Report on the Deliberation Results

March 10, 2015
Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau
Ministry of Health, Labour and Welfare

[Brand name]	Cyramza Injection 100 mg Cyramza Injection 500 mg
[Non-proprietary name]	Ramucirumab (Genetical Recombination) (JAN*)
[Applicant]	Eli Lilly Japan K.K.
[Date of application]	July 25, 2014

[Results of deliberation]
In the meeting held on March 5, 2015, the Second 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. The drug substance and the drug product are both classified as powerful drugs, and the product is classified as a biological product.

[Conditions for approval]
The applicant is required to design and appropriately implement a risk management plan.

**Japanese Accepted Name (modified INN)*

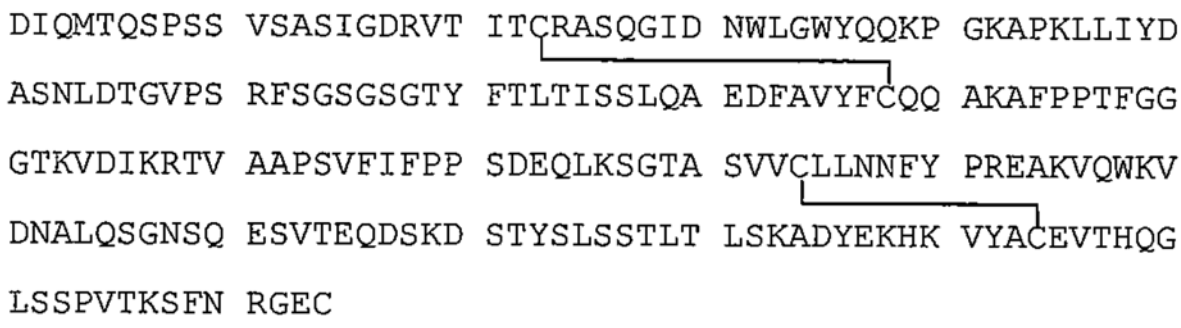
Review Report

February 16, 2015
Pharmaceuticals and Medical Devices Agency

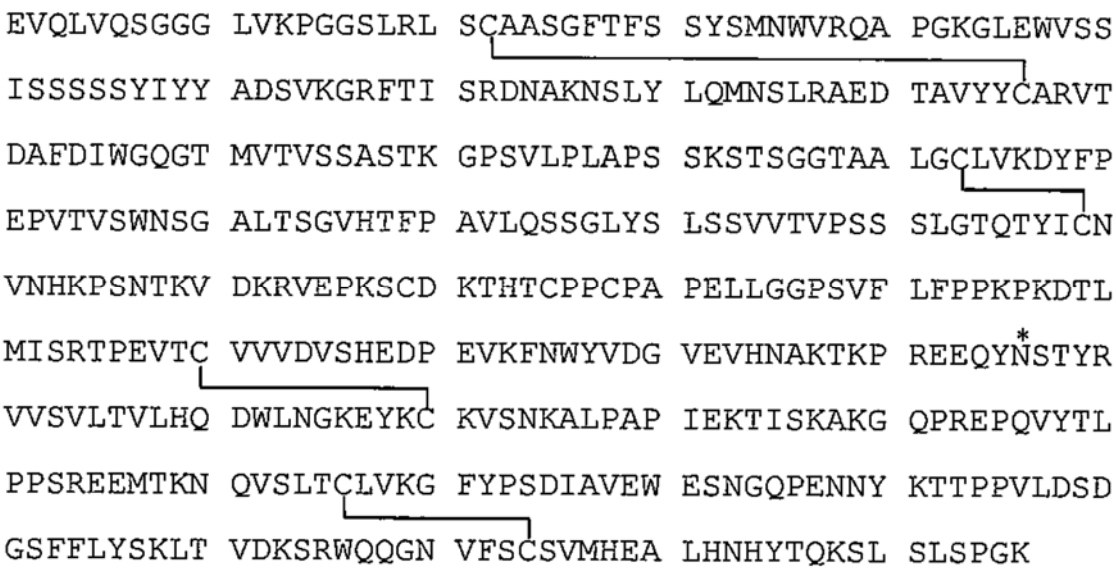
The results of a regulatory review conducted by the Pharmaceuticals and Medical Devices Agency on the following pharmaceutical product submitted for registration are as follows.

[Brand name]	Cyramza Injection 100 mg Cyramza Injection 500 mg
[Non-proprietary name]	Ramucirumab (Genetical Recombination)
[Name of applicant]	Eli Lilly Japan K.K.
[Date of application]	July 25, 2014
[Dosage form/Strength]	Injection: Each 10 mL vial contains 100 mg of Ramucirumab (Genetical Recombination). Each 50 mL vial contains 500 mg of Ramucirumab (Genetical Recombination).
[Application classification]	Prescription drug (1) Drug with a new active ingredient
[Definition]	Ramucirumab is a recombinant human IgG1 monoclonal antibody against the extracellular domain of the human vascular endothelial growth factor receptor-2. Ramucirumab is produced in mouse myeloma (NS0) cells. Ramucirumab is a glycoprotein (molecular weight: ca. 147,000) composed of 2 H-chains (γ1-chain) consisting of 446 amino acid residues each and 2 L-chains (κ-chain) consisting of 214 amino acid residues each.

[Chemical structure]



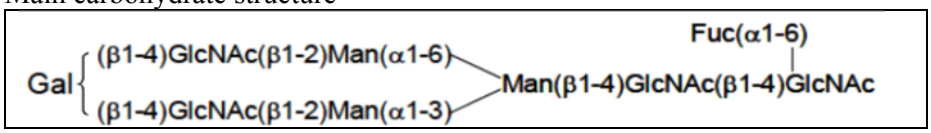
Light chain



Heavy chain

Intramolecular disulfide bonds:	solid line
Intermolecular disulfide bonds:	C214 in light chain - C219 in heavy chain, C225 in heavy chain - C225 in heavy chain, C228 in heavy chain - C228 in heavy chain
Partial processing:	K446 in heavy chain
Glycosylation site:	N296 in heavy chain

Main carbohydrate structure



Gal, Galactose; GlcNAc, N-acetylglucosamine; Man, D-mannose; Fuc, L-fucose

Molecular formula:	$C_{6376}H_{9886}N_{1702}O_{1996}S_{46}$ (protein portion)
Molecular weight:	approx. 147,000

[Items warranting special mention]	Priority Review (Notification No.1010-2 from the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW, dated October 10, 2014)
[Reviewing office]	Office of New Drug V

Review Results

February 16, 2015

[Brand name]	Cyramza Injection 100 mg Cyramza Injection 500 mg
[Non-proprietary name]	Ramucirumab (Genetical Recombination)
[Name of applicant]	Eli Lilly Japan K.K.
[Date of application]	July 25, 2014

[Results of review]
Based on the submitted data, the Pharmaceuticals and Medical Devices Agency (PMDA) has concluded that the efficacy of the product in the treatment of patients with unresectable advanced/recurrent gastric cancer has been demonstrated and its safety is acceptable in view of its observed benefits. Further investigations are needed during the post-marketing surveillance, etc. regarding hypertension, proteinuria, haemorrhage, infusion-related reaction, thromboembolism, gastrointestinal perforation, congestive cardiac failure, neutropenia/leukopenia, posterior reversible encephalopathy syndrome, fistula, disturbance of wound healing, and liver disorder.

As a result of its regulatory review, PMDA has concluded that the product may be approved for the indication and dosage and administration as shown below, with the following conditions.

[Indication]
Unresectable advanced/recurrent gastric cancer

[Dosage and administration]
The usual adult dosage is 8 mg/kg (body weight) of Ramucirumab (Genetical Recombination) given as an intravenous infusion over approximately 60 minutes every 2 weeks. The dose may be adjusted according to the conditions of the patient.

[Conditions for approval]
The applicant is required to design and appropriately implement a risk management plan.

Review Report (1)

December 26, 2014

I. Product Submitted for Registration

[Brand name]	Cyramza Injection 100 mg Cyramza Injection 500 mg
[Non-proprietary name]	Ramucirumab (Genetical Recombination)
[Name of applicant]	Eli Lilly Japan K.K.
[Date of application]	July 25, 2014
[Dosage form/Strength]	Injection: Each 10 mL vial contains 100 mg of Ramucirumab (Genetical Recombination). Each 50 mL vial contains 500 mg of Ramucirumab (Genetical Recombination).
[Proposed indication]	Unresectable advanced/recurrent gastric cancer
[Proposed dosage and administration]	In combination with paclitaxel, the usual adult dosage is 8 mg/kg (body weight) of Ramucirumab (Genetical Recombination) given as an intravenous infusion over approximately 60 minutes every 2 weeks. The dose may be adjusted according to the condition of the patient.

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

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

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

1.(1) Drug overview

Ramucirumab (Genetical Recombination) (hereinafter referred to as ramucirumab) is a human immunoglobulin (Ig) G1 monoclonal antibody against human vascular endothelial growth factor receptor (VEGFR)-2, and was discovered by ImClone Systems. Ramucirumab, by binding to VEGFR-2, inhibits the binding of the vascular endothelial growth factor (VEGF) to VEGFR-2, thereby inhibiting the neovascularization mediated by VEGFR-2 signal pathway, leading to the inhibition of tumor growth.

1.(2) Development history, etc.

In a foreign country, a phase I study (Study I4T-IE-JVBM) involving patients with advanced solid cancer was initiated by ImClone Systems in [redacted] 20[redacted]. Subsequently, Eli Lilly and Company (US) obtained the right to develop ramucirumab in 20[redacted]. For the clinical development for gastric cancer, a phase III study (Study I4T-IE-JVBD [REGARD study]) was started in October 2009 involving patients with metastatic adenocarcinoma of the stomach or gastroesophageal junction, and another phase III study (Study I4T-IE-JVBE [RAINBOW study]) was initiated in December 2010 involving patients with metastatic adenocarcinoma of the stomach or gastroesophageal junction.

In August 2013, a regulatory application for ramucirumab including the pivotal data from the REGARD study was submitted in the US and EU. In the US, ramucirumab was approved in April 2014 for the following indication: "CYRAMZA as a single-agent is indicated for the treatment of patients with advanced or metastatic, gastric or gastro-esophageal junction adenocarcinoma with disease progression on or after prior fluoropyrimidine- or platinum-containing chemotherapy." Subsequently, regulatory application for ramucirumab combination therapy, with the pivotal data from the RAINBOW study, was submitted in the US and EU in May and April, respectively, in 2014. As a result, the indication in the US was changed in November 2014 as follows: CYRAMZA as a single agent, or in combination with paclitaxel, is indicated for the treatment of patients with advanced or metastatic, gastric or gastro-esophageal junction adenocarcinoma with disease progression on or after prior fluoropyrimidine-or platinum-containing chemotherapy."

As of November 2014, ramucirumab has been approved only in the US with the indication for the treatment of gastric cancer.

In Japan, a phase I study (Study I4T-IE-JVBI) in patients with advanced solid cancer was initiated by the applicant in September 2009, and another phase I study (Study I4T-IE-JVBW) involving patients with metastatic adenocarcinoma of the stomach or gastroesophageal junction was also initiated in [redacted] 2010. Subsequently, Japan participated in the RAINBOW study from [redacted] 20[redacted], and now a marketing application for ramucirumab including the pivotal data from the REGARD and RAINBOW studies has been submitted in Japan.

The Japanese brand name proposed at the time of submission was "Cyramza Injection 100 mg, Cyramza Injection 500 mg" but was changed to "Cyramza Injection 100 mg (for intravenous infusion), Cyramza Injection 500 mg (for intravenous infusion)" from the clinical safety viewpoint.

2. Data relating to quality

2.A Summary of the submitted data

2.A.(1) Drug substance

2.A.(1).1) Preparation and control of cell substrate

Among Fab regions that were isolated from the library constructed from healthy human-derived B lymphocytes and exhibit activity against the human vascular endothelial growth factor receptor (VEGFR)-2, a highly affinitive Fab region was selected by codon shuffling. The variable regions of the heavy chain (H chain) and the light chain (L chain) of this Fab region were introduced into expression vectors containing the constant regions of both H and L chains, then the produced 2 types of expression vectors were combined to make a gene expression construct for Ramucirumab (Genetical Recombination) (hereinafter referred to as ramucirumab). The gene expression construct was introduced into mouse bone marrow-derived NS0 cell lines and, among cell lines thus obtained, a clone that is highly productive of anti-VEGFR-2 antibody was selected. A master cell bank (MCB) and a working cell bank (WCB) were prepared using this clone as the original cell line.

The MCB, WCB, and cells at the limit of *in vitro* cell age (CAL) were subjected to characterization (cDNA sequence analysis, Southern blot analysis, determination of the copy number of introduced gene by quantitative PCR), which confirmed the genetic stability throughout the manufacturing period. Also, the MCB, WCB, and CAL were subjected to the following tests: (a) for the MCB, sterility testing, bacteriostatic testing, mycoplasma testing, *in vitro* virus testing, *in vivo* virus testing, extended XC plaque assay, extended S^+L^- focus assay, test for reverse transcriptase activity, test for mouse antibody production, electron microscopy, isozyme analysis, *in vitro* bovine virus testing, *in vitro* porcine virus testing, and *in vitro* bovine polyomavirus testing; (b) for the WCB, sterility testing, bacteriostatic testing, mycoplasma testing, mycoplasmastasis testing, *in vitro* virus testing, *in vivo* latent virus testing, isozyme analysis, and *in vitro* bovine virus testing; and (c) for the CAL, sterility testing, mycoplasma testing, mycoplasmastasis testing, *in vitro* virus testing, *in vivo* latent virus testing, extended XC plaque assay, extended S^+L^- focus assay, test for reverse transcriptase activity, test for mouse antibody production, electron microscopy, mouse retrovirus testing, mouse minute virus testing, isozyme analysis, *in vitro* bovine adventitious virus testing, and *in vitro* porcine virus testing. As a result, neither adventitious virus nor non-viral infectious agents were detected by the tests performed, except for endogenous retroviruses and retrovirus-like particles that are commonly observed in rodent-derived cell lines.

The MCB and WCB are stored in the gas phase of liquid nitrogen or at a temperature below [redacted]°C. There is no plan for generating MCB, but WCB is to be generated as appropriate.

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

[redacted]. The drug substance obtained is stored at 2°C to 8°C in a

multi-layer container.* In the development of ramucirumab, a quality-by-design approach was used mainly to perform the following studies, based on which the control strategy was constructed.

- [redacted].
- Identification of critical process parameters (CPPs) and critical in-process control parameters based on risk assessment, etc.
- Identification of the proven acceptable range of CPPs based on the design of experiments.

[redacted].

The manufacturing process of the drug substance is validated on a commercial scale.

* [redacted].

2.A.(1).3) Safety evaluation of adventitious infective agents

Bovine serum albumin (BSA) is contained in the media used for the preparation of the MCB and WCB and for each culture process. BSA in the medium used for the MCB preparation was derived from cows produced in the US (shipped in [redacted]) and BSA in the media for WCB preparation and for culture process is derived from cows produced in New Zealand.

A purity test was performed on MCB, WCB, and CAL [see "2.A.(1).1) Preparation and control of cell substrate"]. [redacted].

In order to evaluate the viral clearance capacity of the manufacturing process, viral clearance studies were performed using model viruses; the study results confirmed that the manufacturing process has a certain level of viral clearance capacity (the table below).

Results of viral clearance studies

Manufacturing process	Viral clearance index (log_{10})			
	Xenotropic murine leukemia virus	Mouse minute virus	Pseudorabies virus	Bovine diarrhea virus
[redacted]				
[redacted]				
[redacted]				
Viral nanofiltration				
Total viral clearance index	≥20.47	≥17.62	≥22.48	≥8.54

[redacted]

2.A.(1).4) Manufacturing process development (comparability)

The major changes made in the manufacturing process during the drug substance development are as follows (each manufacturing process is referred to as Process A, B, C0, C1, and C2 [manufacturing process for application]):

- [redacted].
- [redacted].
- [redacted].
- [redacted].

With each change of the manufacturing process, the comparability of the quality attributes was evaluated, and the results confirmed the comparability of the drug substance before and after each change.

2.A.(1).5) Characterization

(a) Structure and composition

Primary structure

- It was confirmed that the drug substance has an amino acid sequence identical to that estimated from the cDNA sequence, based on the amino acid analysis, amino-terminal (N-terminal) amino acid sequence analysis by Edman degradation, carboxyl-terminal (C-terminal) amino acid sequence analysis by lysine-C (Lys-C) digestion followed by liquid chromatography-mass spectrometry (LC-MS), and peptide mapping after digestion with trypsin, endoproteinase aspartate-N, and chymotrypsin, by LC-MS and tandem mass spectrometry (MS/MS).

- The results of the N- and C-terminal amino acid sequence analysis showed cyclization of N-terminal glutamic acid residue in the H chains to pyroglutamic acid and heterogeneity due to the deletion of C-terminal Lys residue in the H chains.

Higher order structure

- Comparison of LC-MS pattern and peptide map after Lys-C digestion under reducing and non-reducing conditions, together with LC-MS/MS under reducing and non-reducing conditions, showed that there were 2 disulfide bonds within the L chain and 4 disulfide bonds within the H chain, and 2 disulfide bonds between the H chains and 1 disulfide bond between an L chain and an H chain.

- The analysis of the free sulfhydryl group by specific fluorescent labeling showed that there were [redacted] moles of free sulfhydryl groups per mole of ramucirumab.

- Far-ultraviolet circular dichroism analysis showed a strong absorbance at [redacted] nm, a characteristic feature of β-sheet structure.

- Fourier transform infrared spectroscopy showed a strong absorbance at [redacted] cm^{-1}, a characteristic feature of β-sheet structure.

- Near ultraviolet circular dichroism analysis showed circular dichroic spectra derived from phenylalanine residue in the range from [redacted] to [redacted] nm, derived from tyrosine residue in the range from [redacted] to [redacted] nm, and derived from tryptophan residue in the range from [redacted] to [redacted] nm.

- Fluorescence spectroscopy showed a maximum absorbance at around [redacted] nm, a characteristic feature of folded protein.

- Dynamic light scattering showed a hydrodynamic radius of [redacted] nm, a characteristic feature of folded antibody molecules.

- Differential scanning calorimetry showed transition temperatures of [redacted]°C, [redacted]°C, and [redacted]°C and heat quantity (enthalpy) of [redacted] kcal/mol.

Carbohydrate structure

- [redacted].

(b) Physicochemical properties

Molecular weight

- The molecular weight of PNGase F-treated ramucirumab, determined by LC-MS, was almost identical with the theoretical molecular weight of the protein moiety of ramucirumab.

