaban tosilate hydrate (10, 30, 100 mg/kg/day as edoxaban) or the vehicle was administered orally to male and female cynomolgus monkeys (n = 4/sex/dose) for 4 weeks. One each of females in the 100 mg/kg/day group died and was sacrificed moribund on Day 3 and Day 27 of administration, respectively. Histopathological examination showed accumulation of dark red material in the gastrointestinal tract, bleeding in the lung, thyroid gland, heart, thymus, and peritracheal area, decoloration of the kidney, and dilatation of renal tubules. Bleeding caused by mechanical injury due to gavage, etc., was inferred to have persisted as a result of the anticoagulant effect of edoxaban, leading to moribundity and death, but the cause of the death

could not be definitely identified. In surviving animals, prolongation of PT and APTT was observed in males and females at ≥30 mg/kg/day, and bleeding of adrenals was observed in males of the 100 mg/kg/group. Based on the above, the NOAEL was determined to be 30 mg/kg/day in both males and females.

3.(iii).A.(2).5) Thirteen-week repeated oral dose toxicity study in cynomolgus monkeys (Attached document 4.2.3.3.2-7)

Edoxaban tosilate hydrate (6, 18, 54 mg/kg/day as edoxaban) or the vehicle was administered orally to male and female cynomolgus monkeys (n = 4/sex/dose) for 13 weeks. Prolongation of PT and APTT was observed in males and females at ≥18 mg/kg/day, and transient anemia (decreased red blood cell count, decreased hemoglobin, decreased hematocrit) was observed in females of the 54 mg/kg/day group on Day 28 of administration. Based on the above, the NOAEL was determined to be 54 mg/kg/day in males and 18 mg/kg/day in females.

3.(iii).A.(2).6) Fifty two-week repeated oral dose toxicity study with 13-week recovery in cynomolgus monkeys (Attached document 4.2.3.2-8)

Edoxaban tosilate hydrate (5, 15, 45 mg/kg/day as edoxaban) or the vehicle was administered orally to male and female cynomolgus monkeys (n = 4/sex/dose) for 52 weeks. Several animals died or were sacrificed moribund during the study: 1 female in the 5 mg/kg/day group on Day 178, 1 male and 1 female in the 15 mg/kg/day group on Days 314 and 364, respectively, and 2 females in the 45 mg/kg/day group, one each on Days 72 and 197. Among those animals that died or sacrificed moribund, 1 female in the 5 mg/kg/day group and 1 male in the 15 mg/kg/day group were inferred to have died because of aggravation of systemic conditions due to bleeding caused by mechanical injury due to gavage etc. Pulmonary bleeding and inflammation were observed in the dead female of the 15 mg/kg/day group. The 2 females of the 45 mg/kg/day group did not show any histopathological evidence for the cause of the moribund state. One of them, however, showed prolonged estrous period (bleeding period), severe anemia (decreased red blood cell count, decreased hemoglobin concentration, decreased hematocrit, etc.), and pallor due to anemia, from which the death was inferred to be related to edoxaban. In the other animal, the cause of the moribund state could not be identified. Surviving animals in the 15 mg/kg/day and higher dose groups showed prolongation of PT and APTT, slight decrease in red blood cell count, hemoglobin concentration, and hematocrit, increased reticulocyte count, mild to moderate anisocytosis and deformity of red blood cells, increased mean cell volume, and decreased mean cell hemoglobin concentration. In addition, a slight decrease in the ratio of bone marrow cells to erythroid cells, mild increase in erythroid cells, and hemosiderin-laden macrophages were observed. These hematological changes were not observed after the 13-week recovery period. Based on these findings, the NOAEL was determined to be 5 mg/kg/day in both males and females.

C_{max} and AUC following the administration of edoxaban to cynomolgus monkeys at the NOAEL (5 mg/kg/day) were 263 ng/mL and 3370 ng·h/mL, respectively, in males, and 327 ng/mL and 3237 ng·h/mL, respectively, in females. In contrast, C_{max} and AUC following the administration of edoxaban to humans at the recommended clinical dose (30 mg/day) were 219 ng/mL and 1240 ng·h/mL, respectively. Thus, C_{max} and AUC observed in cynomolgus monkeys were approximately 1.2 to 1.5 times and approximately 2.6 to 2.7 times, respectively, as that observed in humans.

3.(iii).A.(3) Genotoxicity studies (Attached document 4.2.3.3.1-1 to 4, 4.2.3.3.2-1 to 3, 4.2.3.3.2-6)

Genotoxicity studies conducted include a bacterial reverse mutation study, a chromosomal aberration test using cultured mammalian cells (Chinese hamster lung-derived fibroblasts [CHL cells]), a test on human peripheral lymphocyte polyploidy, a micronucleus test in human

peripheral lymphocytes, a micronucleus test using rat bone marrow following a single oral dose, a micronucleus test using rat liver following a single oral dose, a micronucleus test using cynomolgus monkey bone marrow following a 4-week repeated oral dose, and unscheduled DNA synthesis assay following a single oral dose in rats. The chromosomal aberration test using CHL cells showed a significant increase in the number of polyploid cells at ≥1250 μg/mL in groups treated for 6 hours with metabolic activation. The test on human peripheral lymphocyte polyploidy showed a significant increase in the number of polyploid cells at ≥313 μg/mL in groups treated for 3 or 46 hours without metabolic activation and in groups treated for 3 hours with metabolic activation. Given that the chromosomal aberration tests were positive only in samples treated with high edoxaban concentrations and that all other tests were negative, the applicant considered that edoxaban was unlikely to show any genotoxicity in the body.

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

3.(iii).A.(4).1) Medium-term hepatocarcinogenesis study in rats (Attached document 4.2.3.4.2-1; reference data)

N-nitrosodiethylamine (DEN), an initiator of hepatocarcinogenesis (200 mg/kg), or the physiological saline (DEN-untreated) was administered intraperitoneally in a single dose to male F344 rats (n = 10-20). After 2 weeks, edoxaban tosilate hydrate (5, 10, 20 mg/kg/day as edoxaban) or the vehicle was administered orally to DEN-treated animals, and edoxaban tosilate hydrate (20 mg/kg/day as edoxaban) or the vehicle to DEN-untreated animals, for 6 weeks. After DEN treatment, animals in the positive control group were allowed to take ad libitum the food containing 500 ppm of sodium phenobarbital (PB), a hepatocarcinogenesis promoter. At 1 week after the start of edoxaban administration, all animals underwent two-third partial hepatectomy. Two animals in the 20 mg/kg/day group (DEN-treated) died (one death on the day of the hepatectomy and the other death on Day 55 after DEN treatment), and 1 animal in the positive control group died on the next day of the hepatectomy. The deaths were inferred to have been caused by errors in the hepatectomy operation. Histopathological examination performed after edoxaban showed that the number and the area of the foci of the placental-type glutathione *S*-transferase (GST-P)-positive cells in the liver were not higher in any of the treated groups compared with the vehicle control group. Based on these results, the applicant considered that edoxaban did not have the activity to modify the hepatocarcinogenesis even at the dose of 20 mg/kg/day.

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

3.(iii).A.(5).1) Rat study of fertility and early embryonic development to implantation (Attached document 4.2.3.5.1-2)

Edoxaban tosilate hydrate (100, 300, 1000 mg/kg/day as edoxaban) or the vehicle was administered orally to male and female SD rats (n = 19-20/sex/dose) for the following period: from 2 weeks before mating until successful copulation in males, and from 2 weeks before mating until gestation day 7 in females. Edoxaban had no effect on the general toxicity or reproductive competence in parent animals or development of the offspring. Based on the above, the NOAEL was determined to be 1000 mg/kg/day for the general toxicity and reproductive competence of parent animals and for the development of the offspring.

3.(iii).A.(5).2) Rat embryo-fetal development study (Attached document 4.2.3.5.2-2)

Edoxaban tosilate hydrate (30, 100, 300 mg/kg/day as edoxaban) or the vehicle was administered orally to pregnant SD rats (n = 20) from Gestation Days 7 to 17. Animals in the 300 mg/kg/day group showed piloerection, generalized pallor, vaginal discharge, soiled perineal region, and vaginal bleeding. The post-implantation mortality was slightly higher in this group compared with the control group. Based on the above, the NOAEL was determined to be 100 mg/kg/day for the general toxicity and the reproductive competence of parental animals and

for the development of the offspring.

3.(iii).A.(5).3) Rabbit embryo-fetal development study (Attached document 4.2.3.5.2-4)

Edoxaban tosilate hydrate (60, 200, 600 mg/kg/day as edoxaban) was administered orally to pregnant NZW rabbits (n = 21-23) from Gestation Days 7 to 20. Death occurred in 3 animals in the 200 mg/kg/day group and in 4 animals in the 600 mg/kg/day group, and preterm delivery was observed at ≥200 mg/kg/day. These were inferred to have been due to bleeding caused by edoxaban. Animals received at ≥200 mg/kg/day showed decreased defecation, suppressed body weight gain or decreased body weight, and decreased food intake. They also showed increased post-implantation mortality, decreased number and body weight of live fetuses, and an increasing tendency of the biliary variations (missing or small-sized). Animals in the 600 mg/kg/day group showed an increase in the rate of complete 13 ribs and presacral vertebra 27 as skeletal variations. Based on the above, the NOAEL was determined to be 60 mg/kg/day for the general toxicity and the reproductive competence of parental animals and for the development of the offspring.

3.(iii).A.(5).4) Rat study for effects on pre- and postnatal development, including maternal function (Attached document 4.2.3.5.3-2)

Edoxaban tosilate hydrate (3, 10, 30 mg/kg/day as edoxaban) or the vehicle was administered orally to pregnant rats (n = 21-22) from Gestation Day 7 to Parturition Day 20. Vaginal bleeding was observed in 2 animals in the 30 mg/kg/day group during late-stage pregnancy, and reduction in conditioned avoidance behavior in the learning ability test (shuttle box test) was observed in female pups on day 1 of test for learning ability. Based on the above, the NOAEL was determined to be 30 mg/kg/day for the general toxicity of dams and 10 mg/kg/day for reproductive competence and for development of the offspring.

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

3.(iii).A.(6).1) Toxicity studies of metabolites

a. Two-week repeated oral dose toxicity study of metabolite D21-2393 in rats (Attached document 4.2.3.7.5-1)

Metabolite D21-2393 (200, 600, 2000 mg/kg/day) or the vehicle was administered orally to male and female SD rats (n = 10/sex/dose) for 2 weeks. The metabolite had no effect. Thus, the NOAEL was determined to be 2000 mg/kg/day in both males and females.

b. Genotoxicity study of metabolite D21-2393 (Attached document 4.2.3.7.5-2 to 6)

Genotoxicity studies conducted include a bacterial reverse mutation study, a chromosomal aberration test using cultured mammalian cells (CHL cells), a test on human peripheral lymphocyte polyploidy, a micronucleus test using rat bone marrow following a single oral dose, and a micronucleus test using rat bone marrow following 2-week repeated oral dose. In the chromosomal aberration test, a significant increase in the number of polyploidy cells was observed in groups treated with ≥2500 μg/mL of edoxaban for 6 hours regardless of metabolic activation, and in groups treated with 1250 or 2500 μg/mL for 24 hours without metabolic activation. However, all other tests were negative. From these results, the applicant considered that metabolite D21-2393 was unlikely to have genotoxicity in the body.

c. Rat embryo-fetal development study for metabolite D21-2393 (Attached document 4.2.3.7.5-7)

Metabolite D21-2393 (200, 600, 1000 mg/kg/day) or the vehicle was administered orally to pregnant SD rats (n = 19-21) from Gestation Days 7 to 17. The metabolite had no effect on the general toxicity or reproductive competence of dams or on the development of the offspring. Based on the above, the NOAEL was determined to be 1000 mg/kg/day for the general toxicity and the reproductive competence of dams and for the development of the offspring.

d. Two-week repeated oral dose toxicokinetics study (Attached document 4.2.3.7.5-8)

To investigate the systemic exposure to metabolite D21-3231 in repeated oral dose toxicity study of edoxaban, edoxaban tosilate hydrate (54 mg/kg/day as edoxaban) was administered orally to male and female SD rats (n = 5/sex/dose) for 2 weeks, and plasma D21-3231 concentration was measured. C_{max} and $AUC_{0\text{-}24h}$ of D21-3231 on Day 14 of administration were 778 ng/mL and 2750 ng·h/mL, respectively, in males and 612 ng/mL and 2880 ng·h/mL, respectively, in females. These values were approximately 40 to 70 times and approximately 30 times, respectively, as those observed in Study DU176b-PRT019 (C_{max}, 14.9 ng/mL; $AUC_{0\text{-}inf}$, 95.8 ng·h/mL) in which edoxaban tosilate hydrate was administered orally to human subjects in a single dose of 60 mg, which is double the recommended clinical dose (30 mg). From these results, the applicant considered that the toxicity of metabolite D21-3231 also was evaluated in repeated oral dose toxicity studies of edoxaban tosilate hydrate.

3.(iii).A.(6).2) Photosafety study (Attached document 4.2.3.7.7-1, 4.2.3.7.7-2)

Since edoxaban have the absorption spectrum in the ultraviolet-visible spectral region (about 290 nm) and persists in melanin-containing tissues of pigmented animals, such as eye and skin, a photocytotoxicity test using BALB/3T3 cells and a chromosomal aberration test using CHL cells were performed. Both tests were judged negative.

3.(iii).A.(6).3) Ocular function test (Attached document 4.2.3.7.7-3)

Since edoxaban persists in the eye of pigmented animals, effect on the ocular function (intraocular pressure and electroretinogram) was investigated in male and female cynomolgus monkey treated with repeated oral administration of edoxaban tosilate hydrate (15 mg/kg/day as edoxaban) for 39 weeks. Results showed no effect on ocular function.

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

PMDA asked the applicant to explain the mechanism of the increased post-implantation mortality observed in embryo-fetal development studies in rats and rabbits, including the relationship of the numerical aberration of chromosomes to edoxaban, and to explain about the necessity of providing caution and information in the package insert, based on the placental transfer in rats and toxicological findings in fetuses in reproductive and developmental toxicity studies.

The applicant responded as follows:

Regarding the increase in post-implantation mortality observed in the rat embryo-fetal development study, a survey of the historical data of the post-implantation mortality of CD (SD) rats in 48 facilities in Japan showed that the upper limit exceeded 7.5% in 31 facilities (Nakatsuka T et al. *Cong Anom.* 1997;37:47-138), which suggests that the increase (7.5%) observed is within the level that may occur spontaneously, but the exact mechanism for the occurrence is unclear. The increased post-implantation mortality observed in the rabbit embryo-fetal development study is considered to accompany the toxicity in dams, and is unlikely to be related to numerical aberration of chromosomes. In the chromosomal aberration test using CHL cells and in the test on human peripheral lymphocyte polyploidy, edoxaban significantly increased the number of polyploidy cells at 1250 μg/mL and at ≥313 μg/mL, respectively. However, all other genotoxicity tests were negative. Hence, the applicant has concluded that edoxaban is extremely unlikely to induce aneuploidy. In the rabbit embryo-fetal development study, C_{max} was 8.3 μg/mL in the 200 mg/kg/day group in which an increase in post-implantation mortality was noted. Although plasma edoxaban concentration was not measured in the rat embryo-fetal development study, given the edoxaban concentration data obtained in the study for effects on pre- and postnatal development, including maternal function, C_{max} is estimated to be approximately 3 to 4 μg/mL in the 300 mg/kg/day group in which post-implantation deaths were noted. Thus, there is

a wide difference between C_{max} achieved at the dose that caused post-implantation death both in rabbits and rats and the concentration that induces polyploidy cells (≥313 μg/mL). Therefore, from the aspect of the exposure level as well, the increase in post-implantation mortality observed in rats and rabbits is unrelated to numerical aberration-inducing effect of edoxaban observed in *in vitro* systems.

The NOAEL for post-implantation mortality was determined to be 100 mg/kg/day in rats and 60 mg/kg/day in rabbits. When the plasma edoxaban concentration in the rat embryo-fetal development study is compared with the exposure level (C_{max} 218.9 ng/mL, $AUC_{0\text{-}24h}$ 1240 ng·h/mL) observed following a single dose administration of the recommended clinical dose (30 mg) to humans, by referring to the plasma edoxaban concentration (C_{max} and $AUC_{0\text{-}24h}$) of dams in the 30 mg/kg/day group in the rat study for effects on pre- and postnatal development, including maternal function, there is a safety margin of 11.0 times and ≥6.1 times, respectively, compared to the data in rats and 26.6 times and 12.5 times, respectively, compared to the data in rabbits. Furthermore, no fetal bleeding or teratogenicity was observed in embryo-fetal development studies in rats and rabbits, suggesting that edoxaban was unlikely to have any direct effect on fetuses. Therefore, the applicant considered that there was no need to describe such a possibility in the package insert. Nevertheless, since it has been confirmed that edoxaban passes across the placenta and is distributed in fetuses in pregnant rats, the description "Edoxaban is shown to be distributed in fetus in animal experiments (rats)" will be added to the package insert to raise caution.

PMDA considers as follows:
As regards the increased post-implantation mortality observed in rats and rabbits, there is a safety margin of at least 6.1 times in both animal species. In addition, edoxaban is unlikely to pose any clinical problem, provided that usual cautions required for women with child-bearing capacity are exercised in orthopedic surgery of the lower limbs for which edoxaban is indicated and in the accompanying edoxaban administration. On the basis of the above, PMDA accepted the response of the applicant. Other findings observed in toxicity studies are considered to be changes related to bleeding attributed to the pharmacological effect of edoxaban or to those secondary to the bleeding. Therefore, PMDA concluded that there were no toxicological findings that would have serious implications for the safety of edoxaban.

4. Clinical data

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

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

Edoxaban concentrations in plasma and urine and plasma concentrations of main metabolites were measured by a validated LC-MS/MS method (lower limit of quantitation: 0.764 ng/mL for unchanged compound; 0.0792 ng/mL for D21-2393; 0.1 ng/mL for D21-3231, D21-1402, D21-2135).

The drug products used in the following studies were edoxaban tosilate hydrate preparations. The dose is expressed on the basis of edoxaban.

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

In Japanese clinical studies (including global clinical studies conducted jointly in Japan and Taiwan), 3 types of film-coated tablets, containing 5, 15, and 30 mg of edoxaban, respectively, were used. The 15 mg tablets and 30 mg tablets are [redacted].
The to-be-marketed drug products are film-coated tablets containing 30 mg of edoxaban with a score on one side and film-coated tablets containing 15 mg of edoxaban.

4.(i).A.(1).1) Bioequivalence between the to-be-marketed drug products: 15 mg tablets and 30 mg tablets

According to the "Partial Revision of the Guidelines for Bioequivalence Testing of Generic Drugs", Attachment 2 "Guidelines for Bioequivalence Testing of for Different Strengths of Oral Solid Dosage Forms" (PFSB/ELD Notification No. 1124004 dated November 24, 2006), the extent of the formulation change of 15 mg tablets and 30 mg tablets, the to-be-marketed formulations, is level [redacted]. Based on the dissolution test required by the guideline, both drug products were determined to be biologically equivalent.

4.(i).A.(1).2) Bioequivalence between the to-be-marketed 30 mg tablets and 30 mg tablets used in phase III studies

According to the "Partial Revision of the Guidelines for Bioequivalence Testing of Generic Drugs", Attachment 3 "Guidelines for Bioequivalence Testing for Formulation Changes of Oral Solid Dosage Forms" (PFSB/ELD Notification No. 1124004 dated November 24, 2006), the extent of the formulation change of the to-be-marketed 30 mg tablet and 30 mg tablet used in phase III studies is level [redacted]. Based on the dissolution test required by the guideline, both drug products were determined to be biologically equivalent.

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

4.(i).A.(2).1) Study in Japanese subjects

(Protocol No.: DU176b-A-J135, Attached document 5.3.1.1-1)

A 2-group, 2-period, cross-over study was conducted in 34 Japanese healthy adult male subjects (17 subjects per group) to investigate the effect of food consumption on the pharmacokinetics of edoxaban, using the to-be-marketed drug product (washout period, 5-7 days). A to-be-marketed 30-mg tablet was administered orally in a single dose in the fasted state or at 30 minutes after taking a high-fat meal. C_{max} was 230.2 ± 70.6 ng/mL (mean ± standard deviation [SD]) following fasted administration and 257.4 ± 77.0 ng/mL following fed administration, and $AUC_{0\text{-}24h}$ was 1213.6 ± 260.8 ng·h/mL following fasted administration and 1163.4 ± 202.2 ng·h/mL following fed administration. Median t_{max} was 1.0 hour following fasted administration and 1.5 hours following fed administration, and $t_{1/2}$ was 5.0 ± 1.0 hours following fasted administration and 5.4 ± 0.7 hours following fed administration.

The ratio of the geometric least squares mean of C_{max} following fed administration to that following fasted administration was 1.125 (90% confidence interval [CI], 1.005-1.259), and the ratio of the geometric least squares mean of $AUC_{0\text{-}24h}$ following fed administration to that following fasted administration was 0.965 (0.931-1.001).

4.(i).A.(2).2) Study in foreign subjects

(Protocol No.: DU176b-PRT008, Attached document 5.3.1.1-2; Reference data)

A 2-group, 2-period, cross-over study was conducted in 16 Japanese and 16 Caucasian healthy adult male subjects (8 subjects per group) to investigate the effect of food consumption on the pharmacokinetics of edoxaban (washout period ≥6 days). Edoxaban 60 mg (two 30-mg film-coated tablets) was administered orally in a single dose in the fasted state or at 30 minutes after taking a high-fat meal. The ratios of the geometric least squares means of C_{max} and $AUC_{0\text{-}24h}$ in the fed state to those in the fasted state was 1.06 (0.879-1.27) and 1.15 (1.07-1.24), respectively, in Japanese subjects, and 1.22 (0.960-1.55) and 1.15 (1.05-1.27), respectively, in Caucasian subjects. The median t_{max} was later in the fed than the fasted state and was delayed by 1 hour in Japanese subjects and by 0.5 hours in Caucasian subjects. $t_{1/2}$ was not significantly different between fasted and fed administration, either in Japanese or Caucasian subjects.

4.(i).A.(2).3) Effect of inhibition of gastric acid secretion

(Protocol No.: DU176b-PRT012, Attached document 5.3.1.1-3; Reference data)

A 2-group, 2-period, cross-over study was conducted in 32 foreign healthy adult subjects (16 subjects receiving tablets, 16 subjects receiving solution) to investigate the effect of combination with a proton pump inhibitor esomeprazole (EMZ) on the pharmacokinetics of edoxaban (washout period, 10 days). In one dosage regimen, film-coated tablets or liquid solution of edoxaban 60 mg was administered orally in a single dose. In the other dosage regimen, EMZ 20 mg was administered once daily for 4 days and, on Day 4, film-coated tablets or liquid solution of edoxaban 60 mg was administered orally in a single dose. The the geometric least squares mean ratios of C_{max} and the area under the blood concentration-time curve up to the last quantifiable time (AUC_{last}) (edoxaban + EMZ/edoxaban alone) were 1.016 (0.77695-1.3293) and 1.027 (0.91017-1.1593), respectively, for film-coated tablets and 0.921 (0.79564-1.0651) and 1.058 (0.98559-1.1364), respectively, for liquid solution.

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

In the study on the food effect in Japanese subjects using the to-be-marketed drug product (Study DU176b-A-J135), there was no difference in AUC of edoxaban between the fasted state and fed state. In contrast, in the results of population pharmacokinetic study (PPK) analysis, [see "4.(i).A.(2).1) Study in Japanese subjects"], the bioavailability (F) of edoxaban increased by 25% in the fed state compared with the fasted state. PMDA asked the applicant to explain the reasons for the discrepancy.

The applicant explained as follows:
The PPK analysis was planned to evaluate the effect of routinely consumed food on the pharmacokinetics based on the wide range of data pooled from the clinical pharmacology studies with multiple dosing and from clinical studies in Japanese patients undergoing orthopedic surgery of the lower limbs. Therefore, data of food effect studies using high-fat diet (Japanese Study DU176b-A-J135, foreign Study DU176b-PRT008) were excluded from the analysis. The food effect observed in the PPK analysis appears to be partly attributed to the difference in the composition and amount of consumed food from those in Study DU176b-A-J135 using the to-be-marketed drug product. However, the mechanism(s) of how the food affects the absorption of edoxaban from the digestive tract is unknown. All the clinical studies in patients undergoing orthopedic surgery of the lower limbs were conducted under hospitalized conditions. According to the background data of subjects included in the PPK analysis, samples for pharmacokinetic analysis collected on Day 7 of administration and at treatment completion (or discontinuation) were those collected after fed administration in approximately 93% of subjects, which suggests that throughout the treatment period, edoxaban was administered mainly postprandially

PMDA considers as follows:
It is of significance that the food effect was evaluated in the PPK analysis in patients undergoing orthopedic surgery of the lower limbs. However, given the fact that edoxaban was administered postprandially in most of patients, the data have only a limited value in interpreting the effect of food on the bioavailability of the drug. Since little or no difference was observed in the exposure level between fed administration and fasted administration in Study DU176b-A-J135 conducted using the to-be-marketed drug product, the food effect on the pharmacokinetics of edoxaban is unlikely to pose any clinical problem. Therefore, there is no need to specify the timing of administration in relation to food intake in "Dosage and Administration" section.

4.(ii) Summary of clinical pharmacology studies

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

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

4.(ii).A.(1).1) Plasma protein binding rate and distribution rate in blood cells (Attached document 4.2.2.3-5, 4.2.2.3-6)

^{14}C-labeled edoxaban was added to human plasma to obtain final concentrations of 0.2, 1, and 5 μg/mL, and the mixture was incubated at 37°C for 10 minutes. Plasma protein binding rate of edoxaban was 54.3%, 54.4%, and 56.6%, respectively.

^{14}C-edoxaban was added to human blood to obtain final concentrations of 0.2, 1, and 5 μg/mL, and the mixture was incubated at 37°C for 10 minutes. The distribution rate of radioactivity in blood cells was 45.7%, 45.9%, and 47.4%, respectively.

