Report on the Deliberation Results

September 14, 2016

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

Brand Name	Prizbind Intravenous Solution 2.5 g
Non-proprietary Name	Idarucizumab (Genetical Recombination) (JAN*)
Applicant	Nippon Boehringer Ingelheim Co. Ltd.
Date of Application	February 23, 2016

Results of Deliberation

In its meeting held on September 7, 2016, 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 re-examination period is 8 years. Neither the drug product nor its drug substance is classified as a poisonous drug or a powerful drug. The product is classified as a biological product.

Conditions of Approval

The applicant is required to:

1. Develop and appropriately implement a risk management plan.
2. Conduct a use-results survey encompassing all patients treated with the product. Because of the very limited experience in Japanese patients, the survey should be conducted in all patients treated with the product until data are collected on a certain number of patients in order to identify the characteristics of the treated patients, collect data on the safety and efficacy of the product without delay, and take necessary measures to ensure the proper use of the drug product.

**Japanese Accepted Name (modified INN)*

Review Report

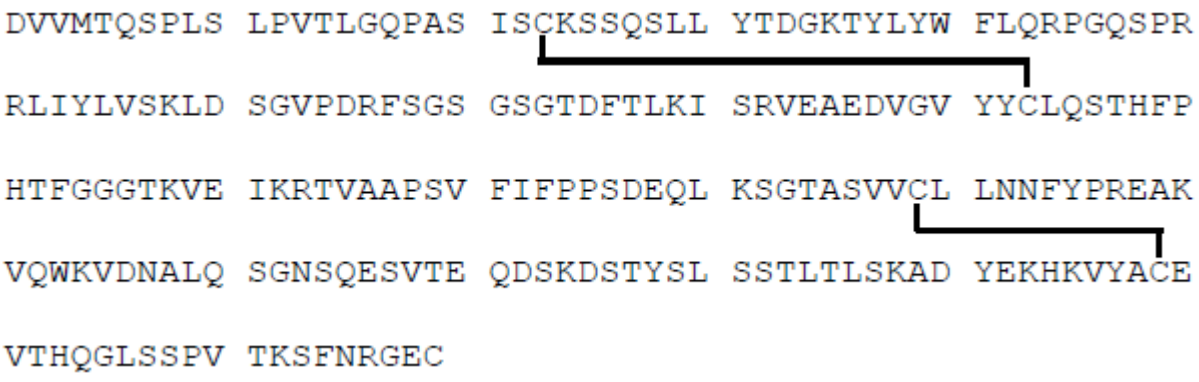
August 26, 2016
Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following pharmaceutical product submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency.

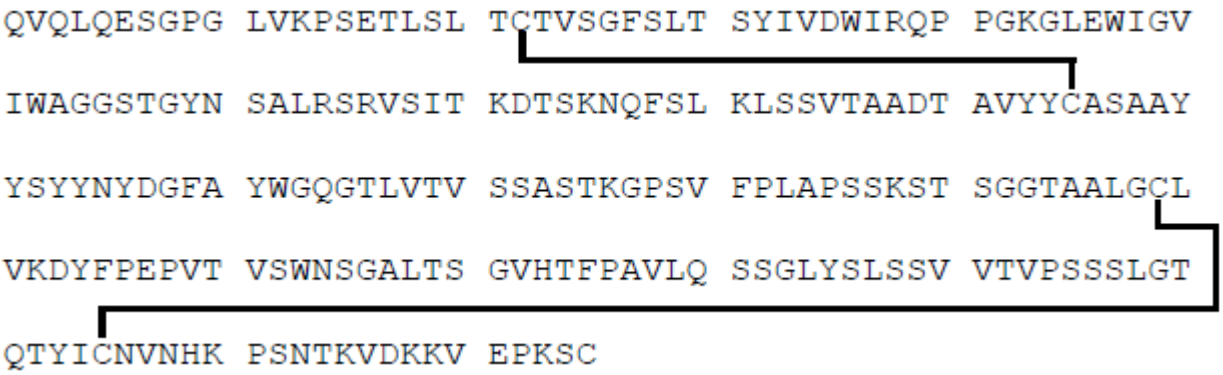
Brand Name	Prizbind Intravenous Solution 2.5 g
Non-proprietary Name	Idarucizumab (Genetical Recombination) (JAN*)
Applicant	Nippon Boehringer Ingelheim Co. Ltd.
Date of Application	February 23, 2016
Dosage Form/Strength	Solution for injection/infusion: each 50 mL vial contains 2.5 g of Idarucizumab (Genetical Recombination)
Application Classification	Prescription drug, (1) Drug containing a new active ingredient
Definition	Idarucizumab is a recombinant humanized monoclonal antibody Fab fragment composed of complementarity-determining regions derived from mouse anti-dabigatran monoclonal antibody and framework regions and constant regions derived from human IgG1. Idarucizumab is a protein composed of an H-chain (γ1-chain) fragment consisting of 225 amino acid residues and an L-chain (κ-chain) consisting of 219 amino acid residues.

[Structure]

Light (L) chain



Heavy (H) chain fragment



Disulfide bond: between cysteine 219 of the L chain and cysteine 225 of the H chain fragment.

Molecular formula: $C_{2131}H_{3299}N_{555}O_{671}S_{11}$ (double chain)

L chain: $C_{1066}H_{1660}N_{284}O_{337}S_{6}$

H chain fragment: $C_{1065}H_{1641}N_{271}O_{334}S_{5}$

Molecular weight: 47782.03

Items Warranting Special Mention Priority review (PSEHB/ELD Notification No. 0330-8 dated March 30, 2016, by the Evaluation and Licensing Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare)

Reviewing Office Office of New Drug II

Review Results

The Pharmaceuticals and Medical Devices Agency (PMDA) has concluded that the data submitted demonstrate the efficacy of the product in reversal of the anticoagulant effects of dabigatran in patients with life-threatening or uncontrolled bleeding and in patients receiving emergency surgery or urgent procedures in which serious bleeding is anticipated, and that its safety is acceptable in view of the benefits indicated by the data submitted, as shown in the Attachment.

As a result of its regulatory review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following conditions. However, PMDA considers that the thromboembolic risk, the risk of hypersensitivity, and other risks associated with the product should be further investigated.

Indication

Reversal of the anticoagulant effects of dabigatran in the following situations:

- Occurrence of life-threatening bleeding or uncontrolled bleeding
- Emergency surgery or urgent procedures in which significant bleeding is anticipated

Dosage and Administration

The usual adult dose is 5 g of Idarucizumab (Genetical Recombination) (2 vials of 2.5 g/50 mL each), administered intravenously as infusions over 5 to 10 minutes per vial or as a bolus injection.

Conditions of Approval

The applicant is required to:

1. Develop and appropriately implement a risk management plan.
2. Conduct a use-results survey encompassing all patients treated with the product. Because of the very limited experience in Japanese patients, the survey should be conducted in all patients treated with the product until data are collected on a certain number of patients in order to identify the characteristics of the treated patients, collect data on the safety and efficacy of the product without delay, and take necessary measures to ensure the proper use of the drug product.

Attachment

Review Report (1)

June 24, 2016

The following is an outline of the data submitted by the applicant and content of the review conducted by the Pharmaceuticals and Medical Devices Agency.

Product Submitted for Approval

Brand Name	Prizbind Intravenous Solution 2.5 g (changed from the proposed name of Prizbind 2.5 g for intravenous injection)
Non-proprietary Name	Idarucizumab (Genetical Recombination)
Applicant	Nippon Boehringer Ingelheim Co. Ltd.
Date of Application	February 23, 2016
Dosage Form/Strength	Solution for injection/infusion: each 50 mL vial contains 2.5 g of Idarucizumab (Genetical Recombination)
Proposed Indication	Reversal of the anticoagulant effects of dabigatran
Proposed Dosage and Administration	The usual adult dose is 5 g of Idarucizumab (Genetical Recombination) (2 vials of 2.5 g/50 mL each), administered intravenously as 2 consecutive infusions over 5 to 10 minutes per vial or as a bolus injection.

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List of Abbreviations

ACT	Activated clotting time
ADA	Anti-drug antibody (Anti-idarucizumab antibody)
ADP	Adenosine diphosphate
AEX	Anion exchange chromatography
aPCC	Activated prothrombin complex concentrate
aPTT	Activated partial thromboplastin time
ASA	Acetylsalicylic acid
Asp-N	Peptidyl-Asp metalloendopeptidase
AUC_{0-24}	Area under the concentration-time curve from time 0 to 24 h
$AUC_{0-\infty}$	Area under the concentration-time curve from time 0 to infinity
AUEC	Area under the effect curve
CAT	Calibrated automated thrombogram
cDNA	Complementary DNA
CEX	Cation exchange chromatography
CGE	Capillary gel electrophoresis
CI	Confidence interval
CIC	Circulating immune complex
CL	Total clearance
CL/F	Apparent clearance
C_{max}	Maximum concentration of analyte in plasma
CQA	Critical quality attribute
CrCL	Creatinine clearance
CV	Coefficient of variation
DE	Dabigatran etexilate
DEMS	Dabigatran etexilate methanesulfonate
DMSO	Dimethylsulfoxide
DNA	Deoxyribonucleic acid
dTT	Diluted thrombin time
DVT	Deep venous thrombosis
ECL	Electrochemiluminescence
ECT	Ecarin clotting time
EC_{50}	50% effective concentration
ELISA	Enzyme-linked immunosorbent assay
E_{max}	Maximum observed or estimated efficacy or PD effect
ESI-Q-TOF-MS	Electrospray ionization-quadrupole-time of flight mass spectrometry
ETP	Endogenous thrombin potential
Fab	Fragment antigen binding
FcRn	Neonatal Fc receptor
fe	Fraction of analyte eliminated in urine
FPA	Fibrinopeptide A
GUSTO	Global Use of Strategies to Open Occluded Arteries
Hb	Hemoglobin
HCP	Host cell protein
HES	Hydroxyethyl starch
HPLC	High performance liquid chromatography
HPSEC	High performance size exclusion chromatography
IC_{50}	50% inhibitory concentration
Idarucizumab	Idarucizumab (Genetical Recombination)
IgG	Immunoglobulin G
IgM	Immunoglobulin M
ISTH	International Society on Thrombosis and Haemostasis
k_a	Association rate constant
K_D	Equilibrium dissociation constant
k_d	Dissociation rate constant
LC-MS	Liquid chromatography-mass spectrometry
LC-MS/MS	Liquid chromatography-tandem mass spectrometry
LLOQ	Lower limit of quantitation
LMWH	Low molecular weight heparin
MCB	Master cell bank
MedDRA	Medical Dictionary for Regulatory Activities
MRT	Mean residence time
NVAF	Non-valvular atrial fibrillation

NZW	New Zealand White
PAR1	Protease activated receptor 1
PAS	Periodic acid-Schiff
PCC	Prothrombin complex concentrate
PD	Pharmacodynamics
PE	Pulmonary embolism
PEG	Polyethylene glycol
P-gp	P-glycoprotein
PK	Pharmacokinetics
Plasma sum dabigatran concentration	Combined plasma concentration of bound and unbound dabigatran and dabigatran metabolites (glucuronides) to plasma protein or idarucizumab
Plasma unbound sum dabigatran concentration	Combined plasma concentration of dabigatran and dabigatran metabolites (glucuronides) unbound to either plasma protein or idarucizumab
PMDA	Pharmaceuticals and Medical Devices Agency
PPCB	Post production cell bank
PPK	Population pharmacokinetics
PPP	Platelet poor plasma
Prizbind	Prizbind Intravenous Solution 2.5 g
PT	Prothrombin time
QbD	Quality by design
Q/F	Apparent intercompartmental clearance
rFVIIa	Recombinant Factor VIIa
RH	Relative humidity
RIPA	Radioimmunoprecipitation assay
ROTEM	Rotational thromboelastometry
SDS	Sodium dodecyl sulfate
SPR	Surface plasmon resonance
TIMI	Thrombolysis in myocardial infarction
TK	Toxicokinetics
TNF	Tumor necrosis factor
t-PA	tissue plasminogen activator
TPN	Total parenteral nutrition
TT	Thrombin time
$t_{1/2}$	Half-life
ULN	Upper limit of normal
UV method	Ultraviolet absorption spectroscopy
V_{SS}	Steady-state volume of distribution
VTE	Venous thromboembolism
WCB	Working cell bank

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

Dabigatran is a selective direct thrombin inhibitor that competitively and reversibly binds to thrombin and exerts its anticoagulant effect by inhibiting the catalytic activity of thrombin to convert fibrinogen to fibrin. In Japan, Prazaxa Capsules containing the prodrug, dabigatran etexilate methanesulfonate (DEMS), as an active ingredient was approved in January 2011. Idarucizumab is a humanized monoclonal antibody fragment discovered by Boehringer Ingelheim in Germany and has a high affinity for dabigatran. Idarucizumab specifically binds to dabigatran and immediately reverses the anticoagulant effects of dabigatran.

Outside Japan, clinical studies of idarucizumab were started in 2012. Idarucizumab was granted an accelerated approval in the US in October 2015 and was approved under accelerated assessment in Europe in November 2015. These approvals were based on clinical study data including the interim data (cutoff date, [redacted]) from a multi-regional phase III study conducted in patients receiving dabigatran and requiring reversal of the anticoagulant effects of dabigatran for emergency surgery or urgent procedures or in situations of life-threatening or uncontrolled bleeding. As of May 2016, idarucizumab has been approved in 7 countries and regions.

In Japan, clinical studies were initiated by Nippon Boehringer Ingelheim Co. Ltd. in 2014, and a marketing approval application was filed with data from clinical studies conducted in and outside Japan and the interim data (cutoff date, [redacted]) from the above-mentioned multi-regional phase III study including data in Japanese patients.

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

2.1 Drug substance

2.1.1 Generation and control of the cell substrate

Dabigatran-protein conjugates prepared by binding dabigatran (hapten) to [redacted] and [redacted] were used to immunize mice. A hybridoma cell line was generated by the fusion of murine myeloma cells with splenocytes from the mice immunized with dabigatran-protein conjugates. A hybridoma clone producing antibodies which specifically bind to the dabigatran-protein conjugates was selected from the hybridoma cell line, and a cDNA encoding the variable domains of the heavy and light chains was isolated from the hybridoma clone. The cDNA was used for humanization and optimization, and gene fragments encoding the variable domains of the heavy and light chains of the humanized Fab were prepared. The expression constructs for the heavy and light chains were generated by the insertion of these gene fragments into each corresponding expression vectors. The 2 expression constructs were transfected into the Chinese hamster ovary (CHO) cell line. The most appropriate clone for production of idarucizumab was selected and used to prepare the MCB and WCB.

The MCB, WCB, and PPCB have been tested for identity and purity according to the following notifications by the Ministry of Health and Welfare: “Viral Safety Evaluation of Biotechnology Products Derived From Cell

Lines of Human or Animal Origin" (PMSB/ELD Notification No. 329 dated February 22, 2000 [ICH Q5A (R1) Guidelines]); "Quality of Biotechnological Products: Analysis of the Expression Construct in Cell Lines Used for Production of r-DNA Derived Protein Products" (PMSB/ELD Notification No. 3 dated January 6, 1998 [ICH Q5B Guidelines]); and "Derivation and Characterisation of Cell Substrates Used for Production of Biotechnological/Biological Products" (PMSB/ELD Notification No. 873 dated July 14, 2000 [ICH Q5D Guidelines]). Genetic stability during manufacturing process has been demonstrated, and no adventitious viruses or non-viral adventitious agents were detected within the range of parameters tested.

The MCB and WCB are stored in the vapor phase of liquid nitrogen. While no new MCB is planned to be prepared, a new WCB will be prepared as appropriate.

2.1.2 Manufacturing process

The manufacturing process for the drug substance consists of the following steps: inoculum cultivation, expanded cultivation, cultivation for production, harvest, [redacted] (Impurity A), [redacted], [redacted], [redacted], [redacted], viral filtration, concentration and replacement of buffer, final preparation/filtration/testing, splitting and pooling, and storage. The manufactured drug substance is stored in a stainless steel container at −20°C.

Steps [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], and [redacted] are defined as critical steps.

Process validation was performed at the commercial scale to validate the manufacturing process for the drug substance.

2.1.3 Safety evaluation of adventitious agents

No raw materials of animal origin, except for the CHO cell line used as the host cells, have been used in the manufacturing process for the drug substance.

The MCB, WCB, and PPCB have been tested for purity [see "2.1.1 Generation and control of the cell substrate"]. Mycoplasma testing, sterility testing, *in vitro* adventitious virus testing, and transmission electron microscopy were performed on the pre-harvest unprocessed bulk manufactured at a commercial scale. No contamination by viral or non-viral adventitious agents was detected within the range of the parameters tested. Tests for mycoplasma, sterility, and *in vitro* adventitious viruses on the unprocessed bulk have been defined as in-process control tests.

Viral clearance studies with model viruses were performed for the purification process and demonstrated that the purification process has a certain level of capacity to remove viruses (Table 1).

Table 1. Results of viral clearance studies

Manufacturing process	Viral reduction factor (log_{10})			
	Murine leukemia virus	Pseudorabies virus	Reovirus type 3	Murine minute virus
[redacted]	>[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	>[redacted]	>[redacted]	[redacted]	[redacted]
[redacted]	>[redacted]	>[redacted]	>[redacted]	>[redacted]
Viral filtration	>[redacted]	>[redacted]	>[redacted]	>[redacted]
Overall virus reduction factor	>20.01	>18.95	>17.03	>16.24

2.1.4 Manufacturing process development

The major changes in the manufacturing process during the development of the drug substance are shown below: the respective manufacturing processes are referred to as the "Non-clinical Manufacturing Process," "Manufacturing Process CMC1," "Manufacturing Process CMC2," "Manufacturing Process CMC3," and "Proposed Manufacturing Process." [redacted]. Formulation made from the drug substance manufactured by [redacted] was used in the phase III study.

- Changes from Non-clinical Manufacturing Process to Manufacturing Process CMC1: Changes in [redacted], [redacted], [redacted] steps.
- Changes from Manufacturing Process CMC1 to Manufacturing Process CMC2: Changes in [redacted] and [redacted].
- Changes from Manufacturing Process CMC2 to Manufacturing Process CMC3: Changes in [redacted] and [redacted].
- Changes from Manufacturing Process CMC3 to the Proposed Manufacturing Process: Changes in [redacted].

When changes were made to the manufacturing process, the comparability of quality attributes was evaluated and the pre- and post-change drug substances were shown to be comparable.

A Quality by design (QbD) approach has been applied to develop the manufacturing process [see "2.3 QbD"].

2.1.5 Characterization

2.1.5.1 Structure and properties

Characterization of the drug substance was performed (Table 2).

Table 2. Attributes tested and methods used in characterization

Attributes		Study methods
Primary structure	Amino acid sequence	Trypsin, chymotrypsin, and Asp-N digestion peptide mapping (LC-MS/MS) Trypsin digestion peptide mapping (matrix-assisted laser desorption/ionization time-of-flight mass spectrometry, LC-MS/MS)
Higher-order structure	Secondary structure, higher-order structure	Far-ultraviolet circular dichroism spectroscopy, Fourier-transform infrared spectroscopy, near-ultraviolet circular dichroism spectroscopy
	Disulfide bond	X-ray crystallography, LC-MS
	Free thiol group	LC-MS
Physicochemical properties	Molecular weight	ESI-Q-TOF-MS
	Extinction coefficient	UV method, Kjeldahl method
	Thermal stability	Differential scanning calorimetry
	Molecular variants	[redacted], [redacted], [redacted], analytical ultracentrifugation, SDS-polyacrylamide gel electrophoresis (silver staining), CGE (non-reducing/reducing) Isoelectric focusing, LC-MS, CEX, ESI-Q-TOF-MS
Biological properties	Binding activity to dabigatran	SPR method
	Inhibitory activity on dabigatran	Thrombin clotting activity

2.1.5.2 Product-related substances and product-related impurities

Based on results of the analyses shown in Section "2.1.5.1 Structure and properties," [redacted], [redacted], and [redacted] were identified as product-related substances. The high-molecular-weight form [redacted], and the low-molecular-weight form [redacted], and the free light chains were identified as product related impurities. These product-related substances and impurities have been controlled with specifications.

2.1.5.3 Process-related impurities

Host cell protein (HCP), host cell DNA, [redacted], Impurity A, [redacted], [redacted], [redacted], and [redacted] were identified as process-related impurities. All of the process-related impurities have been shown to be effectively and consistently removed in the manufacturing process.

2.1.6 Control of drug substance

The specification for the drug substance consists of content, description, identification (peptide map), osmolality, pH, purity ([redacted], [redacted], CGE [under non-reducing and reducing conditions], HCP [enzyme-linked immunosorbent assay (ELISA)] and Impurity A [ELISA]), endotoxins, microbial limits, binding activity to dabigatran, inhibitory activity on dabigatran (thrombin clotting activity), and assay (UV method).

2.1.7 Stability of drug substance

Main stability studies of the drug substance are shown in Table 3. Stability of drug substance has been evaluated mainly with the drug substance manufactured by the Manufacturing Process CMC3.

Table 3. Outline of main stability studies of the drug substance

	No. of batches	Storage condition	Study period	Storage form
Long-term	7	−20°C ± [redacted]°C	24 months [a)]	Stainless steel container
Intermediate	7	5°C ± [redacted]°C	12 months	
Accelerated	7	25°C ± [redacted]°C/60% ± [redacted]% RH	6 months	
Stress	6	40°C ± [redacted]°C/75% ± [redacted]%RH	3 months	[redacted]

[a)] Long-term testing is ongoing (continued for [redacted] months).

The long-term testing showed no obvious changes in the quality attributes during the test period.

The intermediate testing showed decreases in [redacted] ([redacted]) at Month 12.

The accelerated testing showed increases in [redacted], [redacted], and [redacted] and an increasing tendency in [redacted], [redacted], and [redacted]. Besides the above, there were decreases observed in [redacted], [redacted], and [redacted].

The stress testing showed changes in [redacted], in addition to changes observed in the accelerated testing, and an increasing tendency in [redacted].

Based on the above results, a shelf-life of 24 months was established for the drug substance when stored in a stainless steel container at −20°C.

2.2 Drug product

2.2.1 Description and composition of drug product and formulation development

The drug product is a solution for injection containing idarucizumab 2500 mg per 50 mL. The drug product contains the following excipients: glacial acetic acid, polysorbate 20, sodium acetate hydrate, D-sorbitol, and water for injection. The drug product is filled into a glass vial and closed with a butyl rubber stopper.

2.2.2 Manufacturing process

The manufacturing process for the drug product consists of the following steps: thawing; splitting and pooling; sterile filtration; filling and stoppering; capping; visual inspection; release testing; and secondary packaging and storage. [redacted], [redacted], and [redacted] are critical steps.

Process validation for the manufacturing process for the drug product has been performed at a commercial scale.

2.2.3 Manufacturing Process Development

During the development of the drug product, changes were made to the manufacturing scale, the filling step, etc. When changes were made to the manufacturing process for the drug product, the comparability of quality attributes was evaluated and the pre- and post-change drug products were shown to be comparable.

A QbD approach has been applied to develop the manufacturing process [see “2.3 QbD”].

2.2.4 Control of drug product

The specification for the drug product consists of content, description, identification (peptide map), osmolality,

pH, purity ([redacted], [redacted], CGE [under non-reducing and reducing conditions]), endotoxins, extractable volume, foreign insoluble matters, insoluble particulate matters, sterility, polysorbate 20, binding activity to dabigatran, inhibitory activity on dabigatran (thrombin clotting activity), and assay (UV method).

2.2.5 Stability of drug product

Main stability studies of the drug product are shown in Table 4. Stability of drug product has been evaluated with the formulation manufactured by the Proposed Manufacturing Process using the drug substance manufactured by the Manufacturing Process CMC3.

Table 4. Outline of main stability studies of the drug product

	No. of batches	Storage condition	Study period	Storage form
Long-term	4	5°C ± [redacted]°C	24 months [a)]	Butyl rubber stopper and glass vial
Accelerated	4	25°C ± [redacted]°C/60% ± [redacted]%RH	12 months	
Stress (temperature)	4	40°C ± [redacted]°C/75% ± [redacted]%RH	3 months	
Stress (light)	3	Overall illumination of ≥1.2 million lux·h and an integrated near ultraviolet energy of ≥200 W·h/m^2		

[a)] Long-term testing is ongoing (continued for [redacted] months).

The long-term testing showed no obvious changes in the quality attributes during the test period.

The accelerated testing showed increases in [redacted] and an increasing tendency in [redacted], [redacted], and [redacted]. Besides the above, there were decreases observed in [redacted] and a decreasing tendency observed in [redacted].

The stress testing (temperature) showed changes in [redacted], in addition to changes observed in the accelerated testing.

The stress testing (light) revealed that the drug product was photolabile.

Based on the above results, a shelf-life of 24 months was established for the drug product when stored at 2°C to 8°C and protected from light.

2.3 QbD

A QbD approach was applied to develop the drug substance and the drug product, and the quality control strategy has been established with consideration of the following.

- Identification of CQAs

On the basis of data obtained during the development and general scientific knowledge, the following CQAs have been identified from the quality attributes of the drug product, including the product-related substances, product-related impurities, and process-related impurities [see "2.1.5 Characterization"].

CQAs of drug substance: Color, opacity, pH, osmolality, [redacted], HCP, host cell DNA, Impurity A, [redacted], viral contamination, sterility, bioburden, endotoxins, mycoplasma, binding activity to dabigatran, inhibitory activity on dabigatran, and [redacted]

CQAs of drug product: Color, opacity, pH, osmolality, foreign insoluble matters, insoluble particulate matters, [redacted], sterility, endotoxins, [redacted], extractable volume, binding activity to dabigatran, inhibitory activity on dabigatran, and [redacted]

- Process characterization

  Process parameters (input) and performance indicators (output) were classified based on risk assessment, and every step was characterized.

- Establishment of control method

  Control of quality attributes has been established based on the knowledge of the manufacturing process (including the process characterization above), batch analysis data, stability data, and other relevant data. The control of quality attributes consists of the control of process parameters and performance indicators, in-process control, and specifications [see "2.1.5.2 Product-related substances and product-related impurities" and "2.1.5.3 Process-related impurities" for control of product-related impurities and process-related impurities].

2.R Outline of the review by PMDA

Based on the submitted data, PMDA concluded that the quality of the drug substance and the drug product has been controlled appropriately.

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

3.1 Primary pharmacodynamics

3.1.1 *In vitro* evaluation on binding of idarucizumab and dabigatran (CTD 4.2.1.1-08)

The K_D of idarucizumab binding to dabigatran (mean ± standard deviation [SD]) was 2.1 ± 0.7 pmol/L at pH 7.4. The k_a and k_d between idarucizumab and dabigatran (mean ± SD) was $3.4 \pm 0.4 \times 10^5$ $(mol/L)^{-1}s^{-1}$ and 0.7

± 0.08 × $10^{-6}s^{-1}$, respectively. Based on these results, the half-life of idarucizumab-dabigatran complex was estimated to be approximately 260 h. The K_D of dabigatran binding to thrombin at pH 7.7 was reported to be 0.7 nmol/L (*Thrombosis and Haemostasis.* 2007;98:155-62).

The K_D of idarucizumab binding to dabigatran at pH 6.0, 6.7, 7.4, and 8.0 was 62, 9, 4, and 1 pmol/L, respectively.

3.1.2 *In vitro* inhibitory effect of idarucizumab on dabigatran anticoagulant effect

3.1.2.1 Inhibition in human plasma and whole blood (CTD 4.2.1.1-12)

The inhibitory effect of idarucizumab on the anticoagulant activity of dabigatran and its active metabolites was assessed with TT as an indicator which was measured in a modified TT assay.

Thrombin (0.4 U/mL) was added to human plasma spiked with dabigatran (7 nmol/L), dabigatran glucuronide (10 nmol/L), or vehicle (DMSO or 0.1% acetic acid). The TT in the plasma containing dabigatran or dabigatran glucuronide was prolonged by approximately 40 seconds as compared with the plasma containing the vehicle. This TT value observed in the plasma treated with dabigatran or dabigatran glucuronide was defined as a value of 100%, and that with vehicle 0%. Idarucizumab at several concentrations was added to the human plasma treated with dabigatran or dabigatran glucuronide, and TT was measured. IC_{50} of idarucizumab for the TT prolongation by dabigatran and dabigatran glucuronide was 3.1 and 2.4 nmol/L, respectively. The TT prolonged by dabigatran at 7 nmol/L and dabigatran glucuronide at 10 nmol/L was almost completely reversed by idarucizumab at 7 and 10 nmol/L, respectively.

Thrombin (1.5 U/mL) was added to human whole blood and plasma spiked with dabigatran (30 nmol/L) or vehicle (DMSO). The TT in the whole blood and plasma treated with dabigatran was prolonged by approximately 20 and 30 seconds, respectively, as compared with those containing the vehicle. The TT value observed with dabigatran was defined as a value of 100%, and that with vehicle 0%, respectively. IC_{50} of idarucizumab for the TT prolongation by dabigatran in human whole blood and plasma was 11.29 and 10.85 nmol/L, respectively. The TT prolonged by dabigatran at 30 nmol/L was almost completely reversed by idarucizumab at 30 nmol/L.

3.1.2.2 Idarucizumab-related restoration of fibrin and platelet deposition on damaged site (CTD 4.2.1.1-14)

Human blood spiked with dabigatran (390 nmol/L) or vehicle (saline) was perfused through an annular chamber into a damaged vessel segment (endothelium-denuded rabbit aorta) at 600 s^{-1} (shear rate) for 10 minutes, and then the amount of fibrin and platelet deposition onto the damaged vessel was quantified. The dabigatran concentration of 390 nmol/L is equivalent to the mean C_{max} of dabigatran in patients with NVAF treated with DEMS at a dose equivalent to 150 mg DE twice daily (*Thrombosis and Haemostasis.* 2010;103:1116-27).

The percentage of fibrin coverage on the damaged vascular subendothelium (mean ± standard error [SE]) was 9.5% ± 1.4% in the dabigatran-treated group and 67.2% ± 9.8% in the control (saline-treated) group, showing a significant decrease by approximately 86% with dabigatran as compared with the control. The cross section of residual fibrin clot deposited onto the subendothelium (mean ± SE) was 26 ± 3.2 μm^2 in the dabigatran-treated group and 315 ± 75 μm^2 in the control group, showing a significant decrease by ≥90% with dabigatran as compared with the control. The percentage of vessels covered by platelets in the dabigatran-treated group was also significantly lower by approximately 35% than that in the control group (16.9% ± 2.9% in the dabigatran group versus 25.9% ± 2.7% in the control group).

When idarucizumab was added at concentrations of 6300, 21,000, and 63,000 nmol/L to human blood previously treated with dabigatran (390 nmol/L), the percentage of fibrin coverage (mean ± SE) was 61.6% ± 9.2%, 63.3% ± 9.4%, and 58.9% ± 9.7%, respectively, and the cross section of fibrin clot was 272 ± 95, 377 ± 113, and 285 ± 98 μm^2, respectively. These values were similar to those observed in the control group. The percentage of vessels covered by platelets after addition of idarucizumab (mean ± SE) was 24.3% ± 2.5%, 24.1% ± 3.9%, and 24.3% ± 2.3% at 6300, 21,000, and 63,000 nmol/L, respectively, and was similar to that observed in the control group. Addition of idarucizumab (63,000 nmol/L) alone to human blood did not affect fibrin or platelets on the damaged vessels.

3.1.3 Idarucizumab binding to other thrombin substrates

3.1.3.1 Binding to thrombin substrates (CTD 4.2.1.1-08)

Since idarucizumab has structural similarities to thrombin, experiments were performed to determine if idarucizumab had any thrombin-like binding property or enzymatic activity.

Surface plasmon resonance (SPR) experiments were conducted to evaluate the binding of thrombin substrates to idarucizumab (thrombin substrates: factors V and XIII, protein C, von Willebrand factor, S-2238, 10% human plasma, dabigatran, and peptides with a known thrombin cleavage site for factors V, VIII, and XIII, protein C, fibrinogen, and Protease activated receptor 1 [PAR1]). In the experiments, idarucizumab was coupled to a chip, and thrombin substrates at physiological concentrations (except for 1 μmol/L for S-2238 and dabigatran) were flowed over the chip for 60 seconds, followed by dissociation for 120 seconds. The experiments showed no idarucizumab binding to the thrombin substrates, except for dabigatran.

In addition, SPR experiments were performed to compare the binding behavior of idarucizumab-dabigatran complex and that of idarucizumab alone to human serum albumin (0-200 mg/dL), human plasma (0%-25%), and fibrinogen (1 μg/mL). There was no binding to human serum albumin or human plasma proteins in the presence and absence of dabigatran.

3.1.3.2 Thrombin-like enzymatic activity of idarucizumab (CTD 4.2.1.1-07)

Thrombin-like enzymatic activity of idarucizumab in human plasma was assessed with various coagulation tests.

3.1.3.2.1 FPA generation

Human platelet poor plasma (PPP) was spiked with idarucizumab (21,000-63,000 nmol/L), recombinant human thrombin (0.1-5 pmol/L), or vehicle (25 mmol/L sodium acetate solution) and was incubated at 37°C for 1 hour. Fibrinopeptide A (FPA) concentrations were determined with spectrometry at 450 nm. In the recombinant human thrombin groups, FPA concentrations (mean ± SD) increased dose-dependently (6.12 ± 0.97 ng/mL in the 1 pmol/L group; 25.14 ± 2.37 ng/mL in the 5 pmol/L group), showing a significant increase compared with those in the vehicle group (1.83 ± 0.32 ng/mL). No increases in FPA concentration were observed with idarucizumab at any dose (1.45-1.81 ng/mL).

3.1.3.2.2 Fibrinogen activation

Human prothrombin-depleted plasma was spiked with human normal plasma diluted 8-fold with imidazole buffer, and coagulation was induced by addition of a coagulation-inducing reagent containing calcium and thromboplastin. The dilution prolonged the clotting time (mean ± SD) from 22.3 ± 0.82 seconds (at prothrombin concentration of approximately 0.1 mg/mL before dilution) to 52.4 ± 2.98 seconds (at prothrombin concentration of approximately 0.013 mg/mL after dilution). Human prothrombin-depleted plasma was spiked with the above diluted human normal plasma, and idarucizumab (21,000-63,000 nmol/L) or vehicle (25 mmol/L sodium acetate solution) was then added to the human prothrombin-depleted plasma. Coagulation was induced in the same manner as described above. As a result, idarucizumab did not reduce the clotting time (49.27-49.53 seconds).