Electrophoresis

- Isoelectric focusing gel electrophoresis detected [redacted] bands within a pI range from [redacted] to [redacted]. [redacted]. Measurement of the titer of each band showed that all of them had similar biological activity to one another.
- [redacted].
- The drug substance stored for [redacted] months at 38°C to 42°C was subjected to SDS-polyacrylamide gel electrophoresis (SDS-PAGE) under reducing and non-reducing conditions, to N-terminal amino acid sequence analysis, and to MALDI-TOF/MS. The results showed fragments of [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], and [redacted] kDa.

Liquid chromatography

- [redacted].
- [redacted].

Other

- The absorption coefficient (280 nm) was determined to be [redacted] mL/(mg·cm).

(c) Biological properties

- Analysis of the kinetics of VEGFR-2 binding, measured by surface plasmon resonance (SPR), showed an equilibrium dissociation constant of [redacted] pmol/L.
- [redacted].
- [redacted].
- [redacted].

(d) Product-related substances

C-terminal Lys variant of the H chain was handled as the product-related substance.

(e) Impurities

Process-related impurities

[redacted].

Product-related impurities

[redacted].

2.A.(1).6) Control of drug substance

[redacted]. [See "2.B.(1) Peptide mapping"].

2.A.(1).7) Stability of drug substance

The main stability studies for the drug substance are as shown in the table below.

Outline of main stability studies for drug substance

	Manufacturing process	Number of batches	Storage conditions	Study period	Storage configuration
Long-term testing	C1	5	5 ± 3°C	24 months	Multilayered container
	C2	10		[redacted] batches: [redacted] months[*1] [redacted] batches: [redacted] months[*1]	
Accelerated testing	C1	5	[redacted] ± [redacted]°C	[redacted] months	[redacted]
	C2	9		[redacted] batches: [redacted] months [redacted] batches: [redacted] months[*1]	[redacted]
Stress testing	C1	3	[redacted] ± [redacted]°C	[redacted] months	[redacted]
	C2	5			
Photostability testing	C1	1	Overall illuminance of ≥1.2 million lux·h, integrated near ultraviolet energy of ≥200 W·h/m^2	-	Multilayered container[*2]

[*1] The stability study is ongoing. [*2] The control was covered with a sheet of aluminum foil. -, Not applicable.

In the long-term testing, no significant change in the quality attributes was observed throughout the study period in the drug substance manufactured by either Process C1 or C2.

[redacted].

[redacted].

The drug substance was unstable to light in the photostability testing.

Based on the above, a shelf life of 24 months has been proposed for the drug substance when stored at 2°C to 8°C with protection from light in a multilayered container.*

* [redacted].

2.A.(2) Drug product

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

The drug product is an injectable formulation containing 100 mg of ramucirumab in one 10-mL vial or 500 mg of ramucirumab in one 50-mL vial. The drug product contains L-histidine, L-histidine hydrochloride hydrate, glycine, sodium chloride, and polysorbate 80 as excipients. The primary packaging is a glass vial with a rubber cap, and the secondary packaging is a paperboard box.

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

[redacted].

The manufacturing process of the drug product has been validated on a commercial scale.

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

During the drug product development, excipients were changed for better stability.

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

[redacted].

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

The main stability studies for the drug product are as shown in the table below.

Outline of main stability studies for drug product

	Content	Manufacturing process of the drug substance	Number of batches	Storage conditions	Study period	Storage configuration
Long-term testing	100 mg	C1	4	5 ± 3°C, upright and inverted	24 months[*1]	Glass vial
		C2	2		[redacted] months	
	500 mg	C1	4		24 months[*1]	
		C2	1		[redacted] months	
Accelerated testing	100 mg	C1	4	[redacted] ± [redacted]°C, upright	[redacted] months	
		C2	2		[redacted] months	
	500 mg	C1	4		[redacted] months	
		C2	1		[redacted] months	
Photostability testing	100 mg	C1	1	Overall illuminance of ≥1.2 million lux·h, integrated near ultraviolet energy of ≥200 W·h/m^2	-	Unlabeled glass vial,[*2] labeled glass vial,[*2] and secondarily packaged labeled glass vial[*2]
	500 mg	C1	1			

[*1] The stability study is ongoing. [*2] The control is covered with a sheet of aluminum foil. –, Not applicable.

The long-term testing did not show any significant change in the quality attributes throughout the study period.

[redacted].

[redacted].

Based on the above, a shelf life of 24 months has been proposed for the 100 mg formulation and 500 mg formulation when stored at 2°C to 8°C with protection from light in glass vials. The long-term testing will be continued up to [redacted] months.

2.A.(3) Reference material

The primary reference material is prepared from the drug substance and is stored at [redacted]°C to [redacted]°C.

[redacted]

[redacted]

[redacted]

2.B Outline of the review by PMDA

Based on the submitted data and on the results of the following reviews, PMDA concluded that the quality of the drug substance and the drug product was controlled in an appropriate manner.

2.B.(1) Peptide mapping

Peptide mapping allows the detection of changes in the primary structure, post-translational modification, etc. and is useful for the confirmation of the consistency in the structure of ramucirumab. Therefore, PMDA requested the applicant to include peptide mapping in the specifications for the drug substance. The applicant agreed to include peptide mapping in the specifications for the drug substance, and PMDA accepted the response of the applicant.

2.B.(2) New excipient

The drug product contains L-histidine hydrochloride hydrate in an amount exceeding the level that has been used for past intravenous injections. However, PMDA concluded that there is no particular problem in using the excipient (L-histidine hydrochloride hydrate) in the drug product, based on the following reviews.

2.B.(2).1) Specifications and stability

PMDA confirmed that the quality of L-histidine hydrochloride hydrate meets the requirements of the Japanese Pharmacopoeia and that there is no problem in the specifications or stability.

2.B.(2).2) Safety

Based on the review of the submitted data, PMDA concluded that drug product at the proposed dose is unlikely to cause any safety problem.

3. Non-clinical data

3.(i) Summary of pharmacology studies

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

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

3.(i).A.(1).1) Binding characteristics to human vascular endothelial growth factor receptor-2 (Reports 1001-[redacted], PT-1202, IMC01, bTDR275, IMC04, *J Biol Chem.* 2003;278:43496-507 [Reference data], *Leukemia.* 2003;17:604-11 [Reference data], *Structure.* 2011;19:1097-107 [Reference data])

Binding characteristics of Ramucirumab (Genetical Recombination) (hereinafter referred to as ramucirumab) to human vascular endothelial growth factor receptor (VEGFR)-2 recombinant protein was investigated using surface plasmon resonance (SPR) in 4 independent studies. Dissociation constants (K_D) of ramucirumab were 0.01 (n = 1), 0.05 ± 0.01 (n $\geq$ 3), 0.05 ± 0.01 (n $\geq$ 3), and 3.5 ± 0.1 nmol/L (n = 3) in the respective studies. K_D values of the complex of ramucirumab with VEGFR-2 of cynomolgus monkeys, rabbits, and dogs were 2.7 ± 0.1, 9.1 ± 0.2, and 370 ± 50 nmol/L, respectively (n = 3 for each animal). Ramucirumab did not bind to mouse VEGFR-2. In a study using enzyme-linked immunosorbent assay (ELISA), EC_{50} of ramucirumab to human VEGFR-2 was 0.16 nmol/L (n = 1).

The inhibitory effect of ramucirumab against the binding between human vascular endothelial growth factor (VEGF)-A and human VEGFR-2 was investigated in 3 independent studies using ELISA, and IC_{50} values were 0.8, 0.8, and 2.3 nmol/L in the respective studies. IC_{50} values of ramucirumab against the binding of human VEGF-C and VEGF-D with VEGFR-2 were 0.7 and 0.3 nmol/L, respectively.

Affinity of ramucirumab (0.04-25 μg/mL) to 16 different human growth factor receptors, including VEGFR-1 and VEGFR-3, was investigated using ELISA. The results showed that ramucirumab binds only to VEGFR-2.

The epitope for ramucirumab was investigated by X-ray crystallography. Ramucirumab was found to bind to the immunoglobulin-like extracellular domain 3 (Ig D3) of human VEGFR-2. The amino acid sequence of this domain was identical with the sequence of cynomolgus monkey VEGFR-2, except 1 amino acid not included in the epitope.

3.(i).A.(1).2) Inhibition of VEGFR-2 activation (Reports *J Biol Chem.* 2003;278:43496-507 [Reference data], *Biochem Biophys Res Commun.* 2006;345:438-45 [Reference data])

Using human umbilical venous endothelial cells (HUVEC) and porcine aortic endothelial cells (PAE) forced to express human VEGFR-2 (PAE-KDR cell line, VEGFR-2 is also called KDR), the inhibitory effect of ramucirumab against VEGF-A-stimulated VEGFR-2 activation was investigated by immunoblotting. VEGF-A-stimulated autophosphorylation of VEGFR-2 was inhibited by ramucirumab.

The inhibitory effect of the Fab fragments of ramucirumab against VEGF-A-stimulated VEGFR-2 activation was assessed based on the increase in calcium concentration in PAE-KDR cells stimulated by VEGF-A. IC_{50} was 7.3 nmol/L.

3.(i).A.(1).3) Inhibition of VEGF-stimulated cell migration (Report *Leukemia.* 2003;17:604-11 [Reference data])

Human leukemia cell-derived HL60 and HEL cell lines expressing VEGFR-2 and human leukemia cell-derived U937 cell line expressing VEGFR-1 were used to investigate the inhibitory effect of ramucirumab against VEGF-A-stimulated cell migration. Ramucirumab inhibited the migration of HL60 and HEL cell lines but did not inhibit the migration of U937 cell lines. The applicant explained that the results suggest that ramucirumab selectively inhibits the VEGFR-2-mediated effect.

3.(i).A.(1).4) Effect on VEGFR-2 internalization (Report IMC02)

The effect of ramucirumab on the intracellular transfer (internalization) of VEGFR-2 was investigated using PAE-KDR cell line, by measuring the amount of VEGFR-2 remaining on the cell surface by flow cytometry. Ramucirumab reduced the amount of VEGFR-2 on the cell surface. Based on the results, the applicant explained that ramucirumab may also inhibit the function of VEGFR-2 by inducing the internalization of VEGFR-2.

3.(i).A.(1).5) Inhibition of neovascularization (Report IMC03, *Leukemia.* 2003;17:604-11 [Reference data])

(a) *In vitro*

The growth-inhibitory effect of ramucirumab against HUVEC cells was investigated using ^{3}H-labeled thymidine. EC_{50} of ramucirumab was 0.7 nmol/L.

(b) *In vivo*

To investigate the inhibitory effect of ramucirumab against neovascularization, a matrigel containing a mixture of human vascular endothelial precursor cell-derived ECFC cell line and human adipose-derived stem cells was subcutaneously transplanted to athymic mice (nude mice). Intraperitoneal administration of ramucirumab 5 hours before the transplantation of the matrigel inhibited the growth of capillaries in the matrigel as compared with the control (human immunoglobulin (Ig) G4). The applicant explained that the result suggests the inhibitory effect of ramucirumab against neovascularization.

3.(i).A.(1).6) Investigations using anti-mouse VEGFR-2 antibody

Because of the low affinity of ramucirumab to mouse VEGFR-2 [see "3.(i).A.(1).1) Binding characteristics to human vascular endothelial growth factor receptor-2"], anti-mouse VEGFR-2 antibody (DC101) was used in *in vivo* studies in mice.

(a) Binding characteristics to mouse VEGFR-2 (Report 1001-[redacted], *J Natl Cancer Inst.* 2005;97:14-21 [Reference data])

The binding activity of DC101 to mouse VEGFR-2 was investigated by SPR and by ELISA. K_D and EC_{50} were 0.11 and 0.28 nmol/L, respectively. The inhibitory effect of DC101 against the binding of VEGF-A and VEGF-C with mouse VEGFR-2 was investigated by ELISA. IC_{50} values were 0.3 and 0.4 nmol/L, respectively.

(b) Inhibitory effect against VEGFR-2 activation (Reports *Mol Cell Differ.* 1995;3:91-109 [Reference data], *Cancer Cell.* 2012;21:181-95 [Reference data])

Mouse fibroblast-derived NIH3T3 cell line was forced to express mouse *VEGFR-2* gene to investigate the effect of DC101 on VEGF-A-stimulated VEGFR-2 activation. DC101 inhibited VEGF-A-stimulated autophosphorylation of VEGFR-2.

Collecting lymphatic endothelial cells were isolated from NOD/SCID mice* subcutaneously transplanted with human fetal liver-derived 293EBNA cell line that was forced to express VEGF-D. The isolated cells were used to investigate the effect of DC101 on VEGF-D-induced VEGFR-2 activation. Pretreatment with DC101 suppressed VEGF-D-stimulated autophosphorylation of VEGFR-2.

* Mice obtained by mating of a mouse with severe combined immunodeficiency and a non-obese diabetic mouse

(c) Tumor growth inhibitory effect (Reports 5538-[redacted], 5569-[redacted], 5634-[redacted], 2212-[redacted], *Anticancer Res.* 2009;29:1999-2007 [Reference data], *Cancer Res.* 2006;66:3639-48 [Reference data], *Clin Cancer Res.* 2002;8:2714-24 [Reference data], *Clin Cancer Res.* 2000;6:2635-43 [Reference data])

i) Gastric cancer-derived tumor tissue sections and cell lines

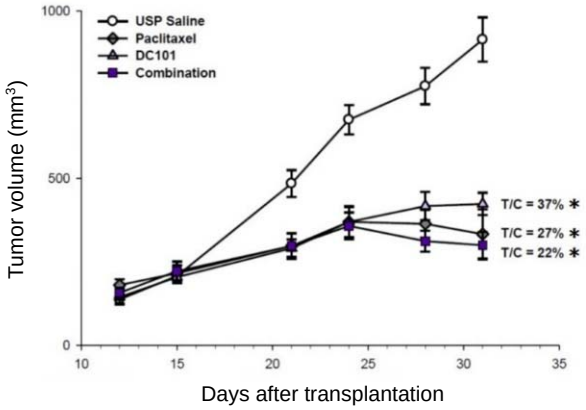
The tumor growth inhibitory effect of DC101 was investigated in nude mice subcutaneously transplanted with 17 different types of tumor tissue sections derived from human gastric cancer patients. Starting from the time when tumor volume reached approximately 150 mm^3 (range, 132-193 mm^3), DC101 (40 mg/kg per dose) was administered intraperitoneally 3 times weekly for a total of 10 times, and tumor volume was calculated. With 7 types of gastric cancer tissue sections, the rate of tumor volume increase in the DC101 group decreased to ≤50% of the rate in the control (human IgG) group. DC101 thus significantly inhibited tumor growth (the table below).

Tumor growth inhibitory effect of DC101 against tumor tissue sections derived from gastric cancer patients

Tumor tissue section	Percentage of tumor volume increase in the DC101 group compared with the control group	*P* value
GAM019	43	0.001
GAF087	17	<0.001
GAF055	37	0.026
GAM110	47	0.003
GAF114	34	0.016
GAM022	25	0.029
GAM139	49	0.005

n = 8; Level of significance, $P < 0.05$ (Dunnett test)

The tumor growth inhibitory effect of combination therapy with DC101 and paclitaxel (PTX) was investigated in nude mice subcutaneously transplanted with MKN-45 cell line derived from human gastric cancer. Starting from the time when the mean tumor volume reached 180 mm^3, DC101 (20 mg/kg twice weekly intraperitoneally) and PTX (20 mg/kg once weekly intravenously) were administered for 3 weeks, and the tumor volume was calculated. Tumor growth was significantly suppressed in the DC101 group and the PTX group as compared with the control (normal saline) group. However, the combination therapy did not show any synergistic effect (the figure below).



Tumor growth-inhibitory effect of DC101 and PTX in mice transplanted with MKN-45 cell line

Mean ± standard error. n = 7 (number of animals treated at the start of administration [because of the ulceration of the tumor, the study was discontinued in the following animals: the control group, 3 animals 31 days after transplantation; the DC101 group, 1 animal 31 days after transplantation; the PTX group, 1 animal 28 days after transplantation and 2 animals 31 days after transplantation; and the combination group, 2 animals 31 days after transplantation]). * $P < 0.001$ against the control (normal saline) group (two-way repeated measures analysis of variance)

ii) Cell lines derived from tumors other than gastric cancer

DC101 exhibited a tumor growth-inhibitory effect in studies conducted in mice transplanted with human pancreatic cancer-derived BxPC-3 cell line, human breast cancer-derived MDA-MB-231 and MDA-MB-435-LM2 cell lines, and human bladder carcinoma-derided 253J B-V cell line.

3.(i).A.(2) Safety pharmacology (Report 1163-110)

Safety pharmacology was investigated in a repeat-dose toxicity study in cynomolgus monkeys regarding the effect of ramucirumab (5, 16, 50 mg/kg) on clinical conditions, body temperature, blood pressure, and electrocardiogram [see "3.(iii).A.(2).2) Thirty nine-week repeat-dose intravenous toxicity study in monkeys"]. No effect of ramucirumab was observed during the study period.

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

Based on the submitted data and the following review, PMDA concluded that ramucirumab is expected to be effective for gastric cancer.

Mechanism of action of ramucirumab and its efficacy on gastric cancer

The applicant explained the mechanism of action of ramucirumab as follows:

Ramucirumab is an antibody against human VEGFR-2. Ramucirumab inhibits the binding of VEGF-A, VEGF-C, and VEGF-D to VEGFR-2 and thereby inhibits VEGFR-2 activation and the growth, migration, and survival of vascular endothelial cells mediated by VEGFR-2 signal pathway. This mechanism inhibits neovascularization in tumors, leading to tumor growth inhibition. In addition, the attenuated VEGFR-2 signal intensity due to internalized VEGFR-2 molecules that are induced by binding of ramucirumab may also contribute to the inhibition of neovascularization.

In the study in nude mice subcutaneously transplanted with tumor tissue sections (17 different types) derived from humans with gastric cancer, the administration of DC101, an anti-mouse VEGFR-2 antibody, exhibited statistically significant inhibitory effect on tumor growth in only 7 types of tumor tissue sections [see "3.(i).A.(1).6).(c) Tumor growth inhibitory effect"]. Therefore, PMDA asked the applicant to explain the reason(s) for failing to achieve the tumor growth inhibitory effect on the remaining 10 types of tumor tissue sections.

The applicant responded as follows:

Sensitivity to tumor growth inhibitory effect via VEGF signal pathway inhibition is reported to vary depending on the level of maturity of blood vessels (*Cancer Res.* 2011;71:7021-8, *Clin Cancer Res.* 2010;16:3887-900.). In fact, among the 17 types of tumor tissue sections studied, the blood vessels in tumor tissue sections highly sensitive to DC101 were immature, while the blood vessels in tumor tissue sections less sensitive to DC101 were mostly in the middle to late stage in maturity. Therefore, it is

inferred that the 10 types of tumor tissue sections were insensitive to DC101 because of mature blood vessels.