4.(ii).A.(1).2) *In vitro* metabolism in human liver (Attached document 5.3.2.2-1 to 4)

a. Metabolism of edoxaban

^{14}C-labeled edoxaban was added to human liver microsomes and to microsomes expressing CYP3A4 among cytochrome P450 (CYP) isomers, and the mixture was incubated at 37°C for 120 minutes in the presence of reduced nicotinamide adeninedinucleotide phosphate (NADPH). As a result, D21-1402, D21-3231, D103-2684, D21-2393, and D21-2135 were identified as metabolites of edoxaban, and another metabolite was tentatively identified as a hydroxymethylated form (hydroxymethylate of *N,N*-dimethylcarbamoyl group in edoxaban). Among them, D21-2393 and D21-3231 were formed in the absence of NADPH as well. In addition, it was shown that mainly CYP3A4 is involved in the formation of D21-1402, D103-2684, and the hydroxymethylated form. It was assumed that D21-2135 was produced nonenzymatically from the hydroxymethylated form of edoxaban, considering the general mechanism of *N*-dealkylation reaction.

b. Effects on metabolic activity of CYP

Effects of edoxaban on specific metabolic activity of each CYP isoform (CYP1A2, 7-ethoxyresorufin *O*-deethylase activity; CYP2A6, coumarin 7-hydroxylase activity; CYP2B6, 7-ethoxy-4-trifluoromethylcoumarin *O*-deethylase activity; CYP2C8/9, tolbutamide 4-methylhydroxylase activity; CYP2C19, (*S*)-mephenytoin 4-hydroxylase activity; CYP2D6, bufuralol 1-hydroxylase activity; CYP2E1, chlorzoxazone 6-hydroxylase activity; CYP3A4, testosterone 6β-hydroxylase activity) was investigated using human liver microsomes. Edoxaban was preincubated with human liver microsomes at 37°C for 5 minutes in the absence of NADPH generating system, followed by addition of NADPH generating system and by further incubation at 37°C. The inhibition rate of edoxaban 1 and 10 μM against the metabolic activity of CYP isoforms was ≤9.7%, assuming the inhibition rate of the vehicle control to be 0%. Edoxaban 100 μM inhibited CYP2C19 activity by 40.2%, CYP2C8/9 activity by 11.1%, and CYP1A2 activity by 10.8%, but had little inhibitory effect on other CYP isoforms. IC_{50} of edoxaban against all CYP isoforms tested was >100 μM. After edoxaban (10 μM) was preincubated with human liver microsomes for 15 minutes in the presence of NADPH generating system, edoxaban had no inhibitory effect on any of the CYP isoforms tested.

c. Effects on drug metabolizing enzyme induction

Edoxaban (0.3-100 μM), D21-2393, or D21-3231 (0.1-30 μM) was incubated with human liver cells for 72 hours, and then mRNA level and enzymatic activity of CYP1A2, CYP3A4, and P-gp (multidrug resistance 1 [human]; MDR1) were measured. For CYP1A2, mRNA level and enzyme activity increased to 13.6- and 12.7-fold, respectively, in the presence of omeprazole 50 μM as the positive control, whereas both increased to ≤0.9-fold and ≤2.6-fold, respectively, in the presence of edoxaban or metabolites at all concentrations tested. For CYP3A4, mRNA level and enzyme activity increased to 48.2- and 29.6-fold, respectively, in the presence of rifampicin 10 μM, the positive control, whereas both increased to ≤2.4-fold and ≤3.1-fold, respectively, in the presence of edoxaban or metabolites at all concentrations tested. For MDR1, mRNA level increased to 1.9-fold in the presence of rifampicin 10 μM as the positive control, and 1.7-fold in the presence of edoxaban 100 μM. However, neither edoxaban

up to 30 μM nor metabolites at any concentration increased the mRNA level.

4.(ii).A.(1).3) Transcellular transport (Attached document 4.2.2.6-1, 4.2.2.6-2)

a. Transcellular transport of edoxaban

The ratio of the apparent permeation coefficient (P_{app}) of ^{14}C-labeled edoxaban (1 μM) from basal to apical side (B to A) and from apical to basal side (A to B) ([B to A]/[A to B]) in human colon cancer-derived Caco-2 cells was 4.53, demonstrating the directional transport. This directional transport was inhibited by MDR1 inhibitors verapamil (100 μM, P_{app} ratio = 1.04) and cyclosporine (10 μM, P_{app} ratio = 0.62). P_{app} of ^{3}H-labeled digoxin, a substrate of MDR1, was 8.23, and this directional transport was completely inhibited by verapamil, a MDR1 inhibitor (100 μM, P_{app} ratio = 0.98). The ratio of P_{app} for transcellular transport of ^{14}C-labeled edoxaban decreased with the increase in substrate concentration, showing that the directional transport was saturable. The Michaelis constant (K_m) under the saturated conditions was 74.9 μM.

b. Inhibition of digoxin transport

The directional transport of ^{3}H-labeled digoxin (1 μM) in Caco-2 cells (P_{app} ratio = 4.60) was concentration-dependently inhibited by edoxaban (1, 3, 10, 30, 100 μM), with P_{app} ratio being 4.50, 4.15, 3.95, 3.24, and 2.44, respectively. IC_{50} was 53.7 μM. The MDR1 inhibitor verapamil (100 μM) completely inhibited the directional transport of digoxin (P_{app} ratio = 0.94).

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

4.(ii).A.(2).1) Studies in Japanese subjects

a. Single-dose study in Japanese and Caucasian subjects (Protocol No.: DU176b-01, Attached document 5.3.3.1-1)

Edoxaban (30, 60, 90, 120, 150 mg) was administered orally in a single dose to 45 Japanese healthy adult male subjects (9 subjects per group) in the fasted state. The median t_{max} of edoxaban was ranging from 1 to 2 hours, C_{max} was 181.80 ± 54.51 (mean ± SD), 257.38 ± 95.68, 394.26 ± 92.45, 519.33 ± 107.28, and 655.24 ± 129.61 ng/mL, respectively, and $AUC_{0\text{-}48h}$ was 923.50 ± 174.36, 1599.18 ± 411.84, 2271.63 ± 381.69, 2914.38 ± 469.39, and 3708.64 ± 770.69 ng·h/mL, respectively. The mean $t_{1/2}$ at each dose was ranging from 7.2 to 9.1 hours. Following a single oral dose of edoxaban (60 mg) after taking an ordinary meal (lipid content, 28.7 g), C_{max} and $AUC_{0\text{-}48h}$ were 435.50 ± 118.18 ng/mL and 1812.20 ± 211.97 ng·h/mL, respectively, and the ratios of the geometric least squares mean of C_{max} and $AUC_{0\text{-}48h}$ following fed administration to those following fasted administration were 1.77 and 1.19, respectively.

Edoxaban (60, 90, 120 mg) was administered orally in a single dose to 27 Caucasian healthy adult male subjects (9 subjects per group) in the fasted state. The median t_{max} was 1 to 1.5 hours, C_{max} was 245.77 ± 78.71, 304.40 ± 91.48, and 429.36 ± 172.10 ng/mL, respectively, and $AUC_{0\text{-}48h}$ was 1580.40 ± 295.62, 1943.69 ± 379.73, and 2778.10 ± 860.02 ng·h/mL, respectively. The mean $t_{1/2}$ at each dose was 10.5 to 10.9 hours.

The mean cumulative urinary excretion rate of edoxaban up to 48 hours after administration was 32.86% to 35.04% in Japanese subjects (30-150 mg) and 28.22% to 31.99% in Caucasian subjects (60-120 mg), and the mean renal clearance (CL_R) was 192.0 to 230.9 mL/min in Japanese subjects and 204.6 to 241.2 mL/min in Caucasian subjects. Following the administration of edoxaban 60 mg in the fed or fasted state, the cumulative urinary excretion rate of edoxaban up to 48 hours after administration was 41.38% in Japanese subjects and 34.74% in Caucasian subjects.

b. Multiple-dose study in Japanese subjects (Protocol No.: DU176b-02, Attached document 5.3.3.1-2)

Edoxaban was administered to 18 Japanese healthy adult male subjects (9 subjects per group)

according to the following dosage regimen: a single oral dose of 60 or 120 mg of edoxaban in the fed state (Day 1), followed by multiple dose of 60 mg twice daily or 120 mg once daily in the fed state from Day 3 to Day 9, then by a single oral dose of 60 mg or 120 mg in the fed state on Day 10. The median t_{max} was 1.00 hour in the 60 mg group both on Day 1 and on Day 10 and, in the 120 mg group, 1.00 hour on Day 1 and 1.50 hours on Day 10. C_{max} on Day 1 was 520.42 ± 114.62 ng/mL in the 60 mg group and 872.98 ± 190.95 ng/mL in the 120 mg group, and C_{max} on Day 10 was 533.14 ± 298.74 and 1091.19 ± 389.27 ng/mL, respectively. The area under the blood concentration-time curve (AUC_{tau}) in the dosing interval was 1780.72 ± 264.40 in the 60 mg group and 4212.92 ± 576.90 ng·h/mL in the 120 mg group on Day 1, and 2108.74 ± 344.91 and 4763.44 ± 861.26 ng·h/mL, respectively, on Day 10. The ratio of AUC_{tau} on Day 10 to that on Day 1 was 1.19 in the 60 mg group and 1.14 in the 120 mg group, and the ratio of C_{max} on Day 10 to that on Day 1 was 1.01 and 1.26, respectively. Mean $t_{1/2}$ was 8.1 hours on Day 1 and 7.7 hours on Day 10 in the 60 mg group, and 7.1 hours on Day 1 and 9.7 hours on Day 10 in the 120 mg group. The trough plasma edoxaban concentration was similar from Day 5, and the plasma edoxaban concentration at 4 hours after administration was similar from Day 3 to Day 10.

The urinary excretion rate of edoxaban up to 48 hours after administration on Day 1 was 38.30% in the 60 mg group and 44.23% in the 120 mg group.

4.(ii).A.(2).2) Studies in foreign subjects

a. Multiple-dose study in British subjects (Protocol No.: DU176-E-PRT001, Attached document 5.3.3.1-5; Reference data)

Edoxaban was administered to 18 Caucasian healthy adult male subjects (9 subjects per group) according to the following dosage regimen: a single oral dose of 60 or 120 mg of edoxaban in the fed state (Day 1), followed by multiple doses of 60 mg twice daily or 120 mg once daily in the fed state from Day 3 to Day 9, then by a single oral dose of 60 mg or 120 mg in the fed state on Day 10. The median t_{max} was 2.00 hours on Day 1 and 3.00 hours on Day 10 in the 60 mg group, and 1.50 hours on Day 1 and 3.50 hours on Day 10 in the 120 mg group. C_{max} on Day 1 was 274 ± 74.0 ng/mL in the 60 mg group and 636 ± 179 ng/mL in the 120 mg group, and C_{max} on Day 10 was 309 ± 54.9 and 686 ± 264 ng/mL, respectively. AUC_{tau} on Day 1 was 1250 ± 169 ng·h/mL in the 60 mg group and 3277 ± 372 ng·h/mL in the 120 mg group, and AUC_{tau} on Day 10 was 1827 ± 309 and 3713 ± 511 ng·h/mL, respectively. Mean $t_{1/2}$ was 10.8 hours on Day 1 and 9.7 hours on Day 10 in the 60 mg group, and 10.0 hours both on Day 1 and Day 10 in the 120 mg group.

b. Multiple-dose study in Chinese subjects (Protocol No.: DU176b-A-A123, Attached document 5.3.3.1-3)

Edoxaban was administered to 8 Chinese healthy adult male subjects according to the following dosage regimen: a single oral dose of 60 mg of edoxaban in the fed state (Day 1), followed by multiple doses of 60 mg twice daily in the fed state from Day 3 up to Day 9, then by a single oral dose of 60 mg in the fed state on Day 10. The median t_{max} was 1.5 hours on Day 1 and 1.75 hours on Day 10, C_{max} was 493.55 ± 182.68 on Day 1 and 474.76 ± 99.30 ng/mL on Day 10, AUC_{tau} was 1761.86 ± 184.48 on Day 1 and 2081.58 ± 308.12 ng·h/mL on Day 10, and mean $t_{1/2}$ was 7.7 hours on Day 1 and 12.6 hours on Day 10.

c. Mass balance study (Protocol No: DU176b-PRT019; Attached document 5.3.3.1-4)

^{14}C-labeled edoxaban (60 mg) was administered orally in a single dose to 6 Caucasian healthy adult male subjects. The ratio of the area under the plasma concentration-time curve from zero to infinity ($AUC_{0\text{-}inf}$) for edoxaban to that for total radioactivity was 0.8126, which suggested that the plasma radioactivity is mostly due to the unchanged compound. In addition to the unchanged compound, D21-3231, edoxaban glucuronide, D21-2393, D103-2684, D21-1402, and D21-2135 were found in the plasma. The ratio of the $AUC_{0\text{-}inf}$ of metabolite to that of the

unchanged compound was the highest for D21-2393 (9.2%), followed by D21-3231 (6.0%).

Of the total radioactivity administered, 62.23% was recovered in feces and 35.36% in urine up to 168 hours after administration. Most of the radioactivity recovered in urine was the unchanged compound; 23.79% of the dose administered was excreted into urine in the form of the unchanged compound up to 48 hours after administration. In addition to the unchanged compounds, the following metabolites were excreted into urine: D21-3231 (percentage of dose administered, 1.85%), edoxaban glucuronide (0.22%), D21-2393 and D103-2684 (co-eluted peak, 1.56%), and D21-1402 (0.45%). The unchanged compound accounted for a majority of radioactivity excreted into feces as well; 53.37% of the administered dose was excreted into feces in the form of the unchanged compound up to 144 hours after administration. D21-2393 and D103-2684 (co-eluted peak, 2.08%), D21-1402 (1.77%), and D21-2135 (0.34%) were also excreted into feces.

4.(ii).A.(3) Pharmacokinetics in patients undergoing orthopedic surgery of the lower limbs

4.(ii).A.(3).1) Plasma concentration in each study

a. Study DU176b-04 (Attached document 5.3.5.1-3)

Edoxaban (5, 15, 30, 60 mg) was administered to Japanese patients undergoing total knee replacement (TKR) once daily for 11 to 14 days. Table 3 shows the plasma edoxaban concentration at pre-dose and at 1 to 3 hours post-dose of edoxaban on Day 7 and at pre-dose on the last day of administration.

Table 3. Plasma edoxaban concentration in the Japanese patients undergoing TKR

Treatment group	Measuring timepoint		No. of subjects evaluated	Drug concentration (ng/mL) Mean ± SD
5 mg	Day 7 of administration	Pre-dose	86	2.39 ± 1.63
		1-3 h post dose	86	27.84 ± 15.87
	Last day of administration	Pre-dose	85	3.48 ± 6.84
15 mg	Day 7 of administration	Pre-dose	89	8.28 ± 6.41
		1-3 h post dose	89	82.84 ± 50.57
	Last day of administration	Pre-dose	90	10.38 ± 8.08
30 mg	Day 7 of administration	Pre-dose	87	16.90 ± 12.27
		1-3 h post dose	87	173.75 ± 97.82
	Last day of administration	Pre-dose	85	19.73 ± 18.65
60 mg	Day 7 of administration	Pre-dose	86	41.03 ± 36.64
		1-3 h post dose	87	354.18 ± 244.40
	Last day of administration	Pre-dose	84	49.21 ± 78.86

b. Study DU176b-B-J209 (Attached document 5.3.5.1-4)

Edoxaban (15, 30 mg) was administered to Japanese and Taiwanese patients undergoing THR once daily for 11 to 14 days. Table 4 shows the plasma edoxaban concentration at pre-dose and at 1 to 3 hours post-dose of edoxaban on Day 7 and at pre-dose on the last day of administration.

Table 4. Plasma edoxaban concentration in the Japanese and Taiwanese patients undergoing THR

Treatment group	Measuring timepoint		No. of subjects evaluated	Drug concentration (ng/mL) Mean ± SD
15 mg	Day 7 of administration	Pre-dose	76	7.61 ± 4.56
		1-3 h post dose	77	85.89 ± 47.47
	Last day of administration	Pre-dose	76	7.54 ± 4.22
30 mg	Day 7 of administration	Pre-dose	71	17.16 ± 19.87
		1-3 h post dose	71	204.03 ± 84.12
	Last day of administration	Pre-dose	68	16.12 ± 10.60

c. Study DU176b-B-J302 (Attached document 5.3.5.1-1)

Edoxaban (30 mg) was administered to Japanese and Taiwanese patients undergoing TKR once daily for 11 to 14 days. Plasma edoxaban concentration before administration on Day 7 (282 evaluable patients) was 17.23 ± 10.32 (mean ± SD) ng/mL.

d. Study DU176b-B-J304 (Attached document 5.3.5.1-2)

Edoxaban (30 mg) was administered to Japanese patients undergoing THR once daily for 11 to 14 days. Plasma edoxaban concentration before administration on Day 7 (250 evaluable subjects) was 17.48 ± 11.81 ng/mL.

e. Study DU176b-B-J303 (Attached document 5.3.5.1-5)

Edoxaban (30 mg) was administered to Japanese patients undergoing hip fracture surgery (HFS) once daily for 11 to 14 days. Plasma edoxaban concentration before administration and at 1 to 3 hours after administration on Day 7 was 24.14 ± 12.46 ng/mL (41 evaluable subjects) and 129.12 ± 110.21 ng/mL (42 evaluable subjects), respectively. Plasma edoxaban concentration before administration on the last day of administration was 23.22 ± 11.04 ng/mL (39 evaluable subjects).

4.(ii).A.(3).2 Population pharmacokinetic analysis (Attached document 5.3.3.5-1)

A PPK analysis was conducted using plasma edoxaban concentration data at 7693 sampling points obtained from a total of 833 subjects, comprising 242 subjects in 6 Japanese and foreign clinical pharmacology studies (DU176-E-PRT001, DU176b-A-A123, DU176b-02, DU176b-01, DU176-E-PRT002, DU176b-A-U120) and 591 subjects in 2 late phase II studies in patients undergoing orthopedic surgery of the lower limbs (DU176b-04, DU176b-B-J209).

The main characteristics of subjects analyzed were as follows: age 58.4 ± 19.0 years (mean ± SD), body weight 63.2 ± 11.8 kg, creatinine clearance (CL_{CR}) 92.1 ± 32.5 mL/min, aspartate aminotransferase (AST) 21.3 ± 6.6 IU/L, alanine aminotransferase (ALT) 19.3 ± 9.6 IU/L, total bilirubin 0.7 ± 0.3 mg/dL, and gamma-glutamyltransferase (γ-GTP) 25.2 ± 22.5 IU/L. Males accounted for 39.6% and females 60.4%, ethnicity was Caucasian in 20.5%, Japanese in 77.8%, and Chienese in 1.7%, and edoxaban was administered in the fasted state in 20.9% of subjects. The above background factors were investigated as covariates.

Plasma edoxaban concentration was described by a 2-compartment model with a first-order absorption process and a first-order elimination process. Relative errors were assumed for inter-subject variability and residual variability. As a result of selection of the covariate model, the following covariates were selected as those affecting the results: CL_{CR} and ethnicity (Asians including Japanese, Caucasians) for apparent total body clearance; body weight and cohort (patients undergoing orthopedic surgery of the lower limbs, healthy adult subjects) for apparent distribution volume of the central compartment; cohort for the absorption rate constant; and

food for relative bioavailability. The final model equations for population parameters were as follows.

$CL/F_i\ (L/h) = 37.7 \times (CL_{CRi}/92)^{0.437} \times \exp\ (Asian_i \times -0.284) \times \exp\ (\eta_1)$

$Vc/F_i\ (L) = 175\ (WT_i/63)^{0.950} \times \exp\ (Population_i \times -0.269) \times \exp\ (\eta_2)$

$Q/F_i\ (L/h) = 10.6 \times \exp\ (\eta_3)$

$Vp/F_i\ (L) = 112 \times \exp\ (\eta_4)$

$ka_i\ (1/h) = 1.63 \times \exp\ (Population_i \times -0.960) \times \exp\ (\eta_5)$

$F1_i = 1 \times \exp\ (Food_i \times 0.227)$

$C_{ij} = C_{ij}^* \cdot (1 + \varepsilon_{ij})$

CL/F: Apparent total body clearance
Vc/F: Apparent distribution volume of the central compartment
WT: Body weight
Q/F: Apparent intercompartmental clearance
Vp/F: Apparent distribution volume of peripheral compartment
ka: Absorption rate constant
$F1_i$: Relative bioavailability (bioavailability after fasted administration was assumed to be 1)
Asian: 0 for Caucasian and 1 for Asian
$Population_i$: 0 for healthy adult subjects, 1 for patients undergoing orthopedic surgery of the lower limbs
Food: 0 for fasted administration, 1 for fed administration
C_{ij}: Observed plasma concentration in subject i at jth measuring timepoint,
C_{ij}^*: Predicted plasma concentration in subject i at jth measuring timepoint
η_i: Random variable that follows a Gaussian distribution with mean 0 and variance ω^2
ε_{ij}: Random variable that follows a Gaussian distribution with mean 0 and variance σ^2

The inter-individual coefficient of variation (CV) for CL/F, Vc/F, Q/F, Vp/F, and ka was 26.1%, 36.6%, 30.8%, 31.9%, and 93.8%, respectively, and the intra-individual CV was 27.5%.

4.(ii).A.(4) Studies on intrinsic factors

4.(ii)A.(4).1 Pharmacokinetics in the elderly and postmenopausal female subjects (Protocol No.: DU176-E-PRT002, Attached document 5.3.3.3-1)

Edoxaban (90 mg) was administered orally in a single dose to 9 Caucasian elderly male subjects (≥65 years) in the fed state (Day 1), followed by multiple oral doses of edoxaban (90 mg) once daily in the fed state from Day 3 to Day 10. As a result, C_{max} was 514 ± 150 and 525 ± 78.8 ng/mL, respectively, on Day 1 and Day 10, AUC_{tau} was 3056 ± 410 and 3598 ± 357 ng·h/mL, respectively, and $t_{1/2}$ was 10.6 ± 1.9 and 11.9 ± 2.2 hours, respectively. Edoxaban was administered in a similar manner to 9 postmenopausal or sterilized female subjects. As a result, C_{max} was 579 ± 92.9 and 522 ± 102 ng/mL, respectively, on Day 1 and Day 10, AUC_{tau} was 3079 ± 413 and 3128 ± 362 ng·h/mL, respectively, and $t_{1/2}$ was 11.2 ± 2.0 and 12.4 ± 2.9 hours, respectively.

Edoxaban was administered in a similar manner to 9 Caucasian healthy adult male subjects (≥18 and ≤51 years). C_{max} was 553 ± 150 and 514 ± 83.4 ng/mL, respectively, on Day 1 and Day 10, AUC_{tau} was 2574 ± 374 and 2836 ± 448 ng·h/mL, respectively, and $t_{1/2}$ was 9.0 ± 2.2 and 9.6 ± 3.2 hours, respectively (Study DU176-E-PRT001, Attached document 5.3.3.1-5).

4.(ii).A.(4).2 Pharmacokinetics in European patients with renal impairment (Protocol No.: DU176b-A-U120, Attached document 5.3.3.3-2)

Edoxaban (15 mg) was administered orally in a single dose to healthy adult subjects (CL_{CR} > 80 mL/min, calculated by Cockcroft-Gault equation), patients with mild renal impairment (50 mL/min ≤ CL_{CR} ≤ 80 mL/min), patients with moderate renal impairment (30 mL/min ≤ CL_{CR} < 50 mL/min), patients with severe renal impairment (CL_{CR} < 30 mL/min and undialyzed), and patients with end stage renal failure (those undergoing peritoneal dialysis) (n = 8 per group). C_{max} was 84.7 ± 26.4, 113 ± 48.9, 115 ± 42.3, 91.9 ± 32.8, and 103 ± 51.6 ng/mL, respectively, $AUC_{0\text{-}inf}$ was 453 ± 102, 636 ± 152, 816 ± 209, 857 ± 199, and 1031 ± 377 ng·h/mL, respectively, and $t_{1/2}$ was 8.6 ± 3.8, 8.2 ± 2.8, 9.4 ± 2.1, 16.9 ± 10.4, and 12.2 ± 5.3 hours,

respectively.

In healthy adult subjects, patients with mild renal impairment, patients with moderate renal impairment, and patients with severe renal impairments (n = 8 per group, except those with moderate impairment [7 subjects]), CL_R of edoxaban was 199 ± 31.3, 128 ± 42.8, 71.6 ± 28.6, and 35.4 ± 14.6 mL/min, respectively, and urinary excretion rate up to 48 hours after administration was 35.1% ± 8.2%, 30.1% ± 6.2%, 20.6% ± 5.4%, and 10.8% ± 3.9%, respectively.

4.(ii).A.(4).3 Pharmacokinetics in European patients with hepatic impairment

(Protocol No.: DU176b-A-E134, Attached document 5.3.3.3-3; Reference data)

Edoxaban (15 mg) was administered orally in a single dose to subjects in the following groups (n = 8 per group): (i) healthy adult subjects matched for background characteristics with patients with mild hepatic impairment (Child-Pugh classification grade A, score 5-6), (ii) patients with mild hepatic impairment, (iii) healthy adult subjects matched for background characteristics with patients with moderate hepatic impairment (Child-Pugh classification grade B, score 7-9), and (iv) patients with moderate hepatic impairment. C_{max} of edoxaban was 77.85, 70.17, 88.84 (geometric mean), and 60.34 ng/mL, respectively, and $AUC_{0\text{-}inf}$ was 494.2, 473.6, 482.1, and 459.0 ng·h/mL, respectively, and $t_{1/2}$ was 5.5, 6.2, 5.2, and 7.2 hours. C_{max} of plasma D21-2393 was 6.3, 6.7, 6.6, and 4.9 ng/mL, and $AUC_{0\text{-}inf}$ was 40.1, 51.3, 43.8, and 43.8 ng·h/mL.

4.(ii).A.(5) Drug-drug interactions

4.(ii).A.(5).1 Digoxin

(Protocol No.: DU176b-PRT014, Attached document 5.3.3.4-1; Reference data)

Twenty-four (24) healthy adult subjects received digoxin orally for 7 days (0.25 mg twice daily for 2 days followed by 0.25 mg once daily for 5 days), followed by the combination of digoxin (0.25 mg once daily) and edoxaban (60 mg once daily) for 7 days (23 subjects). As a result, C_{max} of digoxin increased by 28% (comparison of the geometric least squares means), but AUC_{tau} was not affected.