3.1.3.2.3 Thrombin generation

Human PPP was spiked with idarucizumab (10,500-63,000 nmol/L), an activated coagulation factor concentrate Feiba (factor VIII anti-inhibitor coagulant complex) 0.8 U/mL, or vehicle (25 mmol/L sodium acetate solution) and was incubated at 37°C for 5 minutes. Thrombin generation was then induced by addition of a PPP reagent containing the tissue factor (5 pmol/L) and fluorogenic substrate buffer containing calcium chloride. The lag time, peak thrombin generation level, and ETP were assessed with CAT. The peak thrombin generation level and ETP (mean ± SD) were 241.78 ± 35.02 nmol/L and 1413.74 ± 188.13 nmol/L·min, respectively, in the vehicle group and 576.46 ± 66.72 nmol/L and 3603.80 ± 326.24 nmol/L·min, respectively, in the Feiba group, showing a significant increase in the Feiba group as compared with the vehicle group. In contrast, no increases in the parameters were observed in any idarucizumab dose group. The lag time (i.e., time to the onset of thrombin generation) was comparable between any groups.

3.1.3.2.4 Platelet aggregation

Human platelet-rich plasma was spiked with idarucizumab (63,000 nmol/L) or vehicle (25 mmol/L sodium

acetate solution) and was incubated at 37°C for 5 minutes. A specific PAR1 agonist SFLLRN (2 μmol/L) or purified water was then added to the plasma. Platelet aggregation over 5 minutes was determined with light transmission platelet aggregometry. Platelet aggregation (mean ± SD) was significantly higher in the vehicle + SFLLRN group (198.9 ± 29.1 V·sec) than in the vehicle + purified water group (11.4 ± 3.4 V·sec), whereas no platelet aggregation was observed in the idarucizumab + purified water group (13.4 ± 2.7 V·sec). The extent of platelet aggregation in the idarucizumab + SFLLRN group (198.3 ± 25.3 V·sec) was similar to that in the vehicle + SFLLRN group.

3.1.4 *In vivo* evaluation of idarucizumab

3.1.4.1 Neutralization of anticoagulant activity *in vivo* (CTD 4.2.1.1-03)

Dabigatran or vehicle (saline) was administered intravenously to male Wistar rats (weighing approximately 300 g). Dabigatran was administered by a single intravenous bolus injection at 0.3 μmol/kg, followed by intravenous continuous infusion at 0.1 μmol/kg/h.

Following addition of thrombin (3 U/mL) approximately 20 minutes after the start of administration of dabigatran, TT increased from 23 seconds at baseline to approximately 90 seconds, and aPTT increased from approximately 18 seconds at baseline to approximately 26 seconds (4-10 animals). Twenty minutes after the start of administration of dabigatran or vehicle, the rats were given a single intravenous dose of idarucizumab 0.314 μmol/kg or vehicle (50 mmol/L sodium acetate and 200 mmol/L sorbitol solution). TT and aPTT prolonged by dabigatran returned to the same level as that in the vehicle group within 1 minute after administration of idarucizumab. The restored levels of TT and aPTT were maintained for 30 minutes after administration of idarucizumab during intravenous continuous infusion of dabigatran (4-8 animals).

Plasma sum dabigatran concentration (determined by LC-MS/MS) was 416 to 423 nmol/L at 20 minutes after the start of administration of dabigatran, reached to the peak (approximately 3000 nmol/L) at 5 minutes after administration of idarucizumab, and then decreased to approximately 1000 nmol/L at 30 minutes after administration of idarucizumab (≥2 animals per time point). The applicant discussed the increase in plasma sum dabigatran concentrations after idarucizumab administration as follows: The increases in plasma sum dabigatran concentrations were presumed to reflect the redistribution of dabigatran. Once idarucizumab binds to dabigatran in plasma, dabigatran in the extravascular compartment redistributes into the blood compartment to keep equilibrium. However, no prolonged TT was observed after administration of idarucizumab; this suggests that dabigatran redistributed from the extravascular compartment into the blood compartment may have been inactivated by binding to idarucizumab. Based on the above, the applicant stated that dabigatran distributed in tissues, as well as in plasma, would be neutralized as a consequence.

3.1.4.2 Reversal of dabigatran-induced bleeding in bleeding models

3.1.4.2.1 Reversal of bleeding time in rats (CTD 4.2.1.1-04)

DEMS (DE 30 mg/kg) or vehicle (0.5% hydroxyethylcellulose solution) was administered orally to male and

female Wistar rats (weighing approximately 250 g). Animals were anesthetized at 25 minutes after administration, and single dose of idarucizumab 33 mg/kg or vehicle (50 mmol/L sodium acetate and 200 mmol/L sorbitol solution) was intravenously administered to the animals at 45 minutes after the DEMS administration, which was the time around when plasma dabigatran concentration peaked. A standardized incision was made in the rat tail at 5, 15, 30, and 120 minutes after administration of idarucizumab or vehicle, to measure the time required for hemostasis (6-8 animals). The bleeding time at 5 minutes after administration (mean ± SE) was 163 ± 8 seconds in the control (vehicle + vehicle) group and 375 ± 35 seconds in the DEMS + vehicle group. In contrast, the bleeding time at 5 minutes after administration in the DEMS + idarucizumab group (195 ± 11 seconds) was comparable to that in the control group, and to the bleeding time at 15, 30, and 120 minutes after administration in the DEMS + idarucizumab group.

Blood samples were taken from the carotid artery at 5 minutes before and 5, 15, 30, and 120 minutes after administration of idarucizumab or vehicle to measure the dTT, TT, aPTT, and ECT (2-8 rats). In the DEMS + idarucizumab group, plasma active dabigatran concentration (determined by dTT assay) was 562 ± 80 ng/mL before administration of idarucizumab and 3.86 ± 3.86, 38.98 ± 24.42, and 45.71 ± 17.63 ng/mL, respectively, at 5, 15, and 120 minutes after administration. In the DEMS + vehicle group, the concentration was 436.79 ± 49.91 ng/mL before vehicle administration and 330.24 ± 42.45, 225.31 ± 41.91, and 100.53 ± 33.12 ng/mL, respectively, at 5, 15, and 120 minutes after vehicle administration. TT, aPTT, and ECT were also increased by DEMS administration as compared with those after vehicle administration, but these levels in the DEMS + idarucizumab group returned to the same level as those in the control group at 5 minutes after administration of idarucizumab or vehicle. In the DEMS + idarucizumab group, they increased again and became comparable to those in the DEMS + vehicle group at 120 minutes after idarucizumab administration.

Likewise, plasma sum dabigatran concentration was measured by LC-MS/MS (2-8 animals). In the DEMS + idarucizumab group, plasma sum dabigatran concentration was 617.25 ± 91.95 ng/mL immediately before administration of idarucizumab, increased to 3387.5 ± 368.54 ng/mL at 5 minutes after administration of idarucizumab, and decreased to 1671.25 ± 106.63 ng/mL at 15 minutes after the administration and then to 128.85 ± 17.46 ng/mL at 120 minutes after the administration.

The applicant provided the following explanation:

> The study results also indicate that once dabigatran binds to idarucizumab in plasma, dabigatran in the extravascular compartment redistributes into the blood compartment and then reaches equilibrium immediately. After binding of all administered idarucizumab to dabigatran, the remaining unbound dabigatran equilibrates between the blood compartment and the extravascular compartment again. This is why active dabigatran at low concentrations reappears in plasma when idarucizumab dose is lower than the equimolar dose and the total body load of dabigatran.

3.1.4.2.2 Porcine blunt trauma model in supratherapeutic concentrations of dabigatran (CTD 4.2.1.1-11)

DEMS (DE 30 mg/kg) was administered orally to male Landrace pigs (weighing 37-44 kg) twice daily for 3 days. On Day 4, a catheter was inserted into the jugular vein in animals under anesthesia, and dabigatran (a total intravenous dose of 0.905 mg/kg, administered at 0.77 mg/kg/h for 30 minutes and at 0.52 mg/kg/h for 60 minutes) or Ringer's solution was intravenously infused continuously over 90 minutes. Then, standardized blunt liver injury was made by clamping the middle liver lobe with special forceps at a specified pressure, and the abdomen was closed. Pressure was held on the wound site to allow the wound to bleed for 12 minutes, in order to induce hemorrhagic shock. Administration of Ringer's solution was started in all animals at 5 minutes post injury to maintain blood pressure: Ringer's solution was administered as a bolus injection approximately 1 L, followed by a 120-minute continuous administration at 40 mL/kg/h, and was maintained at 30 mL/kg/h until the end of the study. Idarucizumab 30, 60, 120 mg/kg or saline was administered as an intravenous bolus injection 15 minutes post injury, and blood loss and other relevant parameters were assessed until 240 minutes post injury or unscheduled death (6 animals).

Blood loss (mean ± SD) at 12 minutes post injury was 409 ± 53 mL in the dabigatran-untreated group, whereas blood loss almost doubled in the dabigatran-treated group (786 ± 39 mL). In the control (dabigatran + saline) group, blood loss increased over time to the cumulative amount of 2977 ± 316 mL at 120 minutes, and all animals died by 180 minutes after the injury (a mean survival time of 121 minutes). The cumulative blood loss at 240 minutes in the dabigatran + idarucizumab 30, 60, and 120 mg/kg groups was 1586 ± 619, 1065 ± 97, and 1140 ± 109 mL, respectively, and was reduced by 47%, 64%, and 62%, respectively, as compared with cumulative blood loss at 120 minutes in the dabigatran + saline group. Hemostasis was induced within 15 minutes after idarucizumab administration, and the hemostasis-inducing effect was maintained until the end of the study in the dabigatran + idarucizumab 60 and 120 mg/kg groups. In the dabigatran + idarucizumab 30 mg/kg group, blood loss exceeded 1500 mL in 2 of 6 animals, and 1 animal died 167 minutes after injury.

Trauma-related shock parameters (i.e., lactate levels, base excess levels, and mean arterial pressure) were assessed. In the control group, severe shock occurred due to continuous bleeding, accompanied by increased lactate levels, decreases in base excess levels, and substantially decreased mean arterial pressure. In contrast, these shock parameters were stable in the dabigatran + idarucizumab group. In the dabigatran + idarucizumab 60 and 120 mg/kg groups, lactate levels, base excess levels, and mean arterial pressure at 90 minutes post injury were comparable to those before injury and were maintained up to 240 minutes after injury.

Various coagulation markers such as dTT, ECT, aPTT, and ROTEM or ACT were evaluated. In the dabigatran + idarucizumab 120 mg/kg group, these marker levels returned nearly to the baseline levels within 5 minutes after idarucizumab administration, and the levels were maintained for 240 minutes. In contrast, the reversal of these parameters was sustained only for approximately 5 to 10 minutes and 30 to 60 minutes, respectively, in the dabigatran + idarucizumab 30 and 60 mg/kg groups.

Plasma active dabigatran concentration (determined by dTT assay) was 264 ± 218 ng/mL at 12 hours after the last dose of 3-day oral administration of DEMS and 1161 ± 372 ng/mL immediately after the 90-minute intravenous continuous administration of dabigatran. These values exceeded the median plasma peak concentration of 184 ng/mL in the RE-LY study conducted in patients with NVAF who received a dose equivalent to 150 mg DE twice daily. Plasma active dabigatran concentrations decreased depending on the dose of idarucizumab up to 240 minutes after idarucizumab administration. Plasma sum dabigatran concentration peaked at 15 minutes after idarucizumab administration (30 minutes after injury): 1030 ng/mL in the control group and 5060, 8700, and 7870 ng/mL, respectively, in the dabigatran + idarucizumab 30, 60, and 120 mg/kg groups. Based on the above findings, the applicant attributed the changes in the equilibrium of dabigatran to dabigatran redistribution from the extravascular compartment to the blood compartment. The applicant also provided the following explanation:

> Since idarucizumab 120 mg/kg is approximately equimolar to dabigatran 1.2 mg/kg (a total intravenous dose of 0.905 mg/kg dabigatran in the study), the anticoagulant activity of dabigatran is sufficiently reversed by idarucizumab when the level of idarucizumab is approximately equimolar to the level of dabigatran, because idarucizumab 120 mg/kg is approximately equimolar to dabigatran 1.2 mg/kg (a total intravenous dose of 0.905 mg/kg dabigatran in the study). Meanwhile, the idarucizumab 60 mg/kg group showed cessation of bleeding associated with injury and with the anticoagulant activity of dabigatran, although the anticoagulant activity of dabigatran was not completely reversed. This suggests that full reversal of the anticoagulant activity of dabigatran may not be necessary for hemostasis.

3.1.4.2.3 Split dosing of idarucizumab in a rat tail cut bleeding model (CTD 4.2.1.1-05)

DEMS (DE 30 mg/kg) or vehicle (0.5% hydroxyethylcellulose solution) was administered orally to male and female Wistar rats (weighing <250 g) 3 times every 8 hours. Animals were anesthetized at 25 minutes after the last administration. Idarucizumab 33, 66, and 33 + 33 mg/kg or vehicle (50 mmol/L sodium acetate and 200 mmol/L sorbitol solution or 25 mmol/L sodium acetate solution) was administered as an intravenous bolus injection at 45 minutes after the last administration. Tail bleeding time and anticoagulant activity were assessed (3-6 animals). In the idarucizumab 33 + 33 mg/kg group, idarucizumab was administered in two doses, 33 mg/kg each, 12 minutes apart.

Bleeding time (mean ± SE) at 50 minutes after the last dose of DEMS (315.0 ± 28.72 seconds) was significantly prolonged as compared with that of vehicle (without DEMS) (157.5 ± 7.5 seconds). Bleeding time at 50 minutes after the last dose of DEMS (i.e. 5 minutes after administration of idarucizumab) was 277.5 ± 33.26 seconds in the idarucizumab 33 mg/kg group and 153.8 ± 3.75 seconds in the idarucizumab 66 mg/kg group. Bleeding time at 120 minutes after idarucizumab administration was 277.5 ± 14.36 seconds in the idarucizumab 33 mg/kg group and 180.0 ± 34.64 seconds in the idarucizumab 66 mg/kg group. Bleeding time in the idarucizumab 66 mg/kg group was significantly shorter than that in the control (DEMS + vehicle) group throughout the study period. Bleeding time in the idarucizumab 33 + 33 mg/kg group was 250.0 ± 38.47

seconds at 5 minutes after the first dose of idarucizumab and 195.0 ± 25.98 seconds at 3 minutes after the second dose and was significantly shorter than that in the control group, as with the idarucizumab 66 mg/kg group. Bleeding time at 120 minutes after the first dose of idarucizumab was 195.0 ± 18.57 seconds.

Plasma active dabigatran concentration (determined by dTT assay) was approximately 1000 ng/mL at 40 minutes after the last dose of DEMS. In the control group, plasma active dabigatran concentration gradually decreased to 287.29 ± 33.98 ng/mL at 120 minutes after the last dose of DEMS. In the idarucizumab 33 mg/kg group, plasma active dabigatran concentration was 347.12 ± 70.73 ng/mL and 165.70 ± 30.84 ng/mL, respectively, at 5 and 120 minutes after idarucizumab administration. In the idarucizumab 66 mg/kg group, plasma active dabigatran concentration was 0 ng/mL at both 5 and 120 minutes after idarucizumab administration. In the idarucizumab 33 + 33 mg/kg group, plasma active dabigatran concentration was 90.51 ± 45.55 ng/mL at 5 minutes after the first dose of idarucizumab, 0 ng/mL at 3 minutes after the second dose, and 27.35 ± 13.72 ng/mL at 120 minutes after the first dose.

ECT at 40 minutes after the last dose of DEMS was 94.05 ± 35.96 seconds in the control group, 214.0 ± 34.45 seconds in the idarucizumab 33 mg/kg group, 120.45 ± 6.72 seconds in the idarucizumab 66 mg/kg group, and 132.37 ± 18.02 seconds in the idarucizumab 33 + 33 mg/kg group. ECT was prolonged by DEMS administration as compared with vehicle administration (11.2 ± 0.31 seconds). In the control group, ECT decreased gradually and was 77.20 ± 29.39 seconds and 21.88 ± 0.93 seconds, respectively, at 5 and 120 minutes after dosing. In the idarucizumab 33 mg/kg group, ECT was 42.68 ± 8.02 and 25.43 ± 2.55 seconds, respectively, at 5 and 120 minutes after idarucizumab administration, meaning that ECT was shortened by approximately 83% (at 5 minutes) and 88% (at 120 minutes) as compared with that at 40 minutes after the last dose of DEMS. In the idarucizumab 66 mg/kg group, ECT was 10.05 ± 0.06 seconds (shortened by approximately 92%) and 15.67 ± 0.54 seconds (shortened by approximately 87%), respectively, at 5 and 120 minutes after idarucizumab administration. In the idarucizumab 33 + 33 mg/kg group, ECT was 18.55 ± 3.76 seconds (shortened by approximately 86%) at 5 minutes after the first dose of idarucizumab, 11.48 ± 0.31 seconds (shortened by approximately 91%) at 3 minutes after the second dose, and 17.73 ± 1.50 seconds (shortened by approximately 85.8%) at 120 minutes after the first dose. Similar tendency was observed also for aPTT and TT.

3.1.4.2.4 Split dosing of idarucizumab in a porcine double trauma model (CTD 4.2.1.1-10)

A trauma model was prepared in male Landrace pigs (weighing 36-44 kg) treated with dabigatran, in the same manner as that described in Section "3.1.4.2.2 Porcine blunt trauma model in supratherapeutic concentrations of dabigatran," and idarucizumab 60 and 120 mg/kg was administered 15 minutes after the first injury. At 60 minutes after the first injury, the second injury was made in the liver lobe different from that where the first injury was made. Idarucizumab 60 mg/kg or vehicle (saline) was administered 15 minutes after the second injury. Blood loss, blood cell counts, idarucizumab concentrations, sum dabigatran concentrations, and coagulation parameters (e.g., PT, aPTT, and dTT) were assessed (6 animals each in the idarucizumab 60 + 0

mg/kg, idarucizumab 120 + 0 mg/kg, and idarucizumab 60 + 60 mg/kg groups).

Blood loss following the first injury and blood loss up to 60 minutes after idarucizumab administration were comparable among the idarucizumab 60 + 0 mg/kg, 120 + 0 mg/kg, and 60 + 60 mg/kg groups: blood loss (mean ± SD) following the first injury was 778 ± 40 mL, 815 ± 35 mL, and 790 ± 49 mL, and blood loss up to 60 minutes after idarucizumab was 990 ± 109 mL, 964 ± 74 mL, and 988 ± 84 mL in the respective groups. Following the second injury, blood loss from the second wound site began to increase and reached 3970 ± 610 mL at 300 minutes after the first injury (240 minutes after the second injury) in the idarucizumab 60 + 0 mg/kg group. In the idarucizumab 60 + 0 mg/kg group, the mortality at 5 hours after the first injury was 83%, and the mean survival was 235 ± 55 minutes. However, there was no further bleeding from the first wound site where hemostasis had been obtained by 60 minutes after the first injury and a clot had formed. Meanwhile, blood loss at 300 minutes after the first injury in the idarucizumab 120 + 0 mg/kg and 60 + 60 mg/kg groups was 1659 ± 345 mL and 1426 ± 106 mL, respectively, which were both significantly lower than that in the idarucizumab 60 + 0 mg/kg group. The mortality at 5 hours after the first injury was 0% in both groups. The applicant considered that administration of idarucizumab at approximately equimolar doses (60 + 60 mg/kg and 120 + 0 mg/kg, approximately equimolar to dabigatran 1.2 mg/kg) to the total intravenous dose of dabigatran (0.905 mg/kg) reversed the anticoagulant activity of dabigatran during the study period.

Shock parameters (lactate and base excess levels) were assessed. The idarucizumab 60 + 0 mg/kg group showed an increase over time in lactate levels and decreases in base excess levels and mean arterial pressure. In the idarucizumab 120 + 0 mg/kg and 60 + 60 mg/kg groups, these hemodynamic changes improved with control of blood loss.

Levels of Hb, platelets, and plasma fibrinogen concentration after the second injury were stable in the idarucizumab 120 + 0 mg/kg and 60 + 60 mg/kg groups, whereas these levels were significantly lower in the idarucizumab 60 + 0 mg/kg group than in the idarucizumab 120 + 0 mg/kg and 60 + 60 mg/kg groups.

Coagulation parameters were prolonged by the 3-day oral administration of DEMS. Plasma coagulation parameters (PT, aPTT) were 3 to 5 times higher following intravenous dabigatran administration than the values prior to the administration. Among whole blood coagulation parameters, ROTEM and ACT levels increased to 10- and 3-fold, respectively, following intravenous dabigatran administration. Coagulation parameter levels were completely restored to the levels before dabigatran administration within 5 minutes after the first dose of idarucizumab (60 and 120 mg/kg). In the idarucizumab 120 + 0 mg/kg group, the restored coagulation parameter levels lasted during almost the entire 5-hour assessment period. Meanwhile, following the second injury, coagulation parameters other than aPTT and PT, namely ROTEM and ACT, were prolonged in the idarucizumab 60 mg/kg group. In the idarucizumab 60 + 60 mg/kg group, the second dose of idarucizumab 60 mg/kg restored the coagulation parameter levels nearly to the values before dabigatran administration, and the restored levels lasted as with those in the idarucizumab 120 + 0 mg/kg group. In the

idarucizumab 60 + 0 mg/kg group, all coagulation parameter levels continued to be prolonged. The applicant considered that the prolongation of coagulation parameters was attributed in part to abnormal blood coagulation which was caused by decreases in fibrinogen or platelets secondary to excessive bleeding and redistribution of dabigatran into the plasma.

Plasma active dabigatran concentration (determined by dTT assay) was comparable among the groups (1099-1158 ng/mL) before idarucizumab administration and was 256 ± 130 ng/mL (the mean of the 3 groups) at trough after the 3-day oral administration of DEMS (90 minutes before the first injury). Following intravenous dabigatran administration, plasma active dabigatran concentration reached 1129 ± 160 ng/mL (a supratherapeutic concentration). Dabigatran activity decreased within 5 minutes after idarucizumab administration in a dose dependent manner and remained decreased during the 5-hour assessment period as compared with the plasma active dabigatran concentrations before idarucizumab administration. In the idarucizumab 120 + 0 mg/kg group, plasma active dabigatran concentration completely decreased at 150 minutes after the injury but was 145 ± 100 ng/mL at 300 minutes after the injury. In the idarucizumab 60 mg/kg group, plasma active dabigatran concentration did not decrease completely but decreased to 188 ± 94 ng/mL at 60 minutes after the injury. In the idarucizumab 60 + 0 mg/kg group, plasma active dabigatran concentration was nearly stable at around 200 ng/mL after 60 minutes after the injury and 354 ± 114 ng/mL in 3 animals living at 300 minutes after the injury. In the idarucizumab 60 + 60 mg/kg group, the decreased plasma active dabigatran concentration following the second dose of idarucizumab was maintained afterwards. Plasma sum dabigatran concentration was comparable to plasma active dabigatran concentration before idarucizumab administration. Following idarucizumab administration, however, the concentration increased to approximately ≥8 times that before the injury, and peaked at 15 minutes after idarucizumab administration. Since plasma sum dabigatran concentration decreased with decreasing idarucizumab concentration, the applicant considered that the majority of dabigatran came from the idarucizumab-dabigatran complex.

3.1.4.2.5 Mouse intracranial hemorrhage model (CTD 4.2.1.1-01)

DE 4.5 and 9.0 mg/kg or saline was administered intraperitoneally to male C57BL/6 mice (age of 10-12 weeks), and intracranial hemorrhage was induced by intrastriatal collagenase injection under anesthesia at 1 hour after the administration. Idarucizumab 191, 382, and 764 mg/kg or saline was then administered by tail vein injection at 30 minutes after the collagenase injection. In this model, hematoma enlarged by approximately 80% to 90% during the first 1 to 3 hours after intracranial hemorrhage induction, and idarucizumab was thus administered within 1 hour after intracranial hemorrhage induction. Brain cryosections were prepared 24 hours after intracranial hemorrhage induction, and hematoma volume was quantified (9-20 animals). The hemorrhagic contralateral hemisphere was homogenized, and supernatant after centrifugation was used for Hb quantification with spectrophotometry to quantify intracerebral blood content (4-15 animals).

Hematoma volumes were expanded by administration of DE 4.5 mg/kg as compared with the control group but were significantly reduced by administration of idarucizumab 191 mg/kg. Hematoma volumes were

expanded by administration of DE 9 mg/kg (14.32 μmol/kg) as compared with the control group but were significantly reduced by administration of idarucizumab 764 mg/kg (16 μmol/kg), which was approximately equimolar to the DE dose. However, no significant reduction occurred after administration of idarucizumab 382 mg/kg. Intracerebral blood content was significantly increased by administration of DE 9 mg/kg as compared with the control group and was significantly reduced by administration of idarucizumab 764 mg/kg, which was approximately equimolar to the DE dose. No significant reduction occurred after administration of idarucizumab 382 mg/kg.

3.1.5 Effects of hemodilution with colloidal and crystalloid solutions on binding of idarucizumab to dabigatran (CTD 4.2.1.1-09)

Crystalloids and colloids are used for volume replacement to compensate blood loss in patients with severe hemorrhage. In this study, a crystalloid solution (Ringer's solution) and colloids (starch compounds and gelatin) were administered concomitantly with idarucizumab, to study the effects of the crystalloids and colloids on binding of idarucizumab to dabigatran.

DEMS (DE 30 mg/kg) was administered orally to male Landrace pigs (weighing approximately 45-55 kg) twice daily for 3 days. On Day 4, animals were anesthetized and given a continuous intravenous infusion of dabigatran over 90 minutes (at 0.77 mg/kg/h for 30 minutes and at 0.26 mg/kg/h for 60 minutes). Following completion of dabigatran administration, approximately 50% of total blood volume (65 mL/kg body weight) was withdrawn at 100 mL/min to mimic hemorrhagic shock. Animals were assigned to (a) 60-minute administration of a crystalloid solution, (b) 60-minute administration of a colloidal solution (6% HES 130/0.4, 6% HES 200/0.5, or 4% gelatin), (c) 60-minute retransfusion of washed red blood cells, or (d) no hemodilution (control group) (5 animals/group). Crystalloid solution was administered at 1:1 to blood loss, colloid solutions at 25 mL/kg, and retransfusion at 12 mL/kg. In groups other than the retransfusion and control groups, blood cell counts and Hb concentrations decreased by approximately 50%, and blood was diluted. Plasma fibrinogen levels decreased by approximately 50% in all groups, except for the control group.

Idarucizumab 30 mg/kg was administered immediately after completion of administration of the volume expanders (e.g., a crystalloid solution, colloids, and washed red blood cells), to assess parameters including plasma active dabigatran concentration.

Plasma active dabigatran concentration (determined by dTT assay) (mean ± SD) was 375 ± 163 ng/mL after 3-day oral administration of DEMS and 633 ± 188 ng/mL after 90-minute intravenous infusion of dabigatran on Day 4. In the control group, dabigatran was naturally eliminated (plasma active dabigatran concentrations [determined by dTT assay]: 629 ± 134 ng/mL immediately after intravenous dabigatran infusion; 432 ± 121 ng/mL at 60 minutes post-dose). In the groups treated with the volume expanders, plasma active dabigatran concentration was similar to or slightly higher than that before administration of the fluids. Idarucizumab 30 mg/kg was administered intravenously to these groups following administration of the volume expanders. As

a result, the mean plasma active dabigatran concentration decreased from 620 ± 206 ng/mL, the level before idarucizumab administration, to 44 ± 85 ng/mL within 5 minutes after idarucizumab administration. Plasma active dabigatran concentration returned to a detectable level at 15 minutes after idarucizumab administration and peaked (242 ± 95 ng/mL) at 30 minutes after the administration. Subsequently, plasma active dabigatran concentration decreased again and was 27 ± 48 ng/mL at 24 hours after idarucizumab administration. A comparison between the volume expander groups showed no significant difference in the plasma active dabigatran concentrations until 24 hours after idarucizumab administration.

Plasma sum dabigatran concentration (determined by LC-MS/MS) was comparable to the concentration of plasma active dabigatran before idarucizumab administration but increased to 5 to 8 times higher immediately after idarucizumab administration. Active dabigatran accounted for several percent of the sum dabigatran concentration (44 ng/mL at 5 minutes post-dose). Plasma sum dabigatran concentration was obviously higher in the 4% gelatin and retransfusion groups than in the control group, but the concentrations in the other volume expander groups were comparable to that in the control group. However, no significant difference was found in sum dabigatran concentrations among the volume expanders.

3.2 Secondary pharmacodynamics

3.2.1 Effects on oral and parenteral anticoagulants (CTD 4.2.1.2-01)

Human PPP containing direct thrombin inhibitors (dabigatran 7 nmol/L, hirudin 2 nmol/L, argatroban 150 nmol/L, or melagatran 10 nmol/L) at concentrations prolonging baseline clotting time by approximately 40 seconds was spiked with idarucizumab (62.7 µmol/L) or vehicle (25 mmol/L sodium acetate, 220 mmol/L sorbitol, and 0.02% polysorbate 20 solution). The human PPP was incubated at 37°C for 10 minutes, and then was tested with a modified TT assay. Idarucizumab had no effect on TT prolonged by hirudin or argatroban, but reversed TT prolonged by melagatran, as well as TT prolonged by dabigatran.

In addition, human PPP containing melagatran 10 nmol/L was spiked with idarucizumab at several concentrations (2.5-60 µmol/L) and was tested with a modified TT assay. IC_{50} of idarucizumab for melagatran activity was 7.7 µmol/L, which was weaker than that for dabigatran activity (2-3 nmol/L), but the inhibitory effect was specific.

Human PPP containing factor Xa inhibitors (rivaroxaban and apixaban) at several concentrations (0-500 ng/mL) was spiked with idarucizumab 62.7 µmol/L or vehicle (25 mmol/L sodium acetate, 220 mmol/L sorbitol, and 0.02% polysorbate 20 solution) and was incubated at 37°C for 5 minutes. Anticoagulant activity was assessed with a factor Xa activity assay. Rivaroxaban and apixaban dose-dependently inhibited factor Xa activity, but idarucizumab did not affect the activity of the factor Xa inhibitors at any concentrations.

Human PPP containing several concentrations of heparin (0-2 U/mL) or LMWH (0-5 µg/mL) was spiked with idarucizumab (62.7 µmol/L) or vehicle (25 mmol/L sodium acetate, 220 mmol/L sorbitol, and 0.02%

polysorbate 20 solution). The human PPP was incubated at 37°C for 5 minutes, and then saline was added. Anticoagulant activity was assessed with a factor Xa activity assay. Heparin and LMWH showed concentration-dependent inhibition of factor Xa activity, but idarucizumab did not affect the activity of heparin or LMWH at any concentrations.

A vitamin K antagonist warfarin 0.5 mg/kg or vehicle (0.5% hydroxyethylcellulose solution) was administered orally to male and female Wistar rats (weighing approximately 250 g) once daily for 3 days, and the fourth dose was orally administered 45 minutes before idarucizumab administration (4-5 animals). Animals were anesthetized after the fourth oral administration, and 20 minutes later, were given intravenous idarucizumab 33 mg/kg or vehicle (50 mmol/L sodium acetate and 200 mmol/L sorbitol solution). PT (mean ± SE) at 5 minutes before idarucizumab administration was 10.34 ± 0.20 seconds in the control (vehicle + vehicle) group, 70.78 ± 8.49 seconds in the warfarin + vehicle group, and 114.72 ± 25.53 seconds in the warfarin + idarucizumab group, showing a significant prolongation by warfarin. In the warfarin groups, PT was slightly prolonged over time, while no effects of idarucizumab were observed at any time points until 120 minutes after idarucizumab administration.

3.3 Safety pharmacology

Results of safety pharmacology studies are summarized in Table 5.

Table 5. Summary of results of safety pharmacology studies

Organ system	Test system	Test parameter/method	Dose	Route of administration	Findings	CTD
Central nervous system	Wistar rat (6 males/group)	Irwin screen (panel of functional clinical observation, motor activity)	0, 150, 500 mg/kg	Intravenous	No effects were found in evaluation at pre-dose and at 1 and 24 hours post-dose on Day 1.	4.2.3.2-02
Cardiovascular system	Rhesus monkey (3/sex/group)	Heart rate, electrocardiographic parameters	0/0, 12/150, 12/500, 0/500, 12/0 mg/kg [a)]	Intravenous	No effects were found in evaluation with cardiac telemetry during the period from 90 minutes pre-dose to 6 hours after completion of administration on Day 5 (Day 5 of DEMS administration, which was Day 2 of idarucizumab administration).	4.2.3.2-03
Respiratory system	Wistar rat (8 males/group)	Respiration rate, tidal volume, minute volume	0, 150, 500 mg/kg	Intravenous	No effects were found in evaluation at 0 to 240 minutes post-dose.	4.2.1.3-01

[a)] DEMS (DE)/idarucizumab, administered orally/intravenously. Intravenous administration occurred 1.5 hours after oral dosing.

3.4 Pharmacodynamic drug interactions

3.4.1 Effects on dabigatran- and anticoagulant-induced prolongation of bleeding time (CTD 4.2.1.4-01)

An antiplatelet agent, ASA (100 mg/kg), clopidogrel (4 mg/kg), or ticagrelor (3 mg/kg), or vehicle (0.5% hydroxyethylcellulose solution) was administered orally to male and female Wistar rats (weighing approximately 250 g). DEMS (DE 30 mg/kg) or vehicle (0.5% hydroxyethylcellulose solution) was administered orally 75 minutes following administration of the antiplatelet agents. Anesthesia was started 25 minutes later. Idarucizumab 33 mg/kg or vehicle (saline) was administered intravenously 20 minutes after the

start of anesthesia. A standardized incision was made in the rat tail at 15 minutes after idarucizumab administration, and bleeding time assay was performed by measuring the time required for hemostasis (3-6 animals). Plasma active dabigatran concentrations (determined by dTT assay) were also assessed at 5 minutes before and 15 minutes after idarucizumab administration (3-6 animals).