PMDA considers as follows:
The administration of anti-VEGFR-2 antibody (DC101) demonstrated an inhibitory effect against some of the tumor tissue sections and cell lines derived from patients with gastric cancer, suggesting possible efficacy of ramucirumab in patients with gastric cancer. However, DC101 did not inhibit the growth of some other tumor tissue sections derived from patients with gastric cancer. Considering the explanation of the applicant, data on the relationship between the maturity of blood vessels in tumor tissue and the sensitivity of the tumor tissue to ramucirumab may be critical for the estimation of the efficacy of ramucirumab and for the identification of suitable patients in clinical use. Therefore, relevant information must be further collected and available new findings should be provided to healthcare professionals in an appropriate manner.

3.(ii) Summary of pharmacokinetic studies

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

Pharmacokinetics (PK) of ramucirumab was investigated in cynomolgus monkeys.

3.(ii).A.(1) Analytical methods

3.(ii).A.(1).1) Assay of ramucirumab

Ramucirumab in monkey serum samples was measured by ELISA using solid-phase VEGFR-2 and horseradish peroxidase-labeled anti-human IgG1 antibody.

3.(ii).A.(1).2) Assay of anti-ramucirumab antibody

Anti-ramucirumab antibody in monkey serum samples was measured by (a) double antigen radiometric assay using solid-phase ramucirumab and ^{125}I-labeled ramucirumab and by (b) electrochemical luminescence assay using solid-phase streptavidin, biotin-labeled ramucirumab, and ruthenium-labeled ramucirumab.

3.(ii).A.(2) Absorption

Ramucirumab (4, 12, 40 mg/kg per dose) was administered intravenously on Days 1, 15, 22, and 29 to male and female cynomolgus monkeys, to investigate the serum ramucirumab concentration. PK parameters of ramucirumab following the first dose were as shown in the table below. No clear sex difference was observed in PK parameters of ramucirumab.

The expression of anti-ramucirumab antibody was able to be assessed 29 and 32 days after the start of administration in 3 males and 2 females in the 4 mg/kg group, 5 males and 2 females in the 12 mg/kg group, and 3 each of males and females in the 40 mg/kg group. Of these animals, 2 each of males and females in the 4 mg/kg group, 1 each of male and female in the 12 mg/kg group, and 1 female in the 40mg/kg group tested positive for anti-ramucirumab antibody. In the animals in the 4, 12, and 40 mg/kg groups tested positive for anti-ramucirumab antibody, the serum ramucirumab concentrations before the fourth dose were below the lower limit of quantitation (BLQ) of 1 μg/mL to 8 μg/mL in the 4 mg/kg group, BLQ in the 12 mg/kg group, and 586 μg/mL in the 40 mg/kg group. These serum ramucirumab concentrations were lower than those in animals tested negative for anti-ramucirumab antibody (27, 3-215, 397-644 μg/mL in the 4, 12, and 40 mg/kg groups, respectively).

PK parameters of ramucirumab
(male and female cynomolgus monkeys, single intravenous administration)

Dose (mg/kg)	Sex	n	C_{max} (μg/mL)	C_{168h} (μg/mL)	$AUC_{0-\infty}$ (μg·h/mL)	$t_{1/2}$ (h)	CL (mL/h/kg)	V_{ss} (mL/kg)
4	M	6	119 ± 19	2.8 ± 2.2	7255 ± 1820	54 ± 11	0.57 ± 0.17	45.9 ± 6.9
	F	3	127 ± 34	7.0 ± 7.2	7247 ± 3032	56 ± 25	0.58 ± 0.24	43.9 ± 8.2
12	M	6	422 ± 133	27 ± 14	32,907 ± 4432	99 ± 31	0.32 ± 0.05	50.5 ± 10.7
	F	3	337 ± 72	22 ± 17	28,782 ± 6208	94 ± 31	0.39 ± 0.10	56.0 ± 9.5
40	M	6	1522 ± 273	695 ± 878	168,800 ± 40,858	125 ± 62	0.22 ± 0.06	40.5 ± 6.0
	F	3	1337 ± 152	171 ± 31	127,956 ± 16,783	173 ± 18	0.24 ± 0.04	56.1 ± 7.7

Mean ± standard deviation (SD)

Ramucirumab (5, 16, 50 mg/kg) was administered intravenously at 1-week intervals for 39 weeks to male and female cynomolgus monkeys to investigate serum ramucirumab concentration (the table below).

$AUC_{0-\infty}$ of ramucirumab was higher in females than in males in the 16 mg/kg group while it was higher in males than in females in the 50 mg/kg group. The $AUC_{0-\infty}$ values showed significant variability with no consistent trend in the sex difference among the dose groups. Based on the result, the applicant explained that there was no clear sex difference in the PK of ramucirumab. In all 3 females of the 5 mg/kg group, serum ramucirumab concentrations were BLQ at all blood sampling time points on Week 39, precluding the calculation of PK parameters of ramucirumab on the week.

At the study completion (at Week 39), the expression of anti-ramucirumab antibody was able to be assessed in 1 male and 3 females of the 5 mg/kg group, 3 each of males and females of the 16 mg/kg group, and 3 each of males and females of the 50 mg/kg group. Of these animals, 3 females in the 5 mg/kg group and 1 male in the 16 mg/kg group were positive for anti-ramucirumab antibody. $AUC_{0-\infty}$ values of ramucirumab in anti-ramucirumab antibody-positive animals in the 5 and 16 mg/kg groups 39 weeks after the start of administration were NC* and 1140 (individual value), respectively, which were lower than $AUC_{0-\infty}$ values in antibody-negative animals (20,531 μg·h/mL [individual value] in the 5 mg/kg group and 37,208 ± 29,987 μg·h/mL [mean ± standard deviation (SD)] in the 16 mg/kg group).

* The serum ramucirumab concentrations were BLQ at all blood sampling time points, precluding the calculation of $AUC_{0-\infty}$.

PK parameters of ramucirumab
(male and female cynomolgus monkeys, 39-week repeated intravenous administration)

Time point of measurement	Dose (mg/kg)	Sex	n	C_{max} (μg/mL)	C_{168h} (μg/mL)	$AUC_{0-\infty}$ (μg·h/mL)	$t_{1/2}$ (h)	CL (mL/h/kg)	V_{ss} (mL/kg)
Week 1	5	M	3	107 ± 56	53 ± 32	13,892, 23,897*	65, 183*	0.36, 0.21*	33.9, 58.1*
		F	7	131 ± 32	19 ± 13	8444 ± 2372	55 ± 14	0.65 ± 0.26	45.5 ± 9.6
	16	M	3	523 ± 74	65 ± 51	41,429 ± 9783	75 ± 39	0.40 ± 0.11	40.4 ± 9.9
		F	6	417 ± 104	81 ± 33	40,236 ± 11,866	86 ± 22	0.42 ± 0.10	48.6 ± 8.6
	50	M	3	1284 ± 553	291 ± 147	134,000 ± 53,735	109 ± 13	0.42 ± 0.19	60.3 ± 17.5
		F	6	1656 ± 452	272 ± 69	133,150 ± 34,050	105 ± 49	0.40 ± 0.11	51.4 ± 12.6
Week 39	5	M	3	104 ± 107	19 ± 20	20,531, 302*	80, 5*	0.24, 16.6*	27.5, 79.7*
	16	M	3	334 ± 201	14 ± 18	13,466 ± 14,752	22 ± 20	5.4 ± 7.5	61.4 ± 29.5
		F	3	567 ± 94	103 ± 88	48,927 ± 34,349	72 ± 45	0.61 ± 0.63	33.8 ± 7.0
	50	M	3	2290 ± 1261	688 ± 656	308,857 ± 278,854	83 ± 63	0.91 ± 1.36	28.3 ± 14.5
		F	3	2005 ± 176	331 ± 82	159,067 ± 28,050	84 ± 9	0.32 ± 0.06	35.6 ± 0.71

Mean ± SD, * n = 2 (individual values)

$AUC_{0-\infty}$ of ramucirumab increased more than dose proportionally over the dose range (4-50 mg/kg) used in the above study in cynomolgus monkeys, suggesting the non-linear PK of ramucirumab.

The applicant explained the reason for the non-linearity as follows:
It is assumed that the elimination pathway mediated by the binding to VEGFR-2 is involved in the elimination of ramucirumab, and therefore the elimination pathway may become saturated at higher doses. It is also reported that an increased dose of the antibody induces immune tolerance to an antibody drug, possibly resulting in a decrease in the formation of anti-drug antibody (*Regul Toxicol Pharmacol.* 2009;54:164-82.). In fact, in the repeated dose studies in monkeys, greater numbers of animals in the low dose groups (4 and 5 mg/kg groups) tested positive for anti-ramucirumab antibody than animals in the high dose groups (40 and 50 mg/kg groups) as described above. Thus, it is considered that the dose increase of ramucirumab caused immune tolerance to ramucirumab, which resulted in a decrease in the formation of anti-ramucirumab antibody, leading to a decrease in total body clearance (CL) of ramucirumab and thereby to the non-linearity in PK of ramucirumab.

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

The applicant explained that tissue distribution of ramucirumab was not investigated because ramucirumab is considered to be distributed mainly within the circulating blood based on the following findings.

- In the repeated dose study in cynomolgus monkeys, V_{ss} of ramucirumab [see "3.(ii).A.(2) Absorption"] was similar to the plasma volume of monkeys (45 mL/kg) (*Pharm Res.* 1993;10:1093-5), suggesting minimal extravascular distribution of ramucirumab with only a limited tissue distribution.

- It is reported that VEGFR-2, the target molecule of ramucirumab, is expressed mainly in vascular endothelial and mesothelial cells (*Am J Surg Pathol.* 2012;36:629-39.). In a tissue cross-reactivity study using normal tissues of humans and cynomolgus monkeys, the cross-reactivity of ramucirumab was observed mainly in the vascular endothelium [see "3.(iii).A.(7).1) Tissue cross-reactivity study using normal tissues of humans and cynomolgus monkeys"].

A report suggests that human IgG1 is transferred through the placenta through the neonatal Fc receptor (FcRn) and that the placental transfer of human IgG1 increases during late pregnancy (*Birth Defects Research [Part B]*. 2013;98:459-85). The applicant explained that ramucirumab, a human monoclonal antibody of IgG1 subclass, may cross the placenta into the fetus, and that the placental transfer of ramucirumab may increase during late pregnancy.

3.(ii).A.(4) Metabolism and excretion

The applicant explained that because ramucirumab is a human monoclonal antibody of the IgG1 subclass, it is degraded to low-molecular weight peptides and amino acids and then reused in the body, and, therefore, studies on the metabolism and excretion of ramucirumab were omitted according to a guideline in "Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals" (PFSB/ELD Notification No. 0323-1 dated March 23, 2012).

Since that human IgG1 is reported to be excreted into milk (*J Mammary Gland Biol Neoplasia.* 1996;1:243-9, *J Hum Lact*. 2005;21:439-43, *Am J Gastroenterol*. 2009;104:228-33), the applicant explained that caution would be provided in the package insert that breast-feeding women who are prescribed with ramucirumab should be advised to stop breast feeding.

3.(ii).A.(5) Effect of changes in the manufacturing process of the drug substance on PK

During the development of the drug substance, the manufacturing process was changed 4 times [see "2.A.(1).4) Manufacturing process development (comparability)"]. In order to investigate the effect on PK of the change from Process B to C0, the drug substance (12 mg/kg) manufactured before or after the change in the manufacturing process was administered intravenously in a single dose to male and female cynomolgus monkeys, and serum ramucirumab concentration was measured (the table below). The ratios of the geometric means [90% confidence interval (CI)] of C_{max} and $AUC_{0-\infty}$ of the drug substance manufactured by Process C0 versus the drug substance manufactured by Process B were 1.03 [0.91, 1.17] and 1.02 [0.92, 1.13], respectively, showing no significant difference in PK parameters between before and after the change of the manufacturing process.

The anti-ramucirumab antibody expression was assessed 21 days after administration. Anti-ramucirumab antibody was detected in 15 of 20 animals treated with drug substance manufactured by Process B and 16 of 20 animals treated with drug substance manufactured by Process C0, showing no significant difference in the expression of anti-ramucirumab antibody between the 2 drug substances.

Comparison of PK parameters of ramucirumab following a single intravenous administration of the drug substance manufactured by Process B and C0

Manufacturing process of drug substance	Sex	C_{max} (μg/mL)	t_{max}* (h)	$AUC_{0-\infty}$ (μg·h/mL)	$t_{1/2}$ (h)	V_z (mL/kg)	CL (mL/h/kg)
B	M	403 ± 49.7	12 (6, 12)	35,202 ± 5492	78.1 ± 30.6	38.2 ± 13.6	0.35 ± 0.05
	F	375 ± 97.5	6 (1, 12)	33,957 ± 4590	77.8 ± 24.1	39.6 ± 11.3	0.36 ± 0.04
C0	M	428 ± 143	6 (6, 6)	39,437 ± 10,959	90.1 ± 30.0	39.7 ± 10.0	0.32 ± 0.08
	F	385 ± 64.0	6 (1, 6)	32,199 ± 5436	68.2 ± 14.7	37.4 ± 9.55	0.38 ± 0.06

Mean ± SD, n =10, * Median (range)

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

Based on the submitted data, PMDA concluded that the applicant's explanation of the absorption, distribution, metabolism, and excretion of ramucirumab is acceptable.

3.(iii) Summary of toxicology studies

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

In vivo toxicology studies of ramucirumab were conducted using cynomolgus monkeys because the tissue cross-reactivity of ramucirumab is similar between humans and cynomolgus monkeys [see "3.(iii).A.(7).1) Tissue cross-reactivity study using normal tissues of humans and cynomolgus monkeys"].

3.(iii).A.(1) Single-dose toxicity study

No single-dose toxicity study was conducted. Instead, acute toxicity of ramucirumab was investigated based on the results obtained after the first dose in 5- and 39-week repeat-dose toxicity studies in cynomolgus monkeys [see "3.(iii).A.(2).1) Five-week repeated intravenous toxicity study in monkeys" and "3.(iii).A.(2).2) Thirty nine-week repeated intravenous toxicity study in monkeys"] and in a wound healing study [see "3.(iii).A.(7).2) Wound healing study using a monkey linear incision model"]. No ramucirumab-related toxicity finding was observed at any doses (4-50 mg/kg).

Based on the above, the lethal dose was estimated to be >50 mg/kg.

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

3.(iii).A.(2).1) Five-week repeated intravenous toxicity study in monkeys

Ramucirumab (0 [vehicle; phosphate-buffered normal saline], 4, 12, 40 mg/kg) was administered intravenously for a total of 4 times on Days 1, 15, 22, and 29 to cynomolgus monkeys (n = 2-6/sex/group). Neither death nor treatment-related toxicity was observed during the administration period. The anti-ramucirumab antibody was detected more frequently in the 4 mg/kg group than in the 40 mg/kg group, which was considered not to affect the toxicity evaluation.
Accordingly, the no observed adverse effect level (NOAEL) was determined to be 40 mg/kg.

3.(iii).A.(2).2) Thirty nine-week repeated intravenous toxicity study in monkeys

Ramucirumab (0 [vehicle; phosphate-buffered normal saline], 5, 16, 50 mg/kg) was administered intravenously over 10 or 30 minutes once a week for a total of 39 times to cynomolgus monkeys (n = 3/sex/group). Animals that were subjected to the interim evaluation (n = 3 females/group) received ramucirumab for a total of 11 times, from Week 1 through 10 and in Week 12.

No ramucirumab-related death occurred during the administration period. The expression of anti-ramucirumab antibody was observed [see "3.(ii).A.(2) Absorption"] but was considered not to affect toxicity evaluation.

A pathological examination in the interim evaluation (Week 12) showed mild arteritis in the bilateral kidneys of the animals in the 5 mg/kg group. Also, laboratory tests at Week 26 and Week 39 and the pathological examination in Week 39 showed epiphyseal growth plate thickening and epiphyseal cartilage dysplasia in the femur in the ≥5 mg/kg groups; increased blood urea nitrogen, increased cholesterol, decreased serum albumin, proteinuria, pallor and weight gain of kidney, moderate multifocal to severe diffuse glomerulonephritis, and thymic atrophy in the ≥16 mg/kg groups; and increased serum

creatinine in the 50 mg/kg group. No ramucirumab-related toxicity was observed in the ophthalmological examination, immunophenotyping, or immunogenicity examination.

Based on the above toxicity findings observed in the kidney and bone, the applicant explained as follows:
Arteritis was observed only in 1 animal in the 5 mg/kg group, the lowest dose studied. Vasculitis is reported to develop spontaneously in monkeys (*Toxicol Pathol*. 2006;34:357-63, *Toxicol Pathol*. 2010;38:642-57.).

Therefore the toxicity findings were considered unrelated to ramucirumab. Glomerulonephritis is considered related to proteinuria observed in clinical studies [see "4.(iii).B.(3).4) Proteinuria"].

The toxicity findings in the bone in the use of ramucirumab is unlikely to pose a risk to adult patients because of their closed epiphyseal growth plates.

Accordingly, the NOAEL was determined to be <5 mg/kg. The exposure level ($AUC_{0-\infty}$) at 5 mg/kg was 10,416 μg·h/mL, which was 0.41 times the clinical exposure level.*

* In a Japanese phase II study (Study I4T-JE-JVCL), $AUC_{0-\infty}$ following a single administration of ramucirumab at 8 mg/kg was 25,600 μg·h/mL.

3.(iii).A.(3) Genotoxicity
Since ramucirumab is a biotechnology-derived drug, no genotoxicity study was conducted.

3.(iii).A.(4) Carcinogenicity
Since ramucirumab is a drug aimed at treating unresectable advanced/recurrent gastric cancer, no carcinogenicity study was conducted.

3.(iii).A.(5) Reproductive and developmental toxicity
Extensive knowledge on reproductive and developmental toxicity of ramucirumab is available from past studies with anti-VEGF or -VEGFR antibodies. Therefore reproductive and developmental toxicity studies on ramucirumab were not conducted. The applicant explained that the following published articles suggest possible risks of ramucirumab in clinical use that may affect embryo-fetal development, postnatal development, and the postnatal reproductive system.

Effects on embryo-fetal development
- VEGF and VEGFR are shown to play important roles in the development of embryonic vascular system (*Cell*. 1993;72:835-46, *Development*. 1993;118:489-98, *Proc Natl Acad Sci USA*. 1993;90:7533-7.).

- Homozygous mouse embryos with mutated VEGFR-2 died at an age of 8.5 to 9.5 days (*Nature*. 1995;376:62-6.).