Twenty-three (23) healthy adult subjects received edoxaban (60 mg once daily) orally for 7 days, followed by the combination of edoxaban and digoxin (0.25 mg twice daily for 2 days followed by 0.25 mg once daily for 5 days) for 7 days. As a result, C_{max} of edoxaban increased by 16%, but AUC_{tau} was not affected.

4.(ii).A.(5).2 Ketoconazole

(Protocol No.: DU176b-PRT016, Attached document 5.3.3.4-2; Reference data)

In a 2-group, 2-period cross-over study, 40 healthy adult subjects (20 subjects per group) received ketoconazole (400 mg once daily) orally for 7 days plus a single oral dose of edoxaban (60 mg) concomitantly on Day 4 of ketoconazole administration, or plus a single oral dose of edoxaban (60 mg) alone on Day 4 in the 7-day administration period (washout period, 14 days). C_{max} of edoxaban increased by 89%, and $AUC_{0\text{-}inf}$ by 87%, in combination with ketoconazole compared with edoxaban alone. No difference was observed in $t_{1/2}$ between edoxaban in combination with ketoconazole and edoxaban alone. C_{max} and $AUC_{0\text{-}inf}$ of D21-2393 were increased by 56% and 46%, respectively, in concomitant use.

4.(ii).A.(5).3 Quinidine

(Protocol No.: DU176b-U129, Attached document 5.3.3.4-3; Reference data)

In a 2-group, 2-period cross-over study, 42 healthy adult subjects (21 subjects per group) received quinidine (300 mg) orally 3 times daily for 4 days (300 mg once daily on Day 1 and Day 4) plus a single oral dose of edoxaban (60 mg) in combination with quinidine on Day 3 (Method 1), or edoxaban (60 mg) orally once daily for 4 days plus a single oral dose of

quinidine (300 mg) in combination with edoxaban on Day 3 (Method 2) (washout period, 7-10 days). C_{max} of edoxaban was increased by 85%, and AUC_{0-24h} by 77%, in combination with quinidine (Day 3 in Method 1) compared with edoxaban alone (Day 1 of Method 2). No significant difference was observed in $t_{1/2}$ between edoxaban in combination with quinidine and edoxaban alone. C_{max} and AUC_{0-24h} of D21-2393 were also increased by 82% and 72%, respectively, in combination with quinidine. No difference was observed in C_{max} or AUC_{0-24h} of quinidine between quinidine alone (Day 1 of Method 1) and quinidine in combination with edoxaban (Day 3 of Method 2).

4.(ii).A.(5).4 Verapamil

(Protocol No.: DU176b-A-U130, Attached document 5.3.3.4-4; Reference data)

In a 2-group, 2-period cross-over study, 34 healthy adult subjects (17 subjects per group) received verapamil (240 mg) orally once daily for 11 days plus a single oral dose of edoxaban (60 mg) in combination with verapamil on Day 10 (Method 1), or edoxaban (60 mg) orally once daily for 4 days plus a single oral dose of verapamil (240 mg) in combination with edoxaban on Day 3 (Method 2) (washout period, 7 days). C_{max} and AUC_{0-24h} of edoxaban were both increased by 53% in combination with verapamil (Day 10 of Method 1) compared with edoxaban alone (Day 1 of Method 2). No difference was observed in $t_{1/2}$ between edoxaban in combination with verapamil and edoxaban alone. C_{max} and AUC_{0-24h} of D21-2393 were also increased by 28% and 31%, respectively, in combination with verapamil.

In contrast, C_{max} of verapamil was decreased by 15%, and AUC_{0-24h} by 16%, in combination with edoxaban, whereas no change was observed in C_{max} and AUC_{0-24h} of norverapamil.

4.(ii).A.(5).5 Amiodarone

(Protocol No.: DU176b- A-U131, Attached document 5.3.3.4-5; Reference data)

Thirty (30) healthy adult subjects received a single dose of edoxaban (60 mg), followed by once-daily oral administration of amiodarone (400 mg) for 4 days plus a single oral dose of edoxaban (60 mg) concomitantly on Day 4 of amiodarone administration. C_{max} of edoxaban was increased by 66%, and AUC_{0-inf} by 40%, in combination with amiodarone compared with edoxaban alone. No difference was observed in $t_{1/2}$ between edoxaban in combination with amiodarone and edoxaban alone. C_{max} of D21-2393 was increased by 35%, and AUC_{0-inf} by 22%, in combination with amiodarone.

4.(ii).A.(5).6 Erythromycin

(Protocol No.: DU176b- A-U132, Attached document 5.3.3.4-6; Reference data)

In a 2-group, 2-period, cross-over study, 36 healthy adult subjects received erythromycin (500 mg) orally four times daily for 8 days plus a single oral dose of edoxaban (60 mg) in combination with erythromycin on Day 7, or a single oral dose of edoxaban (60 mg) alone (washout period, 7 days). C_{max} of edoxaban was increased by 68%, and AUC_{0-inf} by 85%, in combination with erythromycin compared with edoxaban alone. No difference was observed in $t_{1/2}$ between edoxaban in combination with erythromycin and edoxaban alone. C_{max} of D21-2393 was increased by 75%, and AUC_{0-inf} by 78%, in combination with erythromycin.

4.(ii).A.(5).7 Atorvastatin

(Protocol No.: DU176b- A-U133, Attached document 5.3.3.4-7; Reference data)

In a 2-group, 2-period, cross-over study, 32 healthy adult subjects received atorvastatin (80 mg) orally once daily for 8 days plus a single oral dose of edoxaban (60 mg) in combination with atorvastatin on Day 7, or a single oral dose of edoxaban (60 mg) alone (washout period ≥7 days). C_{max} of edoxaban was decreased by 14% in combination with atorvastatin, whereas neither AUC_{0-inf} nor $t_{1/2}$ was affected. C_{max} of D21-2393 was decreased by 19%, and AUC_{0-inf} by 10%, in combination with atorvastatin.

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

4.(ii).A.(6).1) Studies in healthy adult subjects

a. Single-dose study in Japanese subjects
(Protocol No.: DU176b-01, Attached document 5.3.3.1-1)

Either a placebo or edoxaban (30, 60, 90, 120, 150 mg) was administered orally in a single dose in the fasted state to 60 Japanese healthy adult male subjects (15 subjects in placebo group, 9 subjects each in each edoxaban group). The median time for prolongation of PT and APTT to reach the maximum level was both 1.00 to 2.00 hours, and PT and APTT prolonged with increasing dose. The mean PT exceeded the upper limit of the reference range (14.8 seconds) up to 8 hours after administration in the 30 mg group and up to 12 hours after administration in the 60 to 150 mg groups. The mean APTT exceeded the upper limit of the reference range (40.0 seconds) from 1 to 4 hours after administration in the 30 mg group, up to 12 hours in the 60 to 120 mg groups, and up to 24 hours in the 150 mg group. The difference in PT and APTT from baseline, international normalized ratio for prothrombin time (PT-INR), and anti-factor Xa activity all increased with increasing plasma edoxaban concentration.

b. Multiple-dose study in Japanese subjects
(Protocol No.: DU176b-02, Attached document 5.3.3.1-2)

Eighteen (18) Japanese healthy adult male subjects (9 subjects per group) received a single oral dose of edoxaban (60, 120 mg) in the fed state (Day 1), then edoxaban (60 mg twice daily or 120 mg once daily) orally in the fed state from Day 3 to Day 9, followed by a single oral dose of edoxaban (60, 120 mg) in the fed state (Day 10). Both PT and APTT were shown to have been prolonged upon measurement on Day 1 and Day 10. The median time for prolongation of PT and APTT to reach the maximum level was 1.0 hour after administration both on Day 1 and Day 10 in both dose groups. No clear difference was observed in the extent of PT prolonged or APTT prolonged between Day 1 and Day 10 in either group. Anti-factor Xa activity increased rapidly after administration. The median time for anti-factor Xa activity to reach the maximum level was approximately 1.0 hour after administration both on Day 1 and on Day 10 in the 60 mg group, and 1.0 hour after administration on Day 1 and 2.0 hours after administration on Day 10 in the 120 mg group. No clear difference was observed in the maximum anti-factor Xa activity between Day 1 and Day 10 in either group.

c. Single dose studies in foreign subjects (Protocol Nos.: DU176b-E-PRT003, 176A-PRT005, DU176b-PRT009, Attached document 5.3.4.1-6 to 8; Reference data)

One-hundred (100) Caucasian healthy adult male subjects (20 subjects per group) received a single oral dose of either a placebo or edoxaban (30, 60, 120 mg) in the fasted state, or single-dose subcutaneous administration of fondaparinux (2.5 mg) in the fasted state. Blood samples were collected under conditions where blood coagulation system was activated by application of pressure on the upper arm. TAT, prothrombin fragment F1+2 (F1+2), and β-thromboglobulin (β-TG) decreased to the lowest levels at 1.5 hours after administration of edoxaban, and remained below the baseline even at 12 hours after administration. TAT, F1+2, and β-TG in blood samples decreased gradually over time in the fondaparinux group as well, but the extent of the decrease was smaller compared with edoxaban groups.

Twelve (12) foreign healthy adult subjects received a single dose of edoxaban (60 mg) in the fasted state. *Ex vivo* antithrombotic effect of edoxaban was detectable at 1.5 hours after administration and persisted for 12 hours. Decreased level of intrinsic thrombin production was observed at 1.5 and 5 hours after administration.

Forty (40) foreign elderly healthy subjects (mean age of 67 years, 10 subjects per group) received twice-daily oral doses of edoxaban (60 mg) in the fed state for 4 days, once-daily

subcutaneous administration of dalteparin sodium (dalteparin, 5000 IU) in the fed state for 4 days, twice-daily oral doses of ximelagatran (24 mg) in the fed state for 4 days, or drinking water (250 mL) for 4 days. In the edoxaban group, decreases in TAT, F1+2, and D-dimer were observed compared with the untreated group (drinking water group). In addition, a decrease in the production of intrinsic thrombin was observed from 1.5 hours after administration, with the maximum decrease being observed at 72 hours after administration. In the dalteparin group, a marked decrease in intrinsic thrombin production was observed at 1.5 and 4 hours after the start of administration, but the extent of the decrease was smaller compared with the edoxaban group. In the ximelagatran group and the untreated group, no clear effect was observed on intrinsic thrombin production.

4.(ii).A.(6).2 Thorough QT study
(Protocol No.: DU176b-PRT021, Attached document 5.3.4.1-2)

In a 4-group, 4-period cross-over study, 64 foreign healthy adult subjects (16 subjects per group) received a single oral dose of edoxaban (90, 180 mg), placebo, or moxifloxacin (400 mg, positive control) (washout period, 7 days). Following the administration of edoxaban (90, 180 mg), the median t_{max} of edoxaban was 1.5 and 1.0 hour, respectively, C_{max} was 293.0 ± 134.6 (mean ± SD) and 414.6 ± 197.1 ng/mL, respectively, and $AUC_{0\text{-}inf}$ was 2570.7 ± 686.9 and 4185.3 ± 1119.9 ng·h/mL, respectively. C_{max} of D21-2393 was 21.7 ± 12.0 and 29.7 ± 19.3 ng/mL, respectively, and $AUC_{0\text{-}inf}$ was 190.5 ± 87.3 and 324.3 ± 171.6 ng·h/mL, respectively.

As regards the difference from placebo group in the least squares mean of the change from baseline in QTcI (QTc interval adjusted for the power unique to each subject), the upper limit of the one-sided 95% CI was <4 msec at all timepoints from 0.5 to 48 hours after administration in the edoxaban 90 and 180 mg groups, whereas in the moxifloxacin 400 mg group, the lower limit of the one-sided 95% CI was >5 msec from 1 to 24 hours after administration.

4.(ii).A.(6).3 Drug-drug interactions (effect on bleeding)

a. Aspirin (Protocol Nos.: DU176b-A-U127, DU176b-PRT017, Attached document 5.3.4.1-1, 5.3.4.1-3; Reference data 5.3.4.1-3)

In a 6-group, 3-period cross-over study, 36 foreign healthy adult subjects (6 subjects per group) were treated with the following 3 dosage regimens according to 6 different orders: (i) aspirin (100 mg) and edoxaban (60 mg) were administered orally in combination once daily for 5 days, (ii) aspirin (100 mg) alone was administered orally once daily for 5 days, and (iii) edoxaban (60 mg) alone was administered orally once daily for 5 days (washout period, 17 days). Compared with the bleeding time observed before administration on Day 1, the bleeding time after administration on Day 5 was 2.0 times longer after concomitant use of edoxaban with aspirin, and 1.2 and 1.5 times longer, respectively, after administration of edoxaban or aspirin alone. No difference was observed in C_{max} or $AUC_{0\text{-}inf}$ of edoxaban or D21-2393 between administration of edoxaban alone and combination with aspirin.

In a 2-cohort, 2-period cross-over study, 56 foreign healthy adult subjects were divided into 2 cohorts (28 subjects per cohort). In Cohort 1, aspirin (325 mg) and edoxaban (60 mg) were administered orally in combination once daily for 5 days and aspirin (325 mg) alone was administered orally once daily for 5 days. In Cohort 2, aspirin (325 mg) and edoxaban (60 mg) were administered orally in combination once daily for 5 days and edoxaban (60 mg) alone was administered orally once daily for 5 days (washout period, 14 days). Compared with the bleeding time observed on Day 1, the bleeding time on Day 5 was 1.8 to 2.0 times longer after concomitant use of edoxaban with aspirin, and 1.4 and 1.3 times longer, respectively, after administration of edoxaban or aspirin alone. Edoxaban had no effect on the activity of aspirin to inhibit platelet aggregation. C_{max} of edoxaban was increased by 35%, and AUC_{tau} by 30%, in combination with aspirin.

b. Naproxen (Protocol No.: DU176b-A-U128, Attached document 5.3.4.1-4; Reference data)

In a 6-group, 3-period cross-over study, 34 foreign healthy adult subjects (5 or 6 subjects per group) were treated with the following 3 dosage regimens according to 6 different orders: (i) naproxen (500 mg) was administered orally twice daily for 2 days and edoxaban (60 mg) was concomitantly administered in a single oral dose on Day 2, (ii) naproxen (500 mg) alone was administered orally twice daily for 2 days, and (iii) edoxaban (60 mg) alone was administered in a single dose (washout period ≥14 days). The bleeding time after concomitant use of edoxaban and naproxen was 1.7 times longer than that observed after administration of edoxaban alone. Edoxaban had no effect on the activity of naproxen to inhibit platelet aggregation. C_{max} or $AUC_{0\text{-}inf}$ of edoxaban or D21-2393 was not affected by combination with naproxen.

c. Warfarin (Protocol No.: DU176b-C-U122, Attached document 5.3.4.1-5; Reference data)

Warfarin was administered orally to 63 Caucasian healthy adult subjects (43 subjects in edoxaban group, 20 subjects in placebo group) for 6 to 16 days at a dose to keep PT-INR within the range from 2.0 to 3.0, after which edoxaban (60 mg) or placebo was administered orally once daily for 5 days. PT-INR (arithmetic mean) increased from baseline level of 2.31 to 3.83 at 1 hour after administration of edoxaban and decreased to 1.81, a level similar to that in the placebo group, at 24 hours after administration. C_{max} and $AUC_{0\text{-}inf}$ of edoxaban were 215.8 ng/mL and 1843.4 ng·h/mL, respectively.

4.(ii).A.(6).4) Studies in patients undergoing orthopedic surgery of the lower limbs

a. Study DU176b-04 (Attached document 5.3.5.1-3)

Japanese patients undergoing TKR received once-daily oral doses of edoxaban (5, 15, 30, 60 mg) or placebo for 11 to 14 days. PT, PT-INR, and APTT prolonged with increasing dose, and prolonged significantly at 1 to 3 hours after administration compared with the trough level on Day 7. Median D-dimer and F1+2 tended to decrease with increasing dose of edoxaban at the trough and at 1 to 3 hours after administration on Day 7, and at the trough on the last day of administration. No clear dose response relationship was observed in TAT at any of the timepoints. In all treatment groups, soluble fibrin level increased before postoperative administration compared with the level before operation, but decreased on Day 7 of administration.

b. Study DU176b-B-J209 (Attached document 5.3.5.1-4)

Japanese and Taiwanese patients undergoing THR received once-daily oral doses of edoxaban (15, 30 mg) for 11 to 14 days, or twice-daily subcutaneous administration of enoxaparin (20 mg) for 11 to 14 days. In edoxaban groups, PT, PT-INR, and APTT prolonged with increasing dose at the trough and at 1 to 3 hours after administration on Day 7 and at the trough on the day of the last dose. D-dimer, F1+2, and soluble fibrin decreased to a greater extent in the edoxaban 30 mg group compared with the edoxaban 15 mg group and the enoxaparin group.

c. Study DU176b-B-J302 (Attached document 5.3.5.1-1)

Japanese and Taiwanese patients undergoing TKR received once-daily oral doses of edoxaban (30 mg) for 11 to 14 days, or twice-daily subcutaneous administration of enoxaparin (20 mg) for 11 to 14 days. In the edoxaban group, PT, PT-INR, and APTT remained at similar levels before administration and at the trough on Day 7 and on the day of the last dose. In the enoxaparin group, in contrast, PT, PT-INR, and APTT tended to become shorter after Day 7 of administration. D-dimer, F1+2, TAT, and soluble fibrin levels decreased after the start of administration in both groups.

d. Study DU176b-B-J304 (Attached document 5.3.5.1-2)

Japanese patients undergoing THR received once-daily oral doses of edoxaban (30 mg) for 11 to 14 days, or twice-daily subcutaneous administration of enoxaparin (20 mg) for 11 to 14 days. In the edoxaban group, PT and PT-INR remained at similar levels before administration and at the trough on Day 7 and on the day of the last dose. In the enoxaparin group, in contrast, they tended to become shorter after Day 7 of administration. APTT prolonged slightly after the start of edoxaban administration but shortened slightly in the enoxaparin group. In the edoxaban group, median F1+2 decreased on Day 7 and on the day of the last dose, and median D-dimer, F1+2, TAT, and soluble fibrin levels tended to decrease after the start of administration.

e. Study DU176b-B-J303 (Attached document 5.3.5.1-5)

Japanese patients undergoing HFS received once-daily oral doses of edoxaban (30 mg) for 11 to 14 days, or twice-daily subcutaneous administration of enoxaparin (20 mg) for 11 to 14 days. In the edoxaban group, PT, PT-INR, and APTT levels were similar before the start of administration and at the trough on Day 7 and on the day of the last dose, while they prolonged at 1 to 3 hours after administration on Day 7. Median D-dimer, F1+2, TAT, and soluble fibrin levels decreased after the trough on Day 7, compared with the level before the start of administration following the operation.

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

4.(ii).B.(1) Ethnic differences in pharmacokinetics

The applicant explained the ethnic differences in the pharmacokinetics of edoxaban as follows:
Pharmacokinetic parameter values in multiple oral doses of edoxaban (60 mg once daily on Day 1 and Day 10, twice daily from Day 3 to Day 9) were similar between Japanese healthy adult male and Chinese healthy adult male subjects. In contrast, in the single-dose study in Japanese and Caucasian healthy adult subjects, C_{max} and AUC were higher in Japanese subjects than in Caucasian subjects within the dose range from 60 to 120 mg. In the PPK analysis, ethnicity (Asians including Japanese, Caucasians) was selected as a covariate for total body clearance. As a result, it was estimated that the total body clearance of Asians including Japanese was 25% smaller compared with Caucasians.

PMDA's view on the ethnic differences in pharmacokinetics is as follows:
Before conducting, as global clinical studies in Japan and Taiwan, the phase II study in patients undergoing THR and the phase III study in patients undergoing TKR, the applicant conducted the phase I study in Chinese subjects and compared the pharmacokinetics between Chinese and Japanese subjects. As far as the results of the study are concerned, there are no differences in pharmacokinetics that would deny the validity of handling the above clinical studies as the global clinical studies in Japan and Taiwan.

4.(ii).B.(2) Appropriateness of dose reduction in patients with renal impairment or in concomitant use with P-gp inhibitor

The "Precautions for Dosage and Administration" section in the proposed package insert sets cut-off level of CL_{CR} for consideration of dose reduction at 50 mL/min, since in patients with renal impairment, blood edoxaban concentration increases, leading to an increased risk of bleeding. PMDA asked the applicant to explain the reason for setting this cut-off level and then determine the necessity of raising cautions to give consideration to dose reduction when using edoxaban in combination with P-gp inhibitors, because P-gp inhibitors increase the AUC of edoxaban to an extent similar to that in patients with moderate to severe renal impairment.

The applicant explained as follows:
In the combined analysis of studies in patients undergoing orthopedic surgery of the lower limbs conducted in Japan and in Taiwan, the incidence of major bleeding or clinically

relevant non-major bleeding in patients with CL_{CR} <50 mL/min was more than 2 times that in patients with CL_{CR} ≥50 mL/min and also exceeded 2 times the incidence in the entire edoxaban 30 mg group. Therefore, CL_{CR} of 50 mL/min was determined as the cut-off value for renal function for considering dose reduction. As regards $AUC_{0\text{-}24h,\ ss}$, $C_{max,\ ss}$ and $C_{min,\ ss}$ calculated based on PPK parameters and empirical Bayes estimate, the ratios of these values after once-daily administration of edoxaban (15 mg) to patients with CL_{CR} <50 mL/min to those after once-daily administration of edoxaban (30 mg) to patients with CL_{CR} ≥50 mL/min were 0.66, 0.60, and 0.81, respectively. From the point of view of safety, since the ratios of these parameter values do not exceed 1, it is unlikely that bleeding risk would be higher when edoxaban 15 mg is administered once daily to patients with CL_{CR} <50 mL/min compared with when edoxaban 30 mg is administered once daily to patients with CL_{CR} ≥50 mL/min. From the point of view of efficacy, since the ratios of these parameter values exceed 0.5, it is ensured that the exposure level achieved by once daily administration of edoxaban 15 mg to patients with CL_{CR} <50 mL/min is equal to, or higher than, the level achieved by once-daily administration of edoxaban 15 mg to patients with CL_{CR} ≥50 mL/min. In the phase II study in Japanese patients undergoing TKR (Japanese TKR phase II study), when edoxaban (15 mg) was administered once daily, a significant decrease in VTE was observed compared with the placebo group. From the results obtained from the phase II study in Japanese and Taiwanese patients undergoing THR (Japanese and Taiwanese THR phase II study), edoxaban is expected to be as effective as enoxaparin, suggesting sufficient efficacy. In the study in Japanese and Taiwanese patients undergoing orthopedic surgery of the lower limbs, the incidence of major bleeding or clinically relevant non-major bleeding did not clearly increase in patients to whom edoxaban was administered in combination with a P-gp inhibitor. Also based on the results of the plasma edoxaban concentration after concomitant use of edoxaban with the P-gp inhibitor, the incidence of major bleeding or clinically relevant non-major bleeding is expected to be within the clinically acceptable range. Therefore, the applicant considered that, instead of encouraging dose reduction, raising caution for concomitant use is appropriate for patients in whom concomitant use of a P-gp inhibitor is required.

As a reason for giving consideration to dose reduction in patients with CL_{CR} <50 mL/min, the applicant points out not only the elevated plasma edoxaban concentration but also the increase in the incidence of bleeding events in these patients. On the other hand, as the reason for denying the necessity for considering dose reduction in concomitant use of edoxaban with a P-gp inhibitor, a drug which causes an increase in plasma edoxaban concentration to a level similar to that observed in patients with renal impairment, the applicant indicated that the incidence of bleeding events did not clearly increase. Thus, the necessity of dose reduction is not determined solely based on the exposure level. Therefore, PMDA considered it difficult to judge that, based on the discussion of the exposure level alone, edoxaban can be administered at a reduced dose to patients with CL_{CR} <30 mL/min, a patient group in whom there has been little experience of edoxaban administration in clinical studies. PMDA asked the applicant to reconsider the appropriateness of edoxaban administration to patients with CL_{CR} <30 mL/min (including patients on haemodialysis), and then re-examine the necessity of providing appropriate cautions if administration is considered feasible.

The applicant explained as follows:
In the European pharmacokinetics study in patients with renal impairment, there was no significant difference in AUC or C_{max} between subjects with CL_{CR} <30 mL/min who received a single oral dose of edoxaban (15 mg) and subjects with CL_{CR} ≥30 and <50 mL/min. However, $t_{1/2}$ prolongation and increased plasma edoxaban concentration at 24 hours after administration were observed in the subjects with CL_{CR} <30 mL/min. $C_{min,\ ss}$ at steady state, calculated from empirical Bayes estimate based on the final model of PPK analysis, in patients with severe renal impairment was approximately twice the level observed when edoxaban (15 mg) was

administered orally to patients with mild renal impairment (50 mL/min ≤ CL_{CR} ≤80 mL/min). Next, using data obtained from 2 phase II studies, a Japanese TKR phase II study and a Japanese and Taiwanese THR phase II study, a logistic regression analysis was performed using the number of bleeding events (major bleeding, clinically relevant non-major bleeding, and minor bleeding) as the objective variable and $AUC_{0\text{-}24h,\,ss}$, $C_{max,\,ss}$ or $C_{min,\,ss}$, calculated from the empirical Bayes estimate based on the final model of PPK analysis, as the explanatory variables. As a result, it was estimated that the incidence of bleeding events would increase with the increase of these pharmacokinetic parameter values. Therefore, a dose reduction of edoxaban is necessary to decrease the bleeding risk in patients with severe renal impairment. From the aspect of the exposure level, if the dose of edoxaban is reduced, it would necessarily be not infeasible to administer edoxaban to patients with severe renal impairment. However, since there is limited clinical experience in these patients, it is necessary to carefully determine the appropriateness of administration by evaluating the risks of VTE and bleeding, and edoxaban should be administered at a reduced dose only if the benefits of administering edoxaban outweighs the risks. As regards patients on hemodialysis, since no clinical study has been conducted in this patient group, it is difficult to propose a recommended dosage and administration. Therefore, information will be provided to the medical practice that edoxaban has not been used in patients on haemodialysis and the dosage regimen in these patients have not been established. As for concomitant use of edoxaban with a P-gp inhibitor, the incidence of bleeding events, including minor bleeding, in the edoxaban 30 mg group was 20.9% (185 of 887 subjects) in subjects who received edoxaban without a P-gp inhibitor and 41.2% (7 of 17 subjects) in subjects who received edoxaban with a P-gp inhibitor, showing a higher incidence in those receiving the concomitant use, albeit small in number of subjects studied. Given that the incidence of bleeding events increases with increasing exposure level of edoxaban and that C_{max} and AUC increase approximately 1.4- to 1.9-fold in concomitant use of edoxaban with a P-gp inhibitor, it is expected that concomitant use of edoxaban with a P-gp inhibitor would increase the bleeding risk. Therefore, it is necessary to caution that dose reduction should be considered. For the above reasons, the caution "a dose reduction of edoxaban should preferably be considered when a P-gp inhibitor is concomitantly administered" will be added to the "Precautions for Concomitant Use" section.