Bleeding time (mean ± SE) in the absence of idarucizumab administration was 138 ± 11, 325 ± 44, 260 ± 36, 345 ± 38, and 383 ± 77 seconds, respectively, in the control (vehicle + vehicle) group, the dabigatran alone group, the dabigatran + ASA group, the dabigatran + clopidogrel group, and the dabigatran + ticagrelor group. Bleeding time was significantly prolonged by the combination of dabigatran and antiplatelet agents. Bleeding time following idarucizumab administration was 160 ± 40 seconds in the dabigatran + ASA group, 240 ± 21 seconds in the dabigatran + clopidogrel group, and 240 ± 21 seconds in the dabigatran + ticagrelor group. Idarucizumab partially reversed the bleeding time prolonged by the combination of dabigatran and antiplatelet agents. In the dabigatran alone group, bleeding time prolonged by dabigatran alone was restored by idarucizumab to 170 ± 17 seconds, which was comparable to that observed in the control group. Plasma active dabigatran concentration was 566.57 ± 104.46, 313.34 ± 114.01, 638.66 ± 132.39, and 547.65 ± 106.26 ng/mL at 5 minutes before idarucizumab administration, respectively, in the dabigatran alone group, the dabigatran + ASA group, the dabigatran + clopidogrel group, and the dabigatran + ticagrelor group. The respective values at 15 minutes following idarucizumab administration were 12.91 ± 12.91, 0 ± 0.00, 68.61 ± 60.24, and 47.07 ± 34.34 ng/mL.

3.4.2 Effects of coagulation factor concentrates on inhibition of dabigatran by idarucizumab *in vitro* (CTD 4.2.1.4-02)

Coagulation factor concentrates are used in urgent procedures for patients with severe hemorrhage. This study evaluated the effects of coagulation factor concentrates on binding of idarucizumab to dabigatran when the concentrates were administered concomitantly with idarucizumab.

Human PPP was spiked with coagulation factor concentrates containing 3 or 4 coagulation factors (e.g., PCCs [1 U/mL], aPCC [1 U/mL], and rFVIIa [100 nmol/L]) or water. Dabigatran at several concentrations (50-1000 ng/mL) or vehicle (DMSO) and idarucizumab 62.7 µmol/L were added to the human PPP, which was then incubated at 37°C for 5 minutes. Normal plasma was added to the human PPP, which was again incubated at 37°C for 1 minute. Thrombin-calcium solution was then added to the human PPP to induce clotting, and dTT was evaluated.

Dabigatran prolonged dTT in a concentration-dependent manner, and the addition of PCCs, aPCC, or rFVIIa had no effects. Following treatment with idarucizumab, dTT prolonged by dabigatran was restored to a level comparable to that observed with vehicle addition, and the addition of PCCs, aPCC, or rFVIIa had no effects.

3.R Outline of the review by PMDA

PMDA's view:

The submitted study data have demonstrated that (a) idarucizumab binds to dabigatran and its active metabolites immediately, and that (b) in various animal models, idarucizumab tended to immediately reduce plasma active dabigatran concentrations and to restore coagulation parameters and bleeding time which were prolonged by dabigatran. PMDA therefore concludes that idarucizumab is expected to restore the coagulant activity inhibited by dabigatran.

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

Plasma idarucizumab concentrations were determined by ELISA, and the lower limit of quantitation (LLOQ) was 15.6 ng/mL (0.33 nmol/L) in rats and 7.8 ng/mL (0.16 nmol/L) in monkeys. Plasma ADA concentrations were determined by electrochemiluminescence (ECL), and the LLOQ was 0.22 ng/mL in rats and 15.1 ng/mL in monkeys.

Values of PK parameters are expressed as mean or mean ± SD unless otherwise specified.

4.1 Absorption

4.1.1 Single dose (CTD 4.2.2.2-01 and -05, 4.2.3.2-01)

Male rats received a single intravenous dose of idarucizumab 20 mg/kg, dabigatran 0.2 mg/kg, or dabigatran 0.2 mg/kg followed by a single intravenous dose of idarucizumab 20 mg/kg 15 minutes later. PK parameters of idarucizumab in the rats are shown in Table 6.

Table 6. PK parameters of idarucizumab (partially modified from the submitted data)

	N	$AUC_{0-\infty}$ (nmol·h/L)	CL (mL/min/kg)	V_{ss} (L/kg)	MRT (h)	$t_{1/2}$ (h)
Idarucizumab alone	3	3730 ± 875	1.95 ± 0.494	0.0688 ± 0.0291	0.570 ± 0.0943	6.68 ± 0.493
Dabigatran + idarucizumab	6 [a)]	2990	2.33	0.0771	0.550	6.34

[a)] No SD for PK parameters was calculated because the number of animals was 3 per time point.

Male and female monkeys received 3 cycles of 4-day administration of oral DEMS (DE 12 mg/kg) or vehicle (i.e., Days 1-4, 15-18, and 29-32). At 1.5 hours after the last dose on the 4th day, the monkeys received intravenous doses of idarucizumab at 30 mg/kg (Day 4), 90 mg/kg (Day 18), and 175 mg/kg (Day 32) (a 14-day recovery period between Days 4 and 18 and between Days 18 and 32). Table 7 shows PK parameters of idarucizumab in the monkeys. ADAs were detected in 2 of 4 animals before the last dose of idarucizumab but did not influence idarucizumab exposure.

Table 7. PK parameters of idarucizumab (partially modified from the submission)

	N	C_{max} [a)] (nmol/L)	AUC_{0-24} [a)] (nmol·h/L)	CL (mL/min/kg)	V_{ss} (L/kg)	MRT (h)	$t_{1/2,\alpha}$ (h)	$t_{1/2,\beta}$ (h)
Idarucizumab 30 mg/kg	2	16100, 14700	11700, 12700	0.873 ± 0.0464	0.0576 ± 0.00692	1.11 ± 0.165	0.394 ± 0.0399	4.26 ± 0.439
Idarucizumab 90 mg/kg	2	38300, 39600	33300, 37700					
Idarucizumab 175 mg/kg	2	81200, 72200	67600, 72200					
Idarucizumab 30 mg/kg + DEMS	2	11400, 11700	9020, 11000	1.01 ± 0.114	0.0671 ± 0.0110	1.12 ± 0.251	0.420 ± 0.0458	4.92 ± 0.632
Idarucizumab 90 mg/kg + DEMS	2	33500, 32900	30300, 35000					
Idarucizumab 175 mg/kg + DEMS	2	65100, 76400	54000, 67000					

[a)] Individual values are shown because only 2 animals were included.

Male monkeys received oral doses of DEMS (DE 12 mg/kg) on Days 1 to 4, 8 to 11, and 30 to 33 and intravenous doses of idarucizumab (group 1, 30 mg/kg on Day 4, 30 + 30 mg/kg on Day 11, and 30 mg/kg on Day 33; group 2, 60 mg/kg on Day 4, 60 + 60 mg/kg on Day 11, and 60 mg/kg on Day 33). PK parameters of idarucizumab in the monkeys are shown in Table 8. ADAs were detected in 6 of 8 animals before the last dose of idarucizumab but did not influence the exposure to idarucizumab.

Table 8. PK parameters of idarucizumab (partially modified from the submitted data)

Idarucizumab dose	N	Time point	Hours after DEMS administration [a)]	C_{max} (nmol/L)	$AUC_{0-\infty}$ (nmol·h/L)	CL (mL/min/kg)	V_{ss} (L/kg)	MRT (h)	$t_{1/2}$ (h)
30 mg/kg	4	Day 4	2.33	10,100 ± 746	11,400 ± 820	0.919 ± 0.0670	0.0739 ± 0.0167	1.34 ± 0.286	5.59 ± 0.717
60 mg/kg	4	Day 4	2.33	15,000 ± 2560	26,100 ± 5320	1.09 ± 0.231	0.107 ± 0.0323	1.61 ± 0.195	5.29 ± 0.348
30 + 30 mg/kg	4	Day 11	1.5 and 3.0	11,300 ± 520	27,100 ± 3610	0.784 ± 0.118	0.0592 ± 0.0181	1.24 ± 0.186	5.62 ± 0.457
60 + 60 mg/kg	4	Day 11	1.5 and 3.0	21,200 ± 5390	54,200 ± 13,600	0.822 ± 0.266	0.0712 ± 0.0411	1.37 ± 0.298	5.32 ± 0.552
30 mg/kg	3	Day 33	1.5	10,100 ± 395	11,600 ± 305	0.902 ± 0.0241	0.0719 ± 0.0103	1.33 ± 0.187	6.15 ± 0.890
60 mg/kg	4	Day 33	1.5	19,700 ± 705	23,700 ± 3360	0.895 ± 0.112	0.0740 ± 0.00866	1.38 ± 0.0899	6.01 ± 0.252

[a)] Hours between the last dose of DEMS and idarucizumab administration in each administration phase.

4.1.2 Repeated dose (CTD 4.2.3.2-02, 05)

Pharmacokinetics (PK) of idarucizumab after repeated intravenous administration was evaluated in repeated-dose toxicity studies.

Table 9 shows PK of idarucizumab in male and female rats receiving 4-week intravenous administration of idarucizumab and male and female monkeys receiving 2-week intravenous administration of idarucizumab and 2-week oral administration of DEMS. After completion of idarucizumab administration, ADAs were detected in 6 of 17 rats in the idarucizumab 150 mg/kg group, 9 of 18 rats in the idarucizumab 500 mg/kg group, in 9 of 10 monkeys in the idarucizumab/DE 150/12 mg/kg group, 3 of 10 monkeys in the idarucizumab/DE 500/12 mg/kg group, and 3 of 10 monkeys in the idarucizumab/DE 500/0 mg/kg group. However, idarucizumab exposure (after the last dose of idarucizumab) did not differ between animals with and without ADA.

Table 9. PK parameters of idarucizumab (partially modified from the submitted data)

Animal species	Idarucizumab dose(mg/kg)	DEMS dose [b] (mg/kg)	Sex	N	Time point	C_{max} (nmol/L)	AUC_{0-24} (nmol·h/L)
Rat	150	0	Male	9[a]	Day 1	52,900	27,200
				9[a]	Day 28	33,300	24,700
			Female	9[a]	Day 1	53,600	26,400
				9[a]	Day 28	51,500	27,800
	500	0	Male	9[a]	Day 1	157,000	82,700
				9[a]	Day 28	197,000	106,000
			Female	9[a]	Day 1	178,000	83,900
				9[a]	Day 28	166,000	109,000
Monkey	150	12	Male	5	Day 1	52,700 ± 6340	54,600 ± 7660
				5	Day 14	59,600 ± 5420	61,700 ± 8600
			Female	5	Day 1	52,700 ± 1590	53,600 ± 4230
				5	Day 14	49,000 ± 6130	51,700 ± 6720
	500	12	Male	5	Day 1	161,000 ± 7620	182,000 ± 20,600
				5	Day 14	181,000 ± 28,300	208,000 ± 38,300
			Female	5	Day 1	168,000 ± 16,500	182,000 ± 16,400
				5	Day 14	164,000 ± 9860	196,000 ± 18,300
	500	0	Male	5	Day 1	170,000 ± 13,100	190,000 ± 17,200
				5	Day 14	163,000 ± 23,400	188,000 ± 8290
			Female	5	Day 1	175,000 ± 11,000	199,000 ± 22,400
				5	Day 14	186,000 ± 19,500	216,000 ± 18,500

[a] No SD for PK parameters was calculated because the number of animals was 3 per time point.
[b] DE dose is shown.

4.2 Distribution

No studies to examine the distribution of idarucizumab were conducted for the present application.

4.3 Metabolism

No studies to examine the metabolism of idarucizumab were conducted for the present application.

4.4 Excretion (CTD 4.2.2.2-01, 05)

Male rats received (a) a single intravenous dose of idarucizumab 20 mg/kg, (b) a single intravenous dose of dabigatran 0.2 mg/kg, or (c) a single intravenous dose of idarucizumab 20 mg/kg after a single intravenous dose of dabigatran 0.2 mg/kg. Table 10 shows the fe of idarucizumab and dabigatran in the rats for up to 48 hours after idarucizumab administration.

Table 10. Fe of idarucizumab and dabigatran (partially modified from the submitted data)

Idarucizumab dose (mg/kg)	Dabigatran dose (mg/kg)	N	fe of idarucizumab (%dose)				fe of dabigatran (%dose)
			0-8 hours	8-24 hours	24-48 hours	0-48 hours	
20	0	3	13.2 ± 6.08	1.12 ± 0.76	0.25 ± 0.38	14.5 ± 6.91	-
20	0.2	3	16.0 ± 5.04	4.18 ± 3.17	0.57 ± 0.85	20.8 ± 6.68	59.3 ± 17.1
0	0.2	3	-	-	-	-	57.2 ± 30.6

-, Not calculated.

Male monkeys received oral DEMS (DE 12 mg/kg) for 4 days and then intravenous idarucizumab (0, 30, 60, 30 + 30, or 60 + 60 mg/kg). The fe of idarucizumab for 48 hours post-dose did not depend on the administered dose of idarucizumab and was 4.89% to 14.6% of the administered dose. The fe of sum dabigatran was 1.43%

± 1.15% of the administered dose in the absence of idarucizumab and 1.56% ± 1.31% of the administered dose in the presence of idarucizumab. Based on the above findings, the applicant considered that idarucizumab did not tend to influence the fe of sum dabigatran.

4.5 Other pharmacokinetic studies (CTD 4.2.2.7-01, 02)

A single intravenous dose of idarucizumab 20 mg/kg was administered to sham-operated rats and 5/6 nephrectomized rats. In the sham-operated and 5/6 nephrectomized rats, $AUC_{0-\infty}$ was 3700 ± 209 and 8580 ± 1890 nmol·h/L, respectively, CL 1.89 ± 0.109 and 0.838 ± 0.168 mL/min/kg, respectively, V_{ss} 0.287 ± 0.0153 and 0.103 ± 0.0225 L/kg, respectively, $t_{1/2,\beta}$ 6.58 ± 0.514 and 6.29 ± 0.351 hours, respectively, and fe 15.8% ± 3.21% and 12.6% ± 3.54%, respectively, of the administered dose.

A single intravenous dose of dabigatran was administered to sham-operated rats, untreated rats, and 5/6 nephrectomized rats, and a single intravenous dose of idarucizumab was given to the rats 5 minutes after the dabigatran administration. PK parameters of idarucizumab in the rats after idarucizumab administration are shown in Table 11.

Table 11. PK parameters of idarucizumab (partially modified from the submitted data)

Rat type	Idarucizumab dose (mg/kg)	Dabigatran dose (mg/kg)	N	C_{max} (nmol/L)	$AUC_{0-\infty}$ (nmol·h/L)	CL (mL/min/kg)
Sham-operated	20	0.4	8	12,500	3660	1.90
	40	0.4	8	23,600	7330	1.90
5/6 nephrectomized	20	0.4	8	12,300	8940	0.780
	40	0.4	8	22,000	18,200	0.767
Untreated	40	0.4	8	20,500	6910	2.02

4.R Outline of the review by PMDA

Distribution and metabolism of idarucizumab have not been investigated in non-clinical studies for the present application, and the applicant provided the following explanation on the distribution and metabolism of idarucizumab:

Distribution: Tissue distribution of idarucizumab is thought to be limited in view of the following: (a) idarucizumab is a Fab of IgG antibody designed to bind specifically to dabigatran, and no idarucizumab-specific staining was observed in rat, monkey, or human tissues in a tissue cross-reactivity study [see "5.4.1 A tissue cross-reactivity study of idarucizumab in normal human, monkey, and rat tissues"]; (b) the V_{ss} of idarucizumab (68.8 ± 29.1 mL/kg in rats and 57.6 ± 6.92 mL/kg in monkeys) was only slightly higher than the plasma volume (39.6 mL/kg and 31.2 mL/kg in rats and 44.8 mL/kg in monkeys) (*J Appl Physiol.* 1994;76(1):485-9; *Pharm Res.* 1993;10(7):1093-6).

Metabolism: Idarucizumab, a Fab of IgG antibody, is presumed to be eliminated via direct excretion into urine and degradation into amino acids through protein catabolism as with other protein-based products. Following administration of idarucizumab to rats and monkeys, the fe of idarucizumab ranged from approximately 10%

to 20% [see “4.4 Excretion”], and the remaining idarucizumab (80%-90%) was presumed to be eliminated by catabolism. The presumption is consistent with findings in literature reporting that following intravenous administration to mice and humans, radiolabeled antibody fragments (e.g., Fab) were taken up mainly by the kidneys and underwent catabolism in the kidneys (*J Nucl Med*. 1996;37(5):829-33; *Cancer Res*. 1995;55(17):3825-34; *Bioconjug Chem*. 2001; 12(2):264-70).

Possibility of placental transfer of idarucizumab: Transcytosis mediated by binding of the Fc domain of IgG to FcRn receptor is presumed to be involved in the active placental transfer of IgG (*Am J Gastroenterol*. 2009;104(1):228-33), and idarucizumab is very unlikely to actively cross the placenta because of the absence of the Fc domain in idarucizumab. In an *in vitro* study using perfused human placenta, abciximab, a Fab fragment of an anti-GPIIb/IIIa IgG1 monoclonal antibody, did not transfer from the maternal circuit to the fetal circuit (*Placenta*. 2003;24:727-38). Following intravenous administration of PEGylated anti-rat TNF-alpha Fab to rats on day 20 of gestation, the extent of transfer to fetuses was negligible (fetal plasma concentration of <0.03 μg/mL [the lower limit of quantification] versus maternal plasma concentration of 23.1 μg/mL). In contrast, after intravenous administration of IgG (cTN3 γ1) to rats on day 20 of gestation, its fetal plasma concentration was as high as 14.6 μg/mL (*Toxicol Sci*. 2011;122(1):170-6). In pregnant women receiving intravenous certolizumab (PEGylated anti-TNFα Fab), infliximab (IgG), or adalimumab (IgG), certolizumab concentration in the fetuses and cords was low (<2 μg/mL, which was <3.9% of maternal plasma certolizumab concentration), whereas infliximab and adalimumab concentrations in the fetuses and cords were higher than their concentrations in maternal plasma (*Clin Gastroenterol Hepatol*. 2013;11(3):286-92). These findings showed that placental transfer of Fab was minimal as compared with IgG, and idarucizumab is thus very unlikely to cross the placenta.

Transfer of idarucizumab to milk: Following administration of cTN3 γ1 (IgG) to lactating rats on day 8 postpartum, cTN3 γ1 concentrations in the milk and pup plasma were high: 2.7 μg/mL and 27.6 μg/mL, respectively (*Toxicol Sci*. 2011;122(1):170-6). Conversely, following intravenous administration of cTN3 PF (PEGylated anti-rat TNFα Fab) to lactating rats on day 8 postpartum, the cTN3 PF concentration in milk was <5% of that in maternal plasma, and the cTN3 PF concentration in pups was below the detectable level (0.02 μg/mL) (*Toxicol Sci*. 2011;122(1):170-6). In lactating women receiving certolizumab (PEGylated anti-TNFα Fab) 400 mg intravenously every 4 weeks, certolizumab was undetectable in any of 5 breast milk samples collected during the period from 4 hours to 2 weeks postdose (*Clin Gastroenterol Hepatol*. 2013;11(3):286-92). These findings suggest that the transfer of Fab to milk is marginal as compared with IgG, and therefore the milk transfer of idarucizumab, Fab of IgG antibody, is very unlikely to occur.

As described above, existing data can provide estimates of distribution and metabolism of idarucizumab. The applicant thus decided not to conduct non-clinical studies on distribution and metabolism for the present application.

PMDA’s view:

Although no non-clinical studies were conducted to investigate the distribution and metabolism of

idarucizumab, the applicant stated that its distribution and metabolism could be estimated from existing data, and the applicant's explanation is reasonable. Based on the submitted data and the applicant's explanation, PMDA considers that non-clinical pharmacokinetics of idarucizumab have been properly assessed.

5. Toxicity and Outline of the Review Conducted by PMDA

The applicant conducted the following toxicity studies with idarucizumab for the present application: a single-dose toxicity study; repeat-dose toxicity studies (including studies investigating renal impairment and formation and deposition of immune complex); a local tolerance study; and other toxicity studies (a tissue cross-reactivity study and a hemocompatibility study).

5.1 Single-dose toxicity (CTD 4.2.3.1-01, reference data)

A single intravenous dose of vehicle (a buffer consisting of 50 mmol/L sodium acetate and 200 mmol/L sorbitol, pH5.5) or idarucizumab 50 or 175 mg/kg was administered to male and female Wister rats. No unscheduled deaths occurred. Clinical chemistry showed high triglyceride levels in male rats in the ≥50 mg/kg groups (up to 1.8-fold that in the control group). The applicant determined the approximate lethal dose to be >175 mg/kg.

5.2 Repeat-dose toxicity

To evaluate the intravenous repeated dose toxicity of idarucizumab, the applicant conducted a 4-week repeated dose toxicity study in rats, a 2-dose and 2-week intravenous toxicity study in combination with oral DEMS in monkeys, and a 2-dose intravenous toxicity study of renal damage in monkeys. No toxic changes were observed in any of the studies, and the applicant determined the no-observed-adverse-effect level (NOAEL) to be 500 mg/kg/day. The exposure parameter values following administration of idarucizumab at 500 mg/kg/day to rats (C_{max}, 181,500 nmol/L; $AUC_{0\text{-}24}$, 107,500 nmol·h/L) were approximately 6.0-fold and 2.5-fold, respectively, of those following 2 doses of idarucizumab 2.5 g administered with a short interval to Japanese healthy subjects (C_{max}, 30,100 nmol/L; $AUC_{0\text{-}\infty}$, 43,300 nmol·h/L).

5.2.1 Four-week intravenous repeated-dose toxicity study in rats (CTD 4.2.3.2-02)

Vehicle (a buffer consisting of 25 mmol/L sodium acetate, 220 mmol/L sorbitol, and 0.02% polysorbate 20; pH5.5) or idarucizumab at 150 or 500 mg/kg/day was repeatedly administered intravenously to male and female Wister rats for 4 weeks (15/sex). Dose-dependent decreases in plasma urea and creatinine were observed in the ≥150 mg/kg groups. However, these findings were judged by the applicant not to represent toxicity, because plasma urea and creatinine levels in the majority of the rats studied were within the range of the historical data from the testing laboratory, and because no relevant histopathological abnormalities were observed. Following 4-week administration, ADAs were detected in all groups including the control group. In the groups analyzed for TK of idarucizumab, ADAs were detected in 15 of 35 animals but did not influence the TK. Accordingly, the ADA development was judged by the applicant to have no impact on toxicity evaluation. No other toxicity findings were identified, and the applicant determined the NOAEL to be 500 mg/kg/day.

5.2.2 Two-dose intravenous toxicity study in combination with DEMS in monkeys (CTD 4.2.3.2-03)

Vehicle (a buffer consisting of 25 mmol/L sodium acetate, 220 mmol/L sorbitol, and 0.02% polysorbate 20; pH5.5) or DEMS (DE)/idarucizumab at 12/150, 12/500, 0/500, or 12/0 mg/kg/day were administered to male and female rhesus monkeys (3/sex). DEMS was orally dosed for 5 consecutive days, and idarucizumab was administered intravenously 2 times in total, namely at 1.5 hours post-dose of DEMS on Days 4 and 5. ADAs were positive in all animals treated with DEMS. The applicant considered that plasma dabigatran might interfere with assay system. In the DEMS/idarucizumab 12/150 and 12/500 mg/kg groups, anticoagulant effect of dabigatran was reversed in all animals, except for 1 of 3 male monkeys in the 12/500 mg/kg group, and no toxicity findings were identified. Hair and weight loss and abnormalities in clinical chemistry and urinalysis were observed in 1 of 2 male monkeys in the 12/500 mg/kg recovery group. In this animal, renal tubular disorder was suggested especially by an imbalanced increase in urea and an increase in plasma inorganic phosphorus, but histopathological examinations revealed only moderately dilated renal cortical tubules and deposition of PAS positive materials in the tubular epithelia and the renal tubular lumens, showing no changes suggestive of any disorders. Immunohistochemical investigation also showed no simian IgM, IgG, or C3 immune complex or human Fab in the kidneys. The absolute kidney weight was low, but the kidney weights relative to brain weight and body weight fell within the range of the control data. Data on TK and reversal of anticoagulant effect of dabigatran in the animal were similar to those in other animals in the same group. Since the relationship between the findings observed in this animal and idarucizumab administration was unclear, an additional toxicity study was conducted in which idarucizumab was administered 2 times after DEMS administration to evaluate the effects on the kidneys [see next section]. The applicant determined that (a) the NOAEL of idarucizumab, in combination with DEMS, was 150 mg/kg/day because the animal receiving 12/500 mg/kg showed abnormal findings, and that (b) the NOAEL of idarucizumab administered alone was 500 mg/kg/day because no toxicity was observed in the DEMS/idarucizumab 0/500 mg/kg group (i.e., with no DEMS administration).

5.2.3 Study of renal damage in monkeys (CTD 4.2.3.2-04)

Vehicle (a buffer consisting of 25 mmol/L sodium acetate, 220 mmol/L sorbitol, and 0.02% polysorbate 20; pH5.5) or DEMS (DE)/idarucizumab at 12/500 or 0/500 mg/kg/day were administered to male and female rhesus monkeys (3/sex). DEMS was orally dosed for 5 consecutive days, and idarucizumab was administered intravenously 2 times in total, namely at 1.5 hours post-dose of DEMS on Days 4 and 5. There were no abnormal clinical signs or laboratory data, and renal parameter data were all within the normal range. Organ weight, necropsy, or histopathological examination showed no abnormal renal findings. Based on the results, the applicant concluded that the renal disorder suspected in the male monkey in the 2-dose intravenous toxicity study in combination with DEMS in monkeys (CTD 4.2.3.2-03) was caused not by administration of DEMS and idarucizumab but by its inherent health problems which already existed before the start of the study. ADAs were detected in 1 of 4 animals in the DEMS/idarucizumab 0/500 mg/kg/day group and 3 of 4 animals in the 12/500 mg/kg/day group at the end of the recovery period. However, since the anticoagulant effects of dabigatran were reversed by the pharmacological effects of idarucizumab, the ADA development was judged

by the applicant to have no impact on toxicity evaluation. Based on the above findings, the applicant determined the NOAEL of idarucizumab to be 500 mg/kg/day with or without concomitant DEMS.

5.2.4 Two-week intravenous repeated-dose toxicity study with DEMS re-administration in monkeys (CTD 4.2.3.2-05)

Vehicle (a buffer consisting of 25 mmol/L sodium acetate, 220 mmol/L sorbitol, and 0.02% polysorbate 20; pH5.5) or DEMS (DE)/idarucizumab 0/500, 12/150, or 12/500 mg/kg/day were repeatedly administered orally (DEMS) and intravenously (idarucizumab) to male and female rhesus monkeys (5/sex). Following 28-day recovery after the completion of the administration, DEMS (DE 0 or 12 mg/kg/day) was re-administered to some animals for 3 days. There were no abnormal clinical signs or laboratory data. The anticoagulant effects induced by DEMS were completely reversed immediately after idarucizumab administration, regardless of development of ADAs, and there were no changes in blood coagulation parameters in the idarucizumab monotherapy (0/500 mg/kg/day) group. Since idarucizumab showed no effect on thrombogenesis markers (i.e., D-dimer and F1 + 2) from baseline through to all post-dose time points, the applicant concluded that idarucizumab does not promote thrombus formation. At the end of recovery period, ADAs were detected in all animals except for animals in the vehicle control group. Anti-dabigatran antibodies were measured by RIPA with ^{3}H-labeled dabigatran before the study and during and after the recovery period. During the recovery period, the antibodies were positive in 3 of 4 animals receiving 0/500 mg/kg/day, 3 of 4 animals receiving 12/150 mg/kg/day, and 4 of 4 animals receiving 12/500 mg/kg/day, but were negative in control animals receiving vehicle. Anti-dabigatran antibodies were positive even in animals receiving no DEMS, and the potential causes were explored. As a result, the applicant considered that a part of idarucizumab-ADA complex existing in plasma bound to ^{3}H-dabigatran, leading to the positive results in the RIPA. A weak positive reaction was also observed in 2 of 4 animals in the 12/500 mg/kg/day group after the recovery period. In light of the longer half-life of idarucizumab-ADA complex in general, the applicant considered that the positive reaction was attributable to the presence of idarucizumab-ADA complex, like during the recovery period. The applicant thus concluded that administration of idarucizumab in combination with DEMS would be very unlikely to generate anti-dabigatran antibodies in monkeys. There were no differences in complement Bb, C3a, and C4a levels among the groups before and after DEMS re-administration after the recovery period. There were also no changes in C1q-conjugated CIC (C1q-CIC) and C3d-conjugated CIC (C3d-CIC) levels which were measured before and during the study. Kidneys from necropsied animals were immunohistochemically assessed for human IgG (idarucizumab) and simian IgG, IgM, and C3. Human IgG was detected in the tubular epithelia of kidneys obtained from animals after idarucizumab administration in all groups, except for the control group, and the extent of the deposition did not differ among the groups. There also were no differences in the extent of other deposits in the renal glomeruli among the groups. Based on these results, the applicant concluded that administration of idarucizumab alone or in combination with DEMS would not cause immune complex formation or deposition of immune complexes in the renal glomeruli in monkeys. In conclusion, the applicant determined the NOAEL of idarucizumab to be 500 mg/kg/day with or without DEMS.

5.3 Local tolerance (CTD 4.2.3.6-01)

Perivascular tolerance of idarucizumab was evaluated in NZW rabbits. Idarucizumab 0.1 mL or 0.9% saline was administered around the marginal veins of the right and left ears of the rabbits. Dermal evaluation and histopathological examinations showed no effects of idarucizumab, and the applicant considered that idarucizumab is locally well tolerated.

5.4 Other toxicity studies

5.4.1 Tissue cross-reactivity in normal human, rhesus monkey, and rat tissues (CTD 4.2.3.7.7-01)

Cross-reactivity of biotin-labeled idarucizumab (2.0 and 10 μg/mL) to normal tissues of humans, resus monkeys and Wistar rats was investigated. No idarucizumab-specific staining was observed in any tissues of the species, and accordingly the applicant concluded that tissue cross-reactivity to idarucizumab is very unlikely to occur.

5.4.2 Hemolysis (CTD 4.2.3.7.7-02, reference data)

Incubation of 0.5 mL human blood with 125 μL idarucizumab (55 mg/mL) yielded no hemolysis.

5.R Outline of the review by PMDA

5.R.1 Anti-dabigatran antibody

PMDA's view:

In the 2-week intravenous repeated-dose toxicity study with DEMS re-administration in monkeys, some animals were positive for anti-dabigatran antibodies measured by RIPA even after the 28-day recovery period. The applicant attributed it to the presence of idarucizumab-ADA complex. However, there were no data showing that there exists a positive level of idarucizumab-ADA complex in plasma throughout the recovery period, and it cannot be concluded that administration of idarucizumab in combination with DEMS would not cause the development of anti-dabigatran antibodies in monkeys. Also in humans, cases have been reported in which individuals were deemed to be positive for anti-dabigatran antibodies as assessed by a modified TT assay. Therefore, in light of the development of anti-dabigatran antibodies, details on provision of precautions and information regarding the resumption of DEMS are discussed in Section "7.R.7 Resumption of DEMS therapy after administration of idarucizumab."

5.R.2 Use in pregnant women

No data from reproductive and developmental toxicity studies have been submitted for the present application. PMDA therefore requested the applicant to discuss the potential risks associated with idarucizumab treatment in pregnant women or women who may be pregnant, taking into consideration of development of ADAs and possible toxicity of immune complexes.

The applicant's response:

Recently developed anticoagulants (e.g., DEMS and factor Xa inhibitors) cause reproductive toxicity in non-

clinical studies; this raises concerns about their potential adverse effects on human fetuses. Precautionary statements are thus provided for their use in pregnant women. Since an *ex vivo* study using a perfused human placenta model showed placental transfer of dabigatran and DEMS (*Obset Gynecol*. 2014;123(6):1256-61), the effects on fetal coagulation system could not be ruled out. DEMS is thus recommended to be used in pregnant women only if no other treatment option is available and the therapeutic benefits overweigh the potential risks. Similar precautionary statements are provided also in the prescribing information in the US and Europe. Therefore, the use of idarucizumab in pregnant women will be limited to those receiving DEMS (because no other treatment option is available and because the potential benefits overweigh the potential risks) who are in life-threatening situations and need immediate reversal of anticoagulant effects of dabigatran. When the anticoagulant effects of dabigatran are reversed by idarucizumab, the blood coagulation system is restored to the original physiological state. In such a state, there are concerns about cardiovascular diseases for which DEMS is indicated. However, since idarucizumab did not accelerate thrombus formation in monkeys treated with idarucizumab in a study, idarucizumab is not considered to promote thrombogenesis in humans, regardless of pregnancy status.

The extent of ADA generation after idarucizumab was very small in healthy adults or patients. Although ADA generation is expected even in pregnant women, the influence of ADA generation on the pharmacological effects of idarucizumab is small, and the incidence of such events is low in general. No adverse events due to development of immune complex have been reported in healthy adults or patients. No deposition of immune complex after administration of idarucizumab was observed in the monkeys which had been clearly positive for ADAs against idarucizumab. Accordingly, formation of immune complex and occurrence of adverse effects due to immune complex are both considered extremely unlikely to emerge in humans because the extent of generation of ADA against idarucizumab is presumed to be very small in humans.

Idarucizumab is a Fab without the Fcγ binding to the FcRn and is thus considered not to cross the placenta via the intracellular uptake mediated by the FcRn. Idarucizumab may cross the placenta by passive diffusion because of its molecular weight (approximately 48 kDa), but in very small amounts (*Placenta*. 2003;24:727-38; *Toxicol Sci.* 2011;122(1):170-6). In addition, no idarucizumab binding to human placental tissues was observed in the tissue cross-reactivity study. Since idarucizumab is deemed to be rapidly eliminated from the maternal plasma after bolus injection, fetal exposure time to idarucizumab is short even if idarucizumab crosses the placenta. Therefore, adverse effects are very unlikely to occur in fetuses.

Based on the above, the applicant determined that reproductive and developmental toxicity studies were not warranted in comprehensive consideration of precautions for use of DEMS in pregnant women.

PMDA's view:

Based on the applicant's explanation, conducting reproductive and developmental studies of idarucizumab was not meaningful, and the applicant's decision to omit reproductive and developmental studies was acceptable. Nevertheless, since effects of idarucizumab on the offspring remain unclear, idarucizumab should not be used

in pregnant women except in urgent situations where idarucizumab is medically necessary to immediately reverse the anticoagulant effects of dabigatran, and the information thereof should be adequately provided to healthcare professionals.