- Mice with VEGF gene hetero-deficiency suffered embryonic death, delayed embryonic development, developmental disorder in forebrain, malformation of the heart, etc. (*Nature*. 1996;380:439-42.).

- Some knockout mice with $VEGF_{120}$ expression alone lacking $VEGF_{164}$ and $VEGF_{188}$ died immediately after birth. Surviving animals suffered impaired myocardial contractility, cardiac hypertrophy, and ischemic cardiomyopathy due to impaired angiogenesis and died within 2 weeks (*Nat Med*. 1999;5:495-502.).

- The administration of anti-VEGF antibody to female rhesus monkeys in the peri-implantation phase caused abortion in 4 of 13 pregnant animals on Gestation Days 18, 133, 135, and 139 (*Reproduction*. 2007;133:1199-211.).

- The administration of anti-VEGFR-2 antibody to female mice in the peri-implantation phase suppressed embryonic development associated with the impaired luteal function (*Endocrinology*. 2005;146:1301-11.).

Effects on postnatal development
- The administration of soluble chimeric VEGFR, a protein that inhibits VEGF, to neonatal mice caused almost complete growth arrest, clinical chemistry findings and histopathological changes suggesting hepatic and renal failure, destruction of alveolar architecture, and death (*Development*. 1999;126:1149-59.).

- The administration of anti-VEGF antibody to neonatal mice caused systemic edema, impaired vascular formation in the renal cortex, impaired nephron development, and abnormality in the glomeruli (*J Clin Invest.* 1997;99:2351-7.).

- The administration of anti-VEGFR-2 antibody to neonatal mice caused impaired alveolar development, alveolar haemorrhage, and increased mortality (*Am J Respir Cell Mol Biol.* 2005;32:420-7.).

Effects on female reproductive system
- VEGF is shown to be expressed in the corpus luteum and is an important factor for regulating angiogenesis in the corpus luteum (*Nat Med*. 1998;4:336-40). It is also important for the development and maintenance of the vascular function of the endometrium and placenta during pregnancy (*Reproduction*. 2001;122:85-90, *Reproduction*. 2009;138:895-902.).

- The administration of anti-VEGF antibody to female marmosets suppressed the growth of vascular endothelial cells in the corpus luteum within the ovaries during the early luteal phase and reduced plasma progesterone concentration that indicates the luteal function (*Endocrinology*. 2000;141:995-1000.).

- The administration of anti-VEGFR-2 antibody or anti-VEGF antibody to female rhesus monkeys caused changes in reproductive hormone levels and prolonged the follicular phase (*J Clin Endocrinol Metab*. 2001;86:768-72, *Endocrinology*. 2002;143:2496-502.).

3.(iii).A.(6) Local tolerance

No local tolerance study was conducted. In the 5- and 39-week repeat-dose toxicity studies in cynomolgus monkeys [see "3.(iii).A.(2).1) Five-week repeated intravenous toxicity study in monkeys" and "3.(iii).A.(2).2) Thirty nine-week repeated intravenous toxicity study in monkeys"], the observation and histopathological examination of the injection site did not show any ramucirumab-related toxicity.

3.(iii).A.(7) Other toxicity studies

3.(iii).A.(7).1) Tissue cross-reactivity study using normal tissues of humans and cynomolgus monkeys

Using frozen sections of normal tissues of humans and cynomolgus monkeys, cross-reactivity of ramucirumab was investigated by immunohistochemical staining using fluorescein isothiocyanate-labeled ramucirumab. The following results were obtained.

- In both human and monkey tissues, ramucirumab was shown to bind mainly to vascular endothelial cells and the retinal tissue, which are reported to be the expression sites of VEGFR-2 (*Cell*. 1993;72:835-46, *Br J Ophthalmol.* 1999;83:486-94.).

- Ramucirumab also bound to tissues of the lung (human), liver (human, monkey), cells of monocyte/macrophage lineage in the lymph node (human) and the spleen (monkey), cerebrospinal meninges, perineurium, alveolar epithelium and glandular epithelium of the salivary gland (human, monkey), pulmonary interstitium and residual epithelium of pituitary Rathke's pouch (human), and choroid plexus epithelium of the brain (monkey). Cross-reactivity was not expected in these cells, tissues, and organs.

The applicant explained that although ramucirumab was shown to bind specifically to the human pulmonary interstitium and retina, safety information obtained from clinical studies of ramucirumab does not suggest any risk of pulmonary or ocular toxicity.

3.(iii).A.(7).2) Wound healing study using a monkey linear incision model

Since ramucirumab inhibits angiogenesis mediated by VEGFR-2 signal pathway, a possible risk of impaired wound healing was a concern. Therefore, the effect of ramucirumab on wound healing was investigated using a cynomolgus monkey linear incision model.

Ramucirumab (0 [vehicle control; aqueous solution containing histidine 10 mmol/L, sodium chloride 75 mmol/L, glycine 133 mmol/L, and 0.01% polysorbate 80 (pH 6.0)], 5, 15, 50 mg/kg) was administered intravenously in a single dose to male cynomolgus monkeys (n = 4/group). Approximately 24 hours after administration (Day 2), a skin full-thickness incision was performed at 8 sites on the back of animals to prepare linear incision model animals. On Days 4, 8, 15, and 22, gross observation for erythema and swelling at the incision site was performed, the wound closure rate was calculated, and a histopathological examination[*1] was performed on the biopsy samples of the skin and subcutaneous tissue collected from 2 incision sites by full thickness punching. The results showed that ramucirumab had no effect on wound healing. The exposure level ($AUC_{0-\infty}$) following the administration of the maximum dose of 50 mg/kg was 180,678 μg·h/mL, which was 7.1 times the clinical exposure level.[*2] The applicant therefore determined that the effect of ramucirumab on wound healing could be evaluated by single-dose administration.

[*1] Evaluated by hematoxylin-eosin staining and by staining with antibody against CD31 expressed in the vascular endothelial cells, after Masson trichrome staining.

[*2] In a Japanese phase II study (Study I4T-JE-JVCL), $AUC_{0-\infty}$ following a single-dose administration of ramucirumab at 8 mg/kg was 25,600 μg·h/mL.

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

Based on the submitted data and the following review, PMDA considers that ramucirumab is acceptable for clinical use but inappropriate for use in pregnant women or women who may possibly be pregnant.

3.(iii).B.(1) Administration of ramucirumab to pregnant women or women who may possibly be pregnant

The proposed package insert submitted for application stated that ramucirumab should be used in pregnant women or women who may possibly be pregnant only if the expected therapeutic benefits outweigh the possible risks associated with treatment. PMDA asked the applicant to explain the reason for this restriction.

The applicant responded as follows:

Published articles suggest that the pharmacological action of ramucirumab may affect the embryo-fetal and postnatal development. However, considering the seriousness of the target disease, the product is clinically important because it has been demonstrated to significantly prolong the overall survival. Therefore, it is appropriate to offer patients opportunities to use ramucirumab when its therapeutic benefits are expected to outweigh the possible risks, as long as the possible negative effect of ramucirumab on embryo-fetal and postnatal development is warned in the package insert.

PMDA considers as follows:

Taking account of the following viewpoints, the use of ramucirumab in pregnant women or women who may possibly pregnant is inappropriate. Therefore, ramucirumab should be contraindicated in these patients.

- Ramucirumab binds to vascular endothelial cells of the human placenta [see "3.(iii).A.(7).1) Tissue cross-reactivity study using normal tissues of humans and cynomolgus monkeys"]. Also, IgG antibody is known to pass through the human placenta [see "3.(ii).A.(3) Distribution"]. In addition to these findings, the negative effects of VEGF and VEGFR inhibition on embryo-fetal and postnatal development [see "3.(iii).A.(5) Reproductive and developmental toxicity"] suggest the risks of fetal death, abortion, and teratogenicity, etc. associated with the administration of ramucirumab.

- Because no study was conducted on the toxicity of ramucirumab in embryo-fetal development, available information is not sufficient for the assessment of the expected therapeutic benefits and the possible risks of ramucirumab.

3.(iii).B.(2) Reversibility of toxicity

In response to the toxicity findings on the kidney and bone observed in the repeat-dose toxicity study [see "3.(iii).A.(2).2) Thirty nine-week repeated intravenous toxicity study in monkeys"], PMDA accepted the applicant's explanation that the possibility of bone toxicity occurring in patients treated with ramucirumab can be excluded. On the other hand, as reversibility of the ramucirumab-induced toxicity in the kidney was not investigated in toxicity studies of ramucirumab despite the possible toxicity in treated patients, PMDA asked the applicant to explain the reason for not having conducted a reversibility study.

The applicant responded as follows:

Since no toxicologically significant findings were observed in the 5-week repeat-dose toxicity study, the available information from published articles, etc. would allow scientific discussion on the reversibility of ramucirumab-induced renal toxicity. Therefore, reversibility was not investigated in the 39-week repeat-dose toxicity study of ramucirumab. Since renal toxicity caused by other drugs inhibiting VEGF-mediated angiogenesis was reversible (e.g., *Toxicol Pathol*. 2008;36:905-16), ramucirumab-induced renal toxicity should also be likely to be reversible.

PMDA considers as follows:

Given that the renal toxicity-related findings (proteinuria) observed in clinical studies were tolerable by monitoring and dose adjustment [see "4.(iii).B.(5).2) Dose adjustment, etc."], ramucirumab may be used in clinical practice. However, the mechanism of the development of glomerulonephritis following treatment with ramucirumab is unknown, and therefore the applicant's explanation that ramucirumab-induced renal toxicity also is likely to be reversible is unacceptable. Therefore, the package insert should highlight the fact that the reversibility of ramucirumab-induced renal toxicity was not investigated in toxicity studies and remains unknown. An additional pathological study should be conducted early to elucidate the mechanism of the development of ramucirumab-induced glomerulonephritis and thereby to investigate the reversibility of the renal toxicity.

If ramucirumab is developed for patients who are growing up, it is necessary to conduct a toxicity study including animals of the recovery group to investigate the reversibility of toxicity findings.

4. Clinical data

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

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

4.(i).A.(1) Analytical methods

4.(i).A.(1).1) Assay of ramucirumab

The amount of Ramucirumab (Genetical Recombination) (hereinafter referred to as ramucirumab) in human serum samples was measured by either of the following methods.

(a) Enzyme-linked immunosorbent assay (ELISA) using solid-phase human vascular endothelial growth factor receptor (VEGFR)-2 and horseradish peroxidase (HRP)-labeled rabbit anti-human immunoglobulin (Ig) Fcγ fragment antibody (lower limit of quantitation, 0.5 μg/mL)

(b) ELISA using solid-phase VEGFR-2-Fc fusion protein and HRP-labeled goat anti-human IgG $F(ab')_2$ antibody (lower limit of quantitation, 1.9-2.5 μg/mL)

The applicant explained as follows:

The methods (a) and (b) were shown to be equivalent by the comparison using the samples containing the reference material. However, when the samples obtained in the Japanese phase I study (Study I4T-IE-JVBW [the JVBW study]) were measured using the both methods, the results were not consistent with each other. Also, since there were some defects in the validation parameters for the method (a), the

results obtained by the method (b) in 9 studies (Study I4T-IE-JVBD [the REGARD study], Study I4T-IE-JVBE [the RAINBOW study], JVBW study, Study I4T-IE-JVBX [the JVBX study], Study I4T-IE-JVBY [the JVBY study], Study I4T-IE-JVBJ [the JVBJ study], Study I4T-IE-JVCC [the JVCC study], Study I4T-IE-JVCA [the JVCA study], Study I4T-JE-JVCL [the JVCL study]) were handled as the primary data for evaluating the pharmacokinetics (PK) of ramucirumab.

4.(i).A.(1).2) Assay of anti-ramucirumab antibody

Anti-ramucirumab antibody in human serum samples was measured by ELISA using biotin-labeled ramucirumab and HRP-labeled streptavidin (detection sensitivity, 3.91 ng/mL).

Neutralizing antibody against anti-ramucirumab antibody was measured by electrochemical luminescence assay using streptavidin, biotin-labeled ramucirumab, and ruthenium-labeled VEGFR-2 (detection sensitivity, 106 ng/mL).

The applicant explained the possibility of ramucirumab in the sample affecting the measurement of anti-ramucirumab antibody, as follows:
Anti-ramucirumab antibody was purified from the serum of a monkey immunized with an excess amount of ramucirumab. The ramucirumab concentration levels that did not affect the measurement of the purified antibody at concentrations of 250, 375, and 500 ng/mL were 313 μg/mL, 499 μg/mL, and >500 μg/mL, respectively. In the REGARD and RAINBOW studies, ramucirumab was administered according to the proposed dosage regimen. The maximum serum ramucirumab concentrations at the measuring time point of anti-ramucirumab antibody were 234 and 177 μg/mL in the REGARD and RAINBOW studies, respectively. Based on the above results, serum ramucirumab was unlikely to have affected the measurement of anti-ramucirumab antibody.

4.(i).A.(2) Changes in the manufacturing processes of the drug substance and the drug product during the development stage

There were changes in the manufacturing processes of the drug substance and the drug product during the development [see "2.A.(1).4) Manufacturing process development (comparability)" and "3.(ii).A.(5) Effect of changes in the manufacturing process of the drug substance on PK"]. The clinical data submitted for the present application were obtained using the formulation manufactured by the following methods: the formulation manufactured by Process A for a foreign phase I study (Study I4T-IE-JVBM [the JVBM study]) and Study I4T-IE-JVBN [the JVBN study]; the formulation manufactured by Process B for the REGARD study, foreign phase I studies (the JVBM and JVBN studies), and a foreign phase II study (Study I4T-IE-JVBJ [the JVBJ study]), etc.; the formulation manufactured by Process C0 for the REGARD study, RAINBOW study, Japanese phase I studies (Study I4T-IE-JVBI [the JVBI study], the JVBW study), foreign phase II studies (Study I4T-IE-JVBK [the JVBK study], the JVBJ study), etc.; and the formulation manufactured by Process C1 for a Japanese phase II study (the JVCL study). The formulation manufactured by Process C2 was submitted for application.

The applicant explained that the changes in the manufacturing process of the drug substance and the drug product do not affect the PK of ramucirumab for the following reasons.

- After each change in the manufacturing process from A through C2, comparability in the quality attributes was evaluated, and the comparability of the drug substance before and after each change was confirmed[see "2.A.(1).4) Manufacturing process development (comparability)"].

- There is no clear difference in the PK of ramucirumab between formulations manufactured by different manufacturing processes, based on (a) the results of the JVBM and JVBN studies using the formulations by Processes A and B, (b) the results of the JVBJ study using the formulations by Processes B and C0, and (c) the results of the JVBW study using the formulation by Process C0 and the JVCL study using the formulation by Process C1.

4.(ii) Summary of clinical pharmacology studies

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

The PK of ramucirumab in cancer patients was investigated in ramucirumab monotherapy as well as in ramucirumab combination therapies with other antineoplastic drugs (e.g., paclitaxel [PTX], PTX +

carboplatin, docetaxel hydrate [DTX], and the combination regimen* of irinotecan hydrochloride [CPT-11] + calcium levofolinate + fluorouracil [5-FU] [FOLFIRI], etc.).

* CPT-11 180 mg/m^2, calcium levofolinate 200 mg/m^2, 5-FU 400 mg/m^2 bolus intravenous infusion, 5-FU 2400 mg/m^2 continuous intravenous infusion

4.(ii).A.(1) Japanese phase II study (5.3.3.2.1, Study I4T-JE-JVCL [December 2013 – ongoing (Only PK data after the first dose were analyzed)])

An open-label, uncontrolled study was conducted to investigate the PK, etc. of ramucirumab in 27 patients (6 patients were included in PK analysis) with metastatic adenocarcinoma of the stomach or gastroesophageal junction with disease progression on or after prior fluoropyrimidine- or platinum-containing chemotherapy. Ramucirumab (8 mg/kg per dose) was administered intravenously at 2-week intervals, and serum ramucirumab concentration was measured. The PK parameters of ramucirumab following the first dose were as shown in the following table. V_{ss} was similar to the plasma volume in humans (approximately 3 L in an adult weighing 70 kg) (*Pharm Res*. 1993;10:1093-5.).

PK parameters of ramucirumab following the first dose

n	C_{max} (μg/mL)	t_{max}[*1] (h)	$AUC_{0-\infty}$ (μg·h/mL)	$t_{1/2}$[*2] (h)	CL (mL/h)	V_z (L)	V_{ss} (L)
6	161 (16)	2.05 (1.07, 2.12)	25,600[*3] (34)	183 (138, 228)	15.0[*3] (20)	3.37[*3] (30)	3.29[*3] (27)

Geometric mean (coefficient of variation [CV]%), [*1] Median (range), [*2] Geometric mean (range), [*3] n = 3

4.(ii).A.(2) Japanese phase I study (5.3.3.2.3, Study I4T-IE-JVBW [December 2010 to October 2011])

An open-label, uncontrolled study was conducted to investigate the PK, etc. of ramucirumab in 6 patients with metastatic adenocarcinoma of the stomach or gastroesophageal junction with disease progression on or after prior fluoropyrimidine- or platinum-containing chemotherapy.

One treatment cycle consisted of 4 weeks. Ramucirumab (8 mg/kg) was administered intravenously on Days 1 and 15, and PTX (80 mg/m^2) was administered intravenously on Days 1, 8, and 15, and the serum ramucirumab concentration was measured (the table below).

The accumulation factors calculated from AUC following the third dose (Day 1 in Cycle 2) were 1.52 and 1.53 (individual values), which were roughly identical to the values estimated from $t_{1/2}$ following the first dose. The geometric means (coefficient of variation [CV]%) of $C_{min,ss}$ of ramucirumab before the third and fifth dose were 44.2 (21) and 66.6 (25) μg/mL, respectively. No anti-ramucirumab antibody was detected.

PK parameter of ramucirumab

Dosing time	n	C_{max} (μg/mL)	t_{max}[*1] (h)	AUC_{0-last} (μg·h/mL)	$AUC_{0-\tau}$ (μg·h/mL)	$AUC_{0-\infty}$ (μg·h/mL)	$t_{1/2}$[*2] (h)	CL (mL/h)	V_z (L)	V_{ss} (L)
First	6	171 (26)	4.00 (1.02, 9.05)	18,500 (35)	18,300 (35)	34,100[*3]	181[*4] (138, 225)	16.6[*3]	3.31[*3]	3.27[*3]
Third	4	282 (15)	1.82 (1.03, 2.15)	-	41,300, 42,600[*5]	-	218[*3]	13.3, 13.8[*5]	4.35[*3]	-

Geometric mean (CV%); -, Not calculated; [*1] Median (range); [*2] Geometric mean (range); [*3] n = 1 (individual value); [*4] n = 4; [*5] n = 2 (individual values)

4.(ii).A.(3) Japanese phase I study (5.3.3.2.6, Study I4T-IE-JVBX [December 2010 to [redacted] 20[redacted]])

An open-label, uncontrolled study was conducted to investigate the PK, etc. of ramucirumab following concomitant use with DTX in 7 patients with recurrent or metastatic breast cancer negative for human epithelial cell growth factor receptor type 2 (HER2).