PMDA considers as follows:
From the aspect of increase in the exposure level, it is understandable to raise caution to give consideration to a dose reduction of edoxaban in patients with decreased renal function and in concomitant use of edoxaban with a P-gp inhibitor. Based on the efficacy and safety evaluated in patients with decreased kidney function, an appropriate method of raising caution will be discussed in "4.(iii).B.(7).1) Patients with renal impairment". Regarding the appropriateness of the method of raising caution to consider dose reduction in concomitant use of edoxaban with a P-gp inhibitor, and regarding the appropriateness of not including, in drugs requiring precautions for concomitant use, amiodarone which increases the C_{max} of edoxaban by 66% and $AUC_{0\text{-}inf}$ by 40% in combination with edoxaban, a final decision will be made taking account of comments raised in the Expert Discussion. The appropriateness of administering edoxaban to patients with CL_{CR} <30 mL/min, a patient group for whom there are only extremely limited use experiences in clinical studies, should be judged carefully. The range of the renal impairment allowing edoxaban administration, the appropriateness of dose administered to patients with decreased kidney function, and the details of caution to be raised will be discussed in "4.(iii).B.(7).1) Patients with renal impairment" and a final decision will be made, also taking account of comments raised in the Expert Discussion.

4.(ii).B.(3) Appropriateness of PPK analysis
The applicant provided discussion on patients requiring edoxaban dose reduction using the results of PPK analysis. In addition, the PPK analysis may possibly reveal the pharmacokinetics

of Japanese patients treatable with edoxaban. Therefore, PMDA conducted the following evaluation on the validity of the PPK analysis.

In the PPK analysis, CL_{CR} and the type of subjects (patients or healthy individuals) were selected as covariates for CL/F and Vc/F of edoxaban. PMDA asked the applicant to explain the possibility that the results of the analysis may have been affected by the facts that among subjects enrolled in phase I studies, patients with decreased kidney function and the elderly were all Caucasian while patients undergoing orthopedic surgery of the lower limbs were all Japanese.

The applicant explained as follows:
The scatter diagram of the empirical Bayes estimate of the pharmacokinetic parameters based on the final model of PPK analysis and the subject background characteristics showed that CL/F tended to be lower in subjects with low CL_{CR}, regardless of the ethnicity. Vc/F tended to be lower in subjects with low body weight regardless of the ethnicity and, among Japanese subjects with the same body weight, Vc/F tended to be lower in patients than in healthy adult subjects. ka tended to be lower in patients than in healthy adult subjects among Japanese and Chinese, while ka in healthy adult subjects was not different among all the ethnicities. Based on the above, the applicant considers that the effect of CL_{CR} on CL/F and the effect of the population (patients undergoing orthopedic surgery of the lower limbs vs. healthy adult subjects) on Vc/F appropriately reflect the data of Japanese subjects. Table 5 shows the parameters estimated by the final model in PPK analysis, using only Japanese data. Results were almost identical with those obtained from the data set including Caucasian and Chinese data.

Table 5. Population parameter values estimated using each data set

Population parameter	Japanese data		Combined Japanese, Chinese, and Caucasian data	
	Estimate	Relative standard error (%)	Estimate	Relative standard error (%)
CL/F (L/h)	38.7	4.3	37.7	2.4
Vc/F (L)	180	4.5	175	3.3
Q/F (L/h)	12.0	9.2	10.6	6.1
Vp/F (L)	116	10.6	112	4.8
ka (1/h)	1.92	12.2	1.63	6.5
CL/F-CLCR	0.497	8.4	0.437	7.0
CL/F-Asian Race	-0.284 (fixed)	-	-0.284	7.9
Vc/F-WT	0.923	16.7	0.950	11.9
Vc/F-Population	-0.344	18.4	-0.269	16.4
ka-Population	-1.18	10.6	-0.960	8.1
F1-Food	0.243	20.4	0.227	14.7
ω2 CL/F	0.0764	13.4	0.068	10.6
ω2 Vc/F	0.0872	21.8	0.134	10.8
ω2 Q/F	0.0889	87.7	0.095	39.2
ω2 Vp/F	0.100	40.0	0.102	15.1
ω2 ka	0.846	19.4	0.880	10.4
σ2	0.0898	6.4	0.076	4.3

Using only the Japanese data, the effect of each of the background factors selected as covariates in the final model of the entire population on each pharmacokinetic parameter was investigated by backward elimination method. Results showed that the effects of all background factors were

also statistically significant.
From these results, the applicant considers that the effect of CL_{CR} on CL/F and the effect of the population on Vc/F appropriately reflect the data of Japanese subjects.

PMDA asked the applicant to explain the reason for the higher estimate of $C_{max, ss}$ in healthy adult subjects despite the fact that Vc/F is lower in patients undergoing orthopedic surgery of the lower limbs than in healthy adult subjects, according to the population mean parameter values.

The applicant explained as follows:
The population is a covariate not only for Vc/F but also for ka. As shown in the last model equation for population parameters and in the population mean parameters, in patients undergoing orthopedic surgery of the lower limbs, Vc/F was 23.6% lower than in healthy adult subjects, but ka was lower by as much as 61.7%, resulting in a higher $C_{max, ss}$ estimate in healthy adult subjects than in patients. Table 6 shows $AUC_{0\text{-}24h}$, C_{max} and C_{min} at steady state estimated for each of the background factors that were covariates for the final population mean parameters.

Table 6. Effect of covariates on pharmacokinetic parameter values at steady state

Covariate		$AUC_{0\text{-}24h, ss}$ (ng·h/mL)	$C_{max, ss}$ (ng/mL)	$C_{min, ss}$ (ng/mL)
Base case [a)]		1410	163.7	12.9
Population	Healthy	1410	177.9	14.3
Meal	Fasted	1124	130.5	10.3
Ethnicity	Caucasian	1061	146.1	6.8
Weight	40 kg	1410	201.3	10.8
	80 kg	1410	140.9	15.4
CL_{CR}	30 mL/min	2164	196.8	31.4
	120 mL/min	1181	152.5	8.7

a: Asian patients undergoing orthopedic surgery of the lower limbs, CL_{CR} 80 mL/min, weight 60 kg, fed administration

PMDA considers as follows:
In this analysis, the population was chosen as a significant covariate. However, since Caucasians were not included in patients undergoing orthopedic surgery of the lower limbs, it is difficult to determine whether the observed difference was due to the health conditions (patients or healthy adult subjects) or to the ethnicity. Although the effect of each covariate of the final model on the pharmacokinetic parameters was investigated using only Japanese data and all effects were confirmed to be statistically significant, the estimated parameter values are not necessarily identical to those estimated from the data of the entire population. The absorption rate and the apparent distribution volume differ between patients undergoing orthopedic surgery of the lower limbs and healthy adults. However, Table 6 shows similar AUC values in the 2 subject groups. Therefore, it is questionable whether or not the quantitative population parameter values obtained in the PPK analysis are appropriate indices showing the difference between Japanese patients undergoing orthopedic surgery of the lower limbs and healthy adult subjects. Nevertheless, according to the scatter diagram presented by the applicant, Japanese patients undergoing orthopedic surgery of the lower limbs included patients with decreased kidney function, the estimated blood edoxaban concentrations in Japanese subjects were in good agreement with observed values, and the results of the PPK analysis using the data of Japanese subjects only were not inconsistent with those of the entire population. Therefore, PMDA has concluded that it is appropriate to estimate plasma edoxaban concentration in Japanese patients undergoing orthopedic surgery of the lower limbs studied in the clinical

studies, based on the results of PPK analysis, and to investigate the relationship between pharmacokinetics and efficacy or safety.

4.(iii) Summary of clinical efficacy and safety

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

As the evaluation data, the results from 9 pharmacokinetic and clinical pharmacology studies (3 Japanese studies, 6 foreign studies) and 5 phase II and phase III studies (3 Japanese studies, 2 Japanese and Taiwanese studies) were submitted [see "4.(i). Summary of biopharmaceutic studies and associated analytical methods" and "4.(ii) Summary of clinical pharmacology studies" for BE and pharmacokinetics].

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

4.(iii).A.(1).1) Japanese single-dose study

(Protocol No.: DU176b-01, Attached document 5.3.3.1-1 [[redacted] 20[redacted]])

In order to investigate the safety, pharmacokinetics, pharmacodynamics, etc., of edoxaban administered orally in a single dose to Japanese and Caucasian subjects, a randomized, single-blind, comparative study was conducted in 96 healthy adult male subjects (60 Japanese, 36 Caucasians). In the study, edoxaban (30, 60, 90, 120, or 150 mg in Japanese subjects; 60, 90, or 120 mg in Caucasian subjects) or placebo was administered orally in a single dose to the subjects in the fasted state (9 subjects in each edoxaban group, 3 subjects in the placebo group). In the Japanese 60 mg group, a fed administration group was also studied by cross-over method. No subjects discontinued the study.

The incidence of adverse events in Japanese subjects was 22.2% (2 of 9 subjects) in the 30 mg group, 11.1% (1 of 9 subjects) in the 60 mg (fasted administration) group, 11.1% (1 of 9 subjects) in the 60 mg (fed administration) group, 11.1% (1 of 9 subjects) in the 90 mg group, 0% (0 of 9 subjects) in the 120 mg group, 11.1% (1 of 9 subjects) in the 150 mg group, and 20.0% (3 of 15 subjects) in the placebo (fasted administration) group. The incidence of adverse events in Caucasian subjects was 22.2% (2 of 9 subjects) in the 60 mg group, 11.1% (1 of 9 subjects) in the 90 mg group, 11.1% (1 of 9 subjects) in the 120 mg group, and 22.2% (2 of 9 subjects) in the placebo group. The adverse event reported by ≥2 subjects in any group was white blood cell count decreased (2 events in 2 subjects) in the Japanese 30 mg group, which was non-serious in both subjects.

4.(iii).A.(1).2) Japanese multiple-dose study

(Protocol No.: DU176b-02, Attached document 5.3.3.1-2 [[redacted] 20[redacted]])

In order to investigate the safety, tolerability, pharmacokinetics, and pharmacodynamics of edoxaban administered orally in multiple doses, a randomized, single-blind, comparative study was conducted in 24 Japanese healthy adult male subjects (9 subjects in the edoxaban group and 3 subjects in the placebo group in each step). In Step 1, edoxaban (60 mg) or placebo was administered once in the morning on Day 1 and Day 10, and twice in the morning and in the evening from Day 3 to Day 9. In Step 2, edoxaban (120 mg) or placebo was administered once in the morning on Day 1 and on Day 3 through Day 10 (8-day consecutive administration). No subjects discontinued the study.

An adverse event (abdominal pain) was observed in 1 subject in the group receiving the placebo in both steps.

4.(iii).A.(1).3) Chinese multiple-dose study (Protocol No.: DU176b-01, Attached document 5.3.3.1-3 [[redacted] 20[redacted] to [redacted] 20[redacted]])

In order to investigate the safety, tolerability, and pharmacokinetics of edoxaban administered orally in multiple doses, a randomized, single-blind, parallel-group, comparative study was

conducted in 11 Chinese healthy adult male subjects (ratio of assignment of edoxaban and placebo, 3:1). No subjects discontinued the study.

Edoxaban (60 mg) or placebo was administered in the fed state once in the morning on Day 1, twice daily at 12-hour interval on Day 3 to Day 9, and once in the morning on Day 10.

Adverse events observed were 1 event in 1 subject of the placebo group and 14 events in 4 subjects of the edoxaban group. Adverse events reported by ≥2 subjects in any group were somnolence (1 of 3 subjects in the placebo group, 2 of 8 subjects in the edoxaban group) and chest pain (0 of 3 subjects in the placebo group, 2 of 8 subjects in the edoxaban group). No serious adverse events were observed.

4.(iii).A.(1).4) Food effect study in Japanese subjects (Protocol No.: DU176b-A-J135, Attached document 5.3.1.1-1 [[redacted] to [redacted] 20[redacted]])

In order to investigate the pharmacokinetics of edoxaban and its active metabolite D21-2393 and effect of food on the pharmacokinetics of edoxaban 30 mg tablet administered orally in a single dose, a randomized, open-label, 2-group, 2-period cross-over, comparative study was conducted in 34 Japanese healthy adult male subjects (washout period 5-7 days). No subjects discontinued the study.

Adverse events were observed in 1 subject in the fasted administration group (nasopharyngitis) and in 5 subjects in the fed administration group (occult blood positive in 4 subjects, ALT increased in 1 subject). No serious adverse events were observed.

4.(iii).A.(1).5) Single-dose study on ^{14}C-labeled edoxaban solution (Protocol No.: DU176b-PRT019, Attached document 5.3.3.1-4 [[redacted] to [redacted] 20[redacted]])

An open-label study was conducted in 6 foreign healthy adult male subjects. In the study, ^{14}C-labeled edoxaban (2.2 MBq [0.57 mSv], 60 mg) was administered orally in a single dose to investigate the pharmacokinetics of edoxaban and its metabolites. No subjects discontinued the study.

Adverse events observed were 8 events in 3 subjects. The adverse event reported by ≥2 subjects was abdominal pain (2 subjects). There were no serious adverse events.

4.(iii).A.(1).6) Drug interaction study with aspirin (Protocol No.: DU176b-A-U127, Attached document 5.3.4.1-1 [[redacted] to [redacted] 20[redacted]])

In order to investigate the effect of concomitant use of edoxaban with a low dose aspirin on bleeding time, pharmacokinetics, safety, etc., a randomized, open-label, 6-group, 3-period cross-over, comparative study was conducted in 36 foreign healthy adult male and female subjects (6 subjects per group). In each group, aspirin 100 mg and edoxaban 60 mg (A), edoxaban 60 mg (B), or aspirin 100 mg (C) was administered once daily for 5 days in 6 different orders (washout period, 17 days). Two subjects discontinued the study. One subject was withdrawn from the study because of increased ALT, AST, and creatinine kinase (CK) observed 1 day before the start of administration in the third period in the ACB order. The other subject withdrew informed consent 1 day before the start of administration in the second period in the BAC order, and was removed from the study accordingly.

The incidence of adverse events was 17.6% (6 of 34 subjects) during treatment with aspirin and edoxaban, 22.9% (8 of 35 subjects) during treatment with edoxaban alone, and 20.0% (7 of 35 subjects) during treatment with aspirin alone. Adverse events reported by ≥2 subjects during any of the treatments were headache (3 subjects during treatment with aspirin and edoxaban, 2 subjects during treatment with edoxaban alone, and 1 subject during treatment with aspirin

alone) and pruritus (2 subjects, 3 subjects, 0 subjects). There were no serious adverse events.

4.(iii).A.(1).7) Thorough QTc study (Protocol No.: DU176b-PRT021, Attached document 5.3.4.1-2 [[redacted] to [redacted] 20[redacted]])

A randomized, 4-group, 4-period, cross-over, comparative study was conducted in 64 foreign healthy adult male and female subjects (16 subjects per group) to investigate QTc interval when a single dose administration of edoxaban (90, 180 mg) resulted in a plasma exposure level reaching or exceeding the clinically expected level, and to evaluate the safety and tolerability. Moxifloxacin 400 mg was used as the positive control. Edoxaban 90 mg (A), edoxaban 180 mg (B), placebo (C), or moxifloxacin 400 mg (D) was administered in the order of ABDC (Group 1), BCAD (Group 2), DACB (Group 3), or CDBA (Group 4). Each study drug was administered orally in a single dose with a washout period of 7 days. Each dose of edoxaban and placebo was administered under blinded conditions, whereas moxifloxacin was administered under non-blinded conditions. Three subjects discontinued the study. One subject (Group 3) withdrew informed consent after administration in period B. Another subject (Group 4) was withdrawn from the study because amphetamine was detected before administration in the period B. Still another subject (Group 4) was withdrawn from the study because of the difficulty in vascular access before administration in the period D.

The incidence of adverse events was 33.9% (21 of 62 subjects) after edoxaban 90 mg administration, 29.0% (18 of 62 subjects) after edoxaban 180 mg administration, 31.7% (20 of 63 subjects) after moxifloxacin administration, and 25.0% (16 of 64 subjects) after placebo administration.

4.(iii).A.(1).8) Pharmacokinetics in the elderly and postmenopausal female subjects (Protocol No.: DU176-E-PRT002, Attached document 5.3.3.3-1 [[redacted] to [redacted] 20[redacted]])

A placebo-controlled, randomized, single-blind, parallel-group, comparative study was conducted in 24 subjects (12 each of elderly male and female subjects) to investigate the safety, tolerability, pharmacokinetics, pharmacodynamics, etc., of edoxaban administered in multiple doses to foreign postmenopausal or sterilized female subjects and to foreign elderly male subjects. Edoxaban (90 mg) or placebo was administered once daily in the morning on Day 1 and on Day 3 through Day 10 (8-day consecutive administration).

The incidence of adverse events was 88.9% (8 of 9 subjects) in both elderly male and elderly female subjects of the edoxaban group and 100.0% (3 of 3 subjects) in both elderly male and elderly female subjects of the placebo group. Adverse events reported by ≥2 subjects in any group were nasopharyngitis (4 elderly male subjects in the edoxaban group, 1 elderly male subject in the placebo group, 0 postmenopausal female subject in the edoxaban group, 0 postmenopausal female subject in the placebo group), headache (5 subjects, 1 subject, 2 subjects, 3 subjects), cough (3 subjects, 0 subject, 0 subject, 0 subject), pharyngolaryngeal pain (2 subjects, 0 subject, 0 subject, 0 subject), dry mouth (2 subjects, 2 subjects, 1 subject, 1 subject), gingival bleeding (0 subject, 0 subject, 2 subjects, 0 subject), nausea (0 subject, 0 subject, 2 subjects, 1 subject), hyperhidrosis (2 subjects, 0 subject, 0 subject, 0 subject), back pain (2 subjects, 0 subject, 2 subjects, 0 subject), and myalgia (1 subject, 0 subject, 2 subjects, 1 subject). There were no serious adverse events.

4.(iii).A.(1).9) Pharmacokinetics in European patients with renal impairment (Protocol No.: DU176b-A-U120, Attached document 5.3.3.3-2 [[redacted] to [redacted] 20[redacted]])

An open-label study was conducted in 40 subjects (8 each of healthy adult subjects, subjects with mild renal impairment, subjects with moderate renal impairment, subjects with severe renal impairment, and patients with end-stage renal failure receiving peritoneal dialysis) with the main objectives of investigating the pharmacokinetics of edoxaban in subjects with various degree of renal function and of investigating the effect of peritoneal dialysis on the pharmacokinetics of

edoxaban. Edoxaban (15 mg) was administered in a single dose. No subjects discontinued the study.
The incidence of adverse events was 12.5% (1 of 8 subjects) in healthy adult subjects, 50.0% (4 of 8 subjects) in subjects with mild renal impairment, 75.0% (6 of 8 subjects) in subjects with moderate renal impairment, 37.5% (3 of 8 subjects) in subjects with severe renal impairment, and 100% (8 of 8 subjects) in patients with end-stage renal failure receiving peritoneal dialysis. Adverse events reported by ≥2 subjects in any group were PT-INR increased (0 healthy adult subject, 1 subject with mild renal impairment, 2 subjects with moderate renal impairment, 2 subjects with sever renal impairment, 6 patients with end-stage renal failure receiving peritoneal dialysis), PT prolonged (0 subject, 1 subject, 2 subjects, 2 subjects, 5 subjects, respectively), APTT prolonged (0 subject, 1 subject, 4 subjects, 1 subject, 1 subject, respectively), and blood lactate dehydrogenase (LDH) increased (0 subject, 0 subject, 2 subjects, 0 subject, 2 subjects, respectively). There were no serious adverse events.

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

4.(iii).A.(2).1) Late phase II study in Japanese patients undergoing TKR (Protocol No.: DU176b-B-J303, Attached document 5.3.5.1-3 [[redacted] to [redacted]])

In order to investigate the dose response of prophylactic effect (efficacy) of edoxaban against deep vein thrombosis (DVT) and pulmonary embolism (PE) and the safety, a randomized, double-blind, parallel-group, comparative study was conducted in a total of 63 study sites in Japan. In the study, edoxaban (5, 15, 30, 60 mg) or placebo was administered orally once daily for 11 to 14 days to Japanese patients undergoing TKR (target sample size; 100 subjects per group, 500 subjects in total).

Patients undergoing first-time unilateral TKR, aged 20 to 84 years, were enrolled in the study. Exclusion criteria were “serum creatinine >1.5 mg/dL”, “AST (GOT) or ALT (GPT) ≥2 times the upper limit of the reference range established by the study site”, and “total bilirubin ≥1.5 times the upper limit of the reference range established by the study site”, among others. From the day of surgery until the end of the study drug administration, or until 1 day (24 hours) after discontinuation, use of antithrombotic drugs (anticoagulants, antiplatelet agents, thrombolytic agents) and other drugs that affect thrombus formation was prohibited. In patients who had undergone epidural anesthesia before the start of the study, the indwelling catheter was to be removed at least 2 hours before the administration of the study drug. During the treatment with the study drug, the use of postoperative epidural anesthesia was prohibited.

Administration of the study drug was to be started at 6 to 24 hours after surgery and, from the next day, the drug was to be taken in the morning as a general rule.

Of 523 randomized subjects, 520 subjects receiving the study drug (102 subjects in the placebo group, 103 subjects in the edoxaban 5 mg group, 106 subjects in the edoxaban 15 mg group, 103 subjects in the edoxaban 30 mg group, 106 subjects in the edoxaban 60 mg group) were included in the safety analysis. Of these, 445 subjects (89 subjects, 88 subjects, 92 subjects, 88 subjects, 88 subjects), excluding 75 subjects (venogram uninterpretable [33], bilateral venogram not performed [18], venogram not performed because of study discontinuation [24]), were included in the full analysis set (FAS), which was the efficacy analysis population.

The primary efficacy endpoint was the percentage of subjects with at least one of the following venous thromboembolic events (VTE) from the start of the study drug administration until the venography at the end of the study drug administration (the incidence of VTE): “asymptomatic DVT (evaluated by the venogram of both lower limbs at the end of the study drug administration)”, “confirmed symptomatic PE”, and “symptomatic DVT confirmed before the

prescribed venography". As the final assessment, the Thromboembolic Event Assessment Committee independent of the sponsor, the investigator, and the coordinating investigator evaluated, under blinded conditions, VTE based on the copies of the test results (e.g., films) collected from each medical institution. The incidence of VTE was 48.3% (43 of 89 subjects) in the placebo group, 29.5% (26 of 88 subjects) in the edoxaban 5 mg group, 26.1% (24 of 92 subjects) in the edoxaban 15 mg group, 12.5% (11 of 88 subjects) in the edoxaban 30 mg group, and 9.1% (8 of 88 subjects) in the edoxaban 60 mg group, showing a dose-response ($P < 0.001$, Cochran-Armitage test, one-sided significance level of 0.025). By assuming that the incidence of VTE monotonically decreased with increasing edoxaban, the incidence of VTE was compared between the placebo group and each edoxaban group by the Shirley-Williams method. As a result, a significant difference was observed in all comparisons ($P \leq 0.005$, one-sided significance level of 0.025 for all comparisons).

Symptomatic PE did not occur in any of the groups, whereas symptomatic DVT was observed in 1 subject in the edoxaban 5 mg group. The incidence of proximal DVT was 4.5% (4 of 89 subjects) in the placebo group, 0.0% (0 of 88 subjects) in the edoxaban 5 mg group, 0.0% (0 of 92 subjects) in the edoxaban 15 mg group, 1.1% (1 of 88 subjects) in the edoxaban 30 mg group, and 1.1% (1 of 88 subjects) in the edoxaban 60 mg group.

As regards safety, "major bleeding" was defined as any of the following bleeding events: "fatal bleeding", "clinically overt bleeding accompanied by a decrease in haemoglobin >2 g/dL", "clinically overt bleeding requiring transfusion >4 units (except autotransfusion of predeposited blood)", "retroperitoneal haemorrhage, intracranial haemorrhage, intraocular haemorrhage, or intrathecal haemorrhage", and "bleeding requiring reoperation". "Clinically relevant non-major bleeding" was defined as any of the following bleeding events that are not classified as major bleeding: "haematoma with a long axis ≥5 cm", "epistaxis or gingival bleeding that is not caused by an extrinsic factor and persists for ≥5 minutes", "bleeding of digestive tract", "frank haematuria that does not disappear even after 24 hours", and "other bleeding that is judged by the investigator or the subinvestigator as clinically significant". "Minor bleeding" was defined as all bleeding events that are not classified either as major bleeding or clinically relevant non-major bleeding. The validity of the judgment of bleeding events reported were re-evaluated under blinded conditions by the Bleeding Event Assessment Committee independent of the sponsor, the investigator, and the coordinating investigator, and the re-evaluation by the committee under blinded conditions was handled as the final one. By taking into account the pharmacological effect of edoxaban, bleeding events that occurred during the period from Day 1 of administration until the next day of the last dose were subjected to calculation of the incidence of the events.

The incidence of major bleeding was 0.0% (0 of 102 subjects) in the placebo group, 0.0% (0 of 103 subjects) in the edoxaban 5 mg group, 0.0% (0 of 106 subjects) in the edoxaban 15 mg group, 0.0% (0 of 103 subjects) in the edoxaban 30 mg group, and 0.9% (1 of 106 subjects, wound haemorrhage) in the edoxaban 60 mg group. The incidence of clinically relevant non-major bleeding was 3.9% (4 of 102 subjects) in the placebo group, 2.9% (3 of 103 subjects) in the edoxaban 5 mg group, 3.8% (4 of 106 subjects) in the edoxaban 15 mg group, 3.9% (4 of 103 subjects) in the 30 mg edoxaban group, and 3.8% (4 of 106 subjects) in the edoxaban 60 mg group. The incidence of all bleeding events was 9.8% (10 of 102 subjects) in the placebo group, 10.7% (11 of 103 subjects) in the edoxaban 5 mg group, 18.9% (20 of 106) in the edoxaban 15 mg group, 19.4% (20 of 103 subjects) in the edoxaban 30 mg group, and 24.5% (26 of 106 subjects) in the edoxaban 60 mg group.