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

6.1 Biopharmaceutic studies and associated analytical methods

Changes were made to the manufacturing process for the drug substance during the development [see "2.1.4 Manufacturing Process Development"]. Among the clinical studies included in the present application, the drug substance manufactured by Manufacturing Process CMC1 or CMC2 was used in Study 1321.1, the drug substance manufactured by CMC2 in Studies 1321.2 and 1321.5, and the drug substance manufactured by [redacted] in Study 1321.3. When changes were made to the manufacturing process from CMC1 to CMC3, the comparability of quality attributes was evaluated and the pre- and post-change drug substances were shown to be comparable. The formulation of the to-be-marketed product is the same as that of the drug product used in all clinical studies.

Idarucizumab concentrations in human plasma were measured by ELISA, and the LLOQ was 1 μg/mL (0.0209 nmol/L). ADAs in human plasma were measured by ECL, and the LLOQ was 11.5 ng/mL. Unbound sum dabigatran concentrations in human plasma were measured by LC-MS/MS, and the LLOQ was 1 ng/mL.

6.2 Clinical pharmacology studies

Results of Study 1321.3 are described based on the interim data as of [redacted], unless otherwise specified. PK parameter values are expressed as geometric mean or geometric mean (geometric CV%), and PD parameter values are expressed as mean or mean ± SD, unless otherwise specified.

6.2.1 Studies in healthy adults

6.2.1.1 Study 1321.5 (CTD 5.3.4.1-03)

Table 12 shows PK parameters of idarucizumab in Japanese healthy adult men who received idarucizumab intravenously at 1, 2, or 4 g over 5 minutes, or at 8 g over 1 hour and Japanese healthy adult men who received idarucizumab (1, 2, or 4 g, or 2 infusions of 2.5 g each [15 minutes apart]) or placebo intravenously at the steady state of plasma dabigatran concentrations. Table 13 shows changes in plasma unbound sum dabigatran concentrations, plasma sum dabigatran concentrations, dTT, ECT, aPTT, and TT in these subjects.

Table 12. PK parameters of idarucizumab following a single intravenous dose of idarucizumab (partially modified from the submitted data)

Idarucizumab dose	DEMS dose [a] (Dose per administration)	N	Administration time	C_{max} (nmol/L)	$AUC_{0-\infty}$ (nmol·h/L)	$t_{1/2}$ (h)	CL (mL/min)	V_{ss} (L)	fe_{0-72} (%)
1 g	-	6	5 min	6810 (10.1)	9150 (15.0)	6.38 (15.4)	38.1 (15.0)	6.21 (14.1)	7.38 (54.9)
2 g	-	6	5 min	15,700 (10.9)	19,500 (17.8)	10.3 (31.4)	35.7 (17.8)	7.45 (26.4)	14.6 (165)
4 g	-	6	5 min	28,100 (14.3)	37,600 (14.4)	7.62 (6.46)	37.1 (14.4)	6.17 (17.7)	24.5 (52.4)
8 g	-	6	1 hour	37,600 (6.88)	76,800 (14.8)	9.70 (9.98)	36.3 (14.8)	6.85 (14.9)	41.3 (25.0)
1 g	220 mg	9	5 min	9510 (33.8)	8590 (14.2)	6.01 (33.3)	40.6 (14.2)	5.57 (28.0)	20.1 (35.1)
2 g	220 mg	9	5 min	17,600 (16.8)	19,200 (18.5)	7.31 (13.5)	36.3 (18.5)	5.45 (19.7)	33.0 (12.5)
4 g	220 mg	9	5 min	30,200 (17.7)	34,500 (16.6)[b]	9.06 (24.1)[b]	40.4 (16.6)[b]	6.38 (27.5)[b]	50.9 (16.4)
2.5 + 2.5 g	220 mg	9	5 min	30,100 (11.5)	43,300 (8.25)	7.91 (9.33)	40.2 (8.25)	6.53 (10.2)	49.3 (18.1)

[a] DE dose is shown. [b] N = 8.

Table 13. Changes in plasma unbound sum dabigatran concentrations, plasma sum dabigatran concentrations, dTT, ECT, aPTT, and TT following a single intravenous dose of idarucizumab (partially modified from the submitted data)

Idarucizumab dose	DEMS dose [e] (Dose per administration)	N	Time since the last dose of DEMS						
			1.92 h [a]	2 h	2.5 h	3 h	6 h	12 h	26 h
Plasma unbound sum dabigatran concentrations (ng/mL)									
0 g	220 mg	12	152 (40.0)	145 (38.3)	165 (38.6) [e]	157 (38.9) [e]	97.2 (35.8)	42.6 (29.4)	12.6 (31.2)
1 g	220 mg	9	184 (38.0)	1.41 (33.7)	ND	34.8 (201)	35.5 (232)	27.6 (54.2)	11.3 (33.7)
2 g	220 mg	9	187 (34.2)	1.33 (17.7)	ND	ND	5.65 (356)	15.0 (67.9)	10.1 (40.2)
4 g	220 mg	9	148 (20.7)	ND	ND	ND	ND	ND	3.97 (28.8)
2.5 + 2.5 g	220 mg	9	164 (28.5)	ND	ND	ND	ND	ND	ND
Plasma sum dabigatran concentrations (nmol/L)									
0 g	220 mg	12	467 (35.4)	474 (34.4)	526 (32.2) [d]	504 (36.2) [d]	303 (30.4)	136 (26.6)	43.3 (26.2)
1 g	220 mg	9	595 (39.5)	1880 (40.5)	3220 (39.3)	2470 (30.4)	416 (29.3)	156 (31.4)	58.4 (22.0)
2 g	220 mg	9	595 (38.4)	2240 (25.8)	3490 (31.2)	2920 (33.6)	526 (32.5)	195 (28.4)	80.3 (20.3)
4 g	220 mg	9	466 (27.6)	1530 (25.4)	2320 (40.4)	1950 (44.0)	499 (44.5)	186 (18.1)	82.9 (18.5)
2.5 + 2.5 g	220 mg	9	534 (28.3)	1690 (33.7)	2670 (40.6) [b]	1800 (48.7) [c]	481 (41.5)	203 (23.7)	94.6 (17.6)
dTT (s)									
0 g	220 mg	12	59.7 ± 11.0	59.2 ± 10.4	61.2 ± 10.8[d]	61.5 ± 9.76[d]	49.0 ± 6.50	39.0 ± 3.29	33.0 ± 1.60
1 g	220 mg	9	64.9 ± 10.1	30.4 ± 0.973	32.0 ± 3.52	37.9 ± 9.10	40.0 ± 6.57	35.3 ± 2.60	32.2 ± 1.08
2 g	220 mg	9	67.7 ± 13.9	30.1 ± 0.618	30.1 ± 0.566	32.0 ± 5.81	35.4 ± 10.9	34.0 ± 3.23	32.2 ± 0.926
4 g	220 mg	9	60.8 ± 6.62	30.5 ± 0.546	30.3 ± 0.798	30.4 ± 0.740	30.8 ± 0.770	30.7 ± 1.37	31.5 ± 1.31
2.5 + 2.5 g	220 mg	9	63.5 ± 7.97	30.5 ± 0.437	30.5 ± 0.648[b]	30.2 ± 0.555[c]	30.4 ± 0.515	30.3 ± 0.431	30.8 ± 0.503
ECT (s)									
0 g	220 mg	12	99.0 ± 20.7	102 ± 21.7	108 ± 21.0[d]	106 ± 25.4[d]	78.2 ± 15.7	54.0 ± 6.32	40.4 ± 5.79
1 g	220 mg	9	115 ± 25.8	33.9 ± 1.12	39.5 ± 8.32	53.6 ± 19.8	59.1 ± 13.9	48.4 ± 5.87	39.7 ± 2.76
2 g	220 mg	9	117 ± 28.0	34.0 ± 1.40	34.5 ± 1.75	38.1 ± 11.5	43.3 ± 18.0	44.2 ± 11.8	38.4 ± 2.02
4 g	220 mg	9	95.3 ± 13.7	33.7 ± 1.60	34.6 ± 1.39	34.1 ± 1.33	33.9 ± 1.50	33.6 ± 1.43	35.2 ± 1.88
2.5 + 2.5 g	220 mg	9	108 ± 19.6	34.2 ± 1.24	34.2 ± 1.21[b]	33.9 ± 0.991[c]	34.5 ± 1.85	33.5 ± 0.936	34.2 ± 1.35
aPTT (s)									
0 g	220 mg	12	74.6 ± 16.0	73.6 ± 15.2	77.6 ± 14.8[d]	80.3 ± 16.7[d]	65.5 ± 13.1	50.9 ± 6.18	40.5 ± 5.12
1 g	220 mg	9	79.1 ± 13.8	33.9 ± 4.61	37.5 ± 9.44	48.0 ± 15.9	55.0 ± 12.2	47.2 ± 8.65	40.5 ± 5.63
2 g	220 mg	9	82.6 ± 17.0	35.4 ± 3.35	35.3 ± 3.37	38.2 ± 10.5	43.1 ± 14.7	41.1 ± 5.71	39.5 ± 3.48
4 g	220 mg	9	71.5 ± 11.6	34.3 ± 5.33	34.1 ± 4.14	34.1 ± 4.10	33.5 ± 4.02	33.4 ± 4.07	35.9 ± 6.18
2.5 + 2.5 g	220 mg	9	72.9 ± 7.55	35.8 ± 3.33	35.4 ± 4.09[b]	35.0 ± 4.16[c]	34.4 ± 3.75	33.1 ± 4.17	35.3 ± 2.94
TT (s)									
0 g	220 mg	12	145 ± 35.6	138 ± 40.2	145 ± 40.2[d]	145 ± 38.0[d]	112 ± 25.5	65.9 ± 13.8	27.3 ± 8.21
1 g	220 mg	9	144 ± 31.3	13.1 ± 0.882	22.3 ± 18.5	45.6 ± 36.1	63.9 ± 34.3	51.0 ± 22.7	26.2 ± 6.46
2 g	220 mg	9	177 ± 49.8	12.6 ± 0.453	12.9 ± 1.02	20.7 ± 24.5	39.7 ± 66.7	33.3 ± 16.9	24.1 ± 7.19
4 g	220 mg	9	145 ± 28.7	12.7 ± 0.559	12.5 ± 0.394	12.4 ± 0.359	12.6 ± 0.584	12.8 ± 0.500	15.7 ± 2.61
2.5 + 2.5 g	220 mg	9	162 ± 27.4	12.8 ± 0.444	12.8 ± 0.545[b]	12.6 ± 0.431[c]	12.6 ± 0.465	12.6 ± 0.370	13.9 ± 1.30

-, not calculated; ND, not determined because the number of samples with concentrations within the detectable range was below two-thirds of the total number. [a)] Before the start of idarucizumab administration. [b)] Values at 2 hours and 20 minutes. [c)] Values at 3 hours and 20 minutes. [d)] N = 9. [e)] DE dose is shown.

ADAs were detected in 4 of 20 subjects before placebo administration and 10 of 60 subjects before idarucizumab administration. ADAs were newly detected after idarucizumab administration in 4 subjects.

6.2.1.2 Study 1321.1 (CTD 5.3.4.1-01)

Table 14 shows PK parameters of idarucizumab in non-Japanese healthy adults who received idarucizumab intravenously at 0.02, 0.06, 0.2, 0.6, 1.2, 2, 3, 4, 6, and 8 g over 1 hour and in those who received idarucizumab intravenously at 1, 2, and 4 g over 5 minutes (Part 1).

Non-Japanese healthy adults received DEMS (DE 220 mg) orally twice daily (in the morning and evening) on Days 1 to 3. On Day 4, they received DEMS (DE 220 mg) orally once in the morning and then, 1 hour and 55 minutes later, received idarucizumab at 1, 2, 4, and 7.5 g (5 g + 2.5 g, 1 hour apart) or placebo intravenously over 5 minutes. PK parameters of idarucizumab are shown in Table 14, changes in plasma unbound sum dabigatran concentrations in Table 15, and $AUEC_{above,2\text{-}12}$ ratio for dTT, ECT, aPTT, and TT in Table 16 (Parts 2 and 3).

Table 14. PK parameters of idarucizumab following a single intravenous dose of idarucizumab (partially modified from the submitted data)

Idarucizumab dose	DEMS dose [a)] (Dose per administration)	N	Administration time	C_{max} (nmol/L)	$AUC_{0\text{-}\infty}$ (nmol·h/L)	$t_{1/2}$ (h)	CL (mL/min)	V_{ss} (L)	fe (%)
0.02 g	0 mg	6	1 h	79.9 (15.1)	146 (19.8)	0.887 (18.1)	47.8 (19.8)	3.67 (14.2)	-
0.06 g	0 mg	6	1 h	257 (11.1)	426 (11.6)	0.978 (12.6)	49.0 (11.6)	3.89 (15.8)	-
0.2 g	0 mg	6	1 h	809 (13.9)	1950 (129)	2.13 (329)	35.6 (129)	5.21 (76.9)	-
0.6 g	0 mg	5	1 h	2440 (13.1)	6970 (75.4)	7.90 (213)	30.0 (75.4)	12.7 (136)	-
1.2 g	0 mg	6	1 h	4520 (9.72)	8780 (4.92)	5.52 (24.1)	47.6 (4.92)	6.98 (19.7)	-
2 g	0 mg	12	1 h	7420 (15.1)	14,500 (15.9)	6.96 (31.9)	47.9 (15.9)	7.51 (24.3)	-
3 g	0 mg	6	1 h	11,700 (10.4)	22,600 (17.6)	7.62 (12.0)	46.3 (17.6)	6.79 (15.6)	-
4 g	0 mg	6	1 h	15,700 (15.6)	31,000 (12.9)	7.65 (12.2)	44.9 (12.9)	6.96 (17.8)	-
6 g	0 mg	6	1 h	22,100 (12.0)	41,200 (11.8)	6.83 (9.80)	50.7 (11.8)	7.64 (11.6)	28.8 (50.1)
8 g	0 mg	5	1 h	33,900 (13.2)	63,800 (15.6)	6.73 (4.77)	43.7 (15.6)	6.25 (7.76)	23.6 (395)
1 g	0 mg	6	5 min	6360 (16.7)	7790 (13.1)	4.54 (17.9)	44.7 (13.1)	5.27 (9.55)	10.7 (76.3)
2 g	0 mg	6	5 min	13,600 (23.4)	16,400 (16.8)	7.42 (33.1)	42.5 (16.8)	6.06 (21.1)	19.1 (73.1)
4 g	0 mg	6	5 min	21,400 (13.1)	25,800 (22.1)	8.11 (11.1)	53.9 (22.1)	8.25 (26.3)	38.9 (23.6)
1 g	220 mg	9	5 min	5410 (13.5)	6480 (17.1)	4.97 (31.1)	53.8 (17.1)	6.30 (22.0)	8.18 (90.6)
2 g	220 mg	9	5 min	12,500 (21.5)	16,600 (10.7)	8.99 (21.6)	41.9 (10.7)	6.90 (29.2)	26.2 (23.4)
4 g	220 mg	8	5 min	25,800 (25.1)	30,900 (14.1)	7.92 (11.3)	45.1 (14.1)	6.37 (21.6)	40.2 (30.5)
7.5 g	220 mg	9	5 min	35,300 (24.4)	62,300 (8.43)	7.03 (15.6)	41.9 (8.43)	-	46.9 (24.9)

-, not calculated. [a)] DE dose is shown.

Table 15. Changes in plasma unbound sum dabigatran concentrations following a single intravenous dose of idarucizumab (partially modified from the submitted data)

Idarucizumab dose	DEMS dose [a] (Dose per administration)	N	Time since the last dose of DEMS				
			1.92 h	2 h	2.5 h	6 h	12 h
Plasma unbound sum dabigatran concentrations (ng/mL)							
0 g	220 mg	9	119 (38.0)	123 (40.8)	130 (47.9)	79.2 (44.6)	38.5 (40.3)
1 g	220 mg	9	136 (51.8)	1.59 (10.7)	ND	15.3 (296)	18.2 (71.1)
2 g	220 mg	9	96.2 (33.3)	ND	ND	ND	ND
4 g	220 mg	8	135 (47.6)	ND	ND	ND	ND

ND, not determined because the number of samples with concentrations within the detectable range was below two-thirds of the total number. [a] DE dose is shown.

Table 16. $AUEC_{above,2\text{-}12}$ ratio (after idarucizumab administration/before idarucizumab administration [Day 3 of DEMS administration]) for coagulation parameters (partially modified from the submitted data)

	Idarucizumab dose	DEMS dose [a] (Dose per administration)	No. of subjects	dTT	ECT	aPTT	TT
Part 2	0 g	220 mg	9	1.01	1.04	1.28	1.08
	1 g	220 mg	9	0.26	0.28	0.46	0.32
	2 g	220 mg	9	0.06	0.07	0.14	0.06
	4 g	220 mg	8	0.02	0.03	0.07	0.00
Part 3	0 g	220 mg	3	1.02	1.22	1.68	1.11
	7.5 g	220 mg	9	0.01	0.02	0.03	0.00

[a] DE dose is shown.

ADAs were detected in 7 of 39 subjects before placebo administration and 12 of 118 subjects before idarucizumab administration. ADAs were newly detected after idarucizumab administration in 7 subjects.

6.2.1.3 Study 1321.2 (CTD 5.3.4.1-02)

A 2-period crossover study (with a 6-day washout period) was conducted in non-Japanese healthy adults (aged 45 to 64 years), healthy elderly subjects (aged 65 to 80 years), subjects with mild renal impairment (CrCL ≥60 to <90 mL/min), and subjects with moderate renal impairment (CrCL ≥30 to <60 mL/min). On Days 1 to 3, oral DEMS was administered twice daily (in the morning and evening) to all subjects. In the morning of Day 4, a single oral dose of DEMS was administered to all subjects. (The healthy adults aged 45 to 64 years received oral DEMS twice daily [in the morning and evening] on Days 5 and 6, and a single oral dose of DEMS on Day 7.) In the morning of Day 4, a 5-min intravenous infusion of idarucizumab or placebo was started at 1 hour and 55 minutes after DEMS administration in all subjects, except for subjects with moderate renal impairment who received two 5-min infusions of idarucizumab or placebo at 1 hour and 55 minutes and at 2 hour and 55 minutes after DEMS administration. The non-Japanese healthy adults (aged 45 to 64 years) who received idarucizumab 2.5 g underwent Period 3 starting at 2 months after the end of Period 2. In Period 3, they received oral DEMS twice daily on Days 1 to 3 and a single oral dose of DEMS on Day 4 (a total of 7 doses) and re-administration of idarucizumab 2.5 g at 1 hour and 55 minutes after the last dose of DEMS. PK parameters of idarucizumab are shown in Table 17. Changes in plasma unbound sum dabigatran concentrations, dTT, ECT, aPTT, and TT are shown in Table 18.

Table 17. PK parameters of idarucizumab following a single intravenous dose of idarucizumab (partially modified from the submitted data)

	Idarucizumab dose	DEMS dose [a] (Dose per administration)	N	C_{max} (nmol/L)	$AUC_{0-\infty}$ (nmol·h/L)	$t_{1/2}$ (h)	CL (mL/min)	V_{ss} (L)	fe (%)
Healthy adults	2.5 g	220 mg	6	15,700 (14.3)	22,200 (12.7)	8.34 (10.1)	39.3 (12.7)	6.61 (11.2)	25.8 (32.6)
	2.5 g (re-administration)	220 mg	6	14,900 (12.0)	20,600 (10.6)	6.67 (5.78)	42.3 (10.6)	6.96 (13.0)	-
	5 g	220 mg	6	25,000 (16.9)	37,000 (18.4)	10.3 (18.9)	47.1 (18.4)	8.86 (24.8)	32.1 (60.0)
Healthy elderly subjects	1 g	220 mg	8	5790 (16.4)	8560 (15.2)	5.84 (60.6)	40.7 (15.2)	6.39 (23.3)	9.43 (69.0)
	5 g	220 mg	8	28,300 (28.9)	43,900 (18.7)	10.8 (15.9)	39.6 (18.7)	8.03 (34.0)	39.8 (13.7)
Subjects with mild renal impairment	1 g	150 mg	6	6940 (19.4)	10,700 (14.1)	9.83 (30.8)	32.7 (14.1)	6.70 (26.9)	12.4 (46.7)
	5 g	150 mg	6	32,100 (17.4)	53,100 (11.1)	9.52 (18.4)	32.8 (11.1)	6.34 (12.6)	32.0 (48.9)
Subjects with moderate renal impairment	2.5 + 2.5 g	150 mg	6	25,600 (11.6)	67,900 (11.6)	10.1 (11.8)	25.7 (11.6)	7.00 (12.4)	30.0 (89.0)

-, not calculated. [a] DE dose is shown.

Table 18. Changes in plasma unbound sum dabigatran concentrations, dTT, ECT, aPTT, and TT following a single intravenous dose of idarucizumab (partially modified from the submitted data)

	Idarucizumab dose	DEMS dose [d] (Dose per administration)	N	Time since the last dose of DEMS						
				1.92 h [a]	2 h	2.5 h	3 h	6 h	12 h	26 h
Plasma unbound sum dabigatran concentrations (ng/mL)										
Healthy adults	0 g	220 mg	12	160 (26.5)	160 (26.4)	155 (29.0)	145 (34.4)	98.4 (35.6)	49.1 (25.9)	16.9 (22.8)
	2.5 g	220 mg	6	158 (21.2)	ND	ND	ND	ND	ND	10.9 (20.9)
	2.5 g (re-administration)	220 mg	6	170 (38.6)	ND [b]	ND	ND	3.20 (154)	18.9 (28.4)[c]	10.9 (59.6)
	5 g	220 mg	6	212 (56.0)	ND	ND	ND	ND	ND	5.44 (99.2)
Healthy elderly subjects	0 g	220 mg	16	202 (39.7)	200 (40.5)	198 (40.9)[f]	183 (39.8)	128 (34.6)	70.4 (32.1)	26.0 (29.7)
	1 g	220 mg	8	189 (37.1)	ND	ND	2.81 (351)	32.2 (102)	35.2 (37.4)	18.7 (14.8)
	5 g	220 mg	8	211 (44.0)	ND	ND	ND	ND	ND	8.31 (70.0)
Subjects with mild renal impairment	0 g	150 mg	12	142 (46.9)	139 (49.1)[f]	137 (46.1)	131 (48.5)	95.5 (46.7)	51.3 (41.8)	19.3 (45.2)
	1 g	150 mg	6	135 (59.9)	ND	ND	ND	13.6 (234)	14.8 (180)	13.5 (57.0)
	5 g	150 mg	6	163 (23.7)	ND	ND	ND	ND	ND	3.87 (86.1)
Subjects with moderate renal impairment	0 g	150 mg	6	209 (29.1)	220 (36.0)	204 (33.5)	209 (31.1)	153 (36.0)	91.7 (26.8)	32.1 (12.4)
	2.5 + 2.5 g	150 mg	6	197 (40.1)	ND	ND	ND	ND	ND	9.94 (163)
dTT (s)										
Healthy adults	0 g	220 mg	12	60.9 ± 7.60	60.3 ± 7.73	60.1 ± 8.78	58.0 ± 7.25	49.8 ± 6.66	40.4 ± 4.07	35.3 ± 2.65
	2.5 g	220 mg	6	60.5 ± 7.04	31.2 ± 1.98	30.9 ± 2.46	31.1 ± 2.24	31.6 ± 2.51	32.8 ± 2.52	33.3 ± 2.63
	2.5 g (re-administration)	220 mg	6	66.3 ± 7.37	34.6 ± 0.543[b]	34.2 ± 0.378	34.0 ± 0.186	35.5 ± 1.16	38.9 ± 6.14[c]	36.3 ± 1.44
	5 g	220 mg	6	65.6 ± 11.7	31.7 ± 1.97	31.4 ± 1.94	31.4 ± 1.98	31.2 ± 2.35	32.5 ± 3.09	32.4 ± 1.17
Healthy elderly subjects	0 g	220 mg	16	68.3 ± 13.8[f]	68.1 ± 13.7	67.7 ± 13.1[f]	66.5 ± 13.1	55.5 ± 9.29	44.6 ± 4.86	36.2 ± 2.97
	1 g	220 mg	8	66.8 ± 14.8	31.6 ± 2.44	31.9 ± 2.80	33.8 ± 6.26	38.8 ± 3.96	38.7 ± 4.51	35.1 ± 3.20
	5 g	220 mg	8	67.3 ± 12.9	32.4 ± 0.667	32.1 ± 0.679	32.2 ± 0.814	32.2 ± 0.743	32.3 ± 1.43	33.5 ± 1.93
Subjects with mild renal impairment	0 g	150 mg	12	60.1 ± 10.4	61.0 ± 14.7	59.0 ± 11.0	57.5 ± 10.3	48.9 ± 8.35	41.1 ± 3.49	34.9 ± 2.03
	1 g	150 mg	6	60.3 ± 9.70	33.1 ± 2.10	33.0 ± 1.83	33.3 ± 1.76	39.4 ± 6.82	36.8 ± 2.79	35.7 ± 2.25
	5 g	150 mg	6	60.4 ± 7.54	30.2 ± 0.388	30.0 ± 0.397	30.1 ± 0.274	30.2 ± 0.407	30.6 ± 1.88	31.2 ± 0.981
Subjects with moderate renal impairment	0 g	150 mg	6	71.7 ± 10.8	70.3 ± 9.50	70.9 ± 11.3	71.0 ± 13.8	60.2 ± 6.21	48.7 ± 3.02	36.3 ± 3.44
	2.5 + 2.5 g	150 mg	6	69.1 ± 11.0	30.6 ± 0.365	30.2 ± 0.525	30.1 ± 0.504	30.2 ± 0.492	30.3 ± 0.500	31.8 ± 2.61
ECT (s)										
Healthy adults	0 g	220 mg	12	97.0 ± 18.4	99.2 ± 21.5	96.8 ± 22.5	92.9 ± 21.0	74.4 ± 15.5	54.4 ± 8.94	40.3 ± 2.40
	2.5 g	220 mg	6	94.4 ± 7.82	33.3 ± 1.94	33.1 ± 2.18	34.0 ± 2.51	33.4 ± 1.92	36.7 ± 1.39	38.9 ± 3.29
	2.5 g (re-administration)	220 mg	6	112 ± 30.7	35.5 ± 2.84[b]	33.0 ± 0.993	33.4 ± 1.32	34.9 ± 4.16	39.1 ± 6.36[c]	39.5 ± 3.68
	5 g	220 mg	6	120 ± 32.2	33.4 ± 1.65	33.1 ± 1.37	32.8 ± 1.39	33.0 ± 1.51	37.5 ± 9.18	36.7 ± 1.81
Healthy elderly subjects	0 g	220 mg	16	127 ± 29.8[f]	128 ± 30.2	125 ± 30.0[f]	119 ± 28.0	90.3 ± 21.9	69.6 ± 10.7	47.9 ± 4.31
	1 g	220 mg	8	111 ± 41.2	36.0 ± 1.88	36.6 ± 2.45	41.0 ± 11.4	53.7 ± 7.82	52.8 ± 5.99	44.6 ± 2.77
	5 g	220 mg	8	123 ± 50.6	35.6 ± 1.57	35.9 ± 2.14	34.9 ± 1.13	42.9 ± 21.4	36.6 ± 2.36	40.3 ± 2.56
Subjects with mild renal impairment	0 g	150 mg	12	96.4 ± 22.5	97.8 ± 24.1	96.5 ± 23.8	90.9 ± 23.9	73.4 ± 17.5	57.3 ± 8.52	42.3 ± 3.46
	1 g	150 mg	6	90.7 ± 22.6	33.0 ± 1.29	33.2 ± 1.4	32.8 ± 1.7	47.8 ± 18.5	41.6 ± 3.86	37.8 ± 1.73
	5 g	150 mg	6	104 ± 13.5	35.8 ± 1.91	35.7 ± 1.51	34.6 ± 1.77	34.6 ± 1.25	35.5 ± 1.05	36.6 ± 1.92
Subjects with moderate renal impairment	0 g	150 mg	6	132 ± 21.7	132 ± 26.1	134 ± 27.8	128 ± 27.7	106 ± 18.5	78.2 ± 6.14	47.8 ± 7.99
	2.5 + 2.5 g	150 mg	6	131 ± 25.9	34.9 ± 1.63	36.7 ± 3.47	36.2 ± 1.84	36.5 ± 2.01	39.6 ± 4.07	41.3 ± 7.99
aPTT (s)										
Healthy adults	0 g	220 mg	12	64.7 ± 10.9	64.9 ± 12.0	64.0 ± 10.8	61.7 ± 11.6	55.1 ± 8.93	42.5 ± 10.5	36.1 ± 5.55
	2.5 g	220 mg	6	67.1 ± 8.50	32.0 ± 1.97	31.0 ± 2.33	32.4 ± 2.96	31.7 ± 3.42	31.9 ± 6.48	39.0 ± 5.82
	2.5 g (re-administration)	220 mg	6	64.3 ± 5.82	30.6 ± 4.93[b]	28.3 ± 2.77	27.7 ± 2.75	28.7 ± 4.80	32.2 ± 6.24[c]	35.3 ± 6.21
	5 g	220 mg	6	66.9 ± 9.84	26.6 ± 5.14	26.4 ± 5.53	26.5 ± 4.78	26.8 ± 5.87	25.6 ± 6.31	28.0 ± 5.92
Healthy elderly subjects	0 g	220 mg	16	70.6 ± 13.5[e]	71.9 ± 11.2	69.6 ± 9.73 [e]	67.6 ± 11.2	60.2 ± 12.7	50.0 ± 7.55	39.9 ± 5.36
	1 g	220 mg	8	73.3 ± 14.1	30.3 ± 3.00	31.0 ± 3.03	32.1 ± 3.56	39.7 ± 9.85	41.4 ± 6.15	36.5 ± 4.37
	5 g	220 mg	8	68.4 ± 17.9	31.1 ± 3.60	31.4 ± 4.39	31.4 ± 4.03	35.7 ± 12.1	29.8 ± 2.29	34.9 ± 3.53

Table 18. Changes in plasma unbound sum dabigatran concentrations, dTT, ECT, aPTT, and TT following a single intravenous dose of idarucizumab (partially modified from the submitted data)

	Idarucizumab dose	DEMS dose [d] (Dose per administration)	N	Time since the last dose of DEMS						
				1.92 h [a]	2 h	2.5 h	3 h	6 h	12 h	26 h
Subjects with mild renal impairment	0 g	150 mg	12	61.6 ± 11.3	60.1 ± 11.2	59.4 ± 10.8	56.4 ± 12.5	51.9 ± 12.1	42.1 ± 8.42	38.1 ± 6.29
	1 g	150 mg	6	57.1 ± 7.12	26.9 ± 4.71	27.2 ± 4.76	27.2 ± 4.90	37.2 ± 11.6	35.0 ± 5.24	33.7 ± 5.49
	5 g	150 mg	6	64.9 ± 7.10	30.0 ± 2.99	30.2 ± 2.59	29.7 ± 2.87	31.2 ± 0.812	29.2 ± 1.08	32.7 ± 0.850
Subjects with moderate renal impairment	0 g	150 mg	6	75.0 ± 8.99	71.0 ± 8.74	72.4 ± 5.67	68.2 ± 9.73	63.9 ± 5.29	52.3 ± 4.64	38.7 ± 5.58
	2.5 + 2.5 g	150 mg	6	71.9 ± 6.49	30.4 ± 5.00	31.2 ± 3.35	31.0 ± 3.99	30.3 ± 2.67	28.5 ± 4.17	33.3 ± 5.64
TT (s)										
Healthy adults	0 g	220 mg	12	118 ± 20.8	119 ± 21.5	116 ± 37.8	108 ± 20.5	88.3 ± 24.8	54.1 ± 17.7	30.2 ± 7.19
	2.5 g	220 mg	6	119 ± 17.9	11.8 ± 0.489	11.5 ± 0.466	12.2 ± 0.691	12.3 ± 0.540	15.5 ± 4.02	24.0 ± 6.36
	2.5 g (re-administration)	220 mg	6	110 ± 20.3	13.2 ± 0.881[b]	12.2 ± 0.234	12.4 ± 0.344	15.1 ± 5.55	26.9 ± 12.8[c]	26.4 ± 8.08
	5 g	220 mg	6	105 ± 46.9	12.8 ± 1.02	15.5 ± 7.64	19.9 ± 18.0	21.0 ± 20.8	25.2 ± 20.4	17.4 ± 4.55
Healthy elderly subjects	0 g	220 mg	16	146 ± 41.3[e]	150 ± 46.4	149 ± 32.9[e]	136 ± 36.7	115 ± 47.0	77.8 ± 23.4	44.4 ± 10.3
	1 g	220 mg	8	151 ± 29.8	12.3 ± 0.530	12.6 ± 1.37	17.3 ± 13.0	51.3 ± 15.8	49.2 ± 10.6	32.8 ± 5.35
	5 g	220 mg	8	143 ± 70.5	12.3 ± 0.498	12.7 ± 0.296	12.4 ± 0.329	28.6 ± 45.4	12.6 ± 0.325	20.6 ± 5.42
Subjects with mild renal impairment	0 g	150 mg	12	118 ± 23.7	105 ± 26.7	116 ± 28.4	100 ± 31.0	96.0 ± 29.7	60.4 ± 15.7	32.7 ± 11.4
	1 g	150 mg	6	115 ± 40.1	13.8 ± 2.02	13.7 ± 2.03	14 ± 2.26	48.2 ± 37.4	32.9 ± 12.5	28.3 ± 7.25
	5 g	150 mg	6	122 ± 38.0	12.0 ± 0.643	12.2 ± 0.459	12.1 ± 0.472	12.2 ± 0.339	12.0 ± 0.647	14.8 ± 2.89
Subjects with moderate renal impairment	0 g	150 mg	6	161 ± 32.6	127 ± 43.0	146 ± 41.6	138 ± 33.3	123 ± 21.5	90.7 ± 9.31	43.2 ± 15.8
	2.5 + 2.5 g	150 mg	6	147 ± 26.6	11.9 ± 0.424	12.2 ± 0.320	12.2 ± 0.479	11.9 ± 0.376	12.6 ± 0.651	20.5 ± 11.0

ND, not determined because the number of samples with concentrations within the detectable range was below two-thirds of the total number. [a] Before the start of idarucizumab administration. [b] Values at 2 hours and 10 minutes. [c] Values at 14 hours. [d] DE dose is shown. [e] N = 15. [f] N = 11.