One treatment cycle consisted of 3 weeks. DTX (75 mg/m^2) was administered on Day 1 and, after 1 hour, ramucirumab (10 mg/kg) was administered intravenously to investigate the serum ramucirumab concentration (the table below). The half-life ($t_{1/2}$) of ramucirumab increased following the fourth dose as compared with the first dose. The accumulation factor calculated from AUC following the third dose

was 1.52, showing accumulated ramucirumab as a result of multiple administration. No anti-ramucirumab antibody was detected.

PK parameters of ramucirumab

Dosing time	n	C_{max} (μg/mL)	t_{max}*1 (h)	AUC*2 (μg·h/mL)	$t_{1/2}$ (h)	CL (mL/h)	V_{ss} (L)
First	7	261 (22)	1.53 (1.08, 5.05)	40,800 (25)	158 (49)	13.6 (24)	2.96 (32)
Fourth	6	335 (22)	2.49 (1.08, 9.03)	55,700 (24)	286 (26)	10.2 (24)	3.92 (18)

Geometric mean (CV%), *1 Median (range), *2 $AUC_{0-\infty}$ in the first dose, $AUC_{0-\tau}$ in the fourth dose

4.(ii).A.(4) Japanese phase I study (5.3.3.2.7, Study I4T-IE-JVBY [February 2011 to March 2012])

An open-label, uncontrolled study was conducted to investigate the PK, etc. of ramucirumab following concomitant use with FOLFIRI in 6 patients with metastatic colorectal cancer with disease progression on or after prior chemotherapy with bevacizumab (genetical recombination), oxaliplatin, and fluoropyrimidine antineoplastics. One treatment cycle consisted of 2 weeks. On Day 1 ramucirumab (8 mg/kg) was administered intravenously, followed by the administration of FOLFIRI 1 hour later, then the serum ramucirumab concentration was measured. The geometric means (CV%) of C_{max} and AUC_{0-C} of ramucirumab following the first dose were 245 (6) μg/mL and 38,400 (15) μg·h/mL,* respectively. No anti-ramucirumab antibody was detected.

* n = 4

4.(ii).A.(5) Foreign phase II study (5.3.5.2.5, Study I4T-IE-JVBJ [January 2009 to January 2012])

An open-label, uncontrolled study was conducted to investigate the PK, etc. of ramucirumab following concomitant use with PTX and carboplatin in 40 patients with stage IIIB or IV non-small-cell lung cancer (39 patients were included in PK analysis). One treatment cycle consisted of 3 weeks. On Day 1 ramucirumab (10 mg/kg) was administered intravenously, followed by intravenous PTX (200 mg/m^2) then by intravenous carboplatin (dose equivalent to AUC 6 mg·min/mL), and serum ramucirumab concentration was measured. The trough concentration of ramucirumab tended to increase with multiple administration, and the trough serum ramucirumab concentration before administration in Cycle 6 was 6.6 times that before administration in Cycle 2. The serum ramucirumab concentration at 1 hour post dose was 25% higher in Cycle 6 as compared with Cycle 1. The anti-ramucirumab antibody was detected in 9 of 35 patients (25.7%) who were tested for the antibody after the start of ramucirumab administration. Of the 9 patients, 8 were assessed as positive for the anti-ramucirumab antibody* (TE-ADA positive). A neutralizing antibody was detected in 1 patient.

* Patients were assessed as positive if antibody titer was >4 times the baseline value, or >1:20 (for patients with missing baseline data or tested negative for the antibody at baseline).

4.(ii).A.(6) Foreign phase III study (5.3.5.1.2, Study I4T-IE-JVBD [REGARD study] [October 2009 – ongoing (data cut-off, July 25, 2012)])

A randomized, double-blind, comparative study was conducted to investigate the efficacy, safety, etc. of ramucirumab in 351 patients (236 patients in the ramucirumab group, 115 patients in the placebo group) (119 patients were included in PK analysis) with metastatic adenocarcinoma of the stomach or gastroesophageal junction with disease progression on or after prior fluoropyrimidine- or platinum-containing chemotherapy. Ramucirumab (8 mg/kg) or placebo was administered intravenously at 2-week intervals, and serum ramucirumab concentration was measured before administration in Cycle 4 and Cycle 7. The geometric means (CV%) of the trough serum ramucirumab concentrations before administration in Cycle 4 and Cycle 7 were 49.5 (80.6) and 74.4 (58.3) μg/mL, respectively. In the ramucirumab group, the anti-ramucirumab antibody was detected in 6 of 138 patients (4.3%) who were tested for the antibody after the start of ramucirumab administration. All of those patients were assessed as TE-ADA positive. No neutralizing antibody was detected.

In the placebo group, the anti-ramucirumab antibody was detected in 3 of 53 patients (5.7%), and 1 of those patients was assessed as TE-ADA positive. The applicant explained that the anti-ramucirumab

antibody assay was performed with a low cut-off point to minimize the false negative rate, and that the low specificity of the assay may have resulted in the detection of anti-ramucirumab antibody in a patient receiving placebo.

4.(ii).A.(7) Global phase III study (5.3.5.1.1, Study I4T-IE-JVBE [RAINBOW study] [December 2010 – ongoing (data cut-off, July 12, 2013)])

A randomized, double-blind, comparative study was conducted to investigate the efficacy, safety, etc. of ramucirumab in combination with PTX in 656 patients (326 patients in the ramucirumab group, 330 patients in the placebo group) (323 patients were included in PK analysis) with metastatic adenocarcinoma of the stomach or gastroesophageal junction with disease progression on or after prior fluoropyrimidine- or platinum-containing chemotherapy.

One treatment cycle consisted of 4 weeks. Ramucirumab (8 mg/kg) or placebo was administered intravenously on Days 1 and 15, PTX (80 mg/m^2) was administered intravenously on Days 1, 8, and 15, and serum ramucirumab concentration was measured. The geometric means (CV%) of the trough serum ramucirumab concentrations before the fourth and seventh doses were 45.0 (50) and 62.8 (47) μg/mL, respectively, and the value before the seventh dose was approximately 40% higher than that before the fourth dose. The geometric means (CV%) of serum ramucirumab concentrations 1 hour after the first and seventh doses were 146 (28) and 216 (30) μg/mL, respectively, showing accumulated ramucirumab as a result of multiple administration.

In the ramucirumab group, the anti-ramucirumab antibody was detected in 7 of 291 patients (2.4%) who were tested for the antibody after the start of ramucirumab administration, and 5 of those patients (1.7%) were assessed as TE-ADA positive. No neutralizing antibody was detected. In the placebo group, the anti-ramucirumab antibody was detected in 13 of 268 patients, and 1 of those patients was assessed as TE-ADA positive.

4.(ii).A.(8) Foreign phase I study (5.3.3.2.4, Study I4T-IE-JVBM [[redacted] 20[redacted] to June 2009])

An open-label, uncontrolled study was conducted to investigate the PK, etc. of ramucirumab in 37 patients with advanced solid cancer. One treatment cycle consisted of 4 weeks. Ramucirumab (2, 4, 6, 8, 10, 13, 16 mg/kg) was administered intravenously at 1-week intervals, and serum ramucirumab concentration was measured (the table below). In all patients in the 2 and 4 mg/kg groups and in 2 patients in the 6 mg/kg group, ramucirumab was administered intravenously in a single dose 2 weeks before the start of Cycle 1, and the PK of ramucirumab following the first dose was investigated. The PK of ramucirumab in multiple administration was investigated in Week 4 in Cycle 1.

The PK of ramucirumab following the first dose showed a non-linear response over the dose range studied (2-16 mg/kg). In multiple administration, PK was analyzed following the fifth dose in the 2 to 6 mg/kg groups. The analysis revealed a more than dose-proportional increase in serum ramucirumab concentrations, with lower CL in the 6 mg/kg group than in the 2 and 4 mg/kg groups. Following the fourth dose, CL was generally constant in the ≥8 mg/kg groups. The applicant explained why serum ramucirumab concentrations increased more than dose proportionally in the dose range from 2 to 6 mg/kg, as follows: the VEGFR-2-mediated elimination pathway is probably involved in the elimination of ramucirumab, and the elimination pathway was saturated with the increase in ramucirumab dose, resulting in decreased CL. The geometric means of the accumulation factors calculated from the AUC following the intravenous administration of ramucirumab (2-16 mg/kg) for 1 cycle at 1-week intervals were 1.66 to 3.07.

The anti-ramucirumab antibody was detected in 2 of 36 patients (5.6%) who were tested for the antibody after the start of ramucirumab administration, and 1 of those patients (2.8%) was assessed as TE-ADA positive. No neutralizing antibody was detected.

PK parameters of ramucirumab

Dosing time	Dose (mg/kg)	n	C_{max} (μg/mL)	t_{max} [*1] (h)	$AUC_{0-\tau}$ (μg·h/mL)	$t_{1/2}$ [*2] (h)	CL (mL/h)	V_{ss} (L)
First	2	6	43.3 (16)	2.61 (1.58, 3.12)	3090 (14)	61.5 (52.5, 78.0)	43.4 (22)	4.12 (16)
	4	4	79.7 (14)	1.53 (1.50, 1.58)	6000 (32)	89.1 (54.9, 120)	40.2 (27)	5.24 (15)
	6	3	192 (10)	3 (1.48, 9.00)	12,900, 13,900[*3*4]	112, 156[*3*4]	-	-
	8	4	299 (12)	1.8 (1.03, 2.10)	25,200 (18)	120[*3*5]	-	-
	10	7	379 (38)	1.5 (1.00, 2.03)	25,300[*6] (20)	-	-	-
	13	5	410 (36)	2.12 (1.17, 9.15)	23,600[*7] (59)	-	-	-
	16	6	545 (24)	2.75 (1.02, 23.88)	42,900[*7] (15)	-	-	-
Fifth	2	3	75.3 (33)	1.80 (1.37, 3.00)	6190 (26)	78.3[*3*5]	25.4 (39)	-
	4	4	142 (49)	3.04 (1.68, 5.00)	10,700 (46)	-	31.6 (36)	-
	6[*3]	2	288, 351	7.00, 96.4	40,800[*5]	-	14.4[*5]	-
Fourth	6[*3]	2	273, 543	1.50, 3.28	24,000, 28,800	-	19.6, 22.4	-
	8	3	557 (21)	2.22 (2.08, 3.00)	44,900 (7)	-	15.3 (23)	-
	10	7	608 (17)	2.05 (1.07, 8.98)	62,500 (19)	184[*3*5]	11.8 (24)	3.06[*3*5]
	13	5	859 (27)	2.00 (1.00, 2.25)	76,800 (24)	-	12.2 (23)	-
	16	4	934 (63)	2.01 (1.73, 3.03)	71,400 (51)	252, 291[*3*4]	17.1 (45)	6.50[*3*5]

Geometric mean (CV%); -, Not calculated; [*1]: Median (range); [*2] Geometric mean (range); [*3] Individual values, [*4] n = 2; *5 n = 1; [*6] n = 5; [*7] n = 4

4.(ii).A.(9) Foreign phase I study (5.3.3.2.5, Study I4T-IE-JVBN [February 2006 to [redacted] 2009])

An open-label, uncontrolled study was conducted to investigate the PK, etc. of ramucirumab in 25 patients with advanced solid cancer. Ramucirumab was administered intravenously at 6, 8, or 10 mg/kg at 2-week intervals in each cycle of 4 weeks, or ramucirumab was administered intravenously at 15 or 20 mg/kg at 3-week intervals in each cycle of 3 weeks, followed by the measurement of serum ramucirumab concentration (the table below).

The accumulation factors calculated from AUC values following 3 doses of ramucirumab (6, 8, 10 mg/kg) at 2-week intervals were 1.21 to 1.66.

The anti-ramucirumab antibody was detected in 4 of 25 patients (16.0%) who were tested for the antibody after the start of ramucirumab administration, and 3 of those patients (12.0%) were assessed as TE-ADA positive. No neutralizing antibody was detected.

PK parameters of ramucirumab

Dosing time	Dose (mg/kg)	Dosing interval	n	C_{max} (μg/mL)	t_{max}[*1] (h)	$AUC_{0-\tau}$ (μg·h/mL)	$t_{1/2}$[*2] (h)	CL (mL/h)	V_{ss} (L)
First	6	2 weeks	4	237 (36)	1.77 (1.50, 3.00)	24,800 (12)	107, 111[*3]	13.9, 20.7[*3]	2.16, 3.16[*3]
	8		5	222 (34)	3.00 (1.00, 5.52)	24,000 (38)	128, 160[*3]	13.7[*4]	2.56[*4]
	10		4	264 (42)	1.52 (1.00, 5.03)	27,700 (33)	130[*5] (118, 148)	30.4[*5] (15)	5.58[*5] (8)
	15	3 weeks	6	664 (31)	3.99 (1.50, 9.08)	59,200 (42)	162[*6] (62.6, 260)	19.8[*6] (37)	4.06[*6] (17)
	20		6	763 (25)	3.43 (1.02, 167.93)	120,000[*6] (31)	-	-	-
Third	6	2 weeks	3	299 (24)	1.50 (1.50, 49.33)	32,200 (40)	-	14.4 (29)	-
	8		4	256 (16)	1.75 (1.00, 2.98)	31,400[*5] (30)	155[*5] (129, 175)	15.8[*5] (33)	2.20[*4]
	10		3	476 (18)	1.00 (0.93, 2.02)	46,800, 52,400[*3]	-	16.1, 17.9[*3]	-

Geometric mean (CV%); -, Not calculated; [*1] Median (range); [*2] Geometric mean (range); [*3] n = 2 (individual values); [*] n = 1 (individual value); [*5] n = 3; [*6] n = 5

4.(ii).A.(10) Japanese phase I study (5.3.3.2.2, Study I4T-IE-JVBI [September 2009 to February 2011])

An open-label, uncontrolled study was conducted to investigate the PK, etc. of ramucirumab in 15 patients with advanced solid cancer. One treatment cycle consisted of 6 weeks. Ramucirumab at 6 or 8 mg/kg was administered intravenously at 2-week intervals, or ramucirumab at 10 mg/kg was administered intravenously at 3-week intervals, followed by the measurement of serum ramucirumab concentration (the table below).

Following the intravenous administration of ramucirumab for 4 times at 2-week intervals or 3 times at 3-week intervals, the accumulation factors of C_{max} and AUC were 0.984 to 2.41 and 1.34 to 1.99, respectively, showing accumulated ramucirumab as a result of multiple administration. No anti-ramucirumab antibody was detected.

PK parameters of ramucirumab

Dosing time	Dose (mg/kg)	Dosing interval	n	C_{max} (μg/mL)	t_{max}[*1] (h)	AUC[*2] (μg·h/mL)	$t_{1/2}$[*3] (h)	CL (mL/h)	V_{ss} (L)
First	6	2 weeks	3	280 (22)	2.05 (1.60, 3.22)	36,900[*4*5]	150 (129, 166)	11.5[*4*5]	1.77[*4*5]
	8		6	356 (34)	2.45 (1.65, 5.10)	73,800[*4*5]	140, 191[*4*6]	8.43[*4*5]	1.67[*4*5]
	10	3 weeks	6	482 (23)	2.59 (1.63, 25.17)	49,600, 73,700[*4*6]	211[*7] (166, 241)	7.83, 9.32[*4*6]	1.84, 2.40[*4*6]
Fourth	6[*4]	2 weeks	1	352	1.55	56,400	-	7.54	-
	8[*4]		2	606, 781	1.62, 1.72	94,900, 110,000	-	3.24, 6.56	-
Third	10[*4]	3 weeks	2	534, 1053	1.78, 3.20	84,800, 122,000	329[*5]	5.00, 5.20	-

Geometric mean (CV%), -, Not calculated; [*1] Median (range); [*2] $AUC_{0-\infty}$ in the first dose, $AUC_{0-\tau}$ in other; [*3] Geometric mean (range); [*4] Individual values, [*5] n = 1, [*6] n = 2, *7 n = 3

4.(ii).A.(11) Drug-drug interactions

4.(ii).A.(11).1 Foreign phase II study (5.3.3.4.1, Study I4T-IE-JVCA [Part A, July 2012 – ongoing (data cut-off, [redacted] 23, 20[redacted]); Part B, July 2012 – ongoing (data cut-off, [redacted] 8, 20[redacted])])

An open-label, uncontrolled study was conducted to investigate the pharmacokinetic interactions between ramucirumab and PTX in 40 patients (24 in Part A, 16 in Part B) (37 patients included in PK analysis) with advanced solid cancer. In Part A, PTX (80 mg/m^2) was administered intravenously on Day 1 of Cycle 1 (2 weeks) and, in Cycle 2 and subsequent cycles (4 weeks each), ramucirumab (8 mg/kg) was administered intravenously on Day 1 and 15, and PTX (80 mg/m^2) intravenously on Days 1, 8, and 15. In Part B, ramucirumab (8 mg/kg) was administered intravenously on Day 1 of Cycle 1 (3

weeks) and, in Cycle 2 and subsequent cycles (4 weeks each), ramucirumab (8 mg/kg) was administered intravenously on Day 1 and 15 (monotherapy), or ramucirumab (8 mg/kg) intravenously on Days 1 and 15 and PTX (80 mg/m^2) intravenously on Day 1, 8, and 15 (combination therapy).

PK parameters of ramucirumab and PTX in monotherapy and combination therapy were as shown in the following tables.