The incidence of all adverse events was 65.7% (67 of 102 subjects) in the placebo group, 75.7% (78 of 103 subjects) in the edoxaban 5 mg group, 80.2% (85 of 106 subjects) in the edoxaban

15 mg group, 75.7% (78 of 103 subjects) in the edoxaban 30 mg group, and 74.5% (79 of 106 subjects) in the edoxaban 60 mg group. Adverse events with an incidence ≥5% in any edoxaban group were nasopharyngitis, insomnia, headache, wound haemorrhage, constipation, diarrhoea, dermatitis contact, erythema, haemorrhage subcutaneous, pruritus, haematuria, ALT increased, AST increased, blood LDH increased, γ-GTP increased, blood urine present, haemoglobin decreased, platelet count increased, and blood alkaline phosphatase (ALP) increased.

Serious adverse events occurred in 5 subjects in the placebo group (tibia fracture, rectal haemorrhage, vertigo positional, ligament rupture, platelet count decreased), in 2 subjects in the edoxaban 5 mg group (pyrexia, compression fracture), in 1 subject in the edoxaban 15 mg group (spinal compression fracture), in 1 subject in the edoxaban 30 mg group (myocardial infarction), and 3 subjects in the edoxaban 60 mg group (nasopharyngitis, joint dislocation, asthma). A causal relationship with the study drug was ruled out except for platelet count decreased in the placebo group and for asthma in the edoxaban 60 mg group.

Adverse events resulting in study discontinuation occurred in 2 subjects in the placebo group (anaemia postoperative/haemarthrosis, haemorrhage subcutaneous/anaemia), 7 subjects in the edoxaban 5 mg group (sciatica, nausea, ligament rupture, DVT, haematuria, ALT increased, gastritis), 4 subjects in the edoxaban 15 mg group (palpitations, haemorrhage subcutaneous, haemarthrosis, post procedural haemorrhage), 2 subjects in the edoxaban 30 mg group (wound haemorrhage, haemoglobin decreased/occult blood positive), and 4 subjects in the edoxaban 60 mg group (epistaxis, wound haemorrhage/anaemia, dizziness/headache, wound haemorrhage).

4.(iii).A.(2).2) Late phase II study in Japanese and Taiwanese patients undergoing THR (Protocol No.: DU176b-04, Attached document 5.3.5.1-4 [[redacted] to [redacted] 20[redacted]])

In order to investigate the efficacy, safety, and dosage regimen of edoxaban and to determine the positioning of edoxaban relative to enoxaparin regarding efficacy and safety, a randomized, parallel-group, comparative study was conducted in a total of 35 study sites in Japan and Taiwan. In the study, edoxaban (15, 30 mg) was administered orally once daily or enoxaparin (2000 IU) was administered subcutaneously twice daily for 11 to 14 days to Japanese and Taiwanese patients undergoing THR (target sample size of 70 subjects per group, 210 subjects in total). In this study, dynamic allocation was employed using study site as the factor.

Patients aged 20 to 84 years who had undergone unilateral THR were enrolled in the study. Exclusion criteria were “patients with severe renal disorder (creatinine clearance <30 mL/min)”, “AST (GOT) or ALT (GPT) ≥2 times the upper limit of the reference range set by the study site”, and “total bilirubin ≥1.5 times the upper limit of the reference range set by the study site”, among others. Prohibited concomitant medications and therapies were the same as those specified in the Japanese TKR phase II study.

In administering the study drug orally to the edoxaban 15 mg group and the 30 mg group, the double-blindness of the dose was to be ensured. The first dose was to be administered at 6 to 24 hours after surgery and, from the next day, the study drug was to be taken in the morning, as a general rule. In the enoxaparin group, the drug was to be administered subcutaneously under unblinded conditions. The first dose was to be administered at 24 to 36 hours after surgery, and the subsequent doses were to be administered every 12 hours, as a general rule.

Of 264 subjects randomized, 261 subjects receiving the study drug (89 subjects in the edoxaban 15 mg group, 85 subjects in the edoxaban 30 mg group, 87 subjects in the enoxaparin group) were included in safety analysis. Of these, 224 subjects (78 subjects, 72 subjects, 74 subjects), excluding 37 subjects with unevaluable venogram (including subjects who discontinued the

study without having venogram taken), were included in the FAS, which was the efficacy analysis population.

The primary efficacy endpoint was the percentage of subjects with at least one of the following VTE from the start of the study drug administration until the venography at the end of the study drug administration (incidence of VTE): "asymptomatic DVT (evaluated by the venogram of both lower limbs at the end of the study drug administration)", "confirmed symptomatic PE", and "symptomatic DVT confirmed before the prescribed venography". As the final assessment, the Thromboembolic Event Assessment Committee independent of the sponsor, the investigator, and the coordinating investigator evaluated, under blinded conditions, VTE based on the copies of the test results (e.g., films) collected from each medical institution. The incidence of VTE was 3.8% (3 of 78 subjects) in the edoxaban 15 mg group, 2.8% (2 of 72 subjects) in the edoxaban 30 mg group, and 4.1% (3 of 74 subjects) in the enoxaparin group.

All cases of VTE observed were distal asymptomatic DVT.

In regards to safety, the validity of the judgment of bleeding events reported were reevaluated under blinded conditions by the Bleeding Event Assessment Committee independent of the sponsor, the investigator, and the coordinating investigator, and the evaluation by the committee was handled as the final one. By taking into account the pharmacological effect of edoxaban, bleeding events that occurred during the period from Day 1 of administration until the next day of the last dose were subjected to calculation of the incidence of the events.

The incidence of major bleeding was 0.0% (0 of 89 subjects) in the edoxaban 15 mg group, 1.2% (1 of 85 subjects) in the edoxaban 30 mg group, and 0.0% (0 of 87 subjects) in the enoxaparin group. The incidence of clinically relevant non-major bleeding was 2.2% (2 of 89 subjects) in the edoxaban 15 mg group, 0.0% (0 of 85 subjects) in the edoxaban 30 mg group, and 2.3% (2 of 87 subjects) in the enoxaparin group. The incidence of all bleeding events was 11.2% (10 of 89 subjects) in the edoxaban 15 mg group, 18.8% (16 of 85 subjects) in the edoxaban 30 mg group, and 17.2% (15 of 87 subjects) in the enoxaparin group.

The incidence of all adverse events was 65.2% (58 of 89 subjects) in the edoxaban 15 mg group, 70.6% (60 of 85 subjects) in the edoxaban 30 mg group, and 82.8% (72 of 87 subjects) in the enoxaparin group. Adverse events with an incidence ≥5% in any of the edoxaban groups were ALT increased, γ-GTP increased, blood urine present, diarrhoea, AST increased, and nasopharyngitis.

Serious adverse events occurred in 1 subject in the edoxaban 15 mg group (dislocation of joint prosthesis), 2 subjects in the edoxaban 30 mg group (vertigo positional and dislocation of joint prosthesis in 1 subject each), and 1 subject in the enoxaparin group (colitis). A causal relationship with the study drug was ruled out for all of the serious adverse events.

Adverse events leading to study discontinuation occurred in 3 subjects in the edoxaban 15 mg group (ALT increased, AST increased/ALT increased, and post procedural haematoma in 1 subject each), 1 subject in the edoxaban 30 mg group (post procedural haematoma), and 6 subjects in the enoxaparin group (erythema, AST increased, pruritus, haemorrhage subcutaneous, AST increased/ALT increased/blood LDH increased/γ-GTP increased, and anaemia in 1 subject each).

Results with the Japanese subpopulation were as follows.

Of 254 Japanese subjects randomized in the study, 251 subjects receiving the study drug (86

subjects in the edoxaban 15 mg group, 82 subjects in the edoxaban 30 mg group, 83 subjects in the enoxaparin group) were included in safety analysis. Of these, 215 subjects (75 subjects in the edoxaban 15 mg group, 70 subjects in the edoxaban 30 mg group, 70 subjects in the enoxaparin group), excluding 36 subjects with unevaluable venogram, were included in the FAS, which was the efficacy analysis population.

As regards the efficacy in the Japanese subpopulation, the incidence of VTE was 4.0% (3 of 75 subjects) in the edoxaban 15 mg group, 2.9% (2 of 70 subjects) in the edoxaban 30 mg group, and 4.3% (3 of 70 subjects) in the enoxaparin group.

As for the safety in the Japanese subpopulation, the incidence of major bleeding was 0.0% (0 of 86 subjects) in the edoxaban 15 mg group, 1.2% (1 of 82 subjects) in the edoxaban 30 mg group, and 0.0% (0 of 83 subjects) in the enoxaparin group, the incidence of clinically relevant non-major bleeding was 2.3% (2 of 86 subjects) in the edoxaban 15 mg group, 0.0% (0 of 82 subjects) in the edoxaban 30 mg group, and 2.4% (2 of 83 subjects) in the enoxaparin group, and the incidence of all bleeding events was 11.6% (10 of 86 subjects) in the edoxaban 15 mg group, 18.3% (15 of 82 subjects) in the edoxaban 30 mg group, and 18.1% (15 of 83 subjects) in the enoxaparin group. The incidence of adverse events was 66.3% (57 of 86 subjects) in the edoxaban 15 mg group, 72.0% (59 of 82 subjects) in the edoxaban 30 mg group, and 83.1% (69 of 83 subjects) in the enoxaparin group.

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

4.(iii).A.(3).1) Phase III study in Japanese and Taiwanese patients undergoing TKR (Protocol No.; DU176b-B-J302, Attached document 5.3.5.1-1 [[redacted] to [redacted] 20[redacted]])

In order to confirm the non-inferiority of edoxaban (30 mg once daily) to enoxaparin (20 mg twice daily) in preventing postoperative VTE, and to compare the safety between edoxaban (30 mg once daily) and enoxaparin (2000 IU twice daily), a randomized, double-blind, parallel-group, comparative study (Japanese and Taiwanese TKR phase III study) was conducted in a total of 71 study sites in Japan and Taiwan. In the study, edoxaban (30 mg) was administered orally once daily, or enoxaparin (20 mg) was administered subcutaneously twice daily, for 11 to 14 days to Japanese and Taiwanese patients undergoing TKR (target sample size of 260 subjects per group, 520 subjects in total).

Patients aged 20 to 84 years who had undergone unilateral TKR were enrolled in the study. The exclusion criteria and prohibited concomitant medications and therapies were the same as those in the Japanese and Taiwanese THR phase IIb study.

The first dose of edoxaban or its placebo was to be done at 6 to 24 hours after surgery and, from the next day, the study drug was to be administered in the morning as a general rule. The first dose of enoxaparin or its placebo was to be done at 24 to 36 hours after surgery, and the subsequent doses were to be done every 12 hours, as a general rule.

Of 716 randomized subjects, 703 subjects receiving the study drug (354 subjects in the edoxaban group, 349 subjects in the enoxaparin group) were included in safety analysis. Of these, 594 subjects (299 subjects, 295 subjects), excluding 109 subjects (55 subjects, 54 subjects) with unevaluable venogram, were included in the FAS, which was the efficacy analysis population.

The primary efficacy endpoint was the percentage of subjects with at least one of the following VTE from the start of the study drug administration until the venography at the end of the study drug administration (incidence of VTE): “asymptomatic DVT (evaluated by the venogram of the operated lower limb at the end of the study drug administration)”, “confirmed symptomatic

PE", and "symptomatic DVT confirmed before the prescribed venography". As the final assessment, the Thromboembolic Event Assessment Committee independent of the sponsor, the investigator, and the coordinating investigator evaluated VTE under blinded conditions based on the copies of the test results (e.g., films) collected from each medical institution. The incidence of VTE was 7.4% (22 of 299 subjects) in the edoxaban group and 13.9% (41 of 295 subjects) in the enoxaparin group, with the between-group difference (incidence in the edoxaban group – incidence in the enoxaparin group) being -6.5% (95% CI, -11.5% to -1.6%). A Z test was performed at a one-sided significance level of 0.025 using the non-inferiority margin of 5% for data in the enoxaparin group. Results showed that the incidence was significantly lower ($P <$ 0.001) in the edoxaban group than in the enoxaparin group, demonstrating the non-inferiority of edoxaban to enoxaparin.

No symptomatic PE occurred. The incidence of symptomatic DVT was 1.3% (4 of 299 subjects) in the edoxaban group and 0.3% (1 of 295 subjects) in the enoxaparin group. The incidence of asymptomatic proximal DVT was 0.0% (0 of 299 subjects) in the edoxaban group and 0.3% (1 of 295 subjects) in the enoxaparin group.

As regards the safety, the validity of the judgment of bleeding events reported was re-evaluated under blinded conditions by the Bleeding Event Assessment Committee independent of the sponsor, the investigator, and the coordinating investigator, and the evaluation by the committee was handled as the final one. By taking into account the pharmacological effect of edoxaban, bleeding events that occurred during the period from Day 1 of administration until the next day of the last dose were subjected to calculation of the incidence of the events.

The incidence of major bleeding was 1.1% (4 of 354 subjects; wound haemorrhage in 2 subjects, haemorrhage subcutaneous and small intestinal haemorrhage in 1 subject each) in the edoxaban group and 0.3% (1 of 349 subjects, haemarthrosis) in the enoxaparin group. The incidence of clinically relevant non-major bleeding was 5.1% (18 of 354 subjects) in the edoxaban group and 3.4% (12 of 349 subjects) in the enoxaparin group, and the incidence of all bleeding events was 22.3% (79 of 354 subjects) in the edoxaban group and 18.9% (66 of 349 subjects) in the enoxaparin group.

The incidence of adverse events was 66.9% (237 of 354 subjects) in the edoxaban group and 73.4% (256 of 349 subjects) in the enoxaparin group. Adverse events with an incidence ≥5% in the edoxaban group were γ-GTP increased (9.3% in the edoxaban group, 18.3% in the enoxaparin group), blood urine present (9.6%, 8.9%), ALT increased (7.1%, 26.9%), haemorrhage subcutaneous (6.2%, 8.0%), and wound haemorrhage (5.1%, 2.9%).

Serious adverse events were observed in 2.8% (10 of 354 subjects) in the edoxaban group, which were postoperative wound infection, stitch abscess, cerebellar infarction, myocardial infarction, melaena, urticaria, haemarthrosis, lumbar vertebral fracture, wound complication, and ligament rupture. The causal relationship with the study drug was ruled out except for haemarthrosis. In the enoxaparin group, serious adverse events were observed in 3.2% (11 of 349 subjects), which were carotid artery stenosis/retinal artery occlusion, convulsion, syncope/hypotension, cyanosis/femoral neck fracture, DVT, gastrointestinal haemorrhage, pyoderma gangrenosum, joint contracture, pyrexia, ALT increased/AST increased, and C-reactive protein increased.

Adverse events leading to study discontinuation occurred in 28 subjects (38 events) in the edoxaban group and in 24 subjects (45 events) in the enoxaparin group. Of these events, those that were observed at least twice in either group were AST increased (1 event in 1 subject of the edoxaban group, 8 events in 8 subjects of the enoxaparin group), wound haemorrhage (6 events

in 6 subjects, 2 events in 2 subjects), ALT increased (1 event in 1 subject, 6 events in 6 subjects), γ-GTP increased (0 event in 0 subject, 6 events in 6 subjects), blood ALP increased (0 event in 0 subject, 3 events in 3 subjects), haemorrhage subcutaneous (5 events in 5 subjects, 1 event in 1 subject), DVT (3 events in 3 subjects, 1 event in 1 subject), haemarthrosis (2 events in 2 subjects, 2 events in 2 subjects), red blood cell count decreased (2 events in 2 subjects, 1 event in 1 subject), haemoglobin decreased (2 events in 2 subjects, 1 event in 1 subject), haematocrit decreased (2 events in 2 subjects, 1 event in 1 subject), blood pressure increased (2 events in 2 subjects, 0 event in 0 subject), haematuria (2 events in 2 subjects, 0 event in 0 subject), blood LDH increased (0 event in 0 subject, 2 events in 2 subjects), and post procedural swelling (0 event in 0 subject, 2 events in 2 subjects).

Results with the Japanese subpopulation were as follows.

Of 656 Japanese subjects randomized, 646 subjects receiving the study drug (323 subjects in the edoxaban group, 323 subjects in the enoxaparin group) were included in safety analysis. Of these, 543 subjects (273 subjects in the edoxaban group, 270 subjects in the enoxaparin group), excluding 103 subjects with unevaluable venogram, were included in the FAS, which was the efficacy analysis population.

Regarding the efficacy in the Japanese subpopulation, the incidence of VTE was 7.3% (20 of 273 subjects) in the edoxaban group and 12.2% (33 of 270 subjects) in the enoxaparin group.

As for safety in the Japanese subpopulation, the incidence of major bleeding was 0.9% (3 of 323 subjects) in the edoxaban group and 0.3% (1 of 323 subjects) in the enoxaparin group, the incidence of clinically relevant non-major bleeding was 5.3% (17 of 323 subjects) in the edoxaban group and 3.7% (12 of 323 subjects) in the enoxaparin group, and the incidence of all bleeding events was 23.2% (75 of 323 subjects) in the edoxaban group and 20.1% (65 of 323 subjects) in the enoxaparin group. The incidence of adverse events was 65.6% (212 of 323 subjects) in the edoxaban group and 73.7% (238 of 323 subjects) in the enoxaparin group.

4.(iii).A.(3).2) Japanese THR phase III study (Protocol No.: DU176b-B-J304, Attached document 5.3.5.1-2 [[redacted] to [redacted]])

In order to confirm the non-inferiority of edoxaban (30 mg once daily) to enoxaparin (20 mg twice daily) in preventing postoperative VTE, and to compare the safety between edoxaban (30 mg once daily) and enoxaparin, a randomized, double-blind, parallel-group, comparative study was conducted in a total of 58 study sites in Japan. In the study, edoxaban (30 mg) was administered orally once daily or enoxaparin (2000 IU) was administered subcutaneously twice daily, for 11 to 14 days (target sample size of 300 subjects per group, 600 subjects in total).

Patients aged 20 to 84 years who had undergone unilateral THR were enrolled in the study. The exclusion criteria and prohibited concomitant medications and therapies were the same as those in the Japanese and Taiwanese THR phase IIb study.

The first dose of edoxaban or its placebo was to be administered at 6 to 24 hours after surgery and, from the next day, the study drug was to be administered in the morning as a general rule. The first dose of enoxaparin or its placebo was to be administered at 24 to 36 hours after surgery, and the subsequent doses were to be administered every 12 hours, as a general rule.

Of 610 subjects randomized, 604 subjects receiving the study drug (303 subjects in the edoxaban group, 301 subjects in the enoxaparin group) were included in safety analysis. Of these, 503 subjects (255 subjects, 248 subjects), excluding 101 subjects (48 subjects, 53 subjects) with unevaluable venogram, were included in the FAS, which was the efficacy analysis population.

The primary efficacy endpoint was the percentage of subjects with at least one of the following VTE from the start of the study drug administration until the venography at the end of the study drug administration (incidence of VTE): “asymptomatic DVT (evaluated by the venogram of the bilateral lower limbs at the end of the study drug administration)”, “confirmed symptomatic PE”, and “symptomatic DVT confirmed before the prescribed venography”. As the final assessment, the Thromboembolic Event Assessment Committee independent of the sponsor, the investigator, and the coordinating investigator evaluated VTE under blinded conditions based on the copies of the test results (e.g., films) collected from each medical institution. The incidence of VTE was 2.4% (6 of 255 subjects) in the edoxaban group and 6.9% (17 of 248 subjects) in the enoxaparin group. The data were subjected to Farrington and Manning test at a one-sided significance level of 0.025 using the non-inferiority margin of 8%, which demonstrated the non-inferiority of edoxaban to enoxaparin ($P < 0.001$).

Neither symptomatic PE nor symptomatic DVT occurred. The incidence of asymptomatic proximal DVT was 0.4% (1 of 255 subjects) in the edoxaban group and 0.8% (2 of 248 subjects) in the enoxaparin group.

As regards the safety, the validity of the judgment of bleeding events reported was reevaluated under blinded conditions by the Bleeding Event Assessment Committee independent of the sponsor, the investigator, and the coordinating investigator, and the evaluation by the committee was handled as the final one. By taking into account the pharmacological effect of edoxaban, bleeding events that occurred during the period from Day 1 of administration until the next day of the last dose were subjected to calculation of the incidence of the events.

The incidence of major bleeding was 0.7% (2 of 303 subjects, haemorrhage subcutaneous and wound haemorrhage in 1 subject each) in the edoxaban group and 2.0% (6 of 301 subjects, haemorrhage subcutaneous and duodenal ulcer haemorrhage in 2 subjects each, haemarthrosis and wound haemorrhage in 1 subject each) in the enoxaparin group. The incidence of clinically relevant non-major bleeding was 2.0% (6 of 303 subjects) in the edoxaban group and 1.7% (5 of 301 subjects) in the enoxaparin group. The incidence of all bleeding events was 20.5% (62 of 303 subjects) in the edoxaban group and 15.9% (48 of 301 subjects) in the enoxaparin group.

The incidence of all adverse events was 65.0% (197 of 303 subjects) in the edoxaban group and 77.1% (232 of 301 subjects) in the enoxaparin group. Adverse events with an incidence ≥5% in the edoxaban group were γ-GTP increased (14.5% in the edoxaban group, 26.2% in the enoxaparin group), ALT increased (11.9%, 41.9%), AST increased (5.6%, 32.2%), and blood urine present (12.5%, 11.3%). Adverse events with an incidence ≥5% only in the enoxaparin group were blood ALP increased (4.6%, 13.3%) and haemorrhage subcutaneous (4.0%, 7.0%).

Serious adverse events were observed in 3.0% (9 of 303 subjects) of subjects in the edoxaban group (femur fracture and dislocation of joint prosthesis in 2 subjects each, herpes zoster, lacunar infarction, orthostatic hypotension, DVT, and pelvic fracture in 1 subject each) and in 3.0% (9 of 301 subjects) of the enoxaparin group (gastroenteritis, postoperative wound infection, abscess jaw, subarachnoid haemorrhage, transient ischaemic attack, DVT/intestinal obstruction, femur fracture, hip fracture, dislocation of joint prosthesis in 1 subject each). In all of the 9 subjects of the edoxaban group, the causal relationship of the study drug with the serious adverse events was ruled out.

Adverse events leading to study discontinuation occurred in 11 subjects (13 events) in the edoxaban group and in 21 subjects (36 events) in the enoxaparin group. Of these events, those

that were observed at least twice in either group were ALT increased (1 event in 1 subject of the edoxaban group, 8 events in 8 subjects of the enoxaparin group), AST increased (0 event in 0 subject, 6 events in 6 subjects), wound haemorrhage (3 events in 3 subjects, 1 event in 1 subject), haemoglobin decreased (1 event in 1 subject, 3 events in 3 subjects), haemorrhage subcutaneous (2 events in 2 subjects, 0 event in 0 subject), bloody discharge (2 events in 2 subjects, 0 event in 0 subject), haematocrit decreased (1 event in 1 subject, 2 events in 2 subjects), red blood cell count decreased (1 event in 1 subject, 2 events in 2 subjects), duodenal ulcer (0 event in 0 subject, 2 events in 2 subjects), and duodenal ulcer haemorrhage (0 event in 0 subject, 2 events in 2 subjects).

4.(iii).A.(3).3) Phase III study in Japanese patients undergoing HFS (Protocol No.: DU176b-B-J303, Attached document 5.3.5.1-5 [[redacted]])

A randomized, open-label study (Japanese HFS phase III study) was conducted in Japanese patients undergoing HFS in a total of 24 study sites in Japan to investigate the safety and efficacy of edoxaban (30 mg) administered once daily for 11 to 14 days, and to determine the positioning of edoxaban relative to enoxaparin* regarding efficacy and safety (target sample size: 60 subjects in the edoxaban group, 30 subjects in the enoxaparin group; 90 subjects in total). In this study, dynamic allocation was employed using the days from the injury to the surgery ("<7 days" or "≥7 days") as the factor.

Including patients aged ≥20 years who were scheduled to undergo surgery for femoral neck fracture or intertrochanteric femoral fracture (trochanteric section of femur, subtrochanteric region) within 10 days, the exclusion criteria and prohibited concomitant medications and therapies were the same as those in the Japanese and Taiwanese THR phase II study.

The first dose of edoxaban was to be administered at 6 to 24 hours after surgery and, from the next day, the study drug was to be administered in the morning as a general rule. The first dose of enoxaparin was to be administered at 24 to 36 hours after surgery, and the subsequent doses were to be administered every 12 hours, as a general rule.

Of 92 randomized subjects, 88 subjects receiving the study drug (59 subjects in the edoxaban group, 29 subjects in the enoxaparin group) were included in safety analysis. Of these, 73 subjects (46 subjects in the edoxaban group, 27 subjects in the enoxaparin group), excluding 15 subjects (13 subjects, 2 subjects) with unevaluable venogram, were included in the FAS, which was the efficacy analysis population.

The primary efficacy endpoints were "major bleeding or clinically relevant non-major bleeding" and "bleeding events (major bleeding, clinically relevant non-major bleeding, minor bleeding)" observed during the period from the start of the study drug administration until the day of post-treatment examination. For the evaluation of bleeding events, the validity of the judgment was reevaluated under blinded conditions by the Bleeding Event Assessment Committee independent of the sponsor, the investigator, and the coordinating investigator, and the evaluation by the committee was handled as the final one. The incidence of "major bleeding or clinically relevant non-major bleeding" observed during the period from the start of the study drug administration until the day of post-treatment examination was 6.8% (4 of 59 subjects) in the edoxaban group (gastrointestinal haemorrhage in 2 subjects, subdural haematoma and post procedural haematoma in 1 subject each) and 10.3% (3 of 29 subjects) in the enoxaparin group (post procedural haematoma in 3 subjects). The incidence of "bleeding events" observed during the same period was 32.2% (19 of 59 subjects) in the edoxaban group and 31.0% (9 of 29 subjects) in the enoxaparin group. The incidence of major bleeding was 3.4% (2 of 59 subjects)

* This group was included for reference purposes and was not the control group for statistical comparison.

in the edoxaban group and 6.9% (2 of 29 subjects) in the enoxaparin group.