ADAs were detected in 6 of 46 subjects after the last dose of idarucizumab.

6.2.1.4 PPK/PD analysis (CTD 5.3.3.5-01)

PPK analysis was performed with plasma idarucizumab concentration data (3572 samples), plasma sum dabigatran concentration data (4439 samples), and plasma unbound sum dabigatran concentration data (4432 samples) obtained from 244 subjects in 3 studies conducted in healthy adults and subjects with renal impairment in and outside of Japan (Studies 1321.1, 1321.2, and 1321.5).

With regard to the distribution of characteristics of subjects in the analysis, the median (minimum, maximum) age was 32 years (20, 76), body weight 73 kg (50.0, 114.0), CrCL (estimated by Cockcroft-Gault equation) 122.70 mL/min (44.11, 212.84), and serum creatinine 76.04 μmol/L (46.86, 110.52). The subject population was as follows: 225 men and 19 women; 169 Caucasians, 73 Asians, and 2 African Americans; and 18 subjects with renal impairment (CrCL ≥30 to <90 mL/min) and 226 subjects without renal impairment. These factors were candidate covariates for PK parameters.

PK of idarucizumab was described by a linear 3-compartment model, and PK of dabigatran was described by a linear two-compartment model with first order absorption incorporating a time-dependent rate constant with a Weibull-like function. The model shown in Figure 1 was used for idarucizumab-dabigatran binding. In the final model, the following factors were selected as covariates: CrCL and race for idarucizumab CL; body

weight for the volume of distribution of central compartment of idarucizumab; CrCL, age, renal impairment, and race for dabigatran CL/F; and renal impairment for dabigatran Q/F.

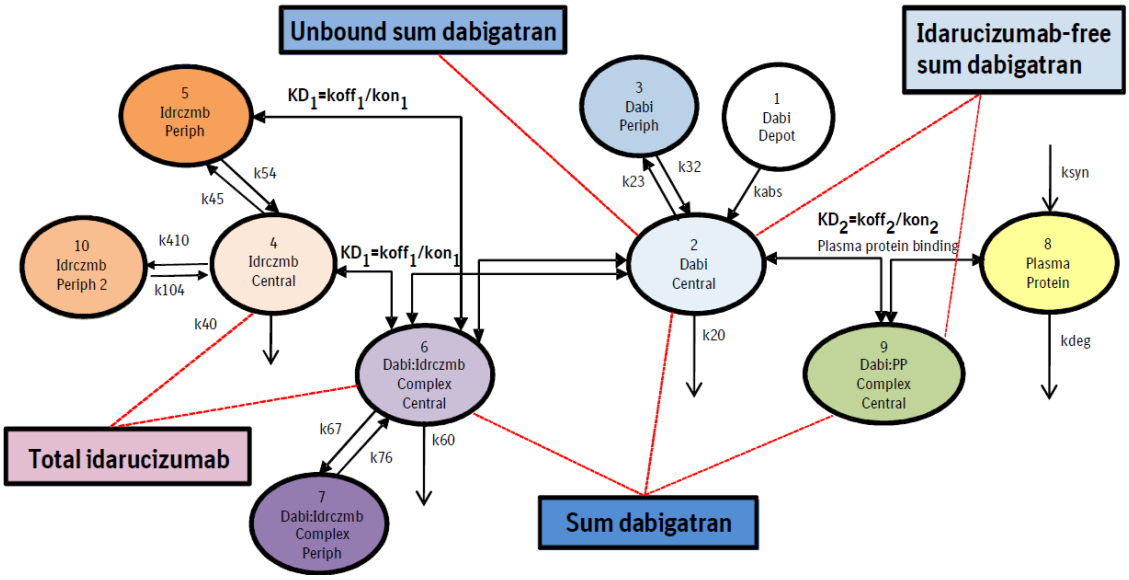

Figure 1. Idarucizumab-dabigatran binding model

A PPK/PD analysis was performed to examine the relationship between the plasma unbound sum dabigatran concentrations and individual coagulation parameters (ECT, dTT, aPTT, and TT). The relationship between plasma unbound sum dabigatran concentrations and ECT and dTT was described by a linear model with an intercept, and the relationship between unbound sum dabigatran concentrations and aPTT and TT was described by a nonlinear maximum effect (E_{max}) model with an intercept. Age, body weight, status/measurements before idarucizumab administration, and studies (Studies 1321.1, 1321.2, and 1321.5) were examined as covariates influencing the relationships between plasma unbound sum dabigatran concentrations and individual coagulation parameters (ECT, dTT, aPTT, and TT). The assessment showed the following significant effects of the covariates: as for ECT, studies (Studies 1321.1 and 1321.5) on the intercept and a study (Study 1321.1) on the slop; as for dTT, status/measurements before idarucizumab administration and a study (Study 1321.5) on the intercept and a study (Study 1321.5) on the slope; as for TT, body weight and a study (Study 1321.1) on the intercept, age on the E_{max}, and body weight on the EC_{50}; as for aPTT, a study (Study 1321.2) on the slope and a study (Study 1321.5) on the E_{max}. However, all covariates were considered to have no clinically significant effects.

6.2.2 Studies in patients

6.2.2.1 Study 1321.3 (CTD 5.3.5.2-01)

Two infusions of Idarucizumab 2.5 g were intravenously administered within a 15-minute interval to patients on anticoagulant therapy with dabigatran who had life-threatening or uncontrolled bleeding requiring urgent medical or surgical intervention (Group A) and those who required emergency surgery or other invasive

procedure for a disease or condition other than bleeding and in whom persistence of anticoagulant effects of dabigatran was undesirable (Group B). PK parameters of idarucizumab are shown in Table 19. Changes in plasma unbound sum dabigatran concentrations, dTT, ECT, aPTT, and TT are shown in Table 20.

Table 19. PK parameters of idarucizumab following a single intravenous dose of idarucizumab (partially modified from the submitted data)

	N	C_{max} (nmol/L)	$AUC_{0-\infty}$ (nmol·h/L)	CL (mL/min)
Group A	134	24,500 (27.7)	72,600 (45.2) [a)]	24.0 (45.3) [a)]
Group B	101	24,800 (34.5)	66,500 (51.1) [b)]	26.2 (51.1) [b)]
Japanese subgroup	4	29,500 (26.5)	59,800, 46300 [c)]	29.1, 37.6 [c)]

[a)] N =109. [b)] N = 77. [c)] Individual values in 2 subjects are shown.

Table 20. Changes in plasma unbound sum dabigatran concentrations, dTT, ECT, aPTT, and TT following a single intravenous dose of idarucizumab (partially modified from the submitted data)

	N	Time since idarucizumab administration						
		Pre-dose	0.333 h	1 h	2 h	4 h	12 h	24 h
Plasma unbound sum dabigatran concentrations (ng/mL) [a)]								
Group A	134	98.4 (232) (N = 134)	1.15 (69.8) (N = 133)	1.21 (113) (N = 129)	1.19 (120) (N = 128)	1.21 (129) (N = 128)	2.10 (386) (N = 125)	4.98 (652) (N = 127)
Group B	104	62.8 (219) (N = 103)	1.21 (91.0) (N = 104)	1.28 (129) (N = 96)	1.32 (162) (N = 96)	1.40 (199) (N = 99)	1.55 (228) (N = 97)	2.34 (238) (N = 91)
Japanese subgroup	4	34.5 (68.2) (N = 4)	1.00 (0) (N = 4)	1.00 (0) (N = 4)	1.00 (0) (N = 4)	1.00 (0) (N = 4)	1.00 (0) (N = 3)	1.00 (0) (N = 4)
dTT (s)								
Group A	136	57.1 ± 25.8 (N = 136)	30.8 ± 6.19 (N = 136)	31.5 ± 9.28 (N = 129)	31.8 ± 11.3 (N = 127)	31.9 ± 12.9 (N = 128)	34.0 ± 16.7 (N = 125)	35.7 ± 14.5 (N = 128)
Group B	104	50.3 ± 33.4 (N = 104)	30.4 ± 7.69 (N = 104)	31.4 ± 12.7 (N = 97)	32.8 ± 17.1 (N = 96)	33.2 ± 18.0 (N = 98)	32.9 ± 16.8 (N = 97)	31.1 ± 4.24 (N = 91)
Japanese subgroup	4	40.9 ± 5.81 (N = 4)	31.4 ± 0.956 (N = 4)	31.6 ± 0.698 (N = 4)	31.7 ± 0.681 (N = 4)	31.9 ± 0.377 (N = 4)	31.6 ± 0.954 (N = 3)	31.6 ± 0.826 (N = 4)
ECT (s)								
Group A	136	133 ± 108 (N = 136)	42.0 ± 33.8 (N = 136)	45.4 ± 44.9 (N = 126)	44.9 ± 46.5 (N = 129)	45.6 ± 49.1 (N = 127)	51.1 ± 60.6 (N = 125)	56.9 ± 57.6 (N = 128)
Group B	104	107 ± 98.2 (N = 104)	41.3 ± 26.9 (N = 104)	44.8 ± 34.4 (N = 97)	46.2 ± 41.7 (N = 95)	51.1 ± 66.2 (N = 98)	49.4 ± 56.1 (N = 97)	44.8 ± 19.2 (N = 91)
Japanese subgroup	4	64.8 ± 20.9 (N = 4)	36.4 ± 0.968 (N = 4)	37.5 ± 3.82 (N = 4)	36.3 ± 0.526 (N = 4)	36.6 ± 2.60 (N = 4)	34.8 ± 0.917 (N = 3)	37.1 ± 3.45 (N = 4)
aPTT (s)								
Group A	136	69.8 ± 54.8 (N = 136)	33.3 ± 11.5 (N = 136)	36.5 ± 40.3 (N = 127)	32.4 ± 13.4 (N = 127)	33.0 ± 15.9 (N = 127)	36.2 ± 21.2 (N = 125)	39.6 ± 19.2 (N = 128)
Group B	104	61.9 ± 56.7 (N = 104)	38.8 ± 48.1 (N = 104)	40.2 ± 35.0 (N = 96)	39.5 ± 30.5 (N = 94)	37.6 ± 29.7 (N = 96)	36.7 ± 25.7 (N = 97)	36.2 ± 16.0 (N = 90)
Japanese subgroup	4	45.9 ± 8.87 (N = 4)	32.9 ± 3.42 (N = 4)	33.1 ± 3.68 (N = 4)	33.0 ± 3.46 (N = 4)	30.5 ± 3.90 (N = 4)	33.5 ± 3.31 (N = 3)	32.7 ± 3.40 (N = 4)
TT (s)								
Group A	135	105 ± 90.4 (N = 134)	16.0 ± 42.1 (N = 135)	16.2 ± 30.7 (N = 126)	17.0 ± 44.3 (N = 127)	17.2 ± 44.9 (N = 126)	22.5 ± 49.8 (N = 125)	30.1 ± 41.0 (N = 128)
Group B	103	77.7 ± 88.8 (N = 103)	11.4 ± 1.84 (N = 102)	19.5 ± 53.1 (N = 95)	20.5 ± 45.4 (N = 93)	20.2 ± 49.4 (N = 96)	20.1 ± 43.2 (N = 97)	17.1 ± 18.2 (N = 91)
Japanese subgroup	4	42.0 ± 18.9 (N = 4)	11.0 ± 0.949 (N = 4)	11.2 ± 1.23 (N = 4)	11.0 ± 0.802 (N = 4)	11.1 ± 0.814 (N = 4)	10.5 ± 0.608 (N = 3)	11.5 ± 1.66 (N = 4)

[a)] Data below the LLOQ were calculated as 1 or 2 ng/mL.

ADAs were detected in 5 of 242 subjects before idarucizumab administration and were newly detected in 3 subjects after idarucizumab administration.

6.R Outline of the review by PMDA

6.R.1 Differences in PK of idarucizumab between Japanese and non-Japanese subjects

The applicant provided the following explanation on differences in PK of idarucizumab between Japanese and non-Japanese subjects:

Idarucizumab was administered alone and in combination with DEMS in Studies 1321.5 and 1321.1, which were conducted in Japanese and non-Japanese healthy subjects, respectively. The ratio of $AUC_{0-\infty}$ of idarucizumab in the Japanese subjects to that in the non-Japanese subjects was in the range of 1.1 to 1.5 in all dose groups, showing that $AUC_{0-\infty}$ in the Japanese subjects was similar to or only slightly higher than that in the non-Japanese subjects. Since there was no difference in the $AUC_{0-\infty}$ values adjusted by body weight between the populations ($AUC_{0-\infty}$ ratio ranging from 0.9 to 1.2), the above difference could be attributed to the difference in body weight. In addition, no major differences were observed in $t_{1/2}$, CL, or V_{ss} of idarucizumab between the Japanese and non-Japanese subjects. $AUC_{0-\infty}$ after administration of the recommended dose of idarucizumab (5 g in total, given in 2 divided doses, 15 minutes apart) in the Japanese healthy subjects was 43,300 nmol·h/L. This value was slightly higher than that after a single dose of idarucizumab 5 g in the non-Japanese healthy adults (37,000 nmol·h/L). However, the values adjusted for body weight were similar in both populations (2,700,000 nmol·h·kg/L in the Japanese healthy subjects and 2,740,000 nmol·h·kg/L in the non-Japanese healthy subjects).

In the PPK analysis, CrCL and race were considered to be factors that might significantly influence CL of idarucizumab. In the model incorporating CrCL, CL of idarucizumab in the Japanese subjects was lower than that in the non-Japanese subjects, but by only approximately 11%. Therefore, this difference was considered to be not clinically meaningful.

Changes in plasma idarucizumab concentrations in 4 Japanese patients in Study 1321.3 were compared with those in the overall study population. The results showed that the changes in plasma idarucizumab concentrations in the 4 Japanese patients generally fell in the 5th to 95th percentile range of changes in plasma idarucizumab concentrations in the overall study population, showing no substantial differences in PK parameters of idarucizumab.

Based on the above, the applicant considered that there were no significant differences in PK of idarucizumab between Japanese and non-Japanese individuals.

PMDA's conclusion:

The applicant discussed that no clinically meaningful differences existed in PK of idarucizumab between Japanese and non-Japanese individuals. Given the submitted data and the applicant's explanation, PMDA considered the applicant's position on the matter to be reasonable. Study 1321.3 revealed no differences in PK between Japanese and non-Japanese subjects, suggesting that Japanese and non-Japanese patients can use the same dosage of idarucizumab without clinically significant problems.

6.R.2 Redistribution of sum dabigatran

The applicant provided the following explanation on the causes of increases in plasma sum dabigatran concentrations after idarucizumab administration:

In Study 1321.2, following administration of idarucizumab 1, 2.5, or 5 g after dabigatran dosing, plasma sum dabigatran concentration increased to approximately 5- to 6-hold higher than that before idarucizumab administration within 30 minutes after idarucizumab administration, and dabigatran was eliminated in a biphasic manner. Idarucizumab exerts its reversal effect by binding to unbound sum dabigatran. Increases in plasma sum dabigatran concentrations observed in the study was probably due to the following mechanism: decreased plasma unbound sum dabigatran concentrations after idarucizumab administration induced a new equilibrium of unbound sum dabigatran in tissues and plasma, which in turn led to redistribution of unbound sum dabigatran or idarucizumab-dabigatran complex from tissues to plasma. Immediately after the administration of idarucizumab, the plasma unbound sum dabigatran concentrations were reduced nearly to the lower limit of quantification, and the anticoagulant effects were completely or almost completely reversed. Thus, plasma sum dabigatran concentrations may increase transiently after idarucizumab administration, but the increase is not clinically significant.

PMDA's view:

The applicant's discussion on the causes of increases in plasma sum dabigatran concentrations after idarucizumab administration is understandable. The applicant explained that transient increases in plasma sum dabigatran concentrations after idarucizumab administration would not be clinically significant. PMDA accepts this explanation because in Study 1321.2 plasma unbound sum dabigatran concentrations decreased close to the lower limit of quantification immediately after idarucizumab administration.

6.R.3 Redistribution of unbound sum dabigatran

Some patients showed a re-elevation of unbound sum dabigatran concentrations after idarucizumab administration. Some subjects in Study 1321.3 had a longer time to the re-elevation and higher re-elevated concentrations than subjects receiving idarucizumab 1 g in the clinical pharmacology studies (Studies 1321.1, 1321.2, and 1321.5). PMDA requested the applicant to explain the reason for the difference.

The applicant's response:

The recurrence of anticoagulant effects of dabigatran after administration of idarucizumab 1 g in healthy subjects was considered to be due to redistribution of unbound sum dabigatran from tissues to plasma. In all of healthy subjects and subjects with renal impairment who received idarucizumab >1 g in phase I studies, a minor amount of unbound sum dabigatran was detected 12 to 36 hours after idarucizumab administration. This timing was roughly the same as that for the re-elevation observed in Study 1321.3. The median CrCL in subjects enrolled in Study 1321.3 was 52.2 mL/min, and the study population included patients with decreased renal function. Since dabigatran is eliminated mainly by the kidneys, unbound sum dabigatran concentration is higher in patients with decreased renal function. When dabigatran is bound to idarucizumab, the idarucizumab-

dabigatran complex is excreted by the same mechanism as that for elimination following administration of idarucizumab alone. In subjects with intact renal function, almost all idarucizumab and idarucizumab-dabigatran complex are taken up by the renal tubular cells after undergoing glomerular filtration, and idarucizumab is considered to be degraded in the renal tubular cells or to be excreted directly in the urine when uptake in the renal tubular cells is saturated. In some patients with renal impairment in Study 1321.3, at 12 hours after idarucizumab administration or later, plasma unbound sum dabigatran concentration elevated again to the level possibly having anticoagulant effects. This fact suggests the following: that more idarucizumab distributes into extravascular tissues in patients with more severe renal impairment; that extravascular idarucizumab inactivates dabigatran by binding to dabigatran, resulting in retention of dabigatran in the body; and that after extravascular degradation of a part of idarucizumab, dabigatran is released again into the blood. The extent of re-elevation of unbound sum dabigatran concentration via this mechanism is considered to be larger with increasing severity of renal impairment, and data from Study 1321.3 suggest that extravascular degradation of idarucizumab occurs approximately 12 to 24 hours after idarucizumab administration. Recurrence of anticoagulant effects of dabigatran might be a concern only when bleeding recurs or persists or when other invasive procedure is required. To handle such a situation, the applicant proposed that additional dosing of idarucizumab 5 g be recommended and included in the section Precautions for Dosage and Administration.

PMDA's view:

It is theoretically possible that the mechanism described by the applicant may cause re-distribution of unbound sum dabigatran from the extravascular tissues into the blood and then may lead to re-elevation of plasma unbound sum dabigatran concentration. Even in patients with moderate renal impairment in Study 1321.2, however, plasma unbound sum dabigatran concentration did not increase again to the level observed in Study 1321.3. Therefore, it cannot be said that the re-elevation always occurs in patients with renal impairment. However, although the cause was unclear, plasma unbound sum dabigatran concentration increased again to the level possibly having anticoagulant effects in some subjects after 12 hours following idarucizumab administration. Additional dosing of idarucizumab would be beneficial to continuously reverse the anticoagulant effects of dabigatran in such patients. In this situation where the exact cause of re-elevation of plasma unbound sum dabigatran to the level possibly having anticoagulant effects is undetermined, the final conclusion on the appropriateness of additional dosing of idarucizumab should be drawn based on whether criteria for the necessity of additional dosing of idarucizumab can be established, and in light of the risks associated with administration of idarucizumab (including development of thrombosis)[see "7.R.3.2 Re-administration"].

6.R.4 Appropriateness of idarucizumab dosage

The applicant provided the following justification for the idarucizumab dosage regimen selected for Study 1321.3:

The required dose of idarucizumab to reverse the anticoagulant effects of dabigatran was determined based on the equimolar binding of idarucizumab to dabigatran (i.e., binding of idarucizumab to dabigatran with a 1:1 stoichiometry) [see "3.1.4 *In vivo* evaluation of idarucizumab"] and the total body loads of dabigatran calculated from plasma dabigatran concentrations and estimated volume of distribution. The plasma dabigatran concentrations used in the calculation were the 99th percentiles of trough and peak concentrations (543 and 861 ng/mL, respectively) observed in the RE-LY study subjects with moderate renal impairment who composed the subgroup with the highest dabigatran concentrations (JACC. 2014; 63(4):321-8). The results suggested that idarucizumab 5 g reverse the anticoagulant effects of dabigatran in 99% of patients with moderate renal impairment in the RE-LY study. In healthy subjects and subjects with mild or moderate renal impairment in phase I studies (Studies 1321.1, 1321.2, and 1321.5), lower idarucizumab doses (1-2.5 g) achieved an immediate and complete reversal effect (defined as decreases in the clotting times of blood coagulation parameters to below ULN), and higher idarucizumab doses could sustain the complete reversal effect. A PPK/PD analysis with PK and PD data from the phase I studies (Studies 1321.1, 1321.2, and 1321.5) was used to estimate the relationship between dabigatran exposure and coagulation response before and after idarucizumab administration. The analysis results suggested that, within the range of data available from the phase I studies (Study 1321.1, 1321.2, and 1321.5), 2 bolus injections of 2.5 g idarucizumab could immediately and completely reverse the anticoagulation effects of dabigatran regardless of renal function or age.

PMDA's view:

Study 1321.3 used the 5 g dose of idarucizumab to achieve a complete reversal, regardless of patient characteristics, on the basis of plasma dabigatran concentrations seen in the RE-LY study. PMDA considered that the applicant's dose selection was justified by the plasma unbound sum dabigatran concentrations and changes in coagulation parameters observed in the phase I studies (Studies 1321.1, 1321.2, and 1321.5). PMDA will make a final decision on the appropriateness of the proposed dosage and administration, based on discussion in Section "7.R.3 Dosage and administration."

6.R.5 Effects of ADAs on idarucizumab PK

The applicant provided the following explanation on the effects of ADAs on idarucizumab PK:

In Studies 1321.1, 1321.2, and 1321.5, ADAs were detected in 11.7% (33 of 283) of subjects before the start of idarucizumab administration. The detected ADAs were generally regarded as nonspecific antibodies and had no influence on the reversal effects of idarucizumab on the prolongation of clotting times (e.g., dTT and ECT) by dabigatran. Also in Studies 1321.1, 1321.2, and 1321.5, ADAs were newly detected after idarucizumab administration in 8.5% (19 of 224) of subjects receiving idarucizumab. The maximum titer of the detected ADAs was 40 (corresponding to an antibody concentration of 3.3 μg/mL) and the antibody response by the ADAs was considered to have little impact on the PK and efficacy of idarucizumab, because of the C_{max} of idarucizumab after administration of the recommended clinical dose of 5 g.

PMDA's view:

There are currently no data suggesting that ADAs detected before the start of idarucizumab administration would influence the idarucizumab PK. There is limited experience on the use of idarucizumab in subjects in whom ADAs newly developed after idarucizumab administration in clinical studies. It is therefore difficult to assess the effects of ADAs newly developing after idarucizumab administration on the idarucizumab PK. Whether measures, including precautionary statements, are needed for ADAs is discussed in Section "7.R.5.3 ADAs" in consideration of the clinical position of idarucizumab.

6.R.6 Timing of resumption of DEMS after idarucizumab administration

Data from Study 1321.3 showed that CL of idarucizumab tended to decrease with increasing severity of renal impairment. PMDA therefore requested the applicant to justify the appropriateness of their claim that DEMS can be resumed 24 hours after idarucizumab administration, regardless of the severity of renal impairment

The applicant's response:

Study 1321.3 was conducted in patients including those with decreased renal function, and changes in plasma idarucizumab concentrations are shown by renal function status in Table 21.

Table 21. Changes in plasma idarucizumab concentrations by CrCL

Time since idarucizumab administration	CrCL category			
	<30 mL/min (N = 50)	≥30 to <50 mL/min (N = 55)	≥50 to <80 mL/min (N = 67)	≥80 mL/min (N = 54)
Plasma idarucizumab concentrations (nmol/L)				
10-30 min	27,300 (24.7)	26,000 (27.7)	23,200 (33.2)	21,000 (35.8)
1 h	20,400 (31.2)	18,300 (31.7)	14,600 (52.4)	12,000 (33.9)
2 h	14,700 (40.0)	11,500 (32.6)	8380 (35.7)	6580 (48.4)
4 h	9560 (50.7)	5430 (52.0)	2940 (87.1)	2140 (77.4)
12 h	1310 (93.5)	578 (76.7)	328 (63.3)	214 (86.1)
24 h	270 (114)	139 (85.0)	89.7 (64.8)	65.3 (73.0)

Plasma idarucizumab concentrations at 24 hours after the second dose of idarucizumab decreased by ≥99% from those at 10 to 30 minutes after the second dose of idarucizumab in all patient subgroups, including patients with severe renal impairment (CrCL <30 mL/min). At 24 hours after idarucizumab administration, the plasma idarucizumab concentration in patients with severe renal impairment was 270 nmol/L. The quantity of idarucizumab with a V_{ss} of 9 L corresponds to <20% of the absorbed dose of dabigatran after a single dose of DEMS (DE 150 mg), and it is assumed that 80% of the absorbed dose of dabigatran exerts anticoagulant effects after resumption. Meanwhile, the value of plasma idarucizumab concentration at 24 hours after administration was that of combined concentrations of idarucizumab bound and unbound to dabigatran, and idarucizumab in plasma may not bind to newly administered dabigatran because a part of idarucizumab has already bound to dabigatran. Therefore, the above value is considered to represent the most conservative assumption. In addition, it has been demonstrated that dabigatran concentrations are higher in patients with severe renal impairment, and unbound dabigatran concentrations elevated again (above the LLOQ) at or before 24 hours after administration in 35 of 50 subjects in Study 1321.3. Unbound dabigatran was detected in the patients

experiencing the re-elevation, which suggests that at 24 hours after administration, idarucizumab bind to dabigatran and there is almost no free idarucizumab.

As shown above, at 24 hours postdose, the residual idarucizumab in blood has limited effects on the anticoagulant effects of resumed dabigatran, regardless of renal function status in patients, and thus DEMS therapy can be resumed at or after the timing.

PMDA's view:
The applicant explained that the effects of residual idarucizumab in plasma at 24 hours postdose on the anticoagulant effects of dabigatran are considered to be limited even in patients with severe renal impairment in whom CL of idarucizumab is reduced. Furthermore, in Japan, treatment with DEMS is contraindicated in patients with severe renal impairment. In light of the above and from the point of view of PK, PMDA considers that the provision of information on the timing of DEMS resumption, i.e., 24 hours after idarucizumab administration, is justified. Meanwhile, whether resumption of DEMS is appropriate should be determined in consideration of the current status of control of bleeding episodes requiring idarucizumab, as well as the risk of recurrence of bleeding. The appropriateness of contents and wording of precautions and information on the timing of DEMS resumption is discussed in Section "7.R.7 Resumption of DEMS therapy after administration of idarucizumab."

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

The applicant submitted evaluation data from 4 clinical studies: 2 phase I studies conducted outside of Japan, a phase I study conducted in Japan, and a multi-regional phase III case series clinical study conducted also in Japan. Results of these studies are described below. As for the multi-regional phase III case series clinical study (Study 1321.3), the interim data as of [redacted], are used to describe the study results, unless otherwise specified [for PK and PD, see Section "6 Summary of Biopharmaceutic Studies, and Associated Analytical Methods, Clinical Pharmacology Studies, and Outline of the Review Conducted by PMDA"].

7.1 Phase I studies

7.1.1 Japanese phase I clinical study (investigation of PD and PK/PD in healthy subjects) (Study 1321.5, CTD 5.3.4.1-03, [January 2014 to August 2014])

Study 1321.5 consisted of 2 parts. Both parts of the study were conducted in Japanese healthy adult men at a study site in Japan.

Part 1 was a randomized, double-blind, within dose groups, dose escalation study to investigate the safety, tolerability, and PK of idarucizumab administered alone intravenously; in this part, idarucizumab or placebo was administered (target sample size, 32 subjects). Eight subjects each were assigned to 4 idarucizumab dose groups: the dose group 1 (1 g), the dose group 2 (2 g), the dose group 3 (4 g), and the dose group 4 (8 g). In each group, 6 subjects were assigned to idarucizumab and 2 subjects to placebo (8 in total). Idarucizumab or placebo was administered intravenously as a 5-min infusion in the dose groups 1 to 3 and as a 1-hour continuous

infusion in the dose group 4.

All 32 subjects received ≥1 dose of idarucizumab or placebo and were included in the safety analysis set.

An adverse event occurred in a subject receiving a 5-min intravenous infusion of placebo (blood creatine phosphokinase increased). There were no deaths, serious adverse events, or adverse events leading to discontinuation of the study drug.

Part 2 was a randomized, double-blind, within dose groups, dose escalation study to investigate the profiles (e.g., safety, tolerability, and PK) of idarucizumab administered as a single intravenous dose at the steady state of dabigatran; in this part, idarucizumab or placebo was administered after DEMS administration (target sample size, 48 subjects). Of 49 volunteers who consented to participate in Part 2 study, 48 were randomly assigned to study treatment. Of the 48 subjects, 12 each were assigned to 4 idarucizumab dose groups: the dose group 5 (1 g), the dose group 6 (2 g), the dose group 7 (4 g), and the dose group 8 (5 g). In each group, 9 subjects were assigned to idarucizumab and 3 subjects to placebo (12 in total). One volunteer was not assigned to study treatment because an adverse event occurred after DEMS administration. All subjects received DEMS (DE 220 mg per administration) orally twice daily on Days 1 to 3 and once on Day 4, followed by a 3-day washout period, and then twice daily on Days 8 to 10 and once on Day 11. Approximately 2 hours after DEMS administration on Day 11, a 5-min intravenous infusion of idarucizumab or placebo was administered in the dose groups 5 to 7, and two 5-min intravenous infusions (15 minutes apart) of idarucizumab 2.5 g or placebo in the dose group 8.

All of the 48 subjects assigned to the study treatment received ≥1 dose of idarucizumab or placebo and were included in the safety analysis set. No adverse events occurred in the subjects.

7.1.2 Foreign phase I studies

7.1.2.1 PD and PK/PD study in healthy subjects (Study 1321.1, CTD 5.3.4.1-01 [September 2012 to November 2013])

Study 1321.1 consisted of 3 parts. All parts of the study were conducted in healthy adult men at a study site in Belgium.

Part 1 was a randomized, double-blind, within dose groups, dose escalation study to investigate the safety, tolerability, and PK of idarucizumab administered alone intravenously; in this part, idarucizumab or placebo was administered (target sample size, 104 subjects). Subjects were assigned to 1 of 13 idarucizumab dose groups: the dose group 1 (0.02 g), the dose group 2 (0.06 g), the dose group 3 (0.2 g), the dose group 4 (0.6 g), the dose group 5 (1.2 g), the dose group 6 (2 g), the dose group 7 (3 g), the dose group 8 (4 g), the dose group 9 (6 g), the dose group 10 (8 g), the dose group 11 (1 g), the dose group 12 (2 g), the dose group 13 (4 g). In the original protocol, each dose group was to include 8 subjects receiving intravenous idarucizumab (6 subjects)

or placebo (2 subjects) as a 1-hour continuous infusion (the dose groups 1 to 10) or as a 5-min infusion (the dose groups 11 to 13). However, because of difficulties in enrollment of subjects, the dose group 4 included only 7 subjects (5 for idarucizumab and 2 for placebo), and the dose group 8 included only 7 subjects (6 for idarucizumab and 1 for placebo). The other dose groups included 8 subjects (6 for idarucizumab and 2 for placebo). In the dose group 7, 8 subjects (6 for idarucizumab and 2 for placebo) mistakenly received the dose for the dose group 6, and as a consequence, they were evaluated as subjects in the dose group 6. Thus, additional 8 subjects were enrolled in this study and were assigned to the dose group 7. A total of 110 subjects were assigned to the dose groups.

All assigned 110 subjects received ≥1 dose of idarucizumab or placebo and were included in the safety analysis set.

The incidence of adverse events was 36.1% (30 of 83 subjects) in the idarucizumab group and 44.4% (12 of 27 subjects) in the placebo group. Adverse events occurring in ≥3 subjects in any group were headache (9 of 83 subjects receiving idarucizumab [dose group 1, 1 of 6; dose group 3, 2 of 6; dose group 6, 2 of 12; dose group 7, 1 of 6; dose group 11, 1 of 6; and dose group 13, 2 of 6] and 2 of 27 subjects receiving placebo), nasopharyngitis (4 of 83 subjects receiving idarucizumab [dose group 2, 1 of 6; dose group 4, 1 of 5; dose group 10, 1 of 6; and dose group 12, 1 of 6] and 2 of 27 receiving placebo), back pain (4 of 83 receiving idarucizumab [dose group 4, 1 of 5; dose group 7, 1 of 6; and dose group 11, 2 of 6] and 1 of 27 receiving placebo), and skin irritation (3 of 83 receiving idarucizumab [dose group 3, 1 of 6; dose group 7, 1 of 6; and dose group 9, 1 of 6] and 2 of 27 receiving placebo). There were no deaths, serious adverse events, or adverse events leading to discontinuation of the study drug.

Parts 2 and 3 were a randomized, double-blind, within dose groups, dose escalation study to investigate the profiles (e.g., safety, tolerability, and PK) of idarucizumab administered as a single intravenous dose at the steady state of dabigatran; in these parts, idarucizumab or placebo was administered after 4-day dosing of DEMS (DE 220 mg per administration, given orally twice daily on Days 1 to 3 and once daily on Day 4) (target sample size, 36 subjects in Part 2 and 12 subjects in Part 3).

In Part 2, subjects were assigned to 1 of 3 idarucizumab dose groups: the dose group 14 (1 g), the dose group 15 (2 g), the dose group 16 (4 g). In the original protocol, each dose group was to include 12 subjects receiving intravenous idarucizumab (9 subjects) or placebo (3 subjects) as a single 5-min intravenous infusion, beginning at 1 hour and 55 minutes after DEMS administration on Day 4. However, because of difficulties in enrollment of subjects, the dose group 16 included only 11 subjects (8 for idarucizumab and 3 for placebo).

All assigned 35 subjects received ≥1 dose of idarucizumab or placebo and were included in the safety analysis set.