PK parameters of ramucirumab

	n	C_{max} (μg/mL)	t_{max}[*1] (h)	$AUC_{0-\infty}$ (μg·h/mL)	$t_{1/2}$[*2] (h)	CL (mL/h)	V_z (L)	V_{ss} (L)
Ramucirumab alone	16	206 (14)	1.75 (1.00, 23.53)	32,100[*3] (29)	157[*3] (77.9, 241)	18.0[*3] (27)	4.08[*3] (25)	3.95[*3] (23)
Ramucirumab + PTX	21	216 (24)	2.37 (1.00, 23.25)	29,100[*4] (28)	139[*4] (78.5, 193)	18.1[*4] (27)	3.61[*4] (24)	3.41[*4] (23)

Geometric mean (CV%), [*1] Median (range), [*2] Geometric mean (range), [*3] n = 15, [*4] n = 13

PK parameters of PTX

	n	C_{max} (μg/mL)	t_{max}[*1] (h)	$AUC_{0-\infty}$ (μg·h/mL)	$t_{1/2}$[*2] (h)	CL (L/h)	V_z (L)	V_{ss} (L)
PTX alone	23	2743 (30)	1.00 (0.97, 1.08)	4280[*3] (29)	11.4[*3] (8.26, 18.9)	33.7[*3] (36)	552[*3] (35)	241[*3] (35)
Ramucirumab + PTX	20	2662 (47)	1.00 (0, 1.63)	4560[*4] (46)	11.4[*4] (6.97, 15.6)	31.9[*4] (52)	526[*4] (48)	226[*4] (72)

Geometric mean (CV%), [*1] Median (range), [*2] Geometric mean (range), [*3] n = 21, [*4] n = 17

The geometric mean ratios [90% confidence interval (CI)] of dose-adjusted C_{max} and $AUC_{0-\infty}$ of ramucirumab in combination with PTX to those of ramucirumab monotherapy were 1.07 [0.93, 1.24] and 1.00 [0.84, 1.19], respectively. The geometric mean ratios [90% CI] of dose-adjusted C_{max} and $AUC_{0-\infty}$ of PTX in combination with ramucirumab to those of PTX monotherapy were 0.97 [0.83, 1.13] and 1.09 [0.93, 1.29], respectively. The applicant explained that these results suggest that PTX does not affect the PK of ramucirumab, and ramucirumab does not affect the PK of PTX.

4.(ii).A.(11).2) Foreign phase II study (5.3.3.4.2, Study I4T-IE-JVCC [July 2012 to March 2014])

An open-label, uncontrolled study was conducted to investigate the effect of ramucirumab on the PK of DTX in 22 patients with advanced solid cancer (18 patients included in PK analysis).

One treatment cycle consisted of 3 weeks. DTX (75 mg/m^2) was administered intravenously on Day 1 in Cycle 1. Ramucirumab (10 mg/kg) and DTX (75 mg/m^2) were administered intravenously on Day 1 in Cycle 2 and subsequent cycles.

The geometric mean ratios [90% CI] of dose-adjusted C_{max} and $AUC_{0-\infty}$ of DTX in combination with ramucirumab to those of DTX monotherapy were 1.14 [0.84, 1.55] and 0.97 [0.84, 1.10], respectively. Based on these results, the applicant explained that ramucirumab does not affect the PK of DTX.

4.(ii).A.(12) Foreign phase II study (5.3.4.2.1, Study I4T-IE-JVBK [November 2009 – ongoing (data cut-off, [redacted] 3, 20[redacted])]); Study on QTc

An open-label, uncontrolled study was conducted to investigate the effect of ramucirumab on the QT interval corrected by the Fridericia method (QTcF) when ramucirumab (10 mg) was administered intravenously at 3-week intervals in 66 patients with advanced solid cancer (61 patients included in PK analysis).

The relationship between serum ramucirumab concentration and change in QTcF from baseline (ΔQTcF) was investigated using a linear mixed effect model. The results did not show any clear relationship. The mean ΔQTcF [90% CI] (msec) at C_{max} (geometric mean ratios [geometric coefficient of variation (%)]) of ramucirumab (571 [41] μg/mL) in Cycle 3 was estimated to be 2.8 [-3.8, 9.5].

Based on the above, the applicant explained that intravenously administered ramucirumab does not have any clinically significant effect on QTc.

4.(ii).A.(13) Population pharmacokinetic (PPK) analysis

A population pharmacokinetic (PPK) analysis was performed using a non-linear mixed effect model (NONMEM ver.7.2), based on the PK data (2782 time points, 497 patients) obtained from the following 8 clinical studies: Japanese phase I studies (the JVBW, JVBX, and JVBY studies), a global phase III study (the RAINBOW study), foreign phase II studies (the JVBJ, JVCA, and JVCC studies), and a foreign phase III study (the REGARD study). The PK of ramucirumab was described by a 2-compartment model with zero order absorption process and the first order elimination processes. The following factors were evaluated as possible covariates for PK parameters of ramucirumab (CL, distribution volume in the central compartment [V_1], distribution volume in the peripheral compartment [V_2]), and inter-compartmental clearance (Q): age, body weight, body mass index (BMI), sex, race, ethnicity, creatinine clearance (CLcr), renal function,[*1] serum albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), total bilirubin (TBI), hepatic function,[*2] cancer type, dose, and treatment duration.

The applicant explained the results of the analysis as follows:

- None of the factors investigated were selected as significant covariates for PK parameters of ramucirumab.

- The estimated values (standard error %) of CL, V_1, V_2, and Q in the last model were 0.014 (2.12) L/h, 3.07 (1.40) L, 2.37 (7.47) L, and 12.9 (13.1) mL/h, respectively.

- The geometric means (CV%) of CL, V_{ss}, and $t_{1/2}$ in each patient estimated by the Bayesian method using the results of the PPK analysis were 14.0 (29.8) mL/h, 5.50 (14.4) L, and 15.0 (24.1) days, respectively.

- In the last model-based simulation, the serum ramucirumab concentration was estimated to achieve a steady state before the sixth dose when ramucirumab (8 mg/kg) was administered at 2-week intervals.

[*1] The severity of renal impairment: normal (CLcr ≥90 mL/min), mild (60 mL/min ≤ CLcr <90 mL/min), moderate (30 mL/min ≤ CLcr <60 mL/min), and severe (15 mL/min ≤ CLcr <30 mL/min)

[*2] The severity of hepatic impairment: normal (TBI ≤ upper limit of normal [ULN] and AST ≤ ULN), mild (TBI ≤1.5 × ULN and AST > ULN, or ULN < TBI ≤1.5 × ULN), and moderate (1.5 × ULN < TBI ≤3 × ULN)

4.(ii).A.(14) PK of ramucirumab in Japanese and non-Japanese patients

Based on the following results, the applicant explained that there was no clear difference in the PK of ramucirumab between Japanese and non-Japanese patients.

- The comparison of the PK data obtained after a single dose of ramucirumab (8 mg/kg) between the Japanese phase II study (the JVCL study) and the foreign phase II study (the JVCA study, part B) [see "4.(ii).A.(1) Japanese phase II study" and "4.(ii).A.(11).1) Foreign phase II study"], as well as the comparison of the PK data after a single dose of ramucirumab (8 mg/kg) in combination with PTX between the Japanese phase I study (the JVBW study) and the foreign phase I study (the JVCA study, part A) [see "4.(ii).A.(2) Japanese phase I study" and "4.(ii).A.(11).1) Foreign phase II study"] showed that the PK of ramucirumab was comparable between Japanese and foreign studies.

- In the PPK analysis, race was not selected as a significant covariate of the PK parameters of ramucirumab [see "4.(ii).A.(13) Population pharmacokinetic (PPK) analysis"].

4.(ii).A.(15) Relationship of exposure level with efficacy and safety

4.(ii).A.(15).1) Relationship between exposure level and efficacy

Based on the results of the RAINBOW study, a relationship of the exposure levels[*1] ($C_{min,1}$,[*2] $C_{min,ss}$, $C_{max,ss}$, $C_{ave,ss}$) of ramucirumab with overall survival (OS) and progression-free survival (PFS) was investigated. The results showed a correlation of the increases in the exposure levels ($C_{min,1}$, $C_{min,ss}$, $C_{max,ss}$, $C_{ave,ss}$) with OS and PFS.

[*1] Estimated from the last model of PPK analysis using the nonlinear mixed effect model (NONMEM ver.7.2) based on the results of RAINBOW study
[*2] The lowest blood ramucirumab concentration after the first dose

4.(ii).A.(15).2) Relationship between exposure level and safety

Based on the results of RAINBOW study, a relationship between the exposure levels[*1] ($C_{min,1}$,[*2] $C_{min,ss}$, $C_{max,ss}$, $C_{ave,ss}$) of ramucirumab and the incidences of Grade ≥3 events that occurred more frequently (with an incidence of ≥10%) in the ramucirumab group than in the placebo group (i.e., Grade ≥3 hypertension, neutropenia, leukopenia) was investigated. The results showed a correlation between the increased exposure levels ($C_{min,1}$, $C_{min,ss}$, $C_{max,ss}$, $C_{ave,ss}$) and the increased incidences of Grade ≥3 hypertension, neutropenia, and leukopenia.

[*1] Estimated from the last model of PPK analysis using the nonlinear mixed effect model (NONMEM ver.7.2) based on the results of RAINBOW study
[*2] The lowest blood ramucirumab concentration after the first dose

4.(ii).A.(16) Effect of impaired hepatic or renal function on PK of ramucirumab

No clinical study was conducted to investigate the PK of ramucirumab in patients with hepatic or renal impairment. The applicant explained that there is no need to adjust the dose of ramucirumab in patients with hepatic or renal impairment for now because the impaired hepatic or renal function is unlikely to affect the PK of ramucirumab for the following reasons.

- Ramucirumab is thought to be eliminated via the pathway mediated by binding with the target antigen and the target antigen-independent pathway. Therefore, impaired hepatic or renal function is unlikely to affect the elimination of ramucirumab.

- Ramucirumab is a high molecular compound (molecular weight, approximately 147,000) and therefore is not renally excreted.

- In the PPK analysis, hepatic function, hepatic function test values (ALT, AST, ALP, serum albumin), renal function, and renal function test value (CLcr) were not selected as covariates for the PK parameters of ramucirumab [see "4.(ii).A.(13) Population pharmacokinetic (PPK) analysis"].

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

Effect of anti-ramucirumab antibody on PK of ramucirumab

Anti-ramucirumab antibody expression was investigated in the following studies: 4 Japanese phase I studies (the JVBI, JVBW, JVBX, and JVBY studies), 2 foreign phase I studies (the JVBM and JVBN studies), 8 foreign phase II studies (the JVBK study, Studies I4T-IE-JVBP, I4T-IE-JVBQ [the JVBQ study], Studies I4T-IE-JVBR, I4T-IE-JVBH, the JVBJ study, Studies I4T-IE-JVBO [the JVBO study], Study I4T-IE-JVBS), 1 foreign phase III study (the REGARD study), and 1 global phase III study (the RAINBOW study). In these clinical studies, the anti-ramucirumab antibody was detected in 64 of 884 patients (7.2%) in whom at least one blood sample was collected after the start of ramucirumab administration, and 53 of those patients (6.0%) were assessed as TE-ADA positive.

The applicant explained the effect of the anti-ramucirumab antibody on the PK of ramucirumab as follows:

The effect of anti-ramucirumab antibody on the PK of ramucirumab was investigated in RAINBOW study, in which ramucirumab was administered at the proposed dosage regimen. Serum ramucirumab concentration was measured in patients in whom the anti-ramucirumab antibody was detected during the administration period. In patients tested positive for the anti-ramucirumab antibody, serum ramucirumab concentrations at the time of anti-ramucirumab antibody measurement ranged from 33.0

to 63.0 μg/mL after the fourth dose and from 23.0 to 43.0 μg/mL after the seventh dose. The concentrations were within the range of the serum ramucirumab concentrations observed in patients tested negative for the anti-ramucirumab antibody at the time point of anti-ramucirumab antibody measurement (below the lower limit of quantitation to 177.0 μg/mL after the fourth dose, 14.5-164.5 μg/mL after the seventh dose).

However, because of the limited number of patients investigated, no conclusion can be drawn on the effect of anti-ramucirumab antibody on the PK of ramucirumab.

PMDA considers as follows:
PMDA accepted the explanation of the applicant. However, information on the effect of the anti-ramucirumab antibody on the PK of ramucirumab should be further collected. New relevant findings should be offered to healthcare professionals in an appropriate manner whenever available.

4.(iii) Summary of clinical efficacy and safety

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

The following data were submitted: efficacy and safety evaluation data consisting of results from a total of 7 studies including 2 Japanese phase I studies, 1 global phase III study, 2 foreign phase I studies, 1 foreign phase II study, and 1 foreign phase III study; and reference data consisting of results from a total of 12 studies including 2 Japanese phase I studies, 9 foreign phase II studies, and 1 foreign phase III study.

List of clinical studies on efficacy and safety

Data category	Region	Study identifier	Phase	Patient population	Sample size	Dosage regimen	Primary endpoints
Evaluation	Japan	I4T-IE-JVBI	I	Patients with advanced solid cancer	15	Ramucirumab was administered intravenously at 6 or 8 mg/kg at 2-week intervals, or at 10 mg/kg at 3-week intervals.	Safety PK
	Japan	I4T-IE-JVBW	I	Patients with metastatic adenocarcinoma of the stomach or gastroesophageal junction with disease progression on or after prior fluoropyrimidine- or platinum-containing chemotherapy	6	In one treatment cycle consisting of 4 weeks, ramucirumab (8 mg/kg) was administered on Days 1 and 15 in combination with PTX (80 mg/m^2 intravenously on Days 1, 8, and 15).	Safety PK
	Global	I4T-IE-JVBE (RAINBOW)	III	Patients with metastatic adenocarcinoma of the stomach or gastroesophageal junction with disease progression on or after prior fluoropyrimidine- or platinum-containing chemotherapy	665 (a) 330 (b) 335	In one treatment cycle consisting of 4 weeks, (a) ramucirumab (8 mg/kg) or (b) placebo was administered intravenously on Days 1 and 15, in combination with PTX (80 mg/m^2 intravenously on Days 1, 8, 15).	Efficacy Safety PK
	Foreign	I4T-IE-JVBM	I	Patients with advanced solid cancer	37	Ramucirumab (2, 4, 6, 8, 10, 13, 16 mg/kg) was administered intravenously at 1-week intervals.	Safety PK
	Foreign	I4T-IE-JVBN	I	Patients with advanced solid cancer	25	Ramucirumab was administered intravenously at 6, 8, or 10 mg/kg at 2-week intervals, or at 15 or 20 mg/kg at 3-week intervals.	Safety PK

Data category	Region	Study identifier	Phase	Patient population	Sample size	Dosage regimen	Primary endpoints
	Foreign	I4T-IE-JVBK	II	Patients with advanced solid cancer	66	Ramucirumab (10 mg/kg) was administered intravenously at 3-week intervals.	Safety
	Foreign	I4T-IE-JVBD (REGARD)	III	Patients with metastatic adenocarcinoma of the stomach or gastroesophageal junction with disease progression on or after prior fluoropyrimidine- or platinum-containing chemotherapy	355 (a) 238 (b) 117	(a) Ramucirumab (8 mg/kg) was administered intravenously at 2-week intervals. (b) Placebo was administered intravenously at 2-week intervals.	Efficacy Safety PK
Reference	Japan	I4T-IE-JVBX	I	Patients with recurrent or metastatic HER2-negative breast cancer	7	Ramucirumab (10 mg/kg) was administered intravenously at 3-week intervals in combination with DTX (75 mg/m^2).	Safety PK
	Japan	I4T-IE-JVBY	I	Patients with metastatic colorectal cancer	6	Ramucirumab (8 mg/kg) was administered intravenously at 2-week intervals in combination with FOLFIRI.	Safety PK
	Foreign	I4T-IE-JVCA	II	Patients with advanced solid cancer	A: 24 B: 16	Part A: PTX (80 mg/m^2) was administered intravenously on Day 1 of Cycle 1 (2 weeks). In Cycle 2 and subsequent cycles (4 weeks each), ramucirumab (8 mg/kg) was administered intravenously on Days 1 and 15 and PTX (80 mg/m^2) on Days 1, 8, and 15. Part B: Ramucirumab (8 mg/kg) was administered intravenously on Day 1 of Cycle 1 (3 weeks). In Cycle 2 and subsequent cycles (4 weeks each), ramucirumab (8 mg/kg) was administered intravenously on Days 1 and 15 (monotherapy), or ramucirumab (8 mg/kg) was administered intravenously on Days 1 and 15 with PTX (80 mg/m^2) on Days 1, 8, and 15 (combination therapy).	Safety PK
	Foreign	I4T-IE-JVCC	II	Patients with advanced solid cancer	22	Ramucirumab (10 mg/kg) was administered intravenously at 3-week intervals in combination with DTX (75 mg/m^2) (DTX alone in Cycle 1).	Safety PK
	Foreign	I4T-IE-JVBP	II	Patients with metastatic renal cell cancer	39	Ramucirumab (8 mg/kg) was administered intravenously at 2-week intervals.	Safety PK
	Foreign	I4T-IE-JVBQ	II	Patients with advanced hepatocellular cancer	42	Ramucirumab (8 mg/kg) was administered intravenously at 2-week intervals.	Safety PK

Data category	Region	Study identifier	Phase	Patient population	Sample size	Dosage regimen	Primary endpoints
	Foreign	I4T-IE-JVBR	II	Patients with recurrent or intractable ovarian cancer	60	Ramucirumab (8 mg/kg) was administered intravenously at 2-week intervals.	Safety
	Foreign	I4T-IE-JVBH	II	Patients with metastatic colorectal cancer	48	Ramucirumab (8 mg/kg) was administered intravenously at 2-week intervals in combination with mFOLFOX6.	Safety PK
	Foreign	I4T-IE-JVBJ	II	Patients with stage IIIB or IV non-small-cell lung cancer	40	Ramucirumab (10 mg/kg) was administered intravenously at 3-week intervals in combination with PTX (200 mg/m^2) and carboplatin (dose equivalent to AUC 6 mg·min/mL).	Safety PK
	Foreign	I4T-IE-JVBO	II	Patients with metastatic malignant melanoma	102 (a) 52 (b) 50	(a) Ramucirumab (10 mg/kg) was administered intravenously at 3-week intervals in combination with dacarbazine (1000 mg/m^2). (b) Ramucirumab (10 mg/kg) was administered intravenously at 3-week intervals.	Safety PK
	Foreign	I4T-IE-JVBS	II	Patients with metastatic, androgen-independent prostatic cancer	132 (a) 66 (b) 66	In one treatment cycle consisting of 3 weeks, (a) ramucirumab (6 mg/kg) or (b) cixutumumab (unapproved in Japan, 6 mg/kg) was administered intravenously on Days 1, 8, and 15 in combination with mitoxantrone (intravenous administration at 12 mg/m^2 on Day 1) and prednisone (unapproved in Japan, twice-daily oral administration of 5 mg).	Safety
	Foreign	I4T-IE-JVBC	III	Patients with recurrent or metastatic breast cancer	1144 (a) 759 (b) 385	(a) Ramucirumab (10 mg/kg) or (b) placebo was administered intravenously at 3-week intervals in combination with DTX (75 mg/m^2).	Safety

PK, Pharmacokinetics; FOLFIRI, Fluorouracil + calcium levofolinate + CPT-11; mFOLFOX6, Fluorouracil + calcium folinate + oxaliplatin; PTX, Paclitaxel; DTX, Docetaxel

The outline of each clinical study was as described below.

Major adverse events other than death reported in each clinical study are described in "4.(iv) Adverse events, etc. observed in clinical studies." PK data, etc. are provided in "4.(i) Summary of biopharmaceutic studies and associated analytical methods" and in "4.(ii) Summary of clinical pharmacology studies."