The incidence of "major bleeding or clinically relevant non-major bleeding" observed during the period from the start of the study drug administration until the next day of the last dose was 3.4% (2 of 59 subjects, gastrointestinal haemorrhage in 2 subjects) in the edoxaban group and 6.9% (2 of 29 subjects, post procedural haematoma in 2 subjects) in the enoxaparin group. The incidence of "bleeding events" observed during the same period was 25.4% (15 of 59 subjects) in the edoxaban group and 17.2% (5 of 29 subjects) in the enoxaparin group. The incidence of "major bleeding" was 1.7% (1 of 59 subjects) in the edoxaban group and 3.4% (1 of 29 subjects) in the enoxaparin group.

As regards efficacy, the Thromboembolic Event Assessment Committee independent of the sponsor, the investigator, and the coordinating investigator evaluated VTE under blinded conditions based on the copies of the test results (e.g., films) collected from each medical institution. The assessment made by the committee was handled as the final one. The incidence of VTE was 6.5% (3 of 46 subjects) in the edoxaban group and 3.7% (1 of 27 subjects) in the enoxaparin group. All were distal asymptomatic DVT. Neither symptomatic PE nor symptomatic DVT was observed.

As regards safety, the incidence of all adverse events was 72.9% (43 of 59 subjects) in the edoxaban group and 82.8% (24 of 29 subjects) in the enoxaparin group. Adverse events with an incidence ≥10% in the edoxaban group were blood urine present and urinary tract infection.

Serious adverse events occurred in 3 subjects in the edoxaban group (fracture displacement in 2 subjects, subdural haematoma in 1 subject) and in 3 subjects in the enoxaparin group (fracture displacement, postoperative wound infection, and thoracic vertebral fracture in 1 subject each). The causal relationship of these serious adverse events with the study drug was ruled out except for subdural haematoma in the edoxaban group and postoperative wound infection in the enoxaparin group.

Adverse events leading to study discontinuation were observed in 3 subjects (3 events) in the edoxaban group (gastrointestinal haemorrhage, 2 evens in 2 subjects; DVT, 1 event in 1 subject) and in 1 subject (1 event) in the enoxaparin group (postoperative wound infection).

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

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

The applicant explained the development history of edoxaban as follows:

Surgical operations as a whole are generally prone to enhance coagulability. In patients undergoing orthopedic surgery of the lower limbs, in particular, venous stasis in the lower limbs is highly likely, compared with other surgeries, during bed rest after surgery because of the restriction of movement of the lower limbs. In addition, the incidence of VTE is increased in many patients who are complicated with risk factors of VTE such as advanced age and obesity. Among orthopedic surgery of the lower limbs, TKR, THR, and HFS are classified as surgeries with a "high risk" of causing VTE in all of the following guidelines: "American College of Chest Physicians: ACCP Guideline, 8th edition" (*Chest.* 2008;133:381S-453S.) (ACCP guideline, 8th edition), "Japanese Guidelines for Prevention of Venous Thromboembolism (Editorial Committee on Japanese Guidelines for Prevention of Venous Thromboembolism)" (Japanese guideline), and "Guideline for prevention of venous thromboembolism (Committee for revision of guideline for preventing pulmonary thromboembolism/deep vein thrombosis [venous thromboembolism] of the Japanese Orthopedic Association)" (JOA guideline). In all these guidelines, prophylactic anticoagulant therapy is recommended for patients undergoing these surgeries. For pharmacological prophylaxis,

unfractionated heparin, warfarin, fondaparinux, and enoxaparin are recommended by the Japanese guideline and JOA guideline. However, since unfractionated heparin has to be injected, it causes significant physical and psychological discomfort for patients and imposes a substantial burden on healthcare professionals who administer the drug. Warfarin, which can be taken orally, has the following disadvantages: (i) it takes a long time until the anticoagulant effect reaches the optimal therapeutic range, (ii) it has a very narrow safety margin, (iii) the efficacy varies substantially among individuals, and (iv) it is prone to be affected by other drugs and food. For these reasons, frequent monitoring of the drug efficacy is essential, making it difficult to use warfarin. Therefore, unfractionated heparin and warfarin have not been widely used for the prophylaxis of postoperative VTE in clinical practices in Japan. Fondaparinux and enoxaparin, drugs approved in recent years, do not require monitoring of blood clotting activity, but require daily subcutaneous administration, thereby imposing a substantial burden on both patients and healthcare professionals. Thus, anticoagulants currently used for the prophylaxis of VTE are fraught with many drawbacks. Therefore, it is of great significance to develop an anticoagulant that can be administered orally, exhibits the effect rapidly, and does not require frequent monitoring of drug efficacy. As regards the positioning of edoxaban, the applicant considers that edoxaban is recommended as the first-choice drug if it is indicated for anticoagulant therapy in patients undergoing TKR, THR, or HFS, each of which is classified as a surgical procedure with a high or very high risk of VTE.

PMDA considers as follows:
For the prophylaxis of VTE after orthopedic surgery of the lower limbs, administration of anticoagulants (e.g., fondaparinux, enoxaparin) is recommended in patients undergoing THR, TKR, or HFS by the ACCP guideline 8th edition, as explained by the applicant. Since neither fondaparinux nor enoxaparin was approved at the time of the issuance of the Japanese guideline, these drugs were not included in the recommended drugs, but THR, TKR, and HFS were listed as surgical procedures with a “high risk” of VTE, and low dose heparin is included in the recommended drugs. In Japan, the use of fondaparinux and enoxaparin was approved in 2007 and 2008, respectively, in patients for whom edoxaban is proposed to be indicated. The JOA guideline issued in 2008 recommends the use of these drugs for anticoagulant therapy. Thus, PMDA considered that the use of anticoagulants in patients undergoing THR, TKR, or HFS is now regarded as an option for preventing postoperative VTE. Therefore, edoxaban, if demonstrated to be at least non-inferior to drugs of the same class in efficacy and safety, may be used as a first-choice drug. Since edoxaban is orally available, it is expected to reduce the burden on patients in administration compared with subcutaneous injection and is thus convenient for patients. On the other hand, it should be borne in mind that the convenience is always accompanied by bleeding risk. Given that edoxaban is an oral drug and is thus prone to be taken under the patient’s perfunctory control after discharge, its proper use and adequate risk management should be considered.

4.(iii).B.(2) Appropriateness of conducting global clinical studies
The Japanese and Taiwanese THR phase II study and the Japanese and Taiwanese TKR phase III study were conducted both in Japan and in Taiwan. Ten of 264 subjects in the Japanese and Taiwanese THR phase II study, and 60 of 716 subjects in the Japanese Taiwanese TKR phase III study, were enrolled and randomized in Taiwan.

The applicant explained the difference in the intrinsic ethnic factors between Japanese and Taiwanese as follows:
The mean body height and mean body weight were similar between Japanese adult subjects (Report of the National Health and Nutrition Survey, 2003) and Taiwanese adult subjects (homepage of Department of Health, Executive Yuan, Taiwan). Comparison of body height and body weight, after taking into account the age of patients undergoing TKR or THR, also showed that they were similar between Japanese and Taiwanese. In addition, it was estimated that there

was little ethnic difference in pharmacokinetics [see "4.(ii).B.(1) Ethnic differences in pharmacokinetics"]. Furthermore, the relationship between plasma edoxaban concentration and pharmacodynamic indices (PT and APTT) following multiple oral doses of edoxaban was similar between Japanese and Chinese healthy adult male subjects.
Next, the applicant explained the differences in extrinsic ethnic factors between Japanese and Taiwanese as follows:
The average life expectancy is similar between Japanese and Taiwanese, and major causes of death are also similar. The percentage of patients undergoing TKR is estimated to be approximately 0.04% of the entire population in Taiwan and approximately 0.03% in Japan, and the percentage of patients undergoing THR is estimated to be approximately 0.03% both in Japan and in Taiwan. In Taiwan, patients remain hospitalized for 5 to 7 days on an average after TKR, which was different from the duration of hospitalization in Japan (14-28 days). However, there was no significant difference between Japan and Taiwan in the anesthesia procedure, duration of surgery, or days from surgery to the start of rehabilitation. In addition, there was no significant difference in the incidence of DVT in patients undergoing TKR or THR, or in the diagnostic method, among Asian countries including Japan and Taiwan. As regards pharmacological prophylaxis against VTE in these patients, fondaparinux and enoxaparin were approved in Japan, and enoxaparin and dalteparin in Taiwan, allowing the use of enoxaparin in both countries. Both in Japan and in Taiwan, physical prophylaxis such as intermittent pneumatic compression, foot pump, elastic stockings, and elastic bandages were used.

In addition to the above, by selecting the study sites where clinical studies in Taiwan can be conducted in accordance with ICH-GCP, the applicant determined that it was appropriate to conduct and evaluate the Japanese and Taiwanese TKR phase III and THR phase II studies as global clinical studies.

In the Japanese and Taiwanese TKR phase III study, the background characteristics of Japanese patients evaluable for safety analysis tended to be similar to those of the entire population. As regards efficacy results, the incidence of VTE was 7.4% (22 of 299 subjects) in the edoxaban group and 13.9% (41 of 295 subjects) in the enoxaparin group in the entire population, and in the Japanese population, 7.3% (20 of 273 subjects) in the edoxaban group and 12.2% (33 of 270 subjects) in the enoxaparin group, showing similar results. As for safety results, the incidence of major bleeding was 1.1% (4 of 354 subjects) in the edoxaban group and 0.3% (1 of 349 subjects) in the enoxaparin group in the entire population, and 0.9% (3 of 323 subjects) in the edoxaban group and 0.3% (1 of 323 subjects) in the enoxaparin group in the Japanese population. The incidence of major bleeding and clinically relevant non-major bleeding combined was 6.2% (22 of 354 subjects) in the edoxaban group and 3.7% (13 of 349 subjects) in the enoxaparin group in the entire population, and 6.2% (20 of 323 subjects) in the edoxaban group and 4.0% (13 of 323 subjects) in the enoxaparin group in the Japanese population, showing similar results. The incidence of bleeding events (major bleeding, clinically relevant non-major bleeding, minor bleeding) was 22.3% (79 of 354 subjects) in the edoxaban group and 18.9% (66 of 349 subjects) in the enoxaparin group in the entire population, and 23.2% (75 of 323 subjects) in the edoxaban group and 20.1% (65 of 323 subjects) in the enoxaparin group in the Japanese population, also showing similar results.

PMDA considers as follows:
Neither intrinsic nor extrinsic ethnic factors show any difference that denies the validity of conducting Japanese and Taiwanese global clinical studies to investigate the VTE-prevention effect after THR and TKR. In addition, in the Japanese and Taiwanese THR phase II study, the number of Taiwanese subjects enrolled in each group was as extremely small as 2 to 4 subjects per group. In addition, VTE, major bleeding, or clinically relevant non-major bleeding did not occur in any of these subjects. Therefore, it is unlikely that inclusion of these subjects significantly affected the incidence of events that served as a critical factor in selecting the dose.

As a result, there is no problem in selecting the dose for the phase III study based on the results of the Japanese and Taiwanese THR phase II study and in conducting the Japanese THR phase III study using the selected dose. In addition, the results of the Japanese and Taiwanese TKR phase III study did not show any particular difference in efficacy or safety endpoints between the Japanese population and the entire population. Therefore, PMDA has concluded that the Japanese and Taiwanese TKR phase III study may be evaluated as a confirmatory study on edoxaban administration in patients undergoing TKR.

4.(iii).B.(3) Efficacy

4.(iii).B.(3).1) Appropriateness of primary endpoint

In the studies that produced evaluation data for patients undergoing THR or TKR, the primary efficacy endpoint was defined as "the percentage of subjects with at least one of the following VTE from the start of the study drug administration until the venography at the end of the study drug administration (incidence of VTE)", where "venous thromboembolic events" were defined as (i) "asymptomatic DVT, (ii) "confirmed symptomatic PE", and (iii) "symptomatic DVT confirmed before the prescribed venography", whereas most of VTE that occurred in the phase III study were asymptomatic distal DVT. Therefore, PMDA asked the applicant to explain the clinical significance of distal DVT.

The applicant explained as follows:

According to the results of autopsies of fatal PE patients in Japan, most of the embolic sources in sudden death due to PE was DVT in the lower limbs, and in 90% of such cases, soleal vein, one of the distal veins, was the source of the thrombus formation (Ro A et al, *The Japanese journal of phlebology.* 2006;17:197-205.). Therefore, in evaluating the VTE-prevention effect of anticoagulants, the effect on the distal DVT that is the original site of the thrombus formation is equally clinically important as that on the proximal DVT. There is a certain relationship between the incidence of symptomatic VTE and that of asymptomatic DVT confirmed by venography (Quinlan DJ et al. *J Thromb Haemost.* 2007;5(7): 1438-43.) and, according to ACCP guideline, 8th edition, DVT detected by a sensitive method such as venography is considered to be an appropriate outcome in the early evaluation of new thromboprophylactic therapies.

PMDA considers as follows:

The difficulty of evaluating the efficacy of edoxaban in preventing symptomatic PE after surgery in the Japanese clinical studies is understandable given the incidence of symptomatic PE. ACCP guideline, 8th edition, appears to recommend, as the outcome of clinically significant thrombosis, to evaluate both confirmed symptomatic VTE and asymptomatic proximal DVT in combination. However, the guideline also acknowledges certain significance in DVT detected in venogram, as suggested by the applicant. Therefore, PMDA considers that the efficacy endpoints established in the clinical studies of edoxaban is acceptable.

4.(iii).B.(3).2) Appropriateness of non-inferiority margin and efficacy of edoxaban

Regarding the rationale for establishing the non-inferiority margin for edoxaban relative to enoxaparin in the incidence of VTE, the primary efficacy endpoint, in the Japanese and Taiwanese TKR phase III study and in the Japanese THR phase III study, the applicant explained as follows:

In the Japanese and Taiwanese TKR phase III study, the non-inferiority margin for the edoxaban group relative to the enoxaparin group was set at 5%, by taking into consideration the clinical significance of edoxaban, including the advantage that edoxaban, thanks to its oral availability and once daily administration, reduces the burden on patients and healthcare professionals compared with enoxaparin which has to be injected twice daily. At the planning of the Japanese and Taiwanese TKR phase III study, the incidence of VTE in the enoxaparin group in this study was assumed to be 21% and, even if the incidence of VTE in the edoxaban group was to exceed this level by up to 5%, edoxaban was considered to be sufficiently effective in

preventing VTE compared to the incidence of VTE (48.3%) in the placebo group in the Japanese TKR phase II study. Therefore, this non-inferiority margin was considered appropriate. On the other hand, the non-inferiority margin for the edoxaban group relative to the enoxaparin group in the Japanese THR phase III study was determined according to the following rationale. By referring to the incidence of VTE in Japanese patients after THR (27.3% [95% CI, 22.2%-32.9%]) given in the Japanese guideline and to the incidence of VTE (4.1%) in the enoxaparin group in the Japanese and Taiwanese THR phase II study, the enoxaparin-induced reduction in the incidence of VTE was estimated to be approximately 18% or more, and the value 8%, which is less than a half of 18%, was considered to be the allowance range for the non-inferiority.

PMDA considers the non-inferiority margin in the Japanese and Taiwanese TKR phase III study and the Japanese THR phase III study, and the efficacy of edoxaban as follows:
Although the clinical significance of reducing the burden on patients and healthcare professionals does not provide a rationale for setting the non-inferiority margin at 5% in the Japanese and Taiwanese TKR phase III study, the non-inferiority margins set for the edoxaban group relative to the enoxaparin group in the primary efficacy endpoint in the Japanese and Taiwanese TKR phase III study and the Japanese THR phase III study are largely appropriate, taking account of the information such as clinical study data available at the planning of each study. On the other hand, since there was a possibility that the risk of VTE may change depending on the background characteristics, etc. of patients enrolled, the efficacy of edoxaban was evaluated, taking account of the absolute value of the incidence in each group in both studies, in addition to the fact that non-inferiority of edoxaban to enoxaparin in terms of the incidence of VTE was demonstrated on the basis of the pre-determined non-inferiority margin. In both the Japanese and Taiwanese TKR phase III study and the Japanese THR phase III study, the incidence of VTE observed for the edoxaban group was considered clinically significant compared with the efficacy observed in the enoxaparin group. Also, the Japanese HFS phase III study was conducted in a limited number of subjects under unblinded conditions, posing a limit to the efficacy evaluation, but no clear difference was observed in the efficacy between edoxaban and enoxaparin in this study. In addition, when the results of the Japanese and Taiwanese TKR phase III study and the Japanese THR phase III study, and the relationship of the efficacy of drugs of the same class in patients undergoing TKR, THR, or HFS are taken into account, edoxaban is expected to be effective in Japanese patients undergoing HFS, as well. Based on the above, PMDA considers that edoxaban has been shown to be effective in the Japanese patients undergoing TKR, THR, or HFS.

4.(iii).B.(4) Bleeding risk

Table 7 shows the incidence of bleeding-related adverse events in the Japanese and Taiwanese clinical studies in patients undergoing orthopedic surgery of the lower limbs. The applicant explained that there was no clear difference in the incidence of bleeding among different surgical procedures.

Table 7. Incidence of bleeding-related adverse events in the Japanese and Taiwanese clinical studies in patients undergoing orthopedic surgery of the lower limbs

		Placebo	5 mg	15 mg	30 mg	60 mg	Enoxaparin
Japanese TKR phase II study	Major bleeding	0.0 (0/102)	0.0 (0/103)	0.0 (0/106)	0.0 (0/103)	0.9 (1/106)	
	Bleeding event	9.8 (10/102)	10.7 (11/103)	18.9 (20/106)	19.4 (20/103)	24.5 (26/106)	
Japanese and Taiwanese THR phase II study	Major bleeding			0.0 (0/89)	1.2 (1/85)		0.0 (0/87)
	Bleeding event			11.2 (10/89)	18.8 (16/85)		17.2 (15/87)
Japanese and Taiwanese TKR phase III study	Major bleeding				1.1 (4/354)		0.3 (1/349)
	Bleeding event				22.3 (79/354)		18.9 (66/349)
Japanese THR phase III study	Major bleeding				0.7 (2/303)		2.0 (6/301)
	Bleeding event				20.5 (62/303)		15.9 (48/301)
Japanese HFS phase III study	Major bleeding				1.7 (1/59)		3.4 (1/29)
	Bleeding event				25.4 (15/59)		17.2 (5/29)

% (n/N)

Regarding the incidence of major bleeding or clinically relevant non-major bleeding, classified by subject background characteristics, in the entire Japanese and Taiwanese clinical studies in patients undergoing orthopedic surgery of the lower limbs, the applicant explained as follows:
Comparison of the incidence between the regions did not show any clear difference between Japan (4.0%, 35 of 870 subjects) and Taiwan (5.9%, 2 of 34 subjects). By age, the incidence was slightly higher in subjects aged ≥75 years (6.1%, 18 of 294 subjects) compared with subjects aged <75 years (3.1%, 19 of 610 subjects). The incidence in male subjects (7.5%, 11 of 147 subjects) was slightly higher compared with female subjects (3.4%, 26 of 757 subjects) and a similar trend was observed also in the enoxaparin group. However, no similar effect of gender was observed in studies in NVAF patients, suggesting that the difference was not a consistent trend observed with edoxaban and thus requires no particular attention to be paid. By body weight, the incidence in subjects weighing ≥50 kg was slightly lower (3.9%, 28 of 725 subjects) compared with subjects weighing <50 kg (5.0%, 9 of 179 subjects). As for renal function, the incidence was 9.3% (8 of 86 subjects) in subjects with CL_{CR} <50 mL/min, 5.0% (20 of 399 subjects) in subjects ≥50 mL/min and <80 mL/min, and 2.1% (9 of 419 subjects) in subjects ≥80 mL/min, showing a tendency for increase with decreasing CL_{CR}. No clear difference was observed in the incidence of major bleeding or clinically relevant non-major bleeding between patient groups classified by duration of surgery (≥2 hours vs. <2 hours), total bleeding volume during surgery, or by primary disease. Nonsteroidal anti-inflammatory drugs (NSAIDs) were concomitantly administered in almost all subjects, precluding the appropriate evaluation of the effect of the concomitant use. P-gp inhibitors were concomitantly administered in only a limited number of subjects, 17 subjects in the 30 mg group and only 26 subjects in all edoxaban groups combined, precluding the thorough evaluation of the effect of the concomitant use. However, a clinically relevant non-major bleeding (occult blood positive) was observed in 1 subject in the 30 mg group who received in concomitant use of a P-gp inhibitor.

PMDA, pointing out the findings in the 3 phase III studies that the incidence of bleeding events in the edoxaban group tended to be higher compared with the enoxaparin group, asked the applicant to explain the bleeding risk caused by edoxaban.

The applicant responded as follows:
Among the phase III studies, there was no consistent tendency in the incidence of major bleeding or clinically relevant non-major bleeding, such as a higher incidence in certain group(s). In addition, there were no fatal bleeding events, intracranial haemorrhages, or surgical site bleeding requiring re-operation in the edoxaban group, nor was there any difference in the site of occurrence or severity of major bleeding between the edoxaban group and the enoxaparin group. On the other hand, the incidence of minor bleeding was higher in the edoxaban group than in the enoxaparin group both in the phase III study and the Japanese and Taiwanese THR phase II study. Among minor bleeding observed in the edoxaban group, blood urine present, haematuria, and wound haemorrhage showed higher incidences in the edoxaban group than in the enoxaparin group. The incidences of anal haemorrhage and haemorrhoidal haemorrhage also tended to be slightly higher in the edoxaban group. In contrast, the incidence of haemorrhage subcutaneous was lower in the edoxaban group. All of these events observed in the edoxaban group were mild in severity, as detailed below. Blood urine present did not require study discontinuation. None of the minor bleeding required interventional treatment, and symptoms resolved or improved except in 1 subject (urinary sediment ±) whose outcome was "unrecovered" in the Japanese THR phase III study. Haematuria did not require discontinuation of the treatment or the study and resolved in all affected subjects. Wound haemorrhage resolved in all subjects without requiring treatment discontinuation or special treatment, except in 1 subject in the Japanese THR phase III study (bleeding occurred from the surgical wound at 2 days after start of administration and the study was discontinued because of the low body weight (40 kg) and low blood count). For anal haemorrhage and haemorrhoidal haemorrhage, topical antihaemorrhoidal drugs were applied to 5 subjects, but no other special treatments or study discontinuation was needed. The symptoms resolved in all subjects. Thus, although the incidence of minor bleeding tended to be higher in the edoxaban group compared with the enoxaparin group, detailed examination of individual events judged as minor bleeding suggests that they are not events of any possible clinical significance.

PMDA considers the bleeding risk caused by edoxaban as follows:
Based on the clinical study data presented, there is no difference in safety profile that may affect the incidence of major bleeding or clinically relevant non-major bleeding between the edoxaban group and the enoxaparin group. Although the incidence of bleeding events as a whole tended to be slightly higher in the edoxaban group, results of the detailed examination of these events did not reveal any problems posing concerns about the safety of edoxaban. However, it cannot be excluded that the difference in the incidence of bleeding events as a whole observed in the clinical studies may suggest the increased bleeding risk with edoxaban compared with enoxaparin. Therefore, it cannot be completely ruled out that, when edoxaban is used in many patients after marketing, the use of the drug may lead to an increase in any risk of major bleeding or clinically relevant non-major bleeding. It is thus essential to continuously pay close attention to the occurrence of bleeding events in the post-marketing surveillance. Occurrence of bleeding should be given due attention from the aspect of the mechanism of action of edoxaban as well. Edoxaban should therefore be used based on the appropriate risk-benefit assessment. Attention should be paid to patient background characteristics such as renal function, body weight, and age, which were shown to increase the bleeding risk in the clinical studies, and caution should be raised regarding these risk factors. Furthermore, because of the oral availability of edoxaban, the product is more likely to be administered continuously even after discharge, compared with approved injectable drugs. Therefore, it is necessary to provide caution and information regarding the appropriate treatment duration and the timing of

treatment termination. The details of the caution statement and of the post-marketing surveillance will be finalized, taking account of comments raised in the Expert Discussion.

4.(iii).B.(5) Indications

Regarding the proposed indications "Prevention of venous thromboembolism in patients undergoing the following orthopedic surgeries of the lower limbs: Total knee replacement, total hip replacement, and hip fracture surgery", PMDA considers as follows:

According to the Japanese guideline, the risk of VTE after orthopedic surgery is classified into low risk, intermediate risk, high risk, and very high risk, and anticoagulant therapy is recommended for surgeries with high to very high risk. Since high-risk surgeries are defined as THR, TKR, and HFS, and very-high-risk surgeries are defined as THR, TKR, and HFS performed on patients with existing VTE or with a thrombotic predisposition. Therefore, anticoagulants used for the prophylaxis of VTE in orthopedic surgery of the lower limbs in Japan should be indicated for all of these surgical procedures in order to practically meet the entire range of use at clinical practices. Clinical studies on edoxaban were conducted, as were the cases with the approved drugs, involving patients who underwent each of the above 3 surgical operations with possibly different VTE risk or bleeding risk from each other, and the results demonstrated the efficacy and safety of edoxaban in each of these surgical procedures. Based on the above, PMDA has concluded that the proposed indications are appropriate.

4.(iii).B.(6) Appropriateness of dosage and administration

4.(iii).B.(6).1) Recommended dosage and administration

Regarding the rationale for the proposed dosage and administration "The usual adult dosage is 30 mg of edoxaban administered orally once daily", the applicant explained as follows:

When VTE-prevention effect and the risk of bleeding events were compared between once-daily administration and twice-daily administration in patients undergoing THR, there was no clear difference in the incidence of VTE or in the incidence of bleeding events between once-daily and twice-daily administration of the same daily dose. Therefore, once-daily administration was determined as appropriate, with consideration given to the expected more favorable compliance. In addition, results of the Japanese study on the food effect on PK showed that although C_{max} following a single oral dose of edoxaban in the fed state slightly increased compared with that after fasted administration, AUC_{0-t} was not affected by food. Therefore, edoxaban may be administered independent of the timing of food intake.