Adverse events occurred in 77.1% (27 of 35) of the subjects, and the incidence of adverse events occurring during the DE treatment period before administration of idarucizumab or placebo was 57.1% (20 of 35 subjects). The incidence of adverse events developing after DEMS administration period was 46.2% (12 of 26) of subjects receiving idarucizumab and 11.1% (1 of 9) of subjects receiving placebo. Adverse events occurring in ≥2 subjects in any group after DEMS therapy period were dizziness (3 of 26 subjects receiving idarucizumab [dose group 14, 1 of 9; dose group 15, 1 of 9; and dose group 16, 1 of 8] and none of 9 subjects receiving placebo), skin irritation (3 of 26 subjects receiving idarucizumab [dose group 15, 2 of 9; and dose group 16, 1 of 8] and none of 9 subjects receiving placebo), and constipation (2 of 26 subjects receiving idarucizumab [dose group 14, 2 of 9] and none of 9 subjects receiving placebo). There were no deaths, serious adverse events, or adverse events leading to discontinuation of the study drug.

In Part 3, 9 subjects were assigned to receive idarucizumab and 3 subjects to placebo. All subjects received 2 intravenous 5-min infusions of idarucizumab (5 g and 2.5 g in this order) or placebo, 1 hour apart, beginning at 1 and 55 minutes after DEMS administration on Day 4.

All assigned 12 subjects received ≥1 dose of idarucizumab or placebo and were included in the safety analysis set.

Adverse events occurred in 33.3% (4 of 12) of the subjects, and the incidence of adverse events occurring during the DEMS therapy period before administration of idarucizumab or placebo was 16.7% (2 of 12 subjects). Adverse events developing after DEMS administration period were asthenia, muscle spasms, epistaxis, and nasopharyngitis in 1 subject each receiving idarucizumab; and infusion site haematoma in 1 subject receiving placebo. There were no deaths, serious adverse events, or adverse events leading to discontinuation of the study drug.

7.1.2.2 PK/PD study in elderly subjects and subjects with renal impairment (Study 1321.2, CTD 5.3.4.1-02 [September 2013 to August 2014])

A randomized, double-blind, dose-comparison, 2-group, 2-way crossover study was conducted at a study site in Belgium in groups of healthy subjects aged 45 to 64 years, healthy elderly subjects aged 65 to 80 years, subjects with mild renal impairment (CrCL ≥60 to <90 mL/min) aged 45 to 80 years, and subjects with moderate renal impairment (CrCL ≥30 to <60 mL/min), to investigate the safety, tolerability, PK, and PD of intravenous idarucizumab, and to establish the idarucizumab doses effective to reverse the anticoagulant effects of dabigatran. In this study, a single infusion of idarucizumab or placebo was administered after DEMS dosing. Table 22 shows the doses of DEMS and idarucizumab administered and the number of subjects in individual groups. Healthy subjects received DEMS orally at doses shown in Table 22 for 7 days (twice daily on Days 1 to 3, 5, and 6 and once daily on Day 4 and Day 7) and a 5-min intravenous infusion of idarucizumab or placebo beginning 1 hour and 55 minutes after DEMS administration on Day 4. Healthy elderly subjects and subjects with renal impairment received DEMS orally at doses shown in Table 22 for 4 days (twice daily for 3 days and

once daily on Day 4) and a 5-min intravenous infusion of idarucizumab or placebo beginning 1 hour and 55 minutes after DEMS administration on Day 4. Subjects with moderate renal impairment received 5-min infusions of idarucizumab or placebo at 1 hour and 55 minutes and 2 hour and 55 minutes after DEMS administration on Day 4. Periods 1 and 2 were separated by ≥6 days of washout period. Only subjects in the idarucizumab 2.5 g group received readministration of idarucizumab 2.5 g in Period 3, 2 months after completing Period 2. There were protocol deviations in 3 subjects with mild renal impairment who were assigned to receive idarucizumab 1 g: they were to receive DE 150 mg on Day 1 of Period 1 but actually received DE 220 mg on the day.

Table 22. Doses of DEMS and idarucizumab by group

	N	DEMS dose [a)] (Dose per administration, mg)	Idarucizumab dose (g)
Healthy subjects (45 to 64 years of age)	6	220	2.5
Healthy subjects (45 to 64 years of age)	6	220	5
Healthy elderly subjects (65 to 80 years of age)	8	220	1
Healthy elderly subjects (65 to 80 years of age)	8	220	5
Subjects with mild renal impairment (45 to 80 years of age)	6	150	1
Subjects with mild renal impairment (45 to 80 years of age)	6	150	5
Subjects with moderate renal impairment (45 to 80 years of age)	6	150	2.5 + 2.5 (1 hour apart)

[a)] DE dose is shown.

All 46 subjects receiving ≥1 dose of idarucizumab or placebo were included in the safety analysis set.

The incidence of adverse events was 67.4% (31 of 46 subjects), and an adverse event occurring in ≥3 subjects after administration of idarucizumab or placebo (during the period from administration of idarucizumab or placebo to the end of study) was headache (in 4 of 46 subjects after idarucizumab administration).

There were no deaths, serious adverse events, or adverse events leading to discontinuation of the study drug.

7.2 Phase III study (RE-VERSE AD study) (Study 1321.3, CTD 5.3.5.2-02 [ongoing since June 2014])

An open-label, uncontrolled, case series study is currently ongoing at 349 study sites in 34 countries (36 sites in Japan) to evaluate the reversal of the anticoagulant effects of dabigatran by idarucizumab and to assess bleeding, clinical outcomes, the safety, and PK of dabigatran after idarucizumab administration. Interim data (cutoff date, [redacted]) were submitted for the application for marketing approval. The target sample size was 200 to 300 subjects at the time of planning of this study. But this was changed during the study (October 28, 2015) to approximately 500 subjects, in order to continue to enroll subjects until either (1) the number of idarucizumab-treated patients reaches the numbers specified by the regulatory authorities in participating countries or (2) idarucizumab is launched in these countries.

Study 1321.3 was conducted in patients on anticoagulant therapy with dabigatran who had life-threatening or uncontrolled bleeding requiring urgent medical or surgical intervention (Group A) and those who required emergency surgery or other invasive procedure for a disease or condition other than bleeding and in whom persistence of anticoagulant effects of dabigatran was undesirable (Group B). The inclusion and exclusion criteria for the groups are shown in Table 23. Subjects were treated with 2 infusions of idarucizumab 2.5 g given less than 15 min apart.

Table 23. Inclusion and exclusion criteria for Study 1321.3

Group A	Group B
Inclusion criteria ・Overt bleeding judged by the physician to require a reversal agent ・Currently taking DE ・≥18 years of age at the time of providing informed consent (≥20 years of age in Japan) ・Signed written informed consent prior to study entry	Inclusion criteria ・Condition requiring emergency surgery or invasive procedure where adequate hemostasis was required. Emergency was defined as "within 8 hours after the condition above." ・Currently taking DE ・≥18 years of age at the time of providing informed consent (≥20 years of age in Japan) ・Signed written informed consent prior to study entry
Exclusion criteria ・Patients with minor bleeding (e.g. epistaxis, hematuria) that could be managed with standard supportive care ・Patients with no clinical signs of bleeding ・Contraindications to study medication including known hypersensitivity to the drug or its excipients (patients with hereditary fructose intolerance were excluded because they may react to sorbitol)	Exclusion criteria ・An elective surgery or procedure, or a surgery or procedure with a low risk of uncontrolled or unmanageable bleeding ・Contraindications to study medication including known hypersensitivity to the drug or its excipients (patients with hereditary fructose intolerance were excluded because they may react to sorbitol)

Reversal of the anticoagulant effects of dabigatran by idarucizumab was defined as "a reduction of clotting times of the coagulation parameters to the normal range," and the primary endpoint was the maximum reversal of the anticoagulant effects of dabigatran by idarucizumab. The maximum reversal was calculated from the equation shown below and was based on value of dTT or ECT at some point between "the end of the first idarucizumab infusion" and "4 hours after the completion of the last idarucizumab infusion (or completion of the first idarucizumab infusion in subjects who did not receive the second infusion)" in individual subjects. The ULN for each coagulation parameter used in this study was determined using the baseline values (i.e., data in the absence of DE) in a total of 208 subjects in Studies 1321.1 and 1321.2. [1)] When values of the maximum reversal calculated using the equation shown below were ≥100%, they were interpreted as complete reversal of the anticoagulant effects, and the calculated maximum reversal values were replaced with 100%.

$$\text{Maximum reversal (\%)} = \frac{\text{predose coagulation test} - \text{minimum postdose coagulation test}}{\text{predose coagulation test} - 110\%\ \text{ULN}} \times 100$$

[1)] The ULN value for each coagulation parameter was calculated as the arithmetic mean baseline + 2 × SD.

7.2.1 Overall study population

The interim data as of [redacted], showed that 243 subjects (137 in Group A and 106 in Group B) received idarucizumab and were included in the treated set. The PD analysis set included subjects with ≥1 evaluable datum for any of PD endpoints or blood coagulation parameters before and after idarucizumab administration. As of [redacted], 154 subjects completed the planned 90-day follow-up period, 20 subjects were being followed up, and 69 subjects withdrew from the study. Main reasons for withdrawal from the study were adverse events in 55 subjects, protocol violation in 4 subjects, and lost to follow-up in 4 subjects.

Patient characteristics in the treated set were as follows: median age (minimum, maximum), 77.0 years (47.0, 96.0); men, 52.7% (128 of 243 subjects); median body weight (minimum, maximum), 73.4 kg (35.0, 169.0); and median CrCL (minimum, maximum), 52.2 mL/min (7.9, 192.9). The daily dose of DEMS (DE) was 110 mg twice daily in 62.1% (151 of 243) of subjects, 150 mg twice daily in 28.8% (70 of 243) of subjects, 75 mg twice daily in 2.5% (6 of 243) of subjects, and others in 6.2% (15 of 243) of subjects. The reasons for use of dabigatran (dabigatran indication) were atrial fibrillation in 94.7% (230 of 243) of subjects, orthopedic surgery in 0.4% (1 of 243) of subjects, VTE in 2.1% (5 of 243) of subjects, and others in 2.9% (7 of 243) of subjects. The median time since the last dose of DEMS (minimum, maximum) was 15.83 hours (1.47, 105.77). The main indications for surgery/interventional procedure in Group B were as follows: fracture (19 subjects); acute cholecystitis, cholelithiasis, or jaundice (7 subjects); wound infection and infective arthritis (6 subjects); acute renal failure and catheter placement for dialysis (5 subjects); and hernia repair (4 subjects).

Baseline values for the primary endpoint: Of 243 subjects in the treated set, 156 (96 in Group A and 60 in Group B) had baseline dTT >110% ULN (39.09 seconds); 188 (116 in Group A and 72 in Group B) had baseline dTT >100% ULN (35.54 seconds); 216 (125 in Group A and 91 in Group B) had baseline ECT >110% ULN (45.39 seconds); and 224 (128 in Group A and 96 in Group B) had baseline ECT >100% ULN (41.26 seconds).

The reversal effect based on dTT and ECT values was evaluated only for patients with baseline coagulation parameter values >110% ULN and was calculated with the above equation (see 7.2). The calculation yielded the median maximum reversal (95% CI) of 100% (100.0-100.0) for both the dTT and ECT in Group A and B populations. As sensitivity analysis, the maximum reversal based on the 100% ULN was calculated. In the calculation, (1) only patients with baseline coagulation parameter values >100% ULN were included, and (2) the “110% ULN” was replaced with “100% ULN” in the above equation. The calculation yielded the median maximum reversal (95% CI) of 100% (100.0-100.0) for both the dTT and ECT in Group A and B populations.

As for the secondary endpoints, the following passage summarizes the maximum reversal effects based on the TT and aPTT in individual patients centrally determined at some point between “the end of the first infusion” and “4 hours after the completion of the second infusion”:

Of 243 subjects in the treated set, 158 (94 in Group A and 64 in Group B) had baseline aPTT >110% ULN (43.78 seconds), 178 (107 in Group A and 71 in Group B) had baseline aPTT >100% ULN (39.80 seconds), 226 (129 in Group A and 97 in Group B) had baseline TT >110% ULN (15.64 seconds), and 230 (131 in Group A and 99 in Group B) had TT >100% ULN (14.22 seconds). Reversal effect based on aPTT and TT was analyzed with the same manner of calculation for the primary endpoint. The maximum reversal based on aPTT was 100% in 95.7% (90 of 94) of subjects in Group A and 93.8% (60 of 64) of subjects in Group B in the analysis using 110% ULN and 91.6% (98 of 107) of subjects in Group A and 91.5% (65 of 71) of subjects in Group B in the analysis using 100% ULN. The maximum reversal based on TT was 100% in 99.2% (128 of 129) of subjects in Group A and 96.9% (94 of 97) of subjects in Group B in the analysis using 110% ULN and 95.4% (125 of 131) of subjects in Group A and 94.9% (94 of 99) of subjects in Group B in the analysis using 100% ULN.

In subjects in Group A, bleeding cessation (confirmed by data on the time to stop bleeding or by the investigator or treating physician) occurred in 76.6% (105 of 137) of patients between the start of first infusion of idarucizumab and 24 hours after the end of the second infusion of idarucizumab. For the remaining 32 patients, no assessment of the bleeding cessation could be made at any time point during the study due to inability to visualize or identify the bleeding site. Of the 32 patients, 6 died before assessment of bleeding. For 105 patients assessable for bleeding, bleeding cessation was confirmed in 77 patients within 24 hours and in 92 patients within 72 hours. In total, 104 subjects had data on the time to stop bleeding and their bleeding could be assessed by the investigator; the median time to stop bleeding was 10.0 hours in these subjects.

In Group B, intra-operative occurrence of bleeding was assessed, and normal hemostasis was achieved in 92.1% (93 of 101) of subjects undergoing surgery, during treatment after completion of administration of idarucizumab 5 g. During treatment, 6.9% (7), 10.0% (1), and 0% (none) of 101 patients were judged to have mildly abnormal hemostasis, moderately abnormal hemostasis, and severely abnormal hemostasis, respectively. The severity of bleeding [2)] occurring within 24 hours post-surgery was assessed as ISTH major in 1.0% (1 of 101) of subjects, TIMI minimal in 1.0% (1 of 101) of subjects, and GUSTO mild in 1.0% (1 of 101) of subjects.

PK data of unbound sum dabigatran were available from 238 patients. In all the 238 patients except for 2 patients, the minimum plasma concentration ($C_{min,1}$) of unbound sum dabigatran decreased to <20 ng/mL at some point between the end of the first infusion of idarucizumab and 4 hours after the completion of the second infusion of idarucizumab, and the median $C_{min,1}$ was below the LLOQ (1 ng/mL).

Changes over time in plasma unbound sum dabigatran concentrations were as follows: the geometric mean (geometric CV%) of the concentrations at baseline was 98.4 ng/mL (232 ng/mL) in Group A and 62.8 ng/mL (219 ng/mL) in Group B. The concentrations decreased to 1.27 ng/mL (102 ng/mL) in Group A and to

[2)] Severity of bleeding was determined by the treating investigator (or subinvestigator) at baseline, and bleeds were rated, whenever possible, using the following 3 bleeding classifications: major or life-threatening (as determined according to the ISTH classification), TIMI classification, and GUSTO classification.

1.47 ng/mL (177 ng/mL) in Group B after the first infusion of idarucizumab (just before the second infusion). The plasma unbound sum dabigatran concentration at baseline ranged from 1.00 to 2590 ng/mL in Group A and 1.00 to 2880 ng/mL in Group B.

The incidence of adverse events reported during the period from the start of the first idarucizumab infusion to 90 days after the last idarucizumab infusion was 91.2% (125 of 137) of subjects in Group A and 82.1% (87 of 106) of subjects in Group B. Adverse events occurring in ≥10% of subjects in either group are shown in Table 24.

Table 24. Adverse events occurring with an incidence of ≥10% in either group (Treated set)

	Group A (N = 137)	Group B (N = 106)	Overall (N = 243)
Urinary tract infection	14.6 (20)	8.5 (9)	11.9 (29)
Pneumonia	10.2 (14)	8.5 (9)	9.5 (23)
Headache	10.2 (14)	0.9 (1)	6.2 (15)
Constipation	11.7 (16)	10.4 (11)	11.1 (27)
Nausea	5.8 (8)	10.4 (11)	7.8 (19)
Pyrexia	10.2 (14)	1.9 (2)	6.6 (16)

% (n)

Adverse events with fatal outcome occurred in 21.2% (29 of 137) of subjects in Group A and 25.5% (27 of 106) of subjects in Group B. Adverse events with fatal outcome occurring in ≥2 subjects in either group were septic shock (2 subjects in Group A and 5 subjects in Group B), pneumonia (3 in Group A and 2 in Group B), haemorrhage intracranial (3 in Group A and 0 in Group B), cardiac arrest (1 in Group A and 3 in Group B), cardiac failure congestive (2 in Group A and 1 in Group B), shock (0 in Group A and 2 in Group B), and general physical health deterioration (2 in Group A and 2 in Group B). The adverse event of cardiac arrest leading to death in 1 subject (Group B) was assessed as related to the study drug.

Serious adverse events occurred in 48.2% (66 of 137) of subjects in Group A and 46.2% (49 of 106) of subjects in Group B. Serious adverse events occurring in ≥3 subjects in either group were pneumonia (8 subjects in Group A and 4 subjects in Group B), septic shock (2 in Group A and 6 in Group B), haemorrhage intracranial (4 in Group A and 0 in Group B), cardiac arrest (1 in Group A and 6 in Group B), cardiac failure (4 in Group A and 0 in Group B), cardiac failure congestive (4 in Group A and 1 in Group B), DVT (4 in Group A and 2 in Group B), PE (4 in Group A and 0 in Group B), renal failure (1 in Group A and 3 in Group B), and subdural haematoma (3 in Group A and 0 in Group B). The serious adverse events of atrial thrombosis (1 event in Group A), DVT (1 event in Group A), PE (1 event in Group A), cerebrovascular accident (1 event in Group B), and cardiac arrest (1 event in Group B) were assessed as related to the study drug.

There were no adverse events leading to discontinuation of the study drug.

7.2.2 Japanese subgroup

As of the cutoff date for the interim data ([redacted]), 4 Japanese patients received idarucizumab (all in

Group A). As of [redacted], 1 of the 4 patients completed the planned 90-day follow-up period, the remaining 3 patients are being followed up, and none of them were withdrawn from the study. Characteristics of the 4 patients are shown in Table 25.

With regard to baseline value for the primary endpoint, 2 Japanese subjects (Patient IDs, 8100601 and 8101301) had baseline dTT >110% ULN, and 3 Japanese subjects (Patient IDs, 8102701, 8100601, and 8101301) had baseline dTT >100% ULN. In addition, 3 Japanese subjects (Patient IDs, 8102701, 8100601, and 8101301) had baseline ECT >110% ULN and >100% ULN. The reversal effect based on dTT and ECT was evaluated only for patients with baseline coagulation parameter values >110% ULN and was calculated with the above equation. As a result of the calculation, the maximum reversal based on the 110% ULN was 100% for both the dTT and ECT in all the evaluable Japanese patients. The maximum reversal based on the 100% ULN was also calculated in the manner in which (1) only Japanese patients with baseline coagulation parameter values >100% ULN were included and (2) the "110% ULN" was replaced with "100% ULN" in the above equation. The calculation yielded the maximum reversal of 100% for both dTT and ECT in all the evaluable Japanese subjects.

With regard to the secondary endpoints, 3 Japanese subjects (Patient IDs, 8102701, 8100601, and 8101301) had baseline aPTT >110% ULN and >100% ULN, and 4 Japanese subjects had baseline TT >110% ULN and >100% ULN. Reversal effect based on aPTT and TT was analyzed, and the maximum reversal (%) assessed with 110% ULN and 100% ULN was 100% for both aPTT and TT in all the evaluable Japanese patients.

Table 25 shows changes in coagulation parameters, time to stop bleeding, changes over time in plasma unbound sum dabigatran concentrations, and adverse events reported in the 4 Japanese patients. There were no deaths, serious adverse events, or adverse events leading to discontinuation of the study drug.

Table 25. Data for Japanese subjects in Study 1321.3

Patient ID	8102701	8101001	8100601	8101301
Age and sex	72 years old, male	82 years old, female	87 years old, female	79 years old, male
Details of bleeding	Lower gastrointestinal hemorrhage	Subarachnoid hemorrhage	Subdural hematoma	Lower urinary tract hemorrhage
Body weight (kg)	63	55	44	80
CrCL (mL/min)	62.7	75.4	31.1	33.8
Dosing regimen for DEMS [a)]	110 mg twice daily	110 mg twice daily	110 mg twice daily	110 mg twice daily
Time between the last DE administration and the idarucizumab administration	11.67 h	21.08 h	21.55 h	29.72 h
Plasma unbound sum dabigatran concentration (ng/mL) (Baseline to 4 hours after idarucizumab administration)	33.1 to 1.00 [b)]	15.1 to 1.00 [b)]	65.4 to 1.00 [b)]	43.5 to 1.00 [b)]
ECT (s) (Baseline to 4 hours after idarucizumab administration)	55.8 to 40.3	41.0 to 34.2	73.3 to 35.9	89.2 to 36.0
dTT (s) (Baseline to 4 hours after idarucizumab administration)	37.7 to 31.9	34.6 to 32.4	43.7 to 31.6	47.5 to 31.6
aPTT (s) (Baseline to 4 hours after idarucizumab administration)	46.5 to 35.8	33.4 to 29.0	49.6 to 30.7	54.0 to 26.6
Time between the start of idarucizumab administration and bleeding cessation	Approx. 2 h (recurrence of bleeding 3 days later)	Not evaluated	Approx. 25 h	Approx. 22 h
Days between the start of idarucizumab administration and the resumption of anticoagulant therapy (anticoagulant drug)	Approx. 3 weeks (DE)	2 days (heparin)	No resumption at 2 months later	None
Adverse events	Intestinal haemorrhage	Urinary tract infection, hypokalaemia, sputum increased, polyuria, blood pressure decreased, and Hb decreased	Delirium and syncope	Abdominal pain

[a)] DE dose is shown. [b)] LLOQ.

7.R Outline of the review by PMDA

7.R.1 Clinical positioning

The applicant's explanation:

In the phase III study (the RE-LY study) evaluating the efficacy and safety of DEMS in approximately 18,000 patients with atrial fibrillation, life-threatening bleeding occurred in 1.5% (175 of 6076) of patients receiving DE 150 mg twice daily. In the Japanese 7th Periodic Safety Report for Prazaxa Capsules 75 mg and 110 mg, the incidence of major bleeding is 0.42% (in 27 of 6408 patients, annual incidence of 0.28%). The incidence of serious bleeding with use of DEMS is low, but there are needs for medications to reverse the anticoagulant effects of dabigatran immediately. Idarucizumab specifically binds to dabigatran, an active metabolite after oral administration of DEMS, and directly and immediately reverses the anticoagulant effect of dabigatran. The current therapies for patients experiencing serious bleeding during DEMS therapy include interruption of

DEMS, pressure hemostasis, or surgical hemostatic interventions, and fluid infusion to improve hemodynamics. There are no therapies so far that can specifically remove dabigatran or directly and specifically reverse the anticoagulant effects of dabigatran. Although oral activated charcoal therapy, gastric lavage, and hemodialysis can remove dabigatran directly, the preference should be given to the use of idarucizumab for reasons including the faster onset of its effects than these therapies. However, blood products or blood transfusion should be considered for cases in which development or worsening of bleeding is caused by factors other than dabigatran. Even for patients eligible for idarucizumab therapy, a combination with blood products or blood transfusion should be considered in patients with massive blood loss and patients who cannot achieve sufficient hemostasis due to factors including injury, vascular rupture, tissue perforation, and concomitant antiplatelets or other medications. For patients who require emergency surgery during treatment with DEMS, idarucizumab should be primarily used to ensure that the emergency surgery can be performed as safely and soon as possible, because idarucizumab can reverse the anticoagulant effects of dabigatran immediately. After administration of idarucizumab, intraoperative bleeding control should be performed in the same manner as for surgery in patients not receiving anticoagulant therapy. Idarucizumab is intended to be indicated only for patients with serious bleeding in whom normal coagulation function should immediately be restored or patients requiring emergency surgery.

PMDA's view:

Idarucizumab is a dabigatran-specific reversal agent expected to remove dabigatran and immediately reverse the anticoagulant effects of dabigatran. The submitted study data have demonstrated the reversal effects of idarucizumab in patients with life-threatening bleeding and patients requiring emergency surgery or urgent procedures [see "7.R.2 Efficacy"], and its safety is acceptable in view of its expected benefits [see "7.R.5 Safety"]. Therefore, it is meaningful to make idarucizumab available for use in clinical practice as the dabigatran-specific reversal agent. However, there are no data from controlled studies showing that idarucizumab improves clinical outcomes in the intended patients, and the risk of thromboembolic events secondary to patients' underlying disease may be increased by treatment with idarucizumab because of immediate reversal of the anticoagulant effects of dabigatran. PMDA thus considers that the appropriateness of the use of idarucizumab should be carefully examined and individually determined for each patient based on the patient characteristics.

Multiple factors are probably involved in the occurrence or worsening of bleeding in patients who experience life-threatening bleeding, and thus, even during treatment with DEMS, decreases in plasma unbound sum dabigatran concentrations after idarucizumab administration do not always result in successful bleeding cessation. Therefore, in principle, the currently used procedures (i.e., hemostasis of the bleeding source, if identified; systemic management; and blood transfusion on an as-needed basis) should be performed even for life-threatening bleeding developing during treatment with DEMS. Idarucizumab should be positioned as an add-on therapy to the currently approved therapies for patients presenting with life-threatening bleeding during treatment with DEMS. The applicant claimed that the priority should be given to idarucizumab therapy, rather than to oral activated charcoal therapy, gastric lavage, or hemodialysis. However, these therapies are not so

generally recommended for patients in the acute phase of serious bleeding, and thus whether idarucizumab has a higher priority than these therapies is unknown. Idarucizumab should be indicated only for bleedings developing during DEMS therapy that meet all the following criteria: (a) life-threatening or serious bleedings affecting the patient clinical course; (b) bleedings presumed to have occurred in the presence of dabigatran anticoagulant effects (according to the time since the last dose of DEMS and hematological findings); and (c) dabigatran anticoagulant effects are deemed to complicate hemostasis.

Emergency surgeries or urgent procedures for which idarucizumab is indicated should be determined individually for each case in clinical practice. In Study 1321.3 enrolling patients planned for various surgeries and procedures, some patients underwent procedures which seemed slightly unsuitable for the indication of idarucizumab. For instance, the use of idarucizumab seems rather unsuitable for patients receiving a less invasive procedure including vessel puncture (e.g., catheter placement), a procedure in which an intervention such as pressure hemostasis can be performed for bleeding, and a procedure in which bleeding, if occurs, is unlikely to become severe. At least, idarucizumab should not be indicated for a procedure or an intervention that is conventionally performed without interruption of DEMS administration. In addition, idarucizumab is basically not indicated for patients on DEMS who receive an elective surgery performed ≥24 hours or ≥2 days after interruption of DEMS (the timing of interruption depends on the level of risk of bleeding), and whether the use of idarucizumab can safely accelerate the timing of surgery has not been evaluated. Also in Study 1321.3, idarucizumab was administered to some patients prior to the use of t-PA after the occurrence of cerebral infarction. The applicant claimed that such cases are eligible for idarucizumab therapy, but the appropriateness of idarucizumab therapy in patients with thrombosis remains undetermined because stroke recurred 30 to 40 minutes after idarucizumab administration in a patient. In light of the mechanism of action of idarucizumab and the evaluation results of Study 1321.3, idarucizumab should be indicated for a surgery meeting all the following: (a) clinically important surgeries that should be performed urgently before elimination of the anticoagulant effects of dabigatran; (b) surgeries that have a higher risk of bleeding associated with its surgical procedure; and (c) surgeries that would result in life-threatening or severe conditions if hemostasis fails.

Based on the above, PMDA considers that it is clinically meaningful to use idarucizumab as an add-on therapy to existing interventions in patients properly selected with consideration of the needs of reversal of anticoagulant effects of dabigatran and the benefits and risks in individual patients.

It should be also noted that the proposed dosage and administration of idarucizumab has been selected based on the assumption that idarucizumab is used to reverse the dabigatran anticoagulant effects in a patient receiving DEMS at the approved dose, and that the efficacy and safety of idarucizumab have not been evaluated for patients receiving an excessive dose of DEMS.

7.R.2 Efficacy

7.R.2.1 Clinical data package

The applicant provided explanation on the appropriateness of participation of Japan in the multi-regional clinical development program and the appropriateness of evaluation of the efficacy and safety of idarucizumab

in Japanese patients based on the data from a multi-regional Study 1321.3.

The applicant's explanation:
First, as for intrinsic ethnic factors, no substantial differences in PK of dabigatran and idarucizumab have been identified between the Japanese and non-Japanese populations. There also seem no major differences in PD of idarucizumab between the Japanese and non-Japanese populations for the following reasons: (a) complete reversal was achieved in both the Japanese and non-Japanese subjects who received idarucizumab 4 g at the steady state of dabigatran after administration of DEMS (DE 220 mg) twice daily in the phase I studies in healthy adults; and (b) following idarucizumab administration, plasma unbound sum dabigatran concentrations decreased close to the LLOQ with no differences in reversal effect based on coagulation markers in both 4 Japanese patients and the overall study population in Study 1321.3 (which enrolled patients, not volunteers). As for extrinsic ethnic factors, there are no large differences between Japan and other countries in interventions provided to patients who present with bleeding or require emergency surgery during treatment with DEMS, and such patients are usually treated with interventions including DEMS interruption, surgical hemostasis, blood transfusion, and use of blood products. In Japan, DEMS is indicated only for treatment of ischemic stroke and systemic embolism in patients with NVAF. In other countries, dabigatran is indicated also for prevention of VTE in patients undergoing orthopedic surgery, treatment of VTE, and reduction of the risk of recurrence of VTE. Of patients enrolled in Study 1321.3, 94.7% (230 of 243) of patients were those with atrial fibrillation for which dabigatran is approved in and outside Japan. The dosage and administration of DEMS differ depending on the indication in foreign countries. Meanwhile, in Study 1321.3, DE was administered at 110 mg twice daily in 62.1% (151 of 243) of subjects, 150 mg twice daily in 28.8% (70 of 243) of subjects, 75 mg twice daily in 2.5% (6 of 243) of subjects, and other doses in 6.2% (15 of 243) of subjects. The dosages used in the majority of the study patients were within the dosage range approved in Japan. Based on the above results of exploration of intrinsic and extrinsic ethnic factors, the participation of Japan in the multi-regional clinical development program for idarucizumab was appropriate, and it was also appropriate that the efficacy and safety of idarucizumab in Japanese patients were evaluated on the basis of data from the multi-regional study.

Study 1321.3 is a multi-regional, case series study with the primary objective of evaluating the reversal effect of idarucizumab on the anticoagulant effects of dabigatran. Since the study was designed to include patients with life-threatening bleeding or patients requiring emergency surgery or urgent procedures, it was ethically difficult to have a group not treated with idarucizumab, a drug with a reversal effect on the anticoagulant effects of dabigatran, and the study was thus conducted as an open-label uncontrolled study. The study sample size of 200 to 300 patients was determined on the basis of feasibility. However, the reversal effect of idarucizumab based on coagulation markers could be demonstrated by evaluation of a relatively small number of subjects (e.g., 10 to 25 subjects). Therefore, the study protocol specified implementation of an interim report. Based on this pre-specified interim report (in 26 subjects), an application for marketing approval of idarucizumab was submitted in the US and Europe. Idarucizumab was approved in the US and Europe in October 2014 and November 2014, respectively. As for Japanese patients, the applicant assumed that the reversal effect of idarucizumab in Japanese patients could be consistent with that in the overall study population if complete

reversal was observed in the first [redacted] consecutive Japanese patients in Study 1321.3. Therefore, in Japan, the applicant decided to submit an application for marketing approval based on interim data with a target sample size of [redacted] Japanese patients.

PMDA's view:
The approved indication and dosage and administration of DEMS are not completely the same in Japan and other countries. In the majority of the subjects in Study 1321.3, however, DEMS was used for treatment of atrial fibrillation, which is an approved indication for DEMS in Japan, and the dosages of DEMS used in the majority of the study subjects were within the dosage range approved in Japan. In addition, as for differences in PK of dabigatran and idarucizumab between Japanese and non-Japanese patients, no significant differences were observed that might make it difficult for Japanese patients to participate in the multi-regional study or to evaluate the PKs. The above and other facts justified the participation of Japanese patients in Study 1321.3. PMDA considers it understandable that Study 1321.3 was conducted with an open-label, uncontrolled design, for the following reasons: (a) the reversal effect of idarucizumab on the anticoagulant effects of dabigatran has been clearly demonstrated in data from the phase I studies; (b) therefore Study 1321.3 was conducted to confirm the reversal effect and to evaluate the safety in patients, not to statistically explore the efficacy of idarucizumab; and (c) the feasibility of the study had to be considered. PMDA considers it acceptable that in Japan, the application for marketing approval was submitted based on the interim data from Study 1321.3 including data in Japanese patients, in light of following facts: (a) major bleeding in patients on DEMS has become a significant clinical issue, and thus there have been needs for early development and approval of a dabigatran-specific reversal agent which can be used in urgent situations; and (b) in the US and Europe, idarucizumab has been approved and launched based on the interim data of Study 1321.3. Since Study 1321.3 intended to enroll patients in urgent situations, PMDA considers it inevitable that the target sample size of Japanese patients was limited because of the difficulties in enrollment of such patients. Based on the above, together with the applicant's explanation, PMDA examined and reviewed the methods of evaluation of efficacy in the very small number of Japanese patients. As a result, PMDA concludes that the reversal effect of idarucizumab on dabigatran can be evaluated, also with data from the phase I studies, if complete reversal is achieved in the first [redacted] consecutive Japanese patients in Study 1321.3.