Evaluation data

(1) Clinical pharmacology

The following clinical pharmacology study in patients with advanced solid cancer was submitted [see "4.(i) Summary of biopharmaceutic studies and associated analytical methods" and "4.(ii) Summary of clinical pharmacology studies"]. A total of 11 patients died during the study period or within 30 days after the last dose. The deaths were all due to the progression of the primary disease.

Foreign phase II study (5.3.4.2.1, Study I4T-IE-JVBK [November 2009 – ongoing (data cut-off, [redacted] 3, 20[redacted])])

(2) Japanese clinical studies

1) Japanese phase I study (5.3.3.2.2, Study I4T-IE-JVBI [September 2009 to February 2011])

An open-label, uncontrolled study was conducted to investigate the safety and PK of ramucirumab in patients with advanced solid cancer (target sample size, 15-18) at a single medical institution in Japan.

One treatment cycle consisted of 6 weeks. Ramucirumab was administered intravenously over 60 minutes at 6 or 8 mg/kg at 2-week intervals or at 10 mg/kg at 3-week intervals.

Of 17 patients enrolled in the study, 1 patient failed to meet the inclusion criteria because of the progression of the primary disease after enrollment, and 1 patient withdrew consent before the administration of ramucirumab. Ramucirumab was administered to a total of 15 patients excluding these 2 patients, and the 15 patients were included in the safety analysis set.

Dose limiting toxicity (DLT) was evaluated in Cycle 1. As no DLT was observed, the maximum tolerated dose (MTD) of ramucirumab was not determined.

The safety analysis revealed that no death occurred during the administration period or within 30 days after the last dose of the study drug.

2) Japanese phase I study (5.3.3.2.3, Study I4T-IE-JVBW [December 2010 to October 2011])

An open-label, uncontrolled study was conducted to investigate the safety and PK of ramucirumab in combination with PTX in patients with metastatic adenocarcinoma of the stomach or gastroesophageal junction with disease progression on or after prior fluoropyrimidine- or platinum-containing chemotherapy (target sample size, 6) at 3 medical institutions in Japan.

One treatment cycle consisted of 4 weeks. Ramucirumab (8 mg/kg) was administered intravenously on Days 1 and 15, and PTX (80 mg/m^2) was administered intravenously on Days 1, 8, and 15.

Of 7 patients enrolled in the study, 6 patients received ramucirumab and were included in the safety analysis set.

DLT was evaluated in Cycle 1. No DLT was observed in this study.

The safety analysis revealed that 1 patient died during the administration period or within 30 days after the last dose of the study drug. The death was due to progression of the primary disease.

(3) Global study

Global phase III study (5.3.5.1.1, Study I4T-IE-JVBE (RAINBOW study) [December 2010 – ongoing (data cut-off, July 12, 2013)])

A randomized, double-blind, comparative study was conducted to compare the efficacy and safety between ramucirumab plus PTX (ramucirumab/PTX) and placebo plus PTX (placebo/PTX) in patients with metastatic adenocarcinoma of the stomach or gastroesophageal junction with disease progression on or after prior fluoropyrimidine- or platinum-containing chemotherapy (target sample size, 663) at 170 medical institutions in 27 countries including Japan.

One treatment cycle consisted of 4 weeks. Ramucirumab (8 mg/kg) or placebo was administered intravenously on Days 1 and 15, in combination with PTX (80 mg/m^2) administered intravenously on Days 1, 8, and 15.

All of the 665 patients (330 in the ramucirumab/PTX group, 335 in the placebo/PTX group) enrolled in the study were included in the intent-to-treat (ITT) population and in the efficacy analysis set. Among patients in the ITT population, 656 patients received the study drug and were included in the safety analysis set. Ramucirumab was administered by mistake to 1 patient who had been randomized to the placebo/PTX group. In the safety analysis, this patient was included in the ramucirumab/PTX group and

thus the safety analysis was performed on 327 patients in the ramucirumab/PTX group and 329 patients in the placebo/PTX group.

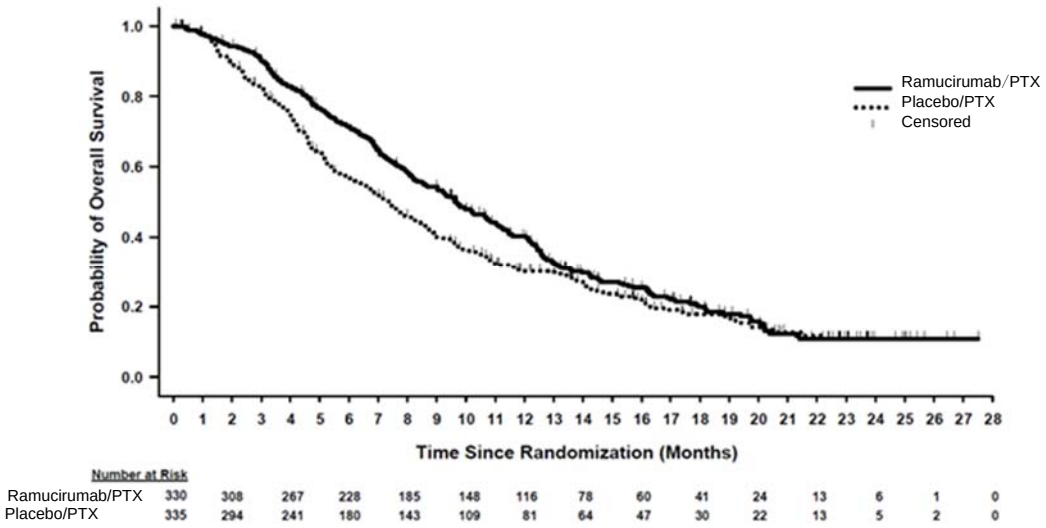
The efficacy analysis revealed the outcome of the primary endpoint of OS and Kaplan-Meier curves as shown in the following table and figure.

Results of OS analysis (ITT population; data cut-off, July 12, 2013)

	Ramucirumab/PTX	Placebo/PTX
Number of patients	330	335
Number of deaths (%)	256 (77.6)	260 (77.6)
Median OS [95% CI] (months)	9.63 [8.48, 10.81]	7.36 [6.31, 8.38]
Hazard ratio [95% CI] *1	0.807 [0.678, 0.962]	
P value (two-sided) *2	0.0169	

*1 Cox proportional-hazards model adjusted for stratification factors (time to progression in the primary treatment [<6 months vs. ≥6 months], presence or absence of measurable lesion [measurable lesion vs. non-measurable lesion], region)

*2 Stratified log-rank test (stratified by time to progression in the primary treatment [<6 months vs. ≥6 months], presence or absence of measurable lesion [measurable lesion vs. non-measurable lesion], region), significance level of 0.05 (two-sided)



Kaplan-Meier curves of OS (ITT population; data cut-off, July 12, 2013)

The safety analysis revealed that 37 patients in the ramucirumab/PTX group and 52 patients in the placebo/PTX group died during the administration period or within 30 days after the last dose of the study drug. Among these fatal cases, 26 patients in the ramucirumab/PTX group and 38 patients in the placebo/PTX group died from the progression of the primary disease. Other causes of deaths were septic shock (3 patients), sepsis (2 patients), gastrointestinal haemorrhage, pulmonary embolism, respiratory failure, gastrointestinal perforation, dehydration, and death* (1 patient each) in the ramucirumab/PTX group; and acute kidney injury (2 patients), septic shock/febrile neutropenia/pulmonary embolism, pulmonary embolism, myocardial infarction, lower respiratory tract infection, intracranial pressure increased, cardiac failure, hypovolaemic shock, hypoalbuminaemia, gastrointestinal haemorrhage, cerebral haemorrhage, drowning, and aspiration (1 patient each) in the placebo/PTX group. A causal relationship to ramucirumab or placebo could not be ruled out for pulmonary embolism, gastrointestinal haemorrhage, and death* (1 patient each) in the ramucirumab/PTX group and acute kidney injury, cardiac failure, pulmonary embolism, septic shock/febrile neutropenia/pulmonary embolism, and cerebral haemorrhage (1 patient each) in the placebo/PTX group.

* The information updated after the data cut-off revealed that the patient had died from the progression of the primary disease. A causal relationship to ramucirumab was therefore ruled out.

(4) Foreign clinical studies

1) Foreign phase I study (5.3.3.2.4, Study I4T-IE-JVBM [[redacted] 20[redacted] to June 2009])

An open-label, uncontrolled study was conducted to investigate the MTD, safety, and PK of ramucirumab in patients with advanced solid cancer (target sample size, 33) at 2 medical institutions overseas.

One treatment cycle consisted of 4 weeks. Ramucirumab (2, 4, 6, 8, 10, 13, 16 mg/kg) was administered intravenously at 1-week intervals. In Cycle 1, the 4-week administration period was followed by a 2-week observation period.

All of the 37 patients enrolled in the study received ramucirumab and were included in the safety analysis set.

DLT was evaluated in Cycle 1. DLT was observed in 1 of 7 patients in the 10 mg/kg group (Grade 3 hypertension) and 1 of 6 patients in the 16 mg/kg group (Grade 3 deep vein thrombosis). Grade 3 hypertension occurred in 1 of 6 patients in the 16 mg/kg group during the observation period after the DLT evaluation period. Therefore, MTD in treatment with ramucirumab at 1-week intervals was determined to be 13 mg/kg.

The safety analysis revealed that 1 patient died during the administration period or within 30 days after the last dose of the study drug. The death was due to the progression of the primary disease.

2) Foreign phase I study (5.3.3.2.5, Study I4T-IE-JVBN [February 2006 to [redacted] 2009])

An open-label, uncontrolled study was conducted to investigate the MTD, safety, and PK of ramucirumab in patients with advanced solid cancer (target sample size, 35) at 3 medical institutions overseas.

Ramucirumab (6, 8, 10 mg/kg) was administered intravenously at 2-week intervals in each cycle of 4 weeks, or ramucirumab (15, 20 mg/kg) was administered intravenously at 3-week intervals in each cycle of 3 weeks.

All of the 25 patients enrolled in the study received ramucirumab and were included in the safety analysis set.

DLT was evaluated in Cycle 1. As no DLT was observed, MTD was not determined.

The safety analysis revealed that 1 patient died during the administration period or within 30 days after the last dose of the study drug. The death was due to the progression of the primary disease.

3) Foreign phase III study (5.3.5.1.2, Study I4T-IE-JVBD (REGARD study) [October 2009 – ongoing (data cut-off, July 25, 2012)])

A randomized, double-blind, comparative study was conducted to compare the efficacy and safety between ramucirumab and placebo under the best supportive care in patients with metastatic adenocarcinoma of the stomach or gastroesophageal junction with disease progression on or after prior fluoropyrimidine- or platinum-containing chemotherapy (target sample size, 348) at 119 medical institutions overseas.

Ramucirumab (8 mg/kg) or placebo was administered intravenously at 2-week intervals.

All of the 355 patients enrolled in the study (238 in the ramucirumab group, 117 in the placebo group) were included in the ITT population and the efficacy analysis set. In total, 351 patients in the ITT population (236 in the ramucirumab group, 115 in the placebo group) who received the study drug were included in the safety analysis set.

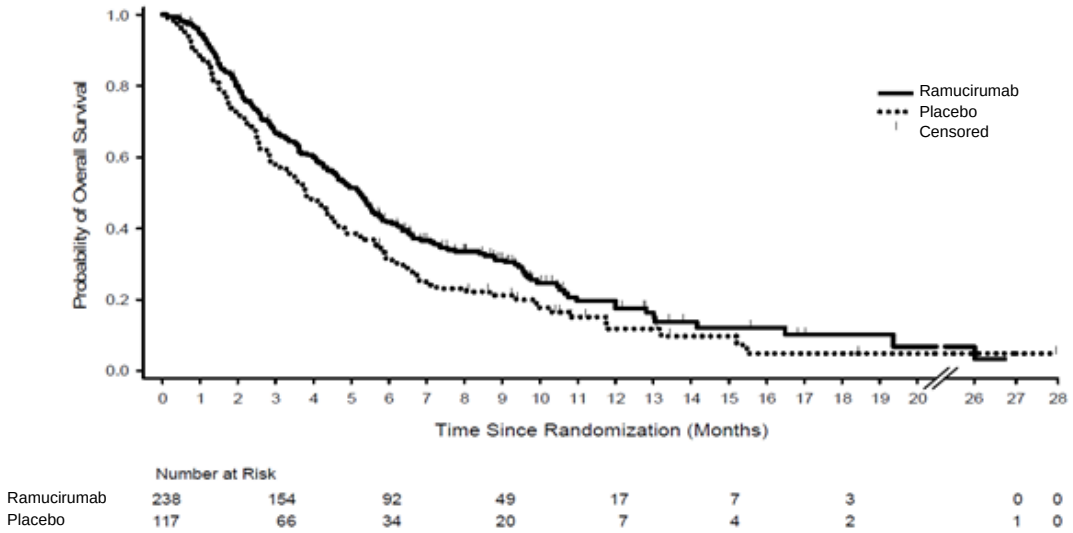
The primary efficacy endpoint of OS and Kaplan-Meier curves were as shown in the following table and figure.

Results of OS analysis (ITT population; data cut-off, July 25, 2012)

	Ramucirumab	Placebo
Number of patients	238	117
Number of deaths (%)	179 (75.2)	99 (84.6)
Median OS [95% CI] (months)	5.2 [4.4, 5.7]	3.8 [2.8, 4.7]
Hazard ratio [95% CI] [*1]	0.776 [0.603, 0.998]	
P value (two-sided) [*2]	0.0473	

[*1] Cox proportional-hazards model adjusted for stratification factors (body weight decrease within past 3 months [≥10% vs. <10%], primary site of lesion [stomach vs. gastroesophageal junction], region)

[*2] Stratified log-rank test (stratified by body weight decrease within past 3 months [≥10% vs. <10%], primary site of lesion [stomach vs. gastroesophageal junction], region), significance level of 0.05 (two-sided)



Kaplan-Meier curves of OS (ITT population; data cut-off, July 25, 2012)

The safety analysis revealed that 48 patients in the ramucirumab group and 30 patients in the placebo group died during the administration period or within 30 days after the last dose of the study drug. Of these fatal cases, 26 patients in the ramucirumab group and 15 patients in the placebo group died from the progression of the primary disease. Other causes of deaths were death[*1] (4 patients), multiorgan failure (3 patients), pneumonia (2 patients), dyspnoea, gastrointestinal haemorrhage, bacteraemia, cardiac arrest, cholangitis, dehydration, gastric cancer, gastric haemorrhage, intestinal perforation, large intestine perforation, multiple injuries, myocardial infarction, and acute kidney injury (1 patient each) in the ramucirumab group; and disease progression, pulmonary embolism, and respiratory failure (2 patients each), dyspnoea, gastrointestinal haemorrhage, lobar pneumonia, gastrointestinal obstruction, large intestine perforation, malignant neoplasm progression, septic shock, sudden death,[*2] and multiorgan failure (1 patient each) in the placebo group. A causal relationship to the study drug or placebo could not be ruled out for pneumonia, gastric haemorrhage, intestinal perforation, myocardial infarction, and large intestine perforation (1 patient each) in the ramucirumab group and pulmonary embolism and large intestine perforation (1 patient) in the placebo group.

[*1] According to the information update dafter the data cut-off, the cause of the death was determined as progression of the primary disease in 3 patients and unknown cause in 1 patient.

[*2] Unknown cause

Reference data

(1) Clinical pharmacology

The following 2 clinical pharmacology studies in patients with advanced solid cancer were submitted [see "4.(i) Summary of biopharmaceutic studies and associated analytical methods" and "4.(ii) Summary of clinical pharmacology studies"]. A total of 4 patients died during the study period or within 30 days after the last dose (all in the JVCA study). The deaths were due to the progression of the primary disease

(3 patients) and acute hepatic failure/acute kidney injury (1 patient). A causal relationship of the deaths to ramucirumab was ruled out for all patients.

1) Foreign phase II study (5.3.3.4.1, Study I4T-IE-JVCA [Part A, July 2012 – ongoing (data cut-off, [redacted] 23, 20[redacted]); part B, July 2012 – ongoing (data cut-off, [redacted] 8, 20[redacted])])
2) Foreign phase II study (5.3.3.4.2, Study I4T-IE-JVCC [July 2012 to March 2014])

(2) Japanese clinical studies
1) Japanese phase I study (5.3.3.2.6, Study I4T-IE-JVBX [December 2010 to [redacted] 20[redacted]])
An open-label, uncontrolled study was conducted to investigate the safety, efficacy, and PK of ramucirumab in combination with DTX in patients with recurrent or metastatic HER2-negative breast cancer (target sample size, 6-12) in 4 medical institutions in Japan.

Of 8 patients enrolled in the study, 7 patients received ramucirumab and were included in the safety analysis set. No death occurred during the administration period or within 30 days after the last dose of the study drug.

2) Japanese phase I study (5.3.3.2.7, Study I4T-IE-JVBY [February 2011 to March 2012])
An open-label, uncontrolled study was conducted to investigate the safety, efficacy, and PK of ramucirumab in combination with FOLFIRI in patients with metastatic colorectal cancer with disease progression on or after prior chemotherapy with bevacizumab, oxaliplatin, and fluoropyrimidine-based antineoplastics (target sample size, 6-9) in 3 medical institutions in Japan.

All of the 6 patients enrolled in the study received ramucirumab and were included in the safety analysis set. No death occurred during the administration period or within 30 days after the last dose of the study drug.

(3) Foreign clinical studies
1) Foreign phase II study (5.3.5.2.1, Study I4T-IE-JVBP [November 2007 to May 2011])
An open-label, uncontrolled study was conducted to investigate the efficacy and safety of ramucirumab in patients with metastatic renal cell cancer with disease progression on or after prior chemotherapy with a tyrosine kinase inhibitor (sunitinib malate or sorafenib tosilate), or those who could not tolerate the chemotherapy (target sample size, 36) in 7 medical institutions overseas.

Of 40 patients enrolled in the study, 39 patients received ramucirumab and were included in the safety analysis set. Of these, 1 patient died during the administration period or within 30 days after the last dose of the study drug. The death was due to multi-organ failure, and a causal relationship of the death to ramucirumab was ruled out.

2) Foreign phase II study (5.3.5.2.2, Study I4T-IE-JVBQ [February 2008 to May 2011])
An open-label, uncontrolled study was conducted to investigate the efficacy and safety of ramucirumab in patients with advanced hepatocellular cancer (target sample size, 40) in 6 medical institutions overseas.

Of 43 patients enrolled in the study, 42 patients received ramucirumab and were included in the safety analysis set. A total of 6 patients died during the administration period or within 30 days after the last dose of the study drug. Of these, 1 patient died from the progression of the primary disease. Other causes of deaths were gastrointestinal haemorrhage, arteriosclerosis, hepatic failure, hepatic encephalopathy, and hepatic malignant neoplasm (1 patient each). A causal relationship to ramucirumab could not be ruled out for gastrointestinal haemorrhage (1 patient).