The daily dose was investigated as follows. In the Japanese TKR phase II study, the incidence of VTE in patients undergoing TKR was 48.3% (43 of 89 subjects) in the placebo group, 29.5% (26 of 88 subjects) in the edoxaban 5 mg group, 26.1% (24 of 92 subjects) in the edoxaban 15 mg group, 12.5% (11 of 88 subjects) in the edoxaban 30 mg group, 9.1% (8 of 88 subjects) in the edoxaban 60 mg group, showing a dose-dependent decrease. In addition, comparison of the incidence of VTE between the placebo group and each dose group by the Shirley-Williams method showed a superiority of edoxaban 5 mg and higher dose groups to the placebo group. As regards safety, although the incidence of major bleeding or of clinically relevant non-major bleeding did not increase with dose, the incidence of bleeding events as a whole increased with dose, 9.8% (10 of 102 subjects) in the placebo group, 10.7% (11 of 103 subjects) in the edoxaban 5 mg group, 18.9% (20 of 106 subjects) in the edoxaban 15 mg group, 19.4% (20 of 103 subjects) in the edoxaban 30 mg group, and 24.5% (26 of 106 subjects) in the edoxaban 60 mg group, with the incidence in the 60 mg group being significantly higher compared with the placebo group. From these results, the appropriate daily dose for patients undergoing TKR was determined as 30 mg and, in the Japanese and Taiwanese TKR phase III study using edoxaban 30 mg, non-inferiority of edoxaban 30 mg to enoxaparin was confirmed.

In the Japanese and Taiwanese THR phase II study, the efficacy and safety of edoxaban in

patients undergoing THR was compared between 30 mg, the dose considered to be the recommended dose in patients undergoing TKR from the results of the Japanese TKR phase II study, and half that dose. As a result, the incidence of VTE was 3.8% (3 of 78 subjects) in the edoxaban 15 mg group, 2.8% (2 of 72 subjects) in the edoxaban 30 mg group, and 4.1% (3 of 74 subjects) in the enoxaparin group, showing that the incidence was similar between the edoxaban groups and the enoxaparin group. The extent of the prolongation of PT, PT-INR, and APTT, the pharmacodynamic indices, measured at 1 to 3 hours after administration on Day 7, was greater in the edoxaban 30 mg group compared with the edoxaban 15 mg group. D-dimer level decreased to a greater extent in the edoxaban 30 mg group compared with the edoxaban 15 mg group. These results suggested a higher anticoagulant effect of 30 mg dose relative to the 15 mg dose. As regards safety, the incidence of major bleeding or clinically relevant non-major bleeding was 2.2% (2 of 89 subjects) in the edoxaban 15 mg group, 1.2% (1 of 85 subjects) in the edoxaban 30 mg group, and 2.3% (2 of 87 subjects) in the enoxaparin group, showing similar results among the groups. The incidence of bleeding events as a whole was 11.2% (10 of 89 subjects) in the edoxaban 15 mg group, 18.8% (16 of 85 subjects) in the edoxaban 30 mg group, and 17.2% (15 of 87 subjects) in the enoxaparin group, showing similar results between the 30 mg and enoxaparin group. From these results, it has been determined that the appropriate dose of edoxaban for patients undergoing THR is 30 mg and, in the Japanese THR phase III study, non-inferiority of edoxaban 30 mg to enoxaparin was confirmed.

Regarding patients undergoing HFS, results of the Japanese HFS phase III study were submitted. The study was conducted using only 30 mg of edoxaban. However, in patients who underwent TKR and also in those who underwent THR, the dose of 30 mg once daily was selected as the recommended dosage regimen based on separate dose-finding studies. In addition, results of the Japanese HFS phase III study showed that the incidence of VTE in the edoxaban 30 mg group was 6.5% (3 of 46 subjects), which was not markedly inferior to the incidence of VTE in the enoxaparin group (3.7%, 1 of 27 subjects). In addition, regarding safety, the incidence of major bleeding or clinically relevant non-major bleeding was 3.4% (2 of 59 subjects) in the edoxaban 30 mg group and 6.9% (2 of 29 subjects) in the enoxaparin group, and the incidence of all bleeding events was 25.4% (15 of 59 subjects) in the edoxaban 30 mg group and 17.2% (5 of 29 subjects) in the enoxaparin group, with each incidence showing no clear difference between the groups. From these results, the applicant considered that it is possible to use the dose 30 mg also in patients undergoing HFS.

Based on the above, the dosage and administration were determined as “The usual adult dosage is 30 mg of edoxaban administered orally once daily” for patients undergoing TKR, THR, or HFS as well.

PMDA considers the dosage regimen of edoxaban as follows:
The efficacy of edoxaban was confirmed in the confirmatory study using once daily dose of 30 mg in 2 patient groups with possibly different VTE risk and bleeding risk, i.e., patients undergoing TKR and those undergoing THR. The efficacy was also suggested in patients undergoing HFS in a study conducted using the same dose. Taking account of these results, the 30 mg dose is appropriate as the clinical dose of edoxaban for preventing VTE in patients undergoing orthopedic surgery of the lower limbs. As regards safety, given that adverse events, bleeding-related events in particular, tend to increase dose-dependently, edoxaban should be used while paying attention to risks such as bleeding due to the use of the drug. Particular caution should be exercised in patients with background characteristics that may increase the frequency of bleeding-related events, including decreased renal function, advanced age, and low body weight, as discussed later. With these reservations, it is appropriate to provide clinical practices with edoxaban 30 mg once daily as the recommended dosage regimen.

4.(iii).B.(6).2) Timing of treatment initiation

Regarding the timing of the start of edoxaban administration, the applicant claimed to specify in the "Precautions for Dosage and Administration" of the proposed package insert that "Administration of edoxaban should be initiated at 6 hours after surgery and upon confirming that there is no bleeding from the surgical wound, etc.", based on the following reasoning: (i) it is essential to start anticoagulant therapy at an early stage in order to prevent VTE after surgery, and (ii) the timing of the treatment initiation was set at 6 to 24 hours after surgery in the Japanese and Taiwanese studies in patients undergoing orthopedic surgery of the lower limbs (Japanese TKR phase II, Japanese and Taiwanese THR phase II, Japanese and Taiwanese TKR phase III, Japanese THR phase III, and Japanese HFS phase III studies).

PMDA considered that the appropriateness of the rules related to the timing of initiation of edoxaban administration should be determined, taking account of the actual timing of the treatment initiation in the clinical studies, not the protocol set for the clinical studies, and asked the applicant to explain the efficacy and safety for each timing of treatment initiation.

The applicant responded as follows:

Among patients in the above 5 studies receiving edoxaban 30 mg, the expected recommended clinical dose, there were only 2 subjects in whom administration was started from 6 to <12 hours after surgery, precluding the evaluation of the efficacy and safety of edoxaban administration initiated during this period. In subjects in the 30 mg group who started the treatment ≥12 hours after surgery, the incidence of VTE was 3.4% (3 of 87 subjects) in patients who started treatment ≥12 and <18 hours after surgery and 6.1% (41 of 671 subjects) in patients who started treatment ≥18 and ≤24 hours after surgery, showing a tendency of increase in the incidence of VTE with the delay in the start of administration from the end of the surgery. A similar tendency was observed in the enoxaparin group. In subjects in the 30 mg group who started treatment ≥12 hours after surgery, the incidence of bleeding events was 14.6% (14 of 96 subjects) in subjects who started treatment ≥12 and <18 hours after surgery and 22.1% (178 of 804 subjects) in subjects who started treatment ≥18 and ≤24 hours after surgery, showing no tendency of increase in the subgroup starting the treatment at an early stage. Similarly, the incidence of major bleeding or clinically relevant non-major bleeding was 4.2% (4 of 96 subjects) and 4.1% (33 of 804 subjects), respectively, showing no difference between subgroups with different timing of treatment initiation. These results suggest that the maximum prevention of VTE can be achieved, without increased bleeding risk, by starting edoxaban administration ≥12 hours after surgery upon confirming that there is no bleeding from the surgical wound, etc. Based on these results, the description in "Precautions for Dosage and Administration" of the proposed package insert will be changed to "Administration of edoxaban should be initiated at least 12 hours after surgery and upon confirming that there is no bleeding from the surgical wound, etc." The reasons for only a limited number of subjects starting the administration from 6 to <12 hours after surgery were considered to be: (i) postoperative anticoagulant therapy is generally initiated after the condition of the surgical wound is confirmed on the next day, and (ii) when epidural anesthesia is used to alleviate the wound pain immediately after surgery, the epidural catheter is removed in the next morning, which is the clinical practice in Japan.

PMDA considers as follows:

In patients undergoing orthopedic surgery of the lower limbs, it is desirable that the anticoagulant action comes into effect when the risk of thrombus formation increases. Therefore, it is appropriate to administer an anticoagulant before or during the surgery. However, given the risk of postoperative bleeding and bleeding risk associated with the use of the epidural catheter, the timing of treatment initiation has little choice but to be determined with the emphasis placed on the actual time window that showed clinically significant efficacy and acceptable safety profile in subjects enrolled in the Japanese and foreign clinical studies of edoxaban. Therefore,

it is appropriate for the applicant to change the proposed package insert regarding on the timing of edoxaban administration, as follows: "Administration of edoxaban should be initiated at least 12 hours after surgery and upon confirming that there is no bleeding from the surgical wound, etc."

4.(iii).B.(6).3) Treatment duration

Regarding the reason for describing in "Precautions for Dosage and Administration" of the proposed package insert that "The efficacy and safety of edoxaban administered for ≥15 days have not been investigated in the Japanese clinical studies in patients undergoing orthopedic surgery of the lower limbs," the applicant explained as follows:

In the Japanese and Taiwanese studies in patients undergoing orthopedic surgery of the lower limbs, the treatment duration was set at 11 to 14 days, which met the treatment duration (not less than 10 days) recommended for anticoagulants in ACCP guideline, 8th edition, and is not significantly different from the treatment duration set for drugs of the same class. However, there is no clear clinical index for judging the timing of ending the administration. In each clinical study, treatment was discontinued before 11 days of administration in some subjects, because of adverse events or necessity of prohibited concomitant medications or therapies, etc., but there were no subjects in whom the administration was discontinued based on the judgment that no further treatment with edoxaban was necessary. Administration of >14 days was not investigated in studies in patients undergoing orthopedic surgery of the lower limbs. However, since ACCP guideline, 8th edition, states that the maximum treatment duration is 35 days for Grade 1A patients undergoing THR or HFS and for Grade 2B patients undergoing TKR, and that the risk of symptomatic VTE persists up to 3 months after THR, it is expected that edoxaban may be administered for >14 days in Japan as well. Among major bleeding and clinically relevant non-major bleeding that occurred in the Japanese and Taiwanese studies in patients undergoing orthopedic surgery of the lower limbs, most of surgery-related bleeding events occurred within 8 days after the start of administration. Also in the Japanese NVAF late phase II study in which edoxaban was administered for 3 months to outpatients with NVAF, albeit different in type from that of the disease discussed here, the incidence of major bleeding or clinically relevant non-major bleeding did not tend to increase markedly with the long-term administration. These results suggest that continued administration of edoxaban after discharge is unlikely to pose any significant safety problem.

PMDA considers as follows:

In the Japanese and Taiwanese studies in patients undergoing orthopedic surgery of the lower limbs, all edoxaban doses were administered on an inpatient basis and the treatment duration was up to 14 days after surgery. Therefore, the efficacy and safety of edoxaban used after discharge or for >14 days after surgery cannot be judged at the present moment. Fondaparinux and enoxaparin, the drugs approved in Japan for patients undergoing orthopedic surgery of the lower limbs, were administered up to 14 days in the Japanese clinical studies. Those comparator drugs are assumed to be used on an inpatient basis because they are injections. As pointed out by the applicant, ACCP guideline, 8th edition, recommends administering anticoagulants for ≥10 days with the maximum duration of 35 days. However, there is no justification for adopting this treatment duration for clinical use of edoxaban in Japan. Based on the above, caution is required for administering edoxaban for >14 days or continuously after discharge to Japanese patients after orthopedic surgery of the lower limbs. When the patient's activities of daily living become possible several days after surgery and the risk of thromboembolism is not necessarily high anymore, continuous administration of the drug without careful consideration should be avoided. Particularly, the possibility that edoxaban may be taken continuously after discharge because of oral availability should be regarded as a new risk not shared by approved injections. Should edoxaban be taken continuously even after discharge, there is a possibility that early detection of adverse drug reactions and their prompt treatment may be more difficult than when

the drug is used on an inpatient basis. Therefore, edoxaban should be used on an outpatient basis only when it is judged necessary upon thorough consideration of risks and benefits. During the review process, the applicant proposed the following draft caution statement for Precautions for Dosage and Administration: "The treatment duration of edoxaban should be determined upon consideration of venous thromboembolism and bleeding risk of individual patients. Edoxaban should not be administered continuously without careful administration after the risk of venous thromboembolism has decreased. In the Japanese clinical studies, the efficacy and safety of edoxaban administered for ≥15 days have not been investigated in patients undergoing orthopedic surgery of the lower limbs." PMDA considers that the caution statement for treatment duration proposed by the applicant is acceptable at the current moment. However, by taking into consideration the appropriateness of information on treatment duration and the oral availability of edoxaban as its characteristics, the appropriateness of cautions against administration without careful consideration and of the measures to be taken for possible administration after discharge will be finalized, taking also account of comments raised in the Expert Discussion.

4.(iii).B.(7) Special patient population

4.(iii).B.(7).1) Patients with renal impairment

The package insert proposed by the applicant contains the description "In patients with renal impairment, blood edoxaban concentration may increase, resulting in an increase in the risk of bleeding. It is therefore desirable to consider dose reduction in patients with creatinine clearance <50 mL/min."

Regarding the reason for determining "CL_{CR} <50 mL/min" as the cut-off level for renal function for dose reduction consideration, the applicant explained as follows:

In the clinical studies of edoxaban, renal function was classified according to CL_{CR} level: normal (>80 mL/min), mild impairment (≥50 mL/min and ≤80 mL/min), moderate impairment (≥30 mL/min and <50 mL/min), and severe impairment (<30 mL/min). In the Study DU176b-A-U120 on pharmacokinetics of edoxaban involving patients with renal impairment who underwent orthopedic surgery of the lower limbs, the efficacy and safety of edoxaban were investigated in patients, classified by severity of renal impairment [see "4.(ii).A.(4) Studies on intrinsic factors" for results of the pharmacokinetic study]. In the combined analysis of the data from the Japanese and Taiwanese studies in patients undergoing orthopedic surgery of the lower limbs, bleeding-related adverse events in the edoxaban 30 mg group were as shown in Tables 8 and 9. The incidence of major bleeding or clinically relevant non-major bleeding in patients with CL_{CR} <50 mL/min was more than twice that observed in patients with CL_{CR} ≥50 mL/min, exceeding the incidence in the entire 30 mg group (4.1%, 37 of 904 subjects). As regards efficacy, there was no clear relationship between the incidence of VTE and CL_{CR} in the Japanese and Taiwanese studies in patients undergoing orthopedic surgery of the lower limbs [Table 10].

Table 8. Incidence of bleeding-related adverse events in the edoxaban 30 mg group in the Japanese and Taiwanese studies in patients undergoing orthopedic surgery of the lower limbs (by CL_{CR})

CL_{CR} (mL/min)	Major or clinically relevant non-major bleeding	Bleeding event
<50	9.3 (8/86)	25.6 (22/86)
≥50	3.5 (29/818)	20.8 (170/818)

% (n/N)

Table 9. Incidence of bleeding-related adverse events in the edoxaban 30 mg group in the Japanese and Taiwanese TKR, Japanese THR, and Japanese HFS phase III studies (by CL_{CR})

CL_{CR} (mL/min)	Japanese and Taiwanese TKR phase III study (major or clinically relevant non-major bleeding)	Japanese THR phase III study (major or clinically relevant non-major bleeding)	Japanese HFS phase III study (major or clinically relevant non-major bleeding)	Japanese and Taiwanese TKR phase III study (bleeding event)	Japanese THR phase III study (bleeding event)	Japanese HFS phase III study (bleeding event)
<50	8.6 (3/35)	11.1 (2/18)	4.2 (1/24)	22.9 (8/35)	33.3 (6/18)	25.0 (6/24)
≥50	6.0 (19/319)	2.1 (6/285)	2.9 (1/35)	22.3 (71/319)	19.6 (56/285)	25.7 (9/35)

% (n/N)

Table 10. Incidences of VTE and bleeding-related adverse events in the Japanese TKR phase II and Japanese and Taiwanese THR phase II studies

	Japanese TKR phase II study			Japanese and Taiwanese THR phase II study		
	Incidence of VTE	Major or clinically relevant non-major bleeding	Bleeding event	Incidence of VTE	Major or clinically relevant non-major bleeding	Bleeding event
Placebo group	48.3 (43/89)	3.9 (4/102)	9.8 (10/102)			
15 mg group	26.1 (24/92)	3.8 (4/106)	18.9 (20/106)	3.8 (3/78)	2.2 (2/89)	11.2 (10/89)
30 mg group	12.5 (11/88)	3.9 (4/103)	19.4 (20/103)	2.8 (2/72)	1.2 (1/85)	18.8 (16/85)
Enoxaparin group				4.1 (3/74)	2.3 (2/87)	17.2 (15/87)

% (n/N)

PMDA asked the applicant to specify the reduced dose and explain the efficacy at that dose.

The applicant explained as follows:
In patients with CL_{CR} <50 mL/min, the dose reduction to 15 mg is appropriate. Using the data of the Japanese TKR phase II study which was used for PPK analysis, a logistic regression analysis was performed using the number of VTE as the objective variable and $AUC_{0\text{-}24h,\ ss}$, $C_{max,\ ss}$ or $C_{min,\ ss}$, calculated from the empirical Bayes estimate based on the final model of PPK analysis, as the explanatory variable. As a result, the incidence of VTE decreased with the increase of these pharmacokinetic parameter values. In patients with decreased renal function or in concomitant use of edoxaban with a P-gp inhibitor, plasma edoxaban concentration is estimated to increase 1.4- to 2-fold. Therefore, when edoxaban is administered to these patients at a reduced dose of 15 mg, the incidence of VTE is expected to be comparable to that observed in other patients treated with 21 to 30 mg of edoxaban. In the Japanese TKR phase II study, the incidence of VTE in the 15 mg group was statistically significantly lower compared with the placebo group (Shirley-Williams method, $P < 0.001$). In addition, in the Japanese and Taiwanese THR phase II study, the incidence of VTE in the 15 mg group was similar to that in the enoxaparin group. Based on the above, the applicant considers that a definite VTE-prevention effect is expected when edoxaban 15 mg is administered to patients with impaired renal function or in concomitant use with a P-gp inhibitor, although the efficacy may be lower compared with 30 mg.

PMDA asked the applicant about the efficacy and safety in subjects who, among those enrolled in the study, had decreased renal function requiring dose reduction, according to the applicant's opinion, and the applicant submitted the data on the incidence of VTE and the incidence of

bleeding classified by renal function.

The applicant, showing the results in subjects with CL_{CR} ≥30 mL/min and <50 mL/min in the Japanese and Taiwanese studies in patients undergoing orthopedic surgery of the lower limbs [Table 11], explained as follows:
Although no detailed comparison can be made because of the limited number of subjects in the edoxaban 15 mg group and the placebo group, the incidence of VTE in the edoxaban 15 mg group was higher compared with the edoxaban 30 mg group and the enoxaparin group, but lower compared with the placebo group. The incidences of major bleeding and clinically relevant non-major bleeding were 2.3% and 9.3%, respectively, in the edoxaban 30 mg group and 0.0% and 0.0%, respectively, in the edoxaban 15 mg group. These results suggest that, in renally impaired patients with CL_{CR} ≥30 mL/min and <50 mL/min, a certain level of VTE-prevention effect can be achieved while lowering the bleeding risk by reducing the edoxaban dose to 15 mg once daily, with consideration given to the risk of VTE and bleeding in individual patients.

Table 11. Incidence of VTE and incidence of bleeding-related adverse events in subjects with CL_{CR} ≥30 mL/min and <50 mL/min in the Japanese and Taiwanese studies in patients undergoing orthopedic surgery of the lower limbs

	Placebo group	15 mg group	30 mg group	Enoxaparin group
Incidence of VTE	50.0 (3/6)	33.3 (4/12)	5.9 (4/68)	13.7 (7/51)
Major bleeding	0.0 (0/8)	0.0 (0/13)	2.3 (2/86)	0.0 (0/61)
Major or clinically relevant non-major bleeding	0.0 (0/8)	0.0 (0/13)	9.3 (8/86)	0.0 (0/61)
Bleeding event	12.5 (1/8)	7.7 (1/13)	25.6 (22/86)	16.4 (10/61)

% (n/N)

PMDA asked the applicant about the appropriateness of administering edoxaban to patients with CL_{CR} <30 mL/min, a subgroup for whom there is little experience of edoxaban administration.

The applicant explained as follows:
In the Japanese TKR phase II study which did not exclude patients with CL_{CR} <30 mL/min, edoxaban was administered to 4 patients with CL_{CR} <30 mL/min (1 subject in the 5 mg group, 3 subjects in the 60 mg group). In 2 subjects in the 60 mg group, bleeding events were observed (epistaxis classified as clinically relevant non-major bleeding, haemorrhage subcutaneous classified as minor bleeding). In the 3 subjects in the 60 mg group, the steady-state exposure level-related pharmacokinetic parameters (calculated based on empirical Bayes estimate) tended to be higher than mean values observed in the 60 mg in the Japanese TKR phase II study. Assuming that edoxaban 15 mg was administered once daily to these subjects, the exposure level would be 1/4 times the observed value, which would be similar to, or less than, the mean value achieved in the 30 mg group. Thus, edoxaban may be administered at a reduced dose even to patients with CL_{CR} <30 mL/min. However, because of little clinical experience in these patients, administration of edoxaban should be carefully decided by balancing the risk of VTE and the bleeding risk, and dose reduction is mandatory even if administration is needed. Therefore, the description in "Precautions for Dosage and Administration" of the proposed package insert will be changed to "In patients with renal impairment, blood edoxaban concentration may increase, resulting in an increased bleeding risk. Therefore, in patients with creatinine clearance of 30 to 50 mL/min, it is desirable to reduce the dose by balancing the risk of VTE and the risk of bleeding in individual patients. In patients with creatinine clearance <30 mL/min, whether or not the use of edoxaban is appropriate should be determined carefully, if administered (there are few experiences of use in patients with creatinine clearance

<30 mL/min).”

PMDA considers as follows:
The reduced dose of edoxaban 15 mg was only used in an extremely limited number of patients with CL_{CR} ≥30 mL/min and <50 mL/min. Therefore, there is a limitation to evaluating the efficacy and safety of such treatment with edoxaban based on the results of clinical studies. However, in the study results obtained, examination of bleeding-related adverse events in subjects classified by renal function showed that bleeding risk may increase in patients with renal impairment compared with those with normal renal function. First, in patients with CL_{CR} ≥30 mL/min and <50 mL/min, the risk of “major bleeding or clinically relevant non-major bleeding” is likely to increase, as stated by the applicant. Thus, appropriate measures are required. The applicant proposed the reduction of the daily dose to 15 mg, as the specific measures. Since the efficacy of edoxaban 15 mg exceeds that of the placebo, and since the dose reduction to 15 mg is expected to decrease the bleeding risk, taking account of the predication based on the pharmacokinetics, it is considered possible to administer edoxaban to patients with CL_{CR} ≥30 mL/min and <50 mL/min, with the recommended dose set at 15 mg. Therefore, it is of significance to provide information that a dose of 15 mg may be selected in considering a dose reduction. Regarding the patients for whom dose reduction should be considered, the applicant claims to include patients with creatinine clearance <30 mL/min in “Precautions for Dosage and Administration.” However, edoxaban has no choice but to be contraindicated in patients with CL_{CR} <30 mL/min, for the following reasons: (i) the safety of edoxaban in patients with CL_{CR} <30 mL/min is little known, (ii) justification for determining the edoxaban-induced bleeding risk solely by simulation based on the exposure level is unclear, (iii) in addition, available benefits may be accompanied by unacceptable risks, and (iv) the risk of VTE can be reduced by physiotherapy, etc., besides anticoagulant therapies. The appropriateness of the above conclusion and the details of the appropriate caution statements will be finalized, taking account of comments raised in the Expert Discussion.

4.(iii).B.(7).2) Low body weight patients

The applicant explained the safety of edoxaban in low body weight patients as follows:
In the Japanese and Taiwanese studies in patients undergoing orthopedic surgery of the lower limbs, examination of the incidence of bleeding-related adverse events by body weight showed that body weight had a small degree of effect on the safety of edoxaban. However, edoxaban has never been administered to patients with body weight <40 kg and, as regards pharmacokinetics, $C_{max,\ ss}$ is expected to increase in patients with low body weight although neither $AUC_{0\text{-}24h,\ ss}$ nor $C_{min,\ ss}$ will increase. Therefore, it is considered necessary to exercise caution in administering edoxaban to these patients while paying attention to the occurrence of bleeding. For this purpose, the description “Patients with body weight <40 kg (Edoxaban has never been used in Japanese clinical studies, the product may increase bleeding risk in low body weight patients.)” will be included in the “Careful Administration” section of the proposed package insert.

Table 12. Incidence of bleeding-related adverse events in the edoxaban 30 mg group in the Japanese and Taiwanese TKR, Japanese THR, and Japanese HFS phase III studies (by body weight)

	<50 kg	≥50 kg
Major or clinically relevant non-major bleeding		
Japanese and Taiwanese TKR phase III study	9.2 (6/65)	5.5 (16/289)
Japanese THR phase III study	3.0 (2/66)	2.5 (6/237)
Japanese HFS phase III study	4.8 (1/21)	2.6 (1/38)
Bleeding events		
Japanese and Taiwanese TKR phase III study	30.8 (20/65)	20.4 (59/289)
Japanese THR phase III study	27.3 (18/66)	18.6 (44/237)
Japanese HFS phase III study	28.6 (6/21)	23.7 (9/38)

% (n/N)

PMDA considers as follows:
In phase III studies, the incidence of bleeding-related adverse events by body weight tended to be higher in patients with the body weight <50 kg for all of categories of bleeding: major bleeding, clinically relevant non-major bleeding, and bleeding events [Table 12]. It is therefore desirable to carefully balance the risks and benefits of edoxaban administration in low body weight patients and, if determined appropriate, to administer the drug carefully while paying due attention to the occurrence of bleeding-related adverse events. Thus, PMDA considers the caution proposed by the applicant is acceptable.