7.R.2.2 Efficacy of idarucizumab in the overall patient population of Study 1321.3
The primary efficacy endpoint of Study 1321.3 was "maximum reversal of the anticoagulant effects of dabigatran by idarucizumab" as determined by dTT or ECT at any time point in the first 4 hours after idarucizumab administration in individual patients. The applicant provided the following explanation on the appropriateness of the evaluation:
The objective of Study 1321.3 was to evaluate the reversal effect of idarucizumab on the anticoagulant effects of dabigatran, and dTT and ECT were evaluated in order to demonstrate the reversal effect on a pharmacodynamic basis. The evaluation time frame of 4 hours after idarucizumab administration was chosen because the anticoagulant effects of dabigatran decrease to baseline in 12 to 72 hours postdose and because, if

evaluation was performed later, evaluation results might reflect the normal dabigatran clearance, rather than the effects of idarucizumab. As a result, the median maximum reversal (as determined by dTT with the threshold of 110% ULN) was 100% in both Groups A and B, and the percentage of patients with a maximum reversal of 100% was 97.4% (97.9% in Group A and 96.7% in Group B). Also, the median maximum reversal (as determined by ECT with the threshold of 110% ULN) was 100% in both Groups A and B, and the percentage of patients with a maximum reversal of 100% was 94.9% (96.0% in Group A and 93.4% in Group B). Plasma unbound sum dabigatran concentrations decreased to <20 ng/mL in 236 of 238 patients, and the median minimum plasma concentration was 1 ng/mL (LLOQ) at 4 hours after completion of administration of idarucizumab 5 g. Scatter plots for the relationship between plasma unbound sum dabigatran concentrations and ECT, dTT, aPTT, and TT in Study 1321.3 indicated a linear relationship between plasma unbound sum dabigatran concentrations and dTT and ECT. A curvilinear relationship was observed between aPTT and plasma unbound sum dabigatran concentrations, but the data varied widely. A linear relationship between TT and plasma unbound sum dabigatran was observed within the range of 0 to 700 ng/mL, but the data varied widely.

Clinical events were assessed as a secondary endpoint. In Group A of Study 1321.3, cessation of bleeding was confirmed in 76.6% (105 of 137) of patients, and bleeding stopped within 24 hours in 56.2% (77 of 137) of patients. In Group B, patients received idarucizumab at a mean time of 3.1 hours before surgery, and "normal or expected hemostasis," "mildly abnormal hemostasis," and "moderately abnormal hemostasis" for intra-operative bleeding was reported in 92.1% (93 of 101), 6.9% (7 of 101), and 1.0% (1 of 101) of patients, respectively. Severely abnormal hemostasis was reported in none of the patients. However, since the same endpoint was not evaluated with data in previous clinical studies or post-marketing setting for DEMS, these results cannot be compared with data from patients not receiving idarucizumab after DEMS therapy.

As shown above, the data from Study 1321.3 demonstrated that idarucizumab could reverse the anticoagulant effects of dabigatran and restore normal hemostatic function.

PMDA asked the applicant to describe the extent and status of reversal observed in patients with a maximum reversal of <100%.

The applicant's explanation:
When 110% ULN was used, the maximum reversal of 100% was not achieved in 4 patients for dTT, 11 for ECT, 8 for aPTT, and 4 for TT. When the more rigorous 100% ULN was used, the maximum reversal (as determined by any of the coagulation markers) was <80% in 6 patients. In these patients, the minimum plasma unbound sum dabigatran concentrations within 4 hours after idarucizumab administration decreased from their baseline levels, and changes in the concentrations in respective patients were as follows: 2590 ng/mL (baseline) to 668 ng/mL (minimum value within 4 hours); 2880 to 669 ng/mL; 78.3 to 1.00 ng/mL; 95.3 to 1.00 ng/mL; 297 to 1.12 ng/mL; and 6.33 ng/mL to "not calculated." Plasma unbound sum dabigatran concentrations did not decline to <20 ng/mL within 4 hours after idarucizumab administration in 2 patients, who had very high

plasma concentrations at baseline.

Only patients with a baseline blood coagulation parameter value of >110%ULN or 100%ULN were defined as "evaluable patients" for the reversal effect. PMDA therefore further asked the applicant to discuss whether idarucizumab was expected to be effective even in patients with low baseline values.

The applicant's response:
The baseline dTT and ECT values were both <110% ULN in 25 patients (12 in Group A and 13 in Group B). In 24 of the 25 patients, the geometric mean of plasma unbound sum dabigatran concentrations before idarucizumab administration was 7.81 ng/mL, and that of their minimum concentrations within 4 hours post-dose was 1.00 ng/mL. (The remaining 1 patient was excluded because of lack of data on plasma unbound sum dabigatran concentrations before idarucizumab administration.) The plasma dabigatran concentration before idarucizumab administration was considered to have little anticoagulant effects. Therefore, idarucizumab is not expected to show its efficacy with this modest decrease in the plasma unbound sum dabigatran concentration (from 7.81 to 1.00 ng/mL). Idarucizumab seems unnecessary in patients with a baseline coagulation parameter value below the ULN because such patients have low plasma dabigatran concentrations. Nevertheless, in the case of an urgent situation, idarucizumab should be administered rather than waiting for laboratory results.

PMDA's view:
The relationship between the primary efficacy endpoint and clinical outcomes in Study 1321.3 remains unclear, and there are no grounds for supporting that the selected endpoints, including the evaluation period, were most appropriate for evaluation. However, as for the objective to evaluate the efficacy of idarucizumab (i.e., reversal of anticoagulant effects of dabigatran), the efficacy of idarucizumab can be evaluated to some extent by investigating data for the endpoint along with changes in plasma unbound sum dabigatran concentrations, because the immediate reversal of dabigatran by idarucizumab has been demonstrated in phase I studies. As a result of such evaluation, the median maximum reversal (the primary endpoint of Study 1321.3) was 100% in the evaluable patients who had dTT and ECT values >110% ULN prior to idarucizumab administration. The plasma unbound sum dabigatran concentration was 81.0 ng/mL (range, 1.00-2880) before idarucizumab administration and declined immediately after idarucizumab administration. Plasma unbound sum dabigatran concentrations decreased also in patients with a maximum reversal of <100%, and these results are considered to suggest the efficacy of idarucizumab. As discussed by the applicant, idarucizumab is not expected to be effective in patients with a baseline value not exceeding the ULN for individual coagulation parameters. The appropriateness of treatment with idarucizumab in such patients is discussed in Section "7.R.4 Indication and intended patient population."

PMDA's conclusion:
Idarucizumab is clinically beneficial since it has been shown to have a reversal effect on the anticoagulant effect of dabigatran, and to be able to reduce the severity of bleeding caused by the anticoagulant effects of

dabigatran.

7.R.2.3 Efficacy in Japanese patients

The applicant provided the following explanation on the efficacy of idarucizumab in Japanese patients:

All 4 Japanese patients evaluated for the primary endpoint in Study 1321.3 achieved complete reversal, showing a decrease in dTT and ECT after idarucizumab administration. No major differences in patient characteristics were observed over the entire study between Groups A and B, while no Japanese patient was enrolled in Group B. The reversal effect of idarucizumab was demonstrated in both groups. Therefore, idarucizumab is expected to have a reversal effect also in Japanese patients requiring emergency surgery or urgent procedure.

PMDA's view:

In Study 1321.3, plasma unbound sum dabigatran concentrations at baseline in 4 Japanese patients were 15.1, 33.1, 43.5, and 65.4 ng/mL. In the patient with the baseline concentration of 15.1 ng/mL, for example, the patient's baseline dTT was 34.6 seconds and showed no marked prolongation in dTT, and these and other findings suggested that the anticoagulant effect of dabigatran was clinically insignificant at the time of idarucizumab administration in the patient. In all Japanese patients, however, plasma unbound sum dabigatran concentrations decreased to 1.00 ng/mL (LLOQ) after administration of idarucizumab 5 g, and blood coagulation parameters showed changes toward restoration of coagulation function. From the point of view of reversal of the anticoagulant effects of dabigatran, the efficacy of idarucizumab has been demonstrated in Japanese patients, as well as in the entire study population.

Study 1321.3 included no Japanese patients receiving idarucizumab prior to emergency surgery, but a situation requiring idarucizumab administration before emergency surgery can occur in Japan as in other countries. PMDA considers that idarucizumab is expected to be effective also in Japanese patients requiring emergency surgery and thus can be used in such patients in Japan, because of the following facts: (1) the efficacy of idarucizumab has been suggested in all of the entire study population, Group A, and Group B in foreign countries; (2) no substantial differences have been identified in PK or PD of dabigatran and idarucizumab between Japanese and non-Japanese patients; and (3) it has been suggested that data on the efficacy of idarucizumab in Japanese patients in Group A tend to be similar to those in the entire study population. Meanwhile, PMDA considers that in the post-marketing surveillance, detailed information should be collected on characteristics of patients judged to require idarucizumab in emergency surgery and on the efficacy and safety of idarucizumab in such patients in clinical practice in Japan. A final decision on details of the intended patient population will be made after discussion in the Expert Discussion.

7.R.3 Dosage and administration

7.R.3.1 Rationale for dosage selection in Study 1321.3 and the proposed dosage and administration

The applicant provided the following explanation about the rationale for the dosage used in Study 1321.3 and for the proposed dosage and administration:

An initial idarucizumab dose was calculated and determined based on the equimolar binding of idarucizumab to dabigatran (i.e., binding of idarucizumab to dabigatran with a 1:1 stoichiometry) and the total body loads of dabigatran observed in patients treated with DE 150 mg twice daily in the RE-LY study (a multi-regional phase III study comparing DEMS and warfarin in patients with NVAF). Idarucizumab 2 g was approximately equimolar to the total body load of dabigatran calculated from its plasma concentration (213 ng/mL) and volume of distribution (66.7 L) at 2 hours after DEMS administration in these patients. In phase I studies, DEMS was administered at DE 220 mg twice daily, which was higher than its clinical dose, and the anticoagulant effects of dabigatran was completely reversed by a single dose of idarucizumab 4 g. The median values of C_{max} of dabigatran observed in these phase I studies were comparable or slightly higher than that in the RE-LY study. In the RE-LY study, however, the dabigatran concentration varied among patients, and some patients showed a higher dabigatran concentration higher than that observed in the phase I studies. The applicant thus considered that a higher dose of idarucizumab was required to reverse the total body load of dabigatran in such patients. Based on the above, the dose of 5 g was selected as an overwhelming dose sufficient to completely reverse the total body load of dabigatran determined on the basis of the dabigatran concentrations observed in almost all patients in the RE-LY study. For Study 1321.3, administration of 2 doses of idarucizumab 2.5 g given ≤15 minutes apart was selected so that blood samples could be collected between the doses, in order to explore the efficacy, PK, and PD following administration of idarucizumab 2.5 g. (The proposed dosage and administration allowed for consecutive infusions of 2 idarucizumab vials.) Each vial was to be administered over 5 to 10 minutes to achieve immediate reversal.

In Study 1321.3 with the above dosing regimen, the reversal effect of idarucizumab on dabigatran was demonstrated, and no safety concerns were identified. Based on the results of Study 1321.3, the following statement was proposed for the dosage and administration section: “The usual adult dose is 5 g of Idarucizumab (Genetical Recombination) (2 vials of 2.5 g/50 mL each), administered intravenously as 2 consecutive infusions over 5 to 10 minutes per vial or as a bolus injection.”

PMDA’s view:

The applicant selected 5 g idarucizumab as an overwhelming dose sufficient to completely reverse dabigatran based on existing data on plasma dabigatran concentrations in patients receiving oral DEMS. The applicant’s selection was understandable in consideration of (a) the clinical position of idarucizumab as a reversal agent to be administered as a single infusion or injection in urgent situations, and (b) the lack of monitoring indices to measure the extent of reversal effect of idarucizumab. In Study 1321.5, immediate and sufficient reversal was achieved after administration of idarucizumab 5 g as compared with the absence of idarucizumab administration. In Study 1321.3, the study results showed improvement in coagulation parameters (e.g., dTT and ECT) within 4 hours after idarucizumab administration as compared with the baseline values and also revealed immediate reduction in plasma unbound sum dabigatran concentrations. These study results suggested that idarucizumab immediately reverses the anticoagulant effects of dabigatran. In addition, there was no trend for clinically significant adverse events to occur frequently in association with the use of idarucizumab [see “7.R.5 Safety”]. Based on the above findings on the efficacy and safety of idarucizumab, PMDA considers that

the proposed idarucizumab dose of 5 g is acceptable in clinical practice.

The protocol of Study 1321.3 specified that idarucizumab 5 g, when divided into 2 doses, should be administered ≤15 minutes apart. The applicant explained that this interval was intended to secure an evaluation time point. Studies conducted in healthy adults demonstrated that complete reversal was achieved after a single dose of idarucizumab 4 g. Based on the above applicant's explanation and results from the studies, the efficacy or safety of idarucizumab is unlikely to be compromised even when 2 vials of idarucizumab are administered without the dose interval specification used in Study 1321.3. Accordingly, PMDA considers that there are no major problems concerning the consecutive infusion of 2 idarucizumab vials.

7.R.3.2 Additional administration

The present application for approval, submitted by the applicant, included the following statement in the section of "Precautions for Dosage and Administration" of the proposed package insert (draft).

Precautions for Dosage and Administration

Plasma concentrations of unbound sum dabigatran or coagulation parameters, such as aPTT, may elevate again within 24 hours after idarucizumab administration in some patients. Additional administration of idarucizumab 5 g should be considered for the patients who meet either of the following:

- Patients presenting with persistence or recurrence of clinically significant bleeding and with an increase in any of the parameters related to coagulation.
- Patients requiring additional emergency surgery or urgent procedure and with an increase in any of the parameters related to coagulation.

The applicant's rationale for the above statements:

In Study 1321.3, additional dosing of idarucizumab was initially permitted several weeks or several years after its initial infusion. However, bleeding recurred during the study period in 2 study sites. The study sites therefore requested that subjects be allowed to receive additional dosing of idarucizumab during the hospitalization period. In response to the request and in view of benefits for the study subjects, additional dosing of idarucizumab was permitted. Later (i.e., after the data cutoff for the interim report), the study protocol was amended to permit additional dosing of idarucizumab.

Details on 2 subjects who received additional dosing of idarucizumab are described below. A 73-year-old man received idarucizumab for gastrointestinal bleeding. At baseline, plasma unbound sum dabigatran concentration was 329 ng/mL, aPTT 87.5 seconds, and CrCL 29.0 mL/min. Plasma unbound sum dabigatran concentrations decreased to 2.66 ng/mL 1 hour after completion of the infusion of idarucizumab 5 g but elevated to 33.4 and 139 ng/mL, respectively, at 12 and 24 hours after the end of the idarucizumab infusion. His aPTT was 33.2 seconds at 10 to 30 minutes after the completion of the infusion. A new gastrointestinal bleeding episode occurred 14 hours after the completion of the infusion. Idarucizumab 5 g was additionally given to the patient 12 hours after the new bleeding episode, and cessation of bleeding was confirmed 1 hour

after the completion of the additional infusion. The aPTT was 71.6 seconds before the additional dosing and 33.8 seconds at 10 to 30 minutes after the completion of the additional infusion. Plasma unbound sum dabigatran concentration was 152 ng/mL before the additional infusion, 1 ng/mL (LLOQ) at 10 to 30 minutes after the completion of the additional infusion, and 61.4 ng/mL at 24 hours after the completion of the additional infusion. He was discharged from hospital 8 days after the additional dosing. The other subject was a 60-year-old man who was treated with idarucizumab for upper gastrointestinal bleeding. At baseline, plasma unbound sum dabigatran concentration was 955 ng/mL, aPTT 283 seconds, and CrCL 25.7 mL/min. Plasma unbound sum dabigatran concentration decreased to 2.09 ng/mL at 1 hour after completion of the infusion of idarucizumab 5 g but elevated to 225 and 272 ng/mL, respectively, at 12 and 24 hours after the completion of idarucizumab infusion. His aPTT was 62.1 seconds at 10 to 30 minutes after the completion of the infusion. Bleeding persisted. Idarucizumab 5 g was additionally administered 2 days after the onset of bleeding episode, and bleeding cessation was confirmed 2 hours after the additional infusion of idarucizumab. His aPTT was 113 seconds before the additional infusion and 47.4 seconds at 10 to 30 minutes after the completion of the additional infusion. Plasma unbound sum dabigatran concentration was 287 ng/mL before the additional infusion, and 1 ng/mL (LLOQ) and 58.5 ng/mL, respectively, at 10 to 30 minutes and 24 hours after completion of the additional infusion. He died of cardiac failure 12 days after the additional idarucizumab infusion.

In these 2 subjects, bleeding stopped after additional dosing of idarucizumab, suggesting that idarucizumab may have prevented recurrence of bleeding. Results from studies conducted in healthy subjects indicate that idarucizumab 5 g is sufficient to completely and sustainably reverse the anticoagulant effects of dabigatran. Meanwhile, plasma dabigatran concentrations may be very high in patients with decreased renal function, concomitant use of a potent P-gp inhibitor, or comorbid diseases. Additional dosing of idarucizumab is likely to be required in patients with such high concentrations, but the characteristics of patients requiring additional dosing of idarucizumab cannot be predicted. Since a certain relationship has been shown between aPTT values and plasma sum dabigatran concentrations, aPTT can be used as an indicator for additional administration of idarucizumab when any signs of re-bleeding are observed. However, there is no established threshold for consideration of additional idarucizumab dosing, and therefore, it is recommended that additional administration of idarucizumab be considered when aPTT is above the reference value in the medical institution.

PMDA’s view on additional dosing of idarucizumab:

In the view of PD and PK, the idarucizumab dose of 5 g has been selected as a dose to completely reverse the total body dabigatran load estimated on the basis of data from the RE-LY study. Taking into account the grounds for the idarucizumab dose selection, together with the fact that DEMS is contraindicated in patients with severe renal impairment in Japan, PMDA considers that plasma dabigatran concentrations are basically within the range that can be reversed by idarucizumab 5 g even in patients with mild or moderate renal impairment or patients concomitantly receiving a medication which may increase plasma dabigatran concentrations. The applicant explained that plasma dabigatran concentrations can be very high in patients with decreased renal function, concomitant use of a potent P-gp inhibitor, or comorbid diseases. However, such patients may have an increased risk of bleeding, and thus DEMS is never used, or, if used, should be given at

a reduced dose in such patients. Meanwhile, in situations of life-threatening bleeding or requiring emergency surgery, the possibility cannot be ruled out that dabigatran may remain in the body to an extent unexpected from the normal clearance of dabigatran, for example, due to rapid worsening of renal function. Actually, in the 2 patients who received additional dosing of idarucizumab in Study 1321.3, plasma unbound sum dabigatran concentrations once decreased after the first infusion of idarucizumab 5 g and then elevated again, which might contribute to the new onset of bleeding and the persistent bleeding. This fact suggests that additional administration of idarucizumab may offer benefits to some patients. Plasma dabigatran concentrations, however, cannot be measured in the current Japanese clinical setting and are not correlated with indicators such as measurable coagulation parameters, and the causes and profiles (e.g., timing and extent) of re-elevation of plasma unbound sum dabigatran concentrations remain unclear. There is no clinically established method to identify a patient for whom additional dosing of idarucizumab should be considered, and the appropriateness of the dose proposed for additional dosing is unclear. Although the applicant proposed the use of aPTT as an index for considerations of additional idarucizumab administration, PMDA considers that no conclusion can be drawn on whether aPTT is an appropriate reference index for consideration of additional dosing of idarucizumab because aPTT levels and plasma dabigatran concentrations are hardly correlated and because the entire results of Study 1321.3 showed a wide variation in aPTT levels. As described above, it is hard to say that the benefits of additional dosing of idarucizumab after the first dosing of idarucizumab 5 g have been clearly demonstrated, and at least for now, there is no evidence to support the recommendation of additional dosing of idarucizumab. A final decision on the appropriateness of additional dosing of idarucizumab will be made after discussion in the Expert Discussion.

7.R.4 Indication and intended patient population

7.R.4.1 Indication

The applicant provided the following explanation about the grounds for the proposed indication “reversal of the anticoagulant effects of dabigatran”:

The phase I studies (Studies 1321.1, 1321.2, and 1321.5) and the phase III study (Study 1321.3, conducted in patients) demonstrated that the anticoagulant effects of dabigatran were immediately reversed by an intravenous infusion of idarucizumab 5 g in healthy subjects, elderly subjects, subjects with renal impairment, and patients with life-threatening bleeding or requiring urgent procedures. The reversal effect of idarucizumab on the anticoagulant effects of dabigatran was demonstrated by measurement of various coagulation parameters and plasma unbound sum dabigatran concentrations. In Study 1321.3, cessation of bleeding was confirmed after administration of idarucizumab in the majority of patients with bleeding, and normal hemostatic function at surgical sites was confirmed after administration of idarucizumab in the majority of patients requiring emergency surgery. The reversal effect of idarucizumab was observed also in 4 Japanese patients. The indication was proposed based on results including the above data from the clinical studies.

PMDA’s view:

The appropriate patients for treatment with idarucizumab are those who are judged to require immediate

reversal of the anticoagulant effects of dabigatran by idarucizumab. The proposed intended patient populations are patients with “life-threatening bleeding or uncontrolled bleeding” and patients “requiring emergency surgery or urgent procedures” in the section “Precautions for Indications” of the package insert. PMDA considers that such specific statement should be provided in the section “Indications” in order to clearly show the intended patient populations. Although no Japanese patients were enrolled in the group of patients requiring emergency surgery in the study, PMDA considers that such patients can be included in the indications because, as described above, idarucizumab is expected to be effective in these patients [see “7.R.2.3 Efficacy in Japanese patients”]. PMDA will make a final decision on the details of wording of the indications, taking into account discussion in the Expert Discussion.

7.R.4.2 Selection of the intended patient population

The mechanism of action of idarucizumab indicates that idarucizumab is expected to be effective only when dabigatran exists and exerts its anticoagulant effects in the body of patients, and therefore, even after DEMS administration, idarucizumab cannot be expected to be effective when dabigatran no longer has clinically meaningful anticoagulant effects. PMDA thus asked the applicant to discuss the relationship between the time from DEMS administration to idarucizumab administration and the efficacy of idarucizumab.

The applicant’s response:

Efficacy data in Study 1321.3 were stratified by the time from the last dose of DEMS to the administration of idarucizumab (<24 hours and ≥24 hours) and were further compared according to renal function status. The analysis results are shown in Table 26.

Table 26. Changes in parameters by time from the last dose of DEMS to the idarucizumab administration and by renal function

Time from the last dose of DEMS to idarucizumab administration		<24 h			≥24 h		
CrCL (mL/min)		<30	≥30 to <50	≥50	<30	≥30 to <50	≥50
Plasma unbound sum dabigatran concentrations (ng/mL)	Baseline	374 (129) 56.6, 2880 (28)	139 (160) 10.1, 2590 (39)	66.5 (150) 1.00, 643 (85)	134 (104) 26.0, 436 (15)	34.3 (171) 3.30, 359 (12)	14.9 (181) 1.00, 69.7 (26)
	4 h after idarucizumab administration	3.88 (2110) 1.00, 1510 (28)	1.30 (189) 1.00, 1700 (37)	1.05 (40.1) 1.00, 30.8 (80)	1.00 (0.763) 1.00, 1.03 (15)	1.00 (0) 1.00, 1.00 (12)	1.00 (0) 1.00, 1.00 (25)
dTT (s)	Baseline	91.3 ± 48.6 39.1, 248 (29)	59.4 ± 28.3 30.6, 194 (40)	47.2 ± 16.2 30.6, 106 (85)	57.1 ± 19.3 34.9, 109 (15)	41.9 ± 15.5 30.8, 88.6 (12)	33.8 ± 3.80 28.8, 41.6 (26)
	4 h after idarucizumab administration	44.3 ± 33.4 24.9, 167 (28)	33.0 ± 21.1 23.7, 159 (38)	30.3 ± 2.15 26.0, 43.2 (80)	29.5 ± 1.99 25.9, 32.9 (15)	29.8 ± 1.78 26.6, 32.6 (12)	31.0 ± 6.54 28.0, 61.2 (24)
ECT (s)	Baseline	263 ± 156 64.0, 500 (29)	140 ± 92.3 37.2, 500 (40)	89.6 ± 55.2 33.9, 315 (85)	135 ± 61.0 61.2, 296 (15)	67.5 ± 30.9 38.9, 140 (12)	48.7 ± 11.1 32.0, 76.1 (26)
	4 h after idarucizumab administration	95.3 ± 128 33.9, 500 (28)	51.3 ± 75.9 31.6, 500 (37)	38.4 ± 3.63 29.4, 52.4 (78)	39.5 ± 3.62 33.8, 46.2 (15)	36.5 ± 2.72 31.6, 40.1 (12)	39.5 ± 8.00 31.5, 71.9 (25)
aPTT (s)	Baseline	116 ± 94.0 41.1, 500 (29)	66.4 ± 35.3 22.3, 215 (40)	52.8 ± 28.5 20.4, 245 (85)	106 ± 121 38.1, 500 (15)	47.6 ± 17.7 34.3, 99.1 (12)	41.1 ± 16.5 27.2, 113 (26)
	4 h after idarucizumab administration	54.8 ± 53.6 18.8, 212 (28)	34.6 ± 23.1 17.2, 168 (38)	30.0 ± 5.46 18.2, 47.4 (78)	33.6 ± 6.92 24.5, 43.0 (15)	29.8 ± 3.46 22.5, 34.1 (12)	32.1 ± 3.69 27.2, 42.7 (23)
TT (s)	Baseline	207 ± 136 52.8, 500 (29)	105 ± 72.7 14.2, 402 (40)	68.2 ± 44.5 10.7, 220 (84)	140 ± 150 32.1, 500 (15)	50.4 ± 37.0 11.7, 156 (12)	29.4 ± 17.9 10.2, 75.2 (25)
	4 h after idarucizumab administration	46.7 ± 90.4 9.40, 384 (28)	24.9 ± 80.3 9.60, 500 (37)	12.2 ± 3.12 8.90, 36.7 (78)	11.7 ± 1.74 9.70, 15.4 (15)	11.2 ± 1.08 9.60, 12.7 (12)	11.4 ± 1.15 9.90, 15.3 (23)

Upper row: geometric mean (geometric CV%) for plasma unbound sum dabigatran concentrations and mean ± SD for other parameters.
Middle row: minimum and maximum.
Lower row: No. of subjects.

In Study 1321.3, the median plasma concentration of unbound sum dabigatran (minimum, maximum) was 35.8 ng/mL (1.00, 436) in patients receiving idarucizumab ≥24 hours after the last dose of DEMS; this value was lower than that in patients receiving idarucizumab <24 hours after the last dose of DEMS (104 ng/mL [1.00, 2880]). The plasma unbound sum dabigatran concentrations in the patients receiving idarucizumab ≥24 hours after the last dose of DEMS depended on their renal function status, and the median plasma concentration of unbound sum dabigatran concentration (minimum, maximum) was 178 ng/mL (26.0, 436) in patients with severe renal impairment, 40.6 ng/mL (3.30, 359) in patients with moderate renal impairment, and 17.1 ng/mL (1.00, 69.7) in patients with mild renal impairment or intact renal function. In patients with severe or moderate renal impairment, plasma unbound sum dabigatran concentration was ≥20 ng/mL, which was regarded as a threshold for the clinically expected anticoagulant effects; this suggested the presence of anticoagulant effects

of dabigatran in at least ≥50% of the patients receiving idarucizumab ≥24 hours after the last dose of DEMS. Also, the median values of coagulation parameters were above the upper limits of normal. It should be noted, however, plasma unbound sum dabigatran concentrations exceeded 20 ng/mL even in some patients with mild renal impairment or intact renal function. In all patients receiving idarucizumab ≥24 hours after the last dose of DEMS, plasma unbound sum dabigatran concentrations decreased to around the LLOQ by 4 hours after idarucizumab administration, indicating complete reversal of the anticoagulant effects of dabigatran. Accordingly, treatment with idarucizumab is clinically meaningful in at least patients with prolonged clotting time at baseline. Plasma dabigatran concentrations can be estimated to some extent from the time after the last dose of DEMS and renal function status at baseline but cannot be predicted completely. Even among patients with intact renal function, some patients had high plasma concentrations of unbound sum dabigatran ≥24 hours after the last dose of DEMS. In patients receiving idarucizumab ≥48 hours after the last dose of DEMS, the median plasma concentration of unbound sum dabigatran (minimum, maximum) before idarucizumab administration was 27.8 ng/mL (1.00, 202), which indicated the majority of these patients had plasma unbound sum dabigatran concentrations at which the anticoagulant effects of dabigatran were maintained. Even such patients, however, showed the reversal effect of idarucizumab on the anticoagulant effects of dabigatran, and thus idarucizumab is expected to be effective.

PMDA's view:

Plasma unbound sum dabigatran concentration decreases over time after administration of dabigatran, and based on the mechanism of action of idarucizumab, administration of idarucizumab is meaningless when plasma dabigatran concentration is sufficiently low. However, it is difficult to measure the plasma dabigatran concentrations in clinical practice. A review on data of coagulation parameters reflecting plasma dabigatran concentrations revealed that in Study 1321.3, the plasma unbound sum dabigatran concentrations before administration of idarucizumab were low in patients with a dTT or ECT value less than the upper limit of normal, and these patients are thought not to need idarucizumab basically. At present, dTT and ECT are not immediately measured in standard medical sites. PMDA considers that patients eligible for idarucizumab therapy should not be selected only on the basis of coagulation parameter data, because of the following facts: (a) other than dTT and ECT, no clinically available coagulation parameters have a proven strong relationship with plasma dabigatran concentrations; and (b) there are factors other than dabigatran that influence coagulation parameters. Then, it was examined whether a population of patients who benefit from idarucizumab can be identified based on renal function status influencing plasma dabigatran concentrations or based on the time since the last dose of DEMS. Changes in plasma unbound sum dabigatran concentration in Study 1321.3 were analyzed in patient groups stratified by the time since the last dose of DEMS and renal function status. In patients with CrCL ≥50 mL/min, for example, the plasma unbound sum dabigatran concentrations decreased in average to as low as 14.9 ng/mL at 24 hours after the last dose of DEMS. Although dabigatran is considered to have no therapeutic effects at this concentration, a wide variation existed among the patients. Thus, no cutoff value was found for specific renal function status or for time since the last dose of DEMS, which are relevant to determine the appropriateness of idarucizumab administration. The $t_{1/2}$ of

dabigatran was approximately 11 hours in Japanese healthy adults and approximately 18 hours in non-Japanese subjects with moderate renal impairment (according to submission data for Prazaxa Capsules 75 mg and 110 mg). The section "Important Precautions" of the current package insert for Prazaxa Capsules 75 mg and 110 mg states that discontinuation of Prazaxa should be considered ≥2 days before major surgery. Accordingly, plasma dabigatran concentration is basically presumed to decrease to a clinically insignificant level 48 hours after the last dose of DEMS. In Study 1321.3, however, the plasma unbound sum dabigatran concentration (geometric mean ± CV% [maximum]) was 23.1 ± 421 ng/mL (202) even in patients who had received the last dose of DMES ≥48 hours earlier, suggesting that plasma dabigatran concentrations could be high exceptionally in such patients. The applicant explained that 9 patients with sum dabigatran concentration exceeding 1000 ng/mL in Study 1321.3 had severe or moderate renal impairment and were receiving a concomitant P-gp inhibitor. This explanation suggested that multiple factors including patient's renal function and concomitant P-gp inhibitors may be involved in the high plasma dabigatran concentrations. Therefore, the presence or absence of these factors should be confirmed before deciding whether to administer idarucizumab to patients receiving the last dose of DEMS some time ago, and idarucizumab should be administered only when its effectiveness is expected. For patients with bleeding during treatment with DEMS, the possibility of other factors influencing bleeding status should be borne in mind, and the appropriateness of idarucizumab therapy should be carefully determined after studying the estimated amount of unbound sum dabigatran in plasma. The following information should be widely disseminated: specific precautions and information for identification of patients to be treated with idarucizumab; and findings on plasma unbound sum dabigatran concentrations and coagulation parameters obtained from clinical studies. PMDA will make a final decision on the specific content of information and approaches, taking account into discussion in the Expert Discussion.

7.R.5 Safety

7.R.5.1 Thromboembolic events

The applicant's explanation:

In Study 1321.3, thrombotic events (myocardial infarction, PE, DVT, systemic embolism) occurred in 5.3% (13 of 243) of patients (8 in Group A and 5 in Group B): DVT in 6 patients, PE in 4, ischaemic stroke in 4, myocardial infarction in 2, and atrial thrombosis in 1 (a single patient may have ≥2 events). Fatal outcome was reported in 2 patients (1 with myocardial infarction and 1 with ischaemic stroke). These events occurred on the day of idarucizumab administration in 1 patient, Day 2 to 7 post-dose in 4 patients, and Day ≥8 post-dose in 8 patients. DEMS is indicated for prevention of thrombosis after orthopedic surgery in some countries, whereas in this study, DEMS was used for treatment of atrial fibrillation in 12 of the 13 patients and for orthopedic surgery in the remaining 1 patient. Anticoagulant therapy was not resumed between administration of idarucizumab and thromboembolic events in 12 patients, while the event recurred after resumption of anticoagulant therapy in 1 patient.

PMDA asked the applicant to explore whether any risk factors can be identified from characteristics of patients who experienced thromboembolic events.

The applicant's response:

The characteristics of the 13 patients with thrombotic events were compared with those of the entire study population. DEMS was used for treatment of atrial fibrillation in 12 of the 13 patients, and the percentage was comparable to that in the entire study population (94.7%, 230 of 243 patients). The median time from the last dose of DEMS to idarucizumab administration was slightly longer in the 13 patients (23.02 hours) than the entire study population (15.83 hours) but did not substantially differ between them. The geometric mean of plasma unbound sum dabigatran concentration just before idarucizumab administration was slightly higher (96.2 ng/mL) in the patients with thrombotic events, than in the entire study population (81 ng/mL). Twelve patients had the common patient characteristic: thromboembolic events occurred before resumption of anticoagulant therapy after idarucizumab administration. Therefore, it was suggested that no resumption of anticoagulant therapy was the most responsible factor for these events.

PMDA's view:

No specific characteristics have been identified in patients with thromboembolic events in Study 1321.3, and details of their clinical courses did not reveal any episode clearly suggesting that administration of idarucizumab may have induced the thromboembolic events. Patients receiving DEMS are already at risk of thromboembolic events, and it can be easily presumed that interruption of anticoagulant therapy increases the thrombotic risk in such patients, regardless of administration of idarucizumab. Therefore, the risk associated with bleeding and the possibility of increased risk of thromboembolic events associated with reversal of anticoagulant effects of dabigatran by idarucizumab should be both carefully evaluated and idarucizumab should be administered only in cases or timing where benefits of idarucizumab are expected to outweigh the potential risks. In view of the thrombotic risk due to underlying diseases, resumption of anticoagulant therapy for underlying diseases should be judged as soon as it is justified that the therapy can be resumed, after bleeding cessation or completion of surgery after idarucizumab administration, and sufficient information should be provided on the resumption. PMDA will make a final decision on details of wording for precautions for risks of thromboembolic events in the package insert for idarucizumab, taking into account discussion in the Expert Discussion. PMDA considers that information on occurrence of thromboembolic events should be collected also in the post-marketing surveillance.

7.R.5.2 Hypersensitivity

In Study 1321.3, the incidence of adverse events probably related to hypersensitivity that occurred during the period from the start of the first infusion of idarucizumab to 90 days after the last idarucizumab administration was 12.3% (30 of 243 subjects; 16 in Group A and 14 in Group B). Among them, adverse events occurring in ≥1% of subjects were pruritus in 1.6% (4 of 243 subjects; 4 in Group A and none in Group B), respiratory failure in 1.2% (3 of 243; 3 in Group A and none in Group B), respiratory distress in 1.2% (3 of 243; 2 in Group A and 1 in Group B), and rash in 1.2% (3 of 243; 1 in Group A and 2 in Group B). Among these adverse events, only rash in 1 subject (in Group A) was assessed as related to the study drug. The adverse event was

mild rash, which occurred 2 days after idarucizumab administration in a 48-year-old man treated with idarucizumab for intracranial hemorrhage, and resolved without any treatment on the following day. Serious adverse events were shock in 2 subjects, respiratory failure in 2 subjects, circulatory collapse in 1 subject, and pneumonitis in 1 subject, and all the serious events were assessed as unrelated to the study drug. After the interim report, anaphylactic reaction was reported in 2 subjects: One subject presented with anaphylactic reaction just after intravenous administration of amoxicillin on the following day of idarucizumab administration, and the event was assessed as unrelated to idarucizumab. The other subject had cerebral hemorrhage and experienced vomiting, decreased consciousness, decreased blood pressure, and eyelid rash after administration of idarucizumab. This subject had received fresh frozen plasma before idarucizumab administration. The subject recovered with administration of epinephrine. On the day of epinephrine administration, TPN was started, and subsequently hypotension with skin eruption occurred. The patient recovered with discontinuation of TPN and administration of antihistamine drugs. However, skin eruption recurred after resumption of TPN. A relationship to idarucizumab was not ruled out. The applicant considered that anaphylactic reaction observed in the above 2 subjects was suspected to be related to drugs other than idarucizumab and that there was no evidence suggesting a relationship to idarucizumab. Based on the above, the applicant claimed that so far, there was no reason that anaphylactic shock needs to be included in the section "Clinically Significant Adverse Reactions" of the package insert.

PMDA's view:

In Study 1321.3, adverse events probably related to hypersensitivity occurred in 12.3% of the subjects. However, the investigators did not assess many of the events as related to idarucizumab because other drugs including blood products were used concomitantly with idarucizumab in many subjects and because effects of other drugs could not be ruled out. Meanwhile, injection site reaction, which was reported as erythema, was observed even in studies in healthy adults, and in Study 1321.3, anaphylactic shock was reported as an adverse event for which a causal relationship to idarucizumab was not ruled out. In addition, hypersensitivity is listed as an adverse reaction requiring precautions in foreign countries. Given the above, PMDA considers that precautions for hypersensitivity as an adverse reaction should be provided in the package insert. Since idarucizumab was investigated in a very limited number of patients, information on occurrence of events related to hypersensitivity in Japanese patients should be collected in activities including a post-marketing surveillance. The applicant proposed that idarucizumab need not be contraindicated but should be used with caution for patients with known hypersensitivity to any ingredients of Prizbind. However, PMDA cannot conclude that idarucizumab can provide such patients with benefits outweighing its potential risks, for the following reasons: (a) adverse reactions may become serious in patients receiving idarucizumab because the target patients of idarucizumab are in poor general condition developing before idarucizumab administration; (b) the safety of idarucizumab has not been established in patients with known hypersensitivity who are theoretically at risk of recurrence of hypersensitivity; and (c) idarucizumab is merely an option to stop bleeding or to reduce the risk of bleeding. Since treatment with idarucizumab is not appropriate at least for patients with known hypersensitivity to idarucizumab, idarucizumab should be contraindicated in such patients. Nevertheless,

PMDA will make a final decision on this matter after discussion in the Expert Discussion.

7.R.5.3 ADAs

The applicant's explanation:

In Study 1321.3, ADAs were measured at baseline and 4 weeks and 3 months after administration of idarucizumab. ADAs were detected in 3.3% (8 of 242) of patients at any time point: all Japanese patients were negative for ADAs. Of the 8 patients, 3 had no detectable pre-existing ADAs and became positive for ADAs after idarucizumab administration. ADA titers were as low as up to 8-fold in the 3 patients. Pre-existing ADAs did not significantly influence the PK or PD of idarucizumab [see "6.R.5 Effects of ADAs on idarucizumab PK"]. With regard to a relationship between ADAs and adverse events such as hypersensitivity, a patient with detectable ADAs experienced mild rash on the groin after idarucizumab administration, and the rash subsequently resolved after lasting for 59 days. The investigator assessed the event as unrelated to the study drug. No relationship was suggested between pre-existing ADA and adverse events considered associated with hypersensitivity by data from other studies.

PMDA's view:

Pre-existing ADAs were detected only in a small percentage of patients, and no clearly clinically significant events have been found in association with ADAs. Therefore ADAs need not be measured before idarucizumab administration. For patients with ADAs detected only after idarucizumab administration, the efficacy and safety of idarucizumab in the presence of the ADAs have not been confirmed. In view of (a) the small percentage of patients with ADAs detected only after idarucizumab administration and (b) the clinical position of idarucizumab [see "7.R.1 Clinical positioning"], patients using DEMS properly are extremely unlikely to receive readministration of idarucizumab in the presence of ADAs developing after idarucizumab administration. Since at present, there is no evidence indicating that idarucizumab should not be used in such patients, PMDA considers that idarucizumab can be used in patients previously treated with idarucizumab but also considers that the applicant should collect all and complete data on patients with re-exposure to idarucizumab and investigate the needs of determination of ADAs or other relevant matters, as appropriate, through the pharmacovigilance activities including a post-marketing surveillance.

7.R.6 Use of idarucizumab in patients with renal impairment

The applicant provided the following explanation on the efficacy and safety of idarucizumab in patients with renal impairment:

The efficacy and safety of idarucizumab were evaluated in patients with various renal function status (severe renal impairment, CrCL <30 mL/min; moderate renal impairment, CrCL ≥30 to <50 mL/min; mild renal impairment, CrCL ≥50 to <80 mL/min; and intact renal function, CrCL ≥80 mL/min) in Study 1321.3. The median maximum reversal (the efficacy endpoint) was 100.0% in all patient groups, regardless of their renal function status. The geometric mean of plasma concentration of unbound sum dabigatran in the respective patient groups changed as follows: 257 ng/mL (at baseline) to 1.58 ng/mL (minimum value within 4 hours

post-dose) in patients with severe renal impairment; 103 to 1.17 ng/mL in patients with moderate renal impairment; 55.3 to 1.00 ng/mL in patients with mild renal impairment; and 35.8 to 1.00 ng/mL in patients with intact renal function. Plasma unbound sum dabigatran concentrations decreased to around the LLOQ in all patient groups. With regard to safety, the incidence of adverse events was 92.2% (47 of 51), 92.7% (51 of 55), 84.1% (58 of 69), 82.1% (46 of 56) of patients, respectively, in the groups of patients with severe, moderate, and mild renal impairment and intact renal function. The incidence of serious adverse events was 62.7% (32 of 51), 45.5% (25 of 55), 42.0% (29 of 69), and 35.7% (20 of 56) of patients, respectively, in the groups of patients with severe, moderate, and mild renal impairment and intact renal function, showing a slightly higher incidence in patients with severe renal impairment. The incidence of adverse events assessed as related to the study drug was 7.8% (4 of 51), 5.5% (3 of 55), 1.4% (1 of 69), and 7.1% (4 of 56) of patients, respectively, in the groups of patients with severe, moderate, and mild renal impairment and intact renal function, showing no difference in the incidence by renal function status. The incidence of bleeding or thrombotic events did not differ by renal function status. Based on the above findings, the efficacy and safety of idarucizumab can be expected in patients, regardless of their renal function status.

PMDA's view:

Since idarucizumab 5 g decreased the plasma unbound sum dabigatran concentrations and coagulation marker levels even in patients with renal impairment in Study 1321.3, the reversal effect of idarucizumab can be expected in such patients. Additionally, no tendency toward increased safety risk was found in patients with renal impairment. In conclusion, idarucizumab can be used in patients with any renal impairment. In Japan, DEMS is contraindicated in patients with severe renal impairment because plasma dabigatran concentrations are elevated, which may lead to an increased risk of bleeding. Therefore, it is also important to ensure that idarucizumab is used only in patients who are using DEMS properly.

7.R.7 Resumption of DEMS therapy after administration of idarucizumab

The applicant provided the following explanation on the reasons that DEMS can be resumed at and after 24 hours after idarucizumab administration:

For patients at a risk of thrombotic events, it is medically crucial to resume DEMS or other antithrombotic drugs after administration of idarucizumab. At 24 hours post-dose of idarucizumab, idarucizumab has very limited effects on the anticoagulant effects of dabigatran because free idarucizumab practically does not exist in plasma, even in patients with renal impairment (including those with CrCL <30 mL/min) who have delayed elimination of idarucizumab. Accordingly, DEMS can be resumed 24 hours after administration of idarucizumab [see "6.R.6 Timing of resumption of DEMS after idarucizumab administration"]. In Study 1321.3, the median and minimum duration from administration of idarucizumab to resumption of DEMS was 15.0 and 1.3 days, respectively, in Group A (36 subjects) and 7.8 and 1.0 days, respectively, in Group B (66 subjects). Although plasma concentrations of unbound sum dabigatran after resumption of DEMS were not measured, no thromboembolic events occurred after resumption of DEMS during the follow-up period (90 days after idarucizumab administration), and there was no increase in the incidences of adverse events after

resumption of DEMS. The applicant provided the following explanation on anti-dabigatran antibodies: In Studies 1321.1, 1321.2, and 1321.5, 7.5% (43 of 574) of samples were screened putative positive for anti-dabigatran antibodies with the modified TT assay. TT values in 4 of the 43 samples were lower by >10% than the threshold. However, the anti-dabigatran antibody levels were assumed to be very low and were considered to be clinically insignificant.

PMDA's view:

It is difficult to draw conclusions about any clinical impact of anti-dabigatran antibodies only based on the anti-dabigatran antibody levels measured in the clinical studies submitted for the present application. Meanwhile, although in a limited number of patients in a limited duration of time, no significant issues emerged regarding the incidence of thromboembolic events in patients with resumption of DEMS in Study 1321.3. Therefore, at this point, it is acceptable to resume DEMS 24 hours or later after idarucizumab administration while PK of idarucizumab is taken into consideration. However, in patients eligible for idarucizumab therapy because of serious bleeding or emergency surgery causing bleeding, their bleeding may not always be controlled to the extent allowing resumption of DEMS at 24 hour after idarucizumab administration. Given the actual time of resumption of DEMS observed in Study 1321.3, physicians should select the type of anticoagulant to be used for anticoagulant resumption (heparin etc. should be considered as an option) and determine the timing of resumption after assessing bleeding risk in individual patients.

7.R.8 Post-marketing investigations

The applicant's explanation:

An all-case surveillance is planned to be conducted in patients confirmed to have been treated with idarucizumab in practical clinical setting, in order to investigate the safety and efficacy of idarucizumab in patients on DEMS who present with uncontrolled bleeding or require emergency surgery or urgent procedures. The registration period is planned to be 3 years, and the planned sample size is 300 patients. Thrombosis and hypersensitivity are the key survey items. The incidence of these events was 5.3% (thrombosis) and 12.3% (hypersensitivity) in Study 1321.3. The sample size of 300 can provide 90% power to detect the difference in the incidences between Japanese patients and the overall study population of Study 1321.3, if the true incidence of thrombosis and hypersensitivity in Japanese patients is approximately 1.5- to 2-fold higher than that in the overall study population.

PMDA's view:

In Study 1321.3 conducted in patients treated with idarucizumab, a very limited number of Japanese patients were enrolled (only 4 patients). Of them, none required emergency surgery or urgent procedures. Therefore, the proposed surveillance should cover all patients receiving idarucizumab, in order (a) to clarify the incidence of the key survey items and others in Japan and the characteristics of patients receiving idarucizumab in the practical clinical setting, because of the limited data on characteristics of patients evaluated in the clinical studies, and (b) to evaluate the relationship between patient characteristics and the safety or efficacy of

idarucizumab. Specifically, the following information should be collected: DEMS dose, time from the last dose of DEMS to administration of idarucizumab, reason for indication of idarucizumab, renal function status, information concerning the clinical course including bleeding site and details on hemostasis in patients with bleeding, and details of surgery and postoperative status of bleeding in patients receiving emergency surgery. In addition, information concerning the usefulness of idarucizumab, timing of resumption of anticoagulant therapy and the safety after the resumption, occurrence of thromboembolic events, concomitant drugs, and cases of re-exposure should be collected. The objectives of the proposed surveillance should be discussed again based on the above, and then the planned sample size should also be re-examined. PMDA will make a final decision on details of the post-marketing surveillance after discussion in the Expert Discussion.

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

Compliance assessment is now under way, and the results and PMDA's conclusion will be reported in the Review Report (2).

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

Based on the submitted data, PMDA has reached the following conclusions: (1) the reversal effect of idarucizumab on the anticoagulant effects of dabigatran has been demonstrated; (2) idarucizumab can reduce severity of bleeding due to the anticoagulant effects of dabigatran in patients on DEMS with life-threatening bleeding or those receiving emergency surgery in which significant hemorrhagic complication is anticipated; and (3) the safety of idarucizumab is acceptable. The use of idarucizumab should be considered as an additional option to existing therapeutic interventions to reverse the anticoagulant effects of dabigatran and to treat bleeding or to reduce the severity of bleeding in patients on DEMS. It is therefore meaningful to make idarucizumab available for use in clinical practice. Appropriate methods of selection of patients to be treated with idarucizumab, specific collection methods for post-marketing information, and other relevant matters should be further investigated.

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

Review Report (2)

August 23, 2016

Product Submitted for Approval

Brand Name	Prizbind Intravenous Solution 2.5 g
Non-proprietary Name	Idarucizumab (Genetical Recombination)
Applicant	Nippon Boehringer Ingelheim Co. Ltd.
Date of Application	February 23, 2016

1. Content of the Review

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

1.1 Clinical positioning of idarucizumab

Prizbind Intravenous Solution 2.5 g (idarucizumab) is a dabigatran-specific reversal agent. The submitted study data have demonstrated the reversal effect of idarucizumab in patients presenting with life-threatening or uncontrolled bleeding or requiring emergency surgery or urgent procedures during treatment with dabigatran etexilate methanesulfonate (DEMS), and its safety is acceptable in view of its expected benefits. Therefore, PMDA concluded that it is meaningful to make idarucizumab available for use in clinical practice. This conclusion was supported by the expert advisors. Meanwhile, PMDA concluded that the appropriateness of the use of idarucizumab should be carefully examined and individually determined for each patient based on the patient characteristics, because there are no data from clinical studies showing that idarucizumab improves clinical outcomes in the patients above, and because the risk of thromboembolic events secondary to patients' underlying disease may be increased by the reversal of the anticoagulant effects of dabigatran by idarucizumab. This conclusion was also supported by the expert advisors. The expert advisors commented as follows: Even in patients with life-threatening or uncontrolled bleeding or patients receiving surgery or procedures that would cause significant bleeding, in view of the existing available therapy options and the urgency of the condition, there seem to be a limited number of circumstances that may require reversal of the anticoagulant effects of dabigatran by idarucizumab. In addition, the possibility that the risk of thromboembolic events may be increased by treatment with idarucizumab cannot be ruled out. Therefore, physicians should be alerted not to have excessive expectations for idarucizumab, not to consider the reversal of anticoagulant effects of DEMS as the first-line intervention, and not to use idarucizumab without careful consideration.

1.2 Efficacy

The following conclusions made by PMDA were supported by the expert advisors: (1) The relationship between the primary efficacy endpoint (the maximum reversal effect) and clinical outcomes in Study 1321.3 remains unclear, but the efficacy of idarucizumab can be evaluated to some extent by investigating the maximum reversal effect along with changes in plasma unbound sum dabigatran concentrations in the evaluation conducted to confirm the reversal effect of idarucizumab on the anticoagulant effects of dabigatran; (2) The reversal effect of idarucizumab on dabigatran in Japanese patients has been suggested by the interim data of Study 1321.3 and by the results from Japanese and non-Japanese phase I clinical studies included in the submitted data; and (3) Idarucizumab has been suggested to be clinically beneficial because it can be assumed to reduce the severity of bleeding due to the anticoagulant effects of dabigatran.

In addition, although no Japanese patients requiring emergency surgery or urgent procedures were enrolled in Study 1321.3, situations requiring idarucizumab administration before emergency surgery or urgent procedures can occur also in Japan, as with other countries. In light of the above, together with the interim data of Study 1321.3 and the results from Japanese and non-Japanese phase I clinical studies, PMDA concluded that idarucizumab is expected to be effective also in Japanese patients requiring emergency surgery or urgent procedures and can be used in such patients. This conclusion was supported by the expert advisors.

1.3 Indication

PMDA concluded that the appropriate patients for treatment with idarucizumab are those requiring immediate reversal of the anticoagulant effects of dabigatran, and that the intended patient populations should be clearly described in the section “Indications” of the package insert. This conclusion was supported by the expert advisors. In addition, the appropriateness of the wording “surgery or procedures” was discussed because “procedures” might be associated with minimally invasive techniques, and the following comments were raised by the expert advisors: (a) the word “procedures” should be removed because the level of techniques is unclear from the word of “procedures” which might be interpreted to include minimally invasive techniques; (b) techniques with a high risk of bleeding are also classified as “procedures” in the coding classification of the National Health Insurance; and (c) the section “Indications” should include the words and phrases which clearly define the intended patients by describing the risk of bleeding or other relevant factors rather than discussing the differentiation of “surgery” and “procedures”; and the wording for “Indication” should include “emergency,” “urgent,” or “in which significant bleeding is anticipated” because such words and phrases will ensure that idarucizumab is administered only to patients receiving highly invasive procedures. Based on the discussion, PMDA concluded that the phrase “Emergency surgery or urgent procedures in which significant bleeding is anticipated” should be included in the wording for “Indication,” and that healthcare professionals in medical practice should be thoroughly informed of the proper use of idarucizumab. The PMDA’s conclusion was supported by the expert advisors.

Based on the above, PMDA concluded that the indication of idarucizumab should be as follows and that the

section “Precautions for Indications” should include the following precautionary statement: “when used for surgery or procedures, idarucizumab should be given only to patients who require urgent reversal of the anticoagulant effect of dabigatran before spontaneous elimination of the effects and who receive surgery or procedures in which uncontrolled bleeding may result in fatal or serious consequence.”

Indication

Reversal of the anticoagulant effects of dabigatran in the following situations:

- Occurrence of life-threatening bleeding or uncontrolled bleeding
- Emergency surgery or urgent procedures in which significant bleeding is anticipated

In addition, the following PMDA’s conclusions were supported by the expert advisors:

(1) Patients eligible for idarucizumab treatment should not be selected only on the basis of coagulation parameter data, for the following reasons:
   (a) The mechanism of action of idarucizumab indicates that idarucizumab is expected to be effective only in patients in whom dabigatran exists at certain levels and exerts its anticoagulant effects in the body of patients. However, it is difficult to immediately measure plasma concentrations of unbound sum dabigatran or certain coagulation parameters (i.e., diluted thrombin time [dTT] and ecarin clotting time [ECT]) in standard medical sites. Other coagulation parameters (e.g., activated partial thromboplastin time [aPTT]) are currently used and available as indices in clinical practice in Japan, but they do not highly correlate with the plasma concentrations of unbound sum dabigatran;
   (b) There are factors other than dabigatran that influence coagulation parameters.

(2) For patients requiring emergency surgery or urgent procedures, idarucizumab should be used only when it is expected to be effective after carefully considering the following:
   (a) The half-life of dabigatran;
   (b) Factors likely to influence the pharmacokinetics of dabigatran (e.g., renal function status, concomitant use of P-glycoprotein [P-gp] inhibitors);
   (c) Perioperative off-treatment period specified in the package insert of Prazaxa Capsules 75 mg and 110 mg:
   (d) The possible presence of other factors having impact on bleeding;
   (e) The estimated level of dabigatran in plasma.

(3) In order to ensure that healthcare professionals can select patients eligible for treatment with idarucizumab (i.e., patients meeting the criteria shown above), the applicant should provide healthcare professionals with specific information which helps them to estimate the level of dabigatran in plasma.

The expert advisors made the following comments:

The residual amount of dabigatran can be estimated from the time since the last dose of dabigatran with reference to the half-life of dabigatran. However, renal tubular secretion mediated by P-gp plays an important

role in elimination of dabigatran, which is particularly affected by the renal blood flow (glomerular filtration rate). The appropriateness of treatment with idarucizumab or the timing of idarucizumab administration should be determined with a full understanding of *in vivo* pharmacokinetics of dabigatran; this information should be adequately provided to healthcare professionals.

Based on the above, PMDA requested the applicant to include the following precautionary statement for selection of patients eligible for treatment with idarucizumab in the section "Precautions for Indications" of the package insert and to provide healthcare professionals in clinical practice with specific information helping them to estimate the level of dabigatran in plasma: "Idarucizumab should be used only in patients in whom the anticoagulant effects of dabigatran are assumed to be present based on the time since the last dose of dabigatran etexilate methanesulfonate, their characteristics (renal function status, concomitant P-glycoprotein inhibitors, and other factors that may affect the pharmacokinetics of dabigatran), and other relevant data." The applicant addressed the request properly.

1.4 Dosage and administration

Data from the Japanese and non-Japanese phase I studies and Study 1321.3 suggested the immediate reversal effect of idarucizumab (genetical recombination) 5 g on the anticoagulant effects of dabigatran, and no tendency toward frequent occurrence of clinically significant adverse events was observed in association with treatment with idarucizumab. Therefore, PMDA concluded that the dose of 5 g idarucizumab is acceptable. This conclusion was supported by the expert advisors.

In situations of life-threatening bleeding or requiring emergency surgery, dabigatran may remain in the body to an extent unexpected from the normal clearance of dabigatran, for example, due to rapid worsening of renal function. Although some patients may benefit from additional administration of idarucizumab, plasma unbound sum dabigatran concentrations are difficult to measure in the current Japanese clinical setting and are not highly correlated with measurable coagulation parameters (e.g., aPTT) as indicators. In addition, the causes, timing, and extent of re-elevation of plasma unbound sum dabigatran concentrations remain unclear. Taken into account the above, PMDA concluded that at least for now, there is no evidence supporting the recommendation of additional dosing of idarucizumab after administration of idarucizumab 5 g, because there is no established method to identify a patient for whom additional dosing of idarucizumab should be considered in its clinical use, and because the appropriateness of the dose proposed for additional dosing is unclear. This conclusion was supported by the expert advisors.

The expert advisors' comment: Much remains unclear about the types of patients likely to show re-elevation of plasma unbound sum dabigatran concentrations, but healthcare professionals should be informed that in Study 1321.3, some patients showed re-elevation of plasma unbound sum dabigatran concentrations and received additional dosing of idarucizumab.

PMDA's response to the expert advisors: The fact that plasma unbound sum dabigatran concentrations elevated again in some patients should be described in the section "Clinical Studies" of the package insert; and there

seem no data available that can be actively provided to healthcare professionals for the dosage and administration of additional idarucizumab dosing, because the additional administration of idarucizumab in Study 1321.3 (interim data) was a protocol deviation, and because the necessity and benefits of additional dosing have not been sufficiently evaluated. This conclusion was supported by the expert advisors.

Based on the above, PMDA has concluded that the dosage and administration statement should be as follows:

Dosage and Administration

The usual adult dose is 5 g of Idarucizumab (Genetical Recombination) (2 vials of 2.5 g/50 mL each), administered intravenously as infusions over 5 to 10 minutes per vial or as a bolus injection.

1.5 Safety

1.5.1 Thromboembolic risk

PMDA concluded that the package insert should include precautionary statements to the following effect:

> Patients receiving DEMS are already at risk of thromboembolic events, and interruption of anticoagulant therapy may increase the thrombotic risk in such patients, regardless of administration of idarucizumab. Idarucizumab should be administered only to patients who would receive its benefits outweighing the potential risks. In view of the thrombotic risk due to underlying diseases, anticoagulant therapy for underlying diseases should be resumed as soon as it is justified after bleeding cessation or completion of surgery after idarucizumab administration.

This conclusion was supported by the expert advisors.

Based on the above, PMDA requested the applicant to include in the section “Important Precautions” of the package insert the following precautionary statement: “Because of the increased risk of thrombosis by reversal of the anticoagulant effects of dabigatran, the resumption of anticoagulant therapy should be considered as soon as medically appropriate after achievement of hemostasis. Dabigatran etexilate methanesulfonate can be resumed 24 hours after administration of idarucizumab, and other anticoagulants can be resumed at any time point after administration of idarucizumab.” The applicant addressed the request properly.

1.5.2 Hypersensitivity

In Study 1321.3, adverse events considered to be related to hypersensitivity occurred, but many of the events were not considered as related to idarucizumab by the investigators, because many subjects used other drugs (including blood products) in combination with idarucizumab and therefore the effects of other drugs could not be ruled out. Meanwhile, injection site reaction (reported as erythema) was observed even in studies in healthy adults, and in Study 1321.3, anaphylactic shock was reported as an adverse event for which a causal relationship to idarucizumab was not ruled out. In addition, hypersensitivity is listed as an adverse reaction requiring precautions in foreign countries. Given the above, PMDA concluded that hypersensitivity should be listed in the section “Clinically Significant Adverse Reactions” to call attention to it. This conclusion was supported by

the expert advisors.

Adverse reactions may become serious in patients receiving idarucizumab because the target patients of idarucizumab are in poor general condition developing before idarucizumab administration. The safety of idarucizumab has not been established in patients with known hypersensitivity who theoretically are at risk of recurrence of hypersensitivity. In addition, idarucizumab is merely an option to stop bleeding or to reduce the risk of bleeding. Because of the above reasons, the conclusion cannot be drawn that idarucizumab can provide such patients with benefits outweighing its potential risks. In light of the above, PMDA concluded that idarucizumab should be contraindicated in patients with at least known hypersensitivity to idarucizumab. The PMDA's conclusion was supported by the expert advisors.

Based on the above, PMDA requested the applicant to include precautionary statements for hypersensitivity including shock and anaphylaxis in the section "Clinically Significant Adverse Reactions" of the package insert and recommended that idarucizumab be contraindicated in patients with known hypersensitivity to any ingredients of Prizbind. The applicant addressed the request and recommendation properly.

1.5.3 Anti-idarucizumab antibodies (anti-drug antibodies)

The following conclusions by PMDA were supported by the expert advisors:

(a) At present, ADAs need not be measured before idarucizumab administration, because in clinical studies pre-existing ADAs were detected only in a small percentage of patients and no clearly clinically significant events were found in association with ADAs.

(b) The efficacy and safety of idarucizumab have not been established in patients receiving readministration of idarucizumab in the presence of the ADAs detected only after idarucizumab administration. The applicant should therefore collect data on patients re-exposed to idarucizumab and investigate, as appropriate, the needs of determination of ADAs through post-marketing surveillance and other pharmacovigilance activities.

Based on the above, PMDA requested the applicant to examine the needs of determination of ADAs on the basis of data available from the post-marketing surveillance and information in and outside Japan. The applicant addressed the request properly.

1.5.4 Resumption of DEMS after administration of idarucizumab

The following conclusion by PMDA was supported by the expert advisors:

The applicant explained that DEMS can be resumed at 24 hours after administration of idarucizumab because there are almost no free idarucizumab in the plasma of patients, including those with renal impairment, at that time point. Some patients were screened putative positive for anti-dabigatran antibodies according to the clinical study data submitted, but in Study 1321.3 none of the patients who resumed DEMS had significant issues including the incidence of thromboembolic events. The above applicant's explanation and the above fact suggest that DEMS can be resumed 24 hour or later after administration of idarucizumab. Meanwhile, however,

it is not always appropriate to say that bleeding can be adequately controlled 24 hours after idarucizumab administration to the extent allowing resumption of DEMS in patients presenting with severe bleeding for which idarucizumab should be indicated or patients receiving emergency surgery in which severe bleeding is anticipated. In light of the above and the actual time of resumption of DEMS in Study 1321.3, PMDA concluded that physicians should select the type of anticoagulant to be used for anticoagulant resumption (heparin etc. should be considered as an option) and determine the timing of resumption after assessing bleeding risk in individual patients.

Based on the above, PMDA requested the applicant to include in the section "Important Precautions" of the package insert the information about the appropriate timing at which DEMS or other anticoagulants can be resumed. The applicant addressed the request properly [see "1.5.1 Thromboembolic risk"].

1.6 Use of idarucizumab in patients with renal impairment

In Study 1321.3, changes by idarucizumab 5 g in plasma unbound sum dabigatran concentrations and coagulation marker levels indicated that the reversal effect of idarucizumab was exerted even in patients with renal impairment, and no specific tendency toward inferior safety profiles was seen in such patients. Given the results, PMDA concluded that idarucizumab can be used in patients with any renal impairment, but it is important that idarucizumab should be used in patients using DEMS properly. This conclusion was supported by the expert advisors. In addition, the expert advisors commented that careful attention should be paid to patients with renal impairment when DEMS is used (rather than when idarucizumab is used), and that this information should be appropriately provided so as to make it clear.

1.7 Risk management plan (draft)

Based on the results of review described in Section "7.R.8 Post-marketing investigations" of the Review Report (1) and discussion in the Expert Discussion, PMDA has concluded that the risk management plan for idarucizumab (draft) should include the safety and efficacy specifications listed in Table 27, and that the applicant should conduct the additional pharmacovigilance activities and risk minimization activities listed in Table 28 and should carry out the drug use-results survey shown in Table 29.

Table 27. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
・Shock and anaphylaxis	・Immunogenicity ・Thromboembolic events	・Re-exposure to idarucizumab
Efficacy specification		
・Efficacy in routine clinical practice		

Table 28. Summary of additional pharmacovigilance activities and additional risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimization activities
・Early post-marketing phase vigilance ・Use-results survey (All-case surveillance) ・Post-marketing clinical study (Study 1321.3) ・Post-marketing clinical study (Study 1321.14 [a])	・Provision of information based on data from the early post-marketing phase vigilance ・Preparation and distribution of documents and leaflets for healthcare professionals

[a] An extension study of Study 1321.3.

Table 29. Outline of use-results survey (all-case surveillance) (draft)

Objective	To evaluate the safety and efficacy of idarucizumab in routine clinical practice
Study method	All-case surveillance (retrospective surveillance)
Population	Patients treated with idarucizumab
Observation period	4 weeks
Registration period	From the market launch of idarucizumab to the termination of the approval conditions
Planned sample size	300 patients
Key survey items	Hypersensitivity (including shock, anaphylaxis, and symptoms and signs of immunogenicity), thromboembolic events
Main survey items	・Patient characteristics ・Details of bleedings ・Details of therapies (details of idarucizumab therapy and concomitant therapies) ・Laboratory data (coagulation parameters) ・Outcomes ・Adverse events

1.8 Appropriateness of the interim report of Study 1321.3

The interim report of Study 1321.3 (cut-off date, [redacted]) submitted for the present application included cases with "missing eCRF pages," cases with "unresolved queries," and cases with "eCRF pages electronically unsigned." The applicant submitted another appendix which describes details of the changes in the data made by [redacted], including results of reconciliation of these unfixed cases. However, the submitted data in this approval application differed from the interim data as of [redacted], which was the date previously agreed between the applicant and PMDA. Therefore, PMDA asked the applicant to provide data to be reflected in the interim data as of [redacted] when the data were processed pursuant to the data handling rules to be followed.

The applicant's explanation:

As for data to be reflected in the interim data as of [redacted], the applicant explained that in some of the cases with "eCRF pages electronically unsigned," outcome of serious adverse events should be changed from "unrecovered" to "death" after the pages were signed, and for cases with missing data for creatinine clearance, the applicant provided the descriptive statistics values which were modified due to changes made by the time of signature. Then, the applicant concluded that there were no changes in its view on the efficacy and safety of idarucizumab if these data were processed in accordance with the data handling rules to be followed.

PMDA reviewed the data which were to be reflected in the interim data as of [redacted] and were provided by the applicant in response to PMDA's request. PMDA then confirmed that these data had no impact on the evaluation described in the Review Report (1).

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

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

The new drug application data were subjected to a document-based compliance inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. The inspection and assessment revealed no noteworthy issues. PMDA thus concluded that there were no obstacles to conducting its review based on the application documents submitted.

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

The new drug application data (CTD 5.3.5.2-02) were subjected to an on-site GCP inspection in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. The inspection revealed no noteworthy issues. PMDA thus concluded that there were no obstacles to conducting its review based on the application documents submitted.

3. Overall Evaluation

Based on the above review, PMDA has concluded that idarucizumab may be approved, with the following conditions, after modifying the proposed indication and the proposed dosage and administration as shown below. Since the product is a drug with a new active ingredient, the re-examination period is 8 years. Neither the drug product nor its drug substance is classified as a poisonous drug or a powerful drug. The product is classified as a biological product.

Indication

Reversal of the anticoagulant effects of dabigatran in the following situations:

- Occurrence of life-threatening bleeding or uncontrolled bleeding
- Emergency surgery or urgent procedures in which significant bleeding is anticipated

Dosage and Administration

The usual adult dose is 5 g of Idarucizumab (Genetical Recombination) (2 vials of 2.5 g/50 mL each), administered intravenously as infusions over 5 to 10 minutes per vial or as a bolus injection.

Conditions of Approval

The applicant is required to:

1. Develop and appropriately implement a risk management plan.
2. Conduct a use-results survey encompassing all patients treated with the product. Because of the very limited

experience in Japanese patients, the survey should be conducted in all patients treated with the product until data are collected on a certain number of patients in order to identify the characteristics of the treated patients, collect data on the safety and efficacy of the product without delay, and take necessary measures to ensure the proper use of the drug product.