4.(iii).B.(7).3) The elderly

The applicant explained the safety of edoxaban in the elderly as follows:
The incidence of bleeding-related adverse events in the edoxaban 30 mg group by age in the Japanese and Taiwanese TKR, Japanese THR, and Japanese HFS phase III studies was as shown in Table 13. The incidence of major bleeding or clinically relevant non-major bleeding tended to be generally higher in subjects aged ≥65 years compared with subjects aged <65 years, and in subjects aged ≥75 years compared with subjects aged <75 years, but the incidence did not far exceed that in the entire 30 mg group. None of the individual adverse events observed in subjects aged ≥65 years, or in subjects aged ≥75 years, showed any significantly higher incidence.

Table 13. Incidence of bleeding-related adverse events in the edoxaban 30 mg group in the Japanese and Taiwanese TKR, Japanese THR, and Japanese HFS phase III studies (by age)

	<65 years	≥65 years	<75 years	≥75 years
Major or clinically relevant non-major bleeding				
Japanese and Taiwanese TKR phase III study	4.9 (2/41)	6.4 (20/313)	5.3 (10/190)	7.3 (12/164)
Japanese THR phase III study	1.1 (2/174)	4.7 (6/129)	2.3 (6/258)	4.4 (2/45)
Japanese HFS phase III study	0.0 (0/11)	4.2 (2/48)	0.0 (0/20)	5.1 (2/39)
Bleeding events				
Japanese and Taiwanese TKR phase III study	19.5 (8/41)	22.7 (71/313)	22.1 (42/190)	22.6 (37/164)
Japanese THR phase III study	17.8 (31/174)	24.0 (31/129)	19.0 (49/258)	28.9 (13/45)
Japanese HFS phase III study	18.2 (2/11)	27.1 (13/48)	15.0 (3/20)	30.8 (12/39)

% (n/N)

The occurrence of bleeding events, which are adverse drug reactions caused by the primary pharmacological action of edoxaban, is considered to be dependent on the plasma edoxaban concentration. In PPK analysis, CL_{CR}, an index of renal function, was selected as the covariate

for the apparent total body clearance of edoxaban, whereas no effect of age was observed. Since CL_{CR} is generally correlated with age, increased exposure level associated with reduced renal function was considered to be a part of the cause for the increased bleeding risk in the elderly, and dose reduction is recommended in these patients, as described above. In addition, since elderly patients have an increased risk of bleeding because of the reduced physiological function, caution is provided for careful administration in the elderly.

PMDA considers that the frequency of bleeding-related adverse events tends to increase in the elderly and it is appropriate to call for careful administration, as proposed by the applicant. As regards the increased bleeding risk associated with the reduced renal function in the elderly, PMDA also considers that the applicant's policy "to ensure the safety by taking measures according to the renal function of individual patients" is appropriate [see "4.(iii).B.(7).1) Patients with renal impairment"].

4.(iii).B.(8) Other safety data

4.(iii).B.(8).1) Spinal/epidural anesthesia and epidural catheter placement

Regarding the use of spinal/epidural anesthesia, the following Warning was included in the proposed package insert: "Administration of edoxaban in combination with spinal/epidural anaesthesia or with lumbar puncture, etc. may cause haematoma at the site of the paracentesis, resulting in paralysis due to neural compression. The concomitant use should be performed with due attention to signs and symptoms of nerve disorder and, if any abnormality is observed, appropriate measures should be taken immediately", together with the following Precautions for Dosage and Administration: "The first dose of edoxaban should be administered at least 2 hours after removal of the epidural catheter or after lumbar puncture. If any of these procedures is given after the first dose, the post-treatment administration of edoxaban should be performed at least 2 hours after the treatment".

The applicant explained the rationale for these descriptions as follows:
In the protocols of the Japanese and Taiwanese studies in patients undergoing orthopedic surgery of the lower limbs, the exclusion criteria after operation included "patients in whom the indwelling epidural catheter cannot be removed within 2 hours before the start of administration," and prohibited concomitant therapies were defined as follows: "If epidural anesthesia is performed before the start of administration, the indwelling catheter should be removed within 2 hours before the start of administration. Post-operative epidural anesthesia during the administration period is prohibited." As a result, the epidural catheter was not used in any of the patients in the Japanese HFS phase III study, whereas it was used in 38.4% to 54.5% of subjects in other studies. The mean duration of the catheter placement was 17 to 18.5 hours after the end of the surgery, and the mean time from the removal of the catheter to the start of administration was 3.3 to 4.5 hours (minimum 2.0 hours). No spinal or extradural haematoma occurred in these studies. Based on the above results and according to ACCP guideline, 8th edition, the requirement "Administration of edoxaban should be initiated at least 2 hours after the removal of the catheter" is included in the "Precautions for Dosage and Administration" section.

During the review process, the applicant changed the description in "Precautions for Dosage and Administration" to "If any of these procedures is given after the first dose or subsequent doses, it should be performed at least 12 hours after the previous dose and at least 2 hours before the next dose." The applicant explained that the change was made because, after a single dose of edoxaban 30 mg, plasma edoxaban concentration and PT changed over time in a similar manner, and PT decreased close to the pre-dose level by 12 hours post-dose.

PMDA considers as follows:
In clinical practice in Japan, spinal/epidural anaesthesia and epidural catheter placement are often performed after orthopedic surgery of the lower limbs. Therefore, due caution should be provided as to these treatments and the appropriate timing of edoxaban administration. Based on the clinical study data thus far obtained, there should be no problem in setting, in the package insert, the same timing of the first dose as that used in clinical studies. With regard to the use of edoxaban in combination with spinal/epidural anaesthesia and to epidural catheter placement and its removal after the first dose or subsequent doses, there is no sufficient safety information because of the lack of clinical experience. These treatments, if necessitated, should be performed under conditions that allow addressing contingencies by referring to the cautions provided by the applicant. In addition, in the post-marketing surveillance, it is necessary to continue to carefully monitor the occurrence of adverse events related to spinal/epidural anesthesia and epidural catheter placement and collect information thereon. The appropriateness of the caution statement will be finalized, taking also account of comments raised in the Expert Discussion.

4.(iii).B.(8).2) Risk of liver disorder caused by edoxaban

The applicant explained the abnormal liver function test results observed after edoxaban administration as follows:
In the Japanese and Taiwanese studies in patients undergoing orthopedic surgery of the lower limbs, the incidence of "ALT ≥3-fold the upper limit of the reference range" was 1.3% (12 of 904 subjects) in the edoxaban 30 mg group and 7.4% (57 of 766 subjects) in the enoxaparin group, the incidence of "AST ≥3-fold the upper limit of the reference range" was 0.9% (8 of 904 subjects) in the edoxaban 30 mg group and 5.2% (40 of 766 subjects) in the enoxaparin group, and the incidence of "total bilirubin ≥2-fold the upper limit of the reference range" was 0.9% (8 of 904 subjects) in the edoxaban 30 mg group and 1.0% (8 of 766 subjects) in the enoxaparin group. There were no events judged as severe hepatic function disorder. The study was discontinued because of the abnormal liver function test values in 0.4% (5 of 1308 subjects) in the edoxaban group and in 2.5% (19 of 766 subjects) in the enoxaparin group. In 2 subjects in the edoxaban 30 mg group, the test values returned to within the reference range after study discontinuation. These results suggested that the frequency of abnormal liver function test, and the severity of the impairment as well, are lower in the edoxaban group compared with the enoxaparin group. Although the invasion by orthopedic surgery of the lower limbs was likely to be a part of the cause for the increased levels of liver function test parameters, results of the toxicological studies of edoxaban did not show any findings suggestive of hepatic function disorder. Therefore, the mechanism of edoxaban causing hepatic function disorder remains unknown. However, examination of adverse events related to hepatic function disorder observed after edoxaban administration and the changes over time of liver function test values in the Japanese and Taiwanese studies in patients undergoing orthopedic surgery of the lower limbs suggested that the risk of liver disorder-related adverse events after edoxaban can be controlled by measuring liver function parameters such as AST, ALT, and total bilirubin by laboratory test routinely performed after orthopedic surgery of the lower limbs and, in case of increased liver function test values, by discontinuing the administration at the discretion of the physician.

PMDA considers that although abnormal liver function test values may be observed after edoxaban administration, there is no increased risk compared with the existing therapies, taking account of the frequency and severity observed in the clinical studies. Therefore, there is no particular need for providing cautions at the current moment, and it will suffice to continue to collect information via the post-marketing surveillance.

4.(iii).B.(9) Post-marketing surveillance etc.

In order to investigate the safety and efficacy of edoxaban in routine use and to detect any new problems in routine use after marketing, the applicant plans to conduct a use-results survey in 2000 patients with the standard observation period of 2 months after the start of treatment. The applicant expects that, of these 2000 patients, 5% (approximately 100 subjects) are patients with moderate renal impairment, 10% (approximately 200 patients) are low body weight patients <40 kg, and 40% (approximately 800 patients) are patients aged ≥75 years. In this survey, the applicant plans to collect information on bleeding events as the priority surveillance item, to investigate the safety and efficacy by gender, age, surgical procedure, and dose, to identify factors related to bleeding adverse events, to investigate the effect of concomitant drugs (e.g., P-gp inhibitors, antiplatelet agents) that may affect bleeding, and to evaluate the safety and efficacy in low body weight patients and in high-risk patients.

PMDA considers that the post-marketing plan of the applicant is largely acceptable. However, it is also necessary to collect information on the duration of edoxaban treatment, adverse events related to spinal/epidural anaesthesia and their relationship with the timing of edoxaban, etc., thereby to continue to investigate the relationship between the efficacy and safety of edoxaban. The details of the post-marketing surveillance, etc., will be further reviewed, taking account of comments raised in 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

A document-based compliance 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, the registration center commissioned by the sponsor had inputted subject background data into electronic case report form (CRF) based on the entries in the registration form informed by the investigator, etc. Since this was found not to have affected the integrity of the study or the evaluation of the study results, PMDA concluded that there should be no problem with conducting a regulatory review based on the submitted 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 (5.3.5.1-1, 5.3.5.1-2, 5.3.5.1-3, 5.3.5.1-4). As a result, protocol deviations (noncompliance with the requirements for the study drug administration or for laboratory test) were found at some clinical trial sites. However, PMDA concluded that there should be no problem with conducting a regulatory review based on the submitted application documents.

3. Application for GMP inspection

Due to the delay in the applicant's application for GMP inspection, the time for regulatory review of edoxaban was extended.

IV. Overall Evaluation

As a result of its review based on the submitted data, PMDA concluded that the efficacy and safety of edoxaban in preventing VTE in patients undergoing TKR, THR, and HFS has been confirmed. Regarding administration of edoxaban in patients who have an increased risk of bleeding and thus require dose reduction, particularly patients with renal disorder, it is necessary to collect appropriate information after marketing. The details of caution statement for the

proper use of edoxaban, information provision, as well as the details of the appropriate post-marketing surveillance will be discussed at the Expert Discussion. PMDA considers that edoxaban may be approved if it can be concluded based on comments from the Expert Discussion that there are no particular problems.

Review Report (2)

February 9, 2011

I. Product Submitted for Registration

[Brand name]	Lixiana Tablets 15 mg and 30 mg
[Non-proprietary name]	Edoxaban Tosilate Hydrate
[Name of applicant]	Daiichi Sankyo Company, Limited
[Date of application]	March 29, 2010

II. Content of the Review

The Expert Discussion and subsequent review by the Pharmaceuticals and Medical Devices Agency (PMDA) are outlined below. The expert advisors for the Expert Discussion were nominated based on their declarations etc., concerning the product submitted for registration, in accordance with the provisions of the "Rules for Convening Expert Discussions etc., by Pharmaceuticals and Medical Devices Agency" (PMDA administrative Rule No. 8/2008 dated December 25, 2008).

(1) Clinical positioning of edoxaban

TKR, THR, and HFS are included in high-risk surgical procedures with increased VTE risk and VTE prophylaxis with anticoagulants is recommended in the major guidelines of Japan and foreign countries that contain descriptions on VTE prophylaxis after orthopedic surgery. Fondaparinux and enoxaparin are approved also in Japan for the prevention of postoperative VTE after these 3 surgical procedures and have already been recognized as options for the prevention of postoperative VTE in clinical practice. Therefore, provided that edoxaban is demonstrated to be at least non-inferior to drugs of the same class, in terms of efficacy and safety, in clinical studies in patients undergoing orthopedic surgery of the lower limbs, edoxaban may be included in the first choice drugs. The above conclusions of PMDA were supported by the expert advisors. It was also pointed out that, since the VTE risk varies, and the amount of bleeding varies widely, among the 3 surgical procedures studied by the applicant, it is of particular significance that they were investigated in separate studies. As regards safety, the expert advisors raised the following comments: (i) Since edoxaban, unlike the approved indirect factor Xa inhibitors that act via antithrombin III, is a novel low molecular weight drug that directly inhibits factor Xa, it is unpredictable whether or not edoxaban has any unknown adverse effects other than bleeding, necessitating the accumulation of information in future, and (ii) caution should be exercised to avoid misunderstanding that, because of the lack of a good index for monitoring the anticoagulant effect of edoxaban, no test is required to ensure the safety.

Since edoxaban is an orally available drug, it is expected to reduce the burden on patients compared with the approved drugs which have to be administered by subcutaneous injection, and is therefore useful for the sake of convenience. However, attention should be paid to the risk of bleeding caused by edoxaban. Taking into account that edoxaban is an oral drug which can be taken after discharge under the control of the patient, its proper use and proper risk management should be worked out. The above conclusions of PMDA were supported by the expert advisors, together with the following comments: (i) Although both anticoagulant effect and bleeding are caused by the primary effect of edoxaban, there is no drug that neutralizes the anti-factor Xa effect of edoxaban, nor an index that can evaluate the excess or deficiency of the effect, thereby underscoring the importance of risk management, and (ii) edoxaban is not by any means safer than existing approved drugs and, under the current status with few clinical experiences, edoxaban should be used by carefully balancing the risks and benefits. In addition, the

following comments were raised by the expert advisors: (i) Since patients are usually discharged in Japan after they can start rehabilitation or walk by themselves, the risk of thromboembolism has been decreased after discharge compared with that during hospitalization. Therefore, it will suffice to administer edoxaban only during the hospitalized period, as is the case with existing drugs of the same class, and (ii) once bleeding occurs, there is no effective means to stop it and, therefore, no further bleeding risk should be imposed on patients by administering edoxaban after discharge when it is more difficult to treat bleeding, if manifest, than during the hospitalization. The expert advisors agreed that edoxaban should be administered under hospitalization, as a general rule.

Based on the above discussion, PMDA instructed the applicant to include the description "Edoxaban should be administered on an inpatient basis, as a general rule." in the Precautions for Dosage and Administration section.

The applicant responded that the above caution would be included in the package insert, and PMDA considered the applicant's response to be appropriate.

(2) Efficacy

Based on the data submitted, there are no differences in intrinsic or extrinsic ethnic factors that deny the appropriateness of conducting the Japanese and Taiwanese global studies to investigate the VTE-prevention effect in Japanese and Taiwanese subjects undergoing THR or TKR. In these studies, the efficacy and safety outcomes observed in the Japanese subpopulation were consistent with those in the entire population. Based on the above results, the expert advisors supported PMDA's conclusion that the data of the Japanese and Taiwanese THR phase II study and the Japanese and Taiwanese TKR phase III study are extrapolatable to Japanese. In the confirmatory studies in patients undergoing THR or TKR, the non-inferiority of edoxaban to enoxaparin was demonstrated using the incidence of VTE as the primary efficacy endpoint. Therefore, PMDA concluded that the VTE-prevention effect was confirmed in patients undergoing THR or TKR. PMDA's conclusion was supported by the expert advisors. Regarding the efficacy of edoxaban in patients undergoing HFS, results of the Japanese HFS phase III study did not show any clear difference in efficacy between edoxaban and enoxaparin, with a proviso that the study was an open-label study conducted in a limited number of subjects. In addition, given the results of the Japanese and Taiwanese TKR phase III study and the Japanese THR phase III study, and the efficacy of edoxaban relative to drugs of the same class in Japanese patients undergoing TKR, THR, and HFS, edoxaban is expected to be effective in Japanese patients undergoing HFS, as well. The expert advisors commented on this conclusion of PMDA, as follows: The Japanese HFS phase III study was not designed, in terms of the target sample size, to demonstrate the non-inferiority of edoxaban to enoxaparin, failing to ensure a sufficient statistical power for between-group comparison. Therefore, it is difficult to conclude from the results of the study that there is no clear difference in the efficacy between edoxaban and enoxaparin in patients undergoing HFS. PMDA responded to this comment as follows: Although the Japanese HFS phase III study was not conducted on a sufficiently large scale to allow statistical comparison with the comparator, the results obtained are unlikely to be accidental, based on the collective judgment of the results of the study, efficacy and safety information that had been obtained before the study, clinical study data of drugs of the same class, and data of clinical studies of edoxaban in patients undergoing TKR and THR. The conclusion of PMDA was finally supported by the expert advisors.

(3) Indications

According to the Japanese guideline, the 3 surgical procedures, THR, TKR, and HFS are classified as those with high VTE risk and, if patients undergoing these surgeries have a thrombotic predisposition, as those with very high VTE risk. The guideline recommends anticoagulant therapy in patients undergoing these surgeries. In order to practically meet the

requirements of anticoagulants used at clinical practices for the prophylaxis of VTE after orthopedic surgery of the lower limbs in Japan, it is essential that the drugs can be used for at least these 3 surgical procedures. Clinical studies of edoxaban were conducted separately in patients undergoing these 3 surgical procedures with possibly different VTE risk or bleeding risk from each other, as were done with existing approved drugs, and the results demonstrated the efficacy and safety of edoxaban in each of these surgical procedures. Therefore, PMDA has concluded that the indication "Prevention of venous thromboembolism in patients undergoing the following orthopedic surgeries of the lower limbs: Total knee replacement, total hip replacement, and hip fracture surgery" is appropriate. The conclusion of PMDA was supported by the expert advisors.

(4) Dosage and administration

1) Recommended dosage and administration

The efficacy of once-daily administration of edoxaban 30 mg was demonstrated in the confirmatory studies in patients undergoing TKR and THR. The efficacy of once-daily administration of 30 mg was also suggested in the study in patients undergoing HFS. From the point of view of safety, given that the incidence of bleeding-related adverse events tends to increase dose-dependently, edoxaban should be used with due caution regarding bleeding risk. However, the incidence of bleeding-related adverse events observed in the edoxaban is clinically acceptable in comparison with those in the enoxaparin group. Based on the above, PMDA concluded that once-daily administration of 30 mg is the appropriate dosage regimen. The conclusion of PMDA was supported by the expert advisors.

2) Precautions for dosage and administration

a. Timing of treatment initiation

In patients undergoing orthopedic surgery of the lower limbs, it is desirable that the anticoagulant action comes into effect when the risk of thrombus formation increases. Therefore, from the efficacy point of view, it is appropriate to administer an anticoagulant before or during the surgery. However, considering the risk of postoperative bleeding and bleeding risk associated with the use of the epidural catheter, etc., the timing of treatment initiation has little choice but to be determined with the emphasis on the actual time window that showed clinically significant efficacy and acceptable safety profile in subjects enrolled in the clinical studies of edoxaban. Based on the above, PMDA concluded that it is appropriate to stipulate the timing of treatment initiation as follows: "Administration of edoxaban should be initiated at least 12 hours after surgery and upon confirming that there is no bleeding from the surgical wound, etc." The conclusion of PMDA was supported by the expert advisors.

b. Treatment duration

The maximum treatment duration evaluated in clinical studies was 14 days after surgery, and the efficacy and safety of edoxaban administered after that period were not investigated. Therefore, when activities of daily living become possible several days after surgery and the risk of thromboembolism is not necessarily high anymore, continuous administration of edoxaban without careful consideration should be avoided. To avoid edoxaban administration for an excessively long term in or outside hospital, an appropriate caution should be provided, with consideration given to the oral availability of edoxaban. Based on the above, PMDA concluded that it is appropriate to provide a caution that "there is no experience of use for ≥15 days" in proposed indications. The conclusion of PMDA was supported by the expert advisors.

c. Edoxaban administration in patients with renal impairment

Plasma edoxaban concentration may increase with decreasing renal function, resulting in an increased bleeding risk. Therefore, based on the efficacy of edoxaban 15 mg in study results submitted, PMDA concluded that dose reduction to 15 mg should be considered in patients

with moderate renal impairment with CL_{CR} ≥30 mL/min <50 mL/min. The conclusion of PMDA was supported by the expert advisors.

As regards patients with severe renal impairment (CL_{CR} <30 mL/min), although these patients may undergo THR, TKR, or HFS, the safety of edoxaban in these patients is unknown and the risks may be unacceptable compared with the benefits obtained. Since VTE risk in these patients can be reduced by physiotherapy, etc., instead of anticoagulant therapy, administration of edoxaban should be contraindicated in these patients. The expert advisors commented on the above conclusion of PMDA, as follows: (i) Given that the objective of edoxaban is the primary prophylaxis of VTE after THR, TKR, and HFS, occurrence of bleeding that may result in serious outcome is unacceptable, raising a question on the appropriateness of actively administering edoxaban even to patients with high bleeding risk, and (ii) since the risk of bleeding of edoxaban is not necessarily lower than that of drugs of the same class and since its effect cannot be neutralized nor monitored, edoxaban should not be recommended to patients with severe renal impairment with uncertain risk of bleeding. Thus, the expert advisors agreed that edoxaban should be contraindicated in patients with CL_{CR} <30 mL/min.

Based on the above discussion, PMDA instructed the applicant to contraindicate edoxaban in "patients with severe renal impairment (creatinine clearance <30 mL/min)" and to include the following caution statement in the "Precautions for Dosage and Administration" section: "In patients with renal impairment, blood edoxaban concentration may increase, resulting in an increased bleeding risk. Therefore, in patients with moderate renal impairment (creatinine clearance of 30-50 mL/min), dose reduction to 15 mg once daily should be considered by balancing the risk of venous thromboembolism and that of bleeding in individual patients."

The applicant responded as follows:
The exposure level (AUC, C_{max}, C_{min}) following once-daily administration of edoxaban 15 mg in patients with CL_{CR} <30 mL/min is estimated to be comparable to that following once-daily administration of edoxaban 30 mg in patients with CL_{CR} ≥50 mL/min, from which the bleeding risk is considered to be within the acceptable range. However, the bleeding risk in patients with severe renal impairment was evaluated using the results of simulation based on the exposure level, and there is little experience of use in these patients in clinical studies. Thus, it cannot be ruled out that edoxaban administration may be associated with unacceptable risk in comparison with the VTE-prevention effect after surgery. Therefore, edoxaban is contraindicated in these patients. Also for patients with moderate renal impairment, the above caution statement will be included in the package insert.

PMDA has concluded that the applicant's proposed measures are appropriate.

d. Drugs requiring careful concomitant use

Considering that verapamil, a drug which increases both C_{max} and AUC of edoxaban by 53% when concomitantly administered, is included in precautions for concomitant use, and that concomitant use of amiodarone, a drug with P-gp-inhibiting activity, also increases C_{max} of edoxaban by 66% and AUC by 40%, amiodarone also should be included in precautions for concomitant use. The conclusion of PMDA was supported by the expert advisors. In addition, the following comment was raised by the expert advisors: Nonsteroidal antiinflammatory analgesics are often administered to patients for whom edoxaban is indicated, and concomitant use with these drugs may excessively enhance the antithrombotic effect. Therefore, these drugs also should be included in precautions for concomitant use.

Based on the above discussion, PMDA instructed the applicant to include amiodarone and nonsteroidal antiinflammatory analgesics in precautions for concomitant use.

The applicant agreed to include amiodarone and nonsteroidal antiinflammatory analgesics with platelet aggregation-inhibiting activity in precautions for concomitant use. PMDA has concluded that the measures proposed by the applicant were appropriate.

e. Spinal/epidural anaesthesia and catheter placement

With regard to the use of edoxaban in combination with spinal/epidural anaesthesia and to epidural catheter placement and its removal after the first dose or subsequent doses, there is no sufficient safety information because of the lack of clinical experience. Therefore, such treatments cannot be recommended. These treatments, if necessitated, should be performed under conditions that allow addressing contingencies by referring to the cautions provided by the applicant that "the treatment should be performed at least 12 hours after the previous dose and at least 2 hours before the next planned dose." The expert advisors commented on this conclusion of PMDA, as follows: (i) Extreme caution is required for bleeding because, once it occurs, it may result in serious sequelae, and (ii) it is likely that spinal/epidural anesthesia and epidural catheter placement are often performed in patients undergoing THR, TKR, and HFS and, although there is no solid evidence, currently there is no better measures than the revised cautions proposed by the applicant. Therefore, PMDA concluded that information should be collected continuously after marketing while providing the revised cautions. This conclusion of PMDA was supported by the expert advisors.

(5) Post-marketing surveillance

The post-marketing surveillance plan (draft) presented by the applicant is largely appropriate. However, it is also necessary to collect information on the duration of edoxaban treatment, adverse events related to spinal/epidural anaesthesia and epidural catheter placement and their relationship with the timing of edoxaban treatment, etc., thereby to continue to investigate the relationship between the efficacy and safety of edoxaban. This conclusion of PMDA was supported by the expert advisors.

Based on the above discussion, PMDA instructed the applicant to re-examine the post-marketing surveillance plan.

The applicant submitted an outline of the revised post-marketing surveillance plan (draft) with modified survey items.

PMDA concluded that, although the post-marketing surveillance plan has to be reviewed in detail, the outline of the plan (draft) presented by the applicant is appropriate, and accepted the response of the applicant.

III. Overall evaluation

As a result of the above review, PMDA concludes that the product may be approved for the following indication and dosage and administration. The re-examination period should be 8 years, the drug substance and the drug product are not classified as poisonous drugs or as powerful drugs, and the product is not classified as a biological product or a specified biological product.

[Indication]	Prevention of venous thromboembolism in patients undergoing the following orthopedic surgeries of the lower limbs: Total knee replacement, total hip replacement, and hip fracture surgery
[Dosage and administration]	The usual adult dosage is 30 mg of edoxaban administered orally once daily.