3) Foreign phase II study (5.3.5.2.3, Study I4T-IE-JVBR [August 2008 to [redacted] 2012])
An open-label, uncontrolled study was conducted to investigate the efficacy and safety of ramucirumab in patients with recurrent or intractable epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal carcinoma who had a history of chemotherapy including platinum-containing antineoplastics (target sample size, 55) in 14 medical institutions overseas.

Of 73 patients enrolled in the study, 60 patients received ramucirumab and were included in the safety analysis set. A total of 5 patients died during the administration period or within 30 days after the last dose of the study drug. Of these, 4 patients died from the progression of the primary disease and 1 patient from intestinal perforation. A causal relationship of the deaths to ramucirumab was ruled out in all patients.

4) Foreign phase II study (5.3.5.2.4, Study I4T-IE-JVBH [April 2009 to August 2011])
An open-label, uncontrolled study was conducted to investigate the efficacy and safety of ramucirumab in combination with fluorouracil, calcium folinate, and oxaliplatin (mFOLFOX6) in patients with metastatic colorectal cancer (target sample size, 45) in 8 medical institutions overseas.

All of the 48 patients enrolled in the study received ramucirumab and were included in the safety analysis set. A total of 2 patients died during the administration period or within 30 days after the last dose of the study drug. The deaths were caused by acute myocardial infarction in 1 patient and cardio-respiratory arrest in the other. A causal relationship of the death to ramucirumab could not be ruled out in either patients.

5) Foreign phase II study (5.3.5.2.5, Study I4T-IE-JVBJ [January 2009 to January 2012])
An open-label, uncontrolled study was conducted to investigate the efficacy and safety of ramucirumab in combination with PTX and carboplatin in patients with stage IIIB or IV non-small-cell lung cancer (target sample size, 40) in 8 medical institutions overseas.

All of the 40 patients enrolled in the study received ramucirumab and were included in the safety analysis set. No death occurred during the administration period or within 30 days after the last dose of the study drug.

6) Foreign phase II study (5.3.5.4.2, Study I4T-IE-JVBO [November 2007 to ■ 2011])
An open-label, randomized, comparative study was conducted to compare the efficacy and safety between ramucirumab alone and in combination with dacarbazine in patients with metastatic malignant melanoma (target sample size, 104) in 14 medical institutions overseas.

Of 106 patients enrolled in the study (52 in the ramucirumab group, 54 in the ramucirumab/dacarbazine [DTIC] group), 102 patients (50 in the ramucirumab group, 52 in the ramucirumab/DTIC group) received the study drug and were included in the safety analysis set. During the administration period or within 30 days after the last dose of the study drug, 3 patients in the ramucirumab group and 1 patient in the ramucirumab/DTIC group died. A death in the ramucirumab group (1 patient) was due to the progression of the primary disease. Other causes of deaths were hepatic failure (2 patients) in the ramucirumab group and cardiac arrest (1 patient) in the ramucirumab/DTIC group. A causal relationship of the deaths to ramucirumab could not be ruled out for 1 patient with hepatic failure in the ramucirumab group and for 1 patient with cardiac arrest in the ramucirumab/DTIC group.

7) Foreign phase II study (5.3.5.4.3, Study I4T-IE-JVBS [August 2008 to September 2011])
An open-label, randomized, comparative study was conducted to compare the efficacy and safety of ramucirumab and cixutumumab (unapproved in Japan), in combination with mitoxantrone and prednisone (unapproved in Japan) in patients with androgen-independent, metastatic prostate cancer (target sample size, 132) in 28 medical institutions overseas.

Of 138 patients enrolled in the study (69 in the ramucirumab group, 69 in the cixutumumab group), 132 patients (66 in the ramucirumab group, 66 in the cixutumumab group) received the study drug and were included in the safety analysis set. In the ramucirumab group, 6 patients died during the administration period or within 30 days after the last dose of the study drug. Of these, 2 patients died from the progression of the primary disease. Other causes of deaths were septic shock, pneumonia aspiration, intraventricular haemorrhage, and neutropenia (1 patient each). A causal relationship of the deaths to ramucirumab could not be ruled out for 1 patient with septic shock and 1 patient with pneumonia aspiration.

8) Foreign phase III study (5.3.5.4.1, Study I4T-IE-JVBC [August 2008 – ongoing (data cut-off, [redacted] 31, 20[redacted])])

A double-blind, randomized, comparative study was conducted to investigate the efficacy and safety of ramucirumab in combination with DTX in patients with HER2-negative, recurrent, or metastatic breast cancer (target sample size, 1113) in 177 medical institutions overseas.

Of 1455 patients enrolled in the study, 1144 patients (759 in the ramucirumab group, 385 in the placebo group) were included in the ITT population excluding 311 patients who were judged ineligible at screening. In total, 1134 patients in the ITT population, (752 in the ramucirumab group, 382 in the placebo group) received the study drug and were included in the safety analysis set. During the administration period or within 30 days after the last dose of the study drug, 24 patients in the ramucirumab group and 7 patients in the placebo group died. Of these, 10 patients in the ramucirumab group and 4 patients in the placebo group died from the progression of the primary disease. Other Causes of deaths were acute kidney injury (2 patients), sepsis, death,[*1] febrile neutropenia, hepatic encephalopathy, tumour embolism, acute tonsillitis, pneumonia, neutropenic infection, sudden death,[*2] enterocolitis, and hepatic failure (1 patient each) in the ramucirumab group, and hepatic failure, multi-organ failure, and pulmonary embolism (1 patient each) in the placebo group. A causal relationship of the deaths to ramucirumab or placebo could not be ruled out for the patients with acute kidney injury, neutropenic infection, or enterocolitis (1 patient each) and the patient who died[*1] in the ramucirumab group and for the patient with hepatic failure in the placebo group.

[*1] The cause of death was unknown, but considered to be possibly related to cardiac disease or a cerebrovascular event. A causal relationship to ramucirumab could not be ruled out.
[*2] Cause unknown

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

4.(iii).B.(1) Data for review

PMDA considered that, among the submitted data, clinical data from the RAINBOW and REGARD studies are most important for evaluating the efficacy and safety of ramucirumab. The RAINBOW study (a global phase III study) investigated the efficacy and safety of ramucirumab in patients with unresectable advanced/recurrent gastric or gastro-esophageal junction adenocarcinoma with disease progression on or after prior fluoropyrimidine- and platinum-containing chemotherapy. The REGARD study (a foreign phase III study) investigated the efficacy and safety of ramucirumab in patients with unresectable advanced/recurrent gastric or gastro-esophageal junction adenocarcinoma with disease progression on or after prior fluoropyrimidine- or platinum-containing chemotherapy. The evaluations were primarily based on the data of these studies.

4.(iii).B.(2) Efficacy

Based on the following review, PMDA concluded that the efficacy of ramucirumab had been demonstrated in patients with unresectable advanced/recurrent gastric or gastro-esophageal junction adenocarcinoma with disease progression on or after prior fluoropyrimidine- and platinum-containing chemotherapy.

4.(iii).B.(2).1) Use of control group

The applicant explained the rationale for the control or comparator in the RAINBOW and REGARD studies as follows:

In 2008, when the REGARD study was planned, the efficacy of monotherapy with CPT-11 or taxane antineoplastic was suggested by a small-scale open-label, uncontrolled, phase II study in patients with unresectable advanced/recurrent gastric cancer who received previously chemotherapy. However, no standard therapy had been established at that time. Also, the then-applicable US National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN guidelines), Gastric Cancer (v.2. 2009) recommended best supportive care as one of the treatment options for these patients, in addition to the chemotherapy with CPT-11 or taxane antineoplastic agent.

In this context, placebo was selected as the control in the REGARD study. On the other hand, in the RAINBOW study, the efficacy and safety of ramucirumab were investigated in combination with an antineoplastic, which was recommended as a treatment option. From the following safety aspects, once-

weekly administration of PTX (80 mg/m^2) was selected as the comparator (intravenous administration on Days 1, 8, and 15 in each cycle consisting of 4 weeks).

- Hematologic toxicity and non-hematologic toxicity of CPT-11 and DTX were frequently reported in patients with unresectable advanced/recurrent gastric cancer who previously received chemotherapy (e.g., *Jpn J Clin Oncol*. 2004;34:8-13, *Jpn J Clin Oncol.* 2007;37:936-41.).

- The efficacy and safety of PTX in patients with unresectable advanced/recurrent gastric cancer who previously received chemotherapy were investigated mainly at the dose of 80 mg/m^2 at 1-week intervals or the dose of 210 or 225 mg/m^2 at 3-week intervals (e.g., *Anticancer Drugs*. 1998;9:307-10). No data are available from a clinical study that prospectively compared the efficacy and safety of PTX between 1-week interval and 3-week interval. However, a retrospective comparison with an external control revealed that the incidence of Grade 4 neutropenia was higher in patients receiving PTX at 3-week intervals than in patients receiving at 1-week intervals (*Gastric Cancer*. 2002;5:90-5, *Gastric Cancer*. 2006;9:14-8).

After RAINBOW study was initiated, the results of an open-label, randomized, phase III study were reported (*J Clin Oncol*. 2013;31:4438-44.). This study compared the group receiving PTX (80 mg/m^2) at 1-week intervals with the group receiving CPT-11 in patients with unresectable advanced/recurrent gastric cancer who previously received chemotherapy. The results did not show any significant difference in OS between the two groups. Therefore, the applicant considers that the selection of 1-week-interval PTX (80 mg/m^2) as concomitant drug was appropriate from the viewpoint of efficacy as well.

PMDA accepted the explanation of the applicant.

4.(iii).B.(2).2) Efficacy endpoints and evaluation results

Given that treatment of patients with unresectable advanced or recurrent cancer of the stomach or gastroesophageal junction is performed with the expectation of life prolongation, it was appropriate that OS was selected as the primary endpoint in the RAINBOW and REGARD studies.

Also, based on the results of the following studies, PMDA concluded that the efficacy of ramucirumab/PTX combination therapy and of ramucirumab monotherapy was demonstrated.

- The RAINBOW study demonstrated the superiority of the ramucirumab/PTX group in OS to the placebo/PTX group [see "4.(iii).A. *Evaluation data* (3) Global study"].

- The REGARD study demonstrated the superiority of the ramucirumab group in OS to the placebo group [see "4.(iii).A. *Evaluation data* (4).3) Foreign phase III study].

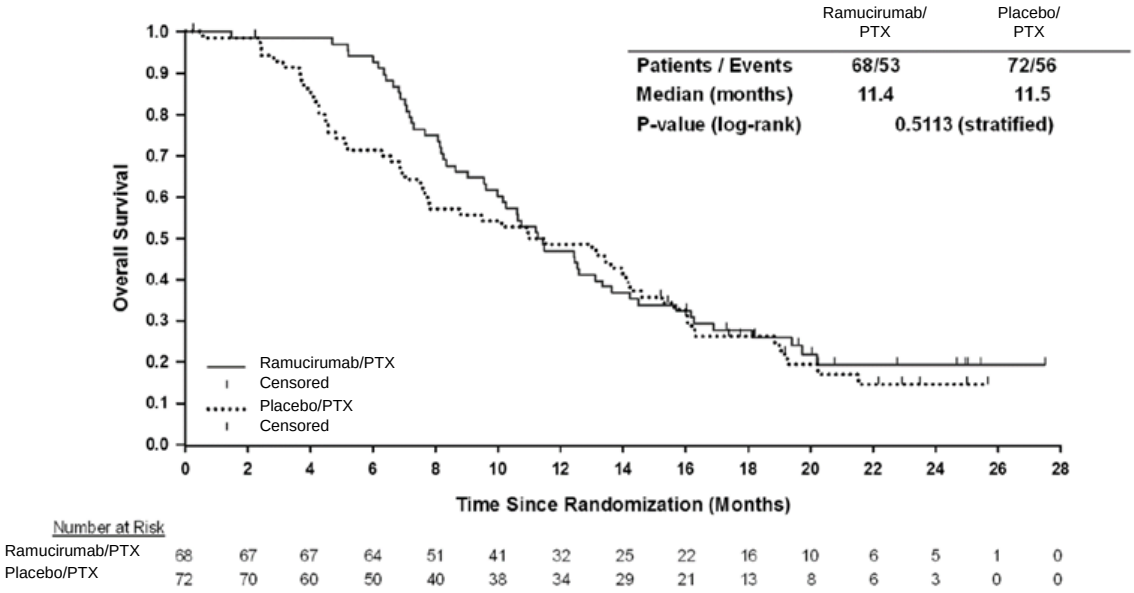
4.(iii).B.(2).3) Efficacy in Japanese patients

In RAINBOW study, the results of OS and Kaplan-Meier curves in the Japanese population were as shown in the following table and figure. The applicant explained that a Japanese phase II study (JVCL study) is ongoing aiming to confirm the efficacy and safety of ramucirumab monotherapy in Japanese patients with adenocarcinoma of the stomach or gastroesophageal junction.

Results of OS analysis in Japanese patients
(RAINBOW study, ITT population, data cut-off on July 12, 2013)

	Ramucirumab/PTX	Placebo/PTX
Number of patients	68	72
Number of deaths (%)	53 (77.9)	56 (77.8)
Median OS [95% CI] (months)	11.35 [9.63, 13.34]	11.53 [7.59, 14.16]
Hazard ratio [95% CI][*1]	0.880 [0.603, 1.284]	
P value (two-sided)[*2]	0.5113	

[*1] Cox proportional-hazards model adjusted for stratification factors (time to progression in the primary treatment [<6 months vs. ≥6 months], presence or absence of measurable lesion [measurable lesion vs. non-measurable lesion])
[*2] Stratified log-rank test (stratified by time to progression in the primary treatment [<6 months vs. ≥6 months], presence or absence of measurable lesion [measurable lesion vs. non-measurable lesion])



Kaplan-Meier curves of OS in Japanese patients (ITT population; data cut-off, July 12, 2013)

PMDA considers as follows:
The RAINBOW study shows a similar tendency in OS in the Japanese population and the entire study population, based on Kaplan-Meier curves, etc. Therefore, ramucirumab is expected to be effective in Japanese patients as well. The results of Japanese phase II study (JVCL study) are expected to provide important information on ramucirumab monotherapy in Japanese patients, and therefore the study must be completed so that necessary measures are taken based on the study results.

4.(iii).B.(3) Safety [for adverse events, see "4.(iv) Adverse events, etc., observed in clinical studies"]

As a result of the following review, PMDA considers that caution should be exercised for the following adverse events in the use of ramucirumab: hypertension, proteinuria, haemorrhage, infusion-related reaction (IRR), thromboembolism, gastrointestinal perforation, cardiac failure congestive, neutropenia/leukopenia, posterior reversible encephalopathy syndrome (RPLS), fistula, disturbance of wound healing, and liver disorder.

PMDA has concluded that ramucirumab monotherapy and ramucirumab/PTX combination therapy are tolerable, provided that physicians with sufficient knowledge and experience of cancer chemotherapy take appropriate measures, such as monitoring and controlling of adverse events as well as the interruption, reduction, or discontinuation of ramucirumab and the concomitant drug.

4.(iii).B.(3).1) Safety profile of ramucirumab

Based on the safety information obtained from the RAINBOW and REGARD studies, the applicant explained the safety profile of ramucirumab as follows:
The outline of the safety in the RAINBOW and REGARD studies was as shown in the following table.

Summary of safety (RAINBOW and REGARD studies)

	Number of patients (%)			
	RAINBOW study		REGARD study	
	Ramucirumab/PTX N = 327	Placebo/PTX N = 329	Ramucirumab N= 236	Placebo N = 115
All adverse events	324 (99.1)	322 (97.9)	223 (94.5)	101 (87.8)
Grade ≥3 adverse events	267 (81.7)	206 (62.6)	134 (56.8)	67 (58.3)
Adverse events resulting in death*	39 (11.9)	51 (15.5)	22 (9.3)	15 (13.0)
Serious adverse events	153 (46.8)	139 (42.2)	106 (44.9)	51 (44.3)
Adverse events leading to treatment discontinuation*				
Ramucirumab (or placebo)	68 (20.8)	68 (20.7)	25 (10.5)	7 (6.0)
PTX	91 (27.8)	76 (23.1)	-	-
Adverse events leading to treatment interruption or dose reduction				
Ramucirumab (or placebo)	151 (46.2)	91 (27.7)	37 (15.7)	8 (7.0)
PTX	233 (71.3)	178 (54.1)	-	-

-, Not applicable; * In the REGARD study, adverse events resulting in death were counted based on the report of fatal cases, and adverse events leading to treatment discontinuation were counted based on the data of treatment completion.

i) RAINBOW study

In the RAINBOW study, adverse events with an incidence of ≥10% either in the ramucirumab/PTX group or in the placebo/PTX group were as shown in the following table.

Adverse events with an incidence of ≥10% in either group (RAINBOW study)

Preferred term (MedDRA/J ver.16.0)	Number of patients (%)			
	Ramucirumab/PTX N = 327		Placebo/PTX N = 329	
	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	324 (99.1)	267 (81.7)	322 (97.9)	206 (62.6)
Neutropenia	178 (54.4)	133 (40.7)	102 (31.0)	62 (18.8)
Decreased appetite	131 (40.1)	10 (3.1)	105 (31.9)	13 (4.0)
Fatigue	130 (39.8)	23 (7.0)	106 (32.2)	13 (4.0)
Nausea	115 (35.2)	6 (1.8)	108 (32.8)	8 (2.4)
Anaemia	111 (33.9)	30 (9.2)	117 (35.6)	34 (10.3)
Leukopenia	111 (33.9)	57 (17.4)	69 (21.0)	22 (6.7)
Alopecia	107 (32.7)	0	127 (38.6)	1 (0.3)
Diarrhoea	106 (32.4)	12 (3.7)	76 (23.1)	5 (1.5)
Abdominal pain	101 (30.9)	18 (5.5)	67 (20.4)	11 (3.3)
Epistaxis	100 (30.6)	0	23 (7.0)	0
Vomiting	88 (26.9)	10 (3.1)	68 (20.7)	12 (3.6)
Oedema peripheral	82 (25.1)	5 (1.5)	45 (13.7)	2 (0.6)
Hypertension	78 (23.9)	46 (14.1)	16 (4.9)	8 (2.4)
Constipation	70 (21.4)	0	71 (21.6)	2 (0.6)
Asthenia	69 (21.1)	18 (5.5)	45 (13.7)	6 (1.8)
Stomatitis	64 (19.6)	2 (0.6)	24 (7.3)	2 (0.6)
Pyrexia	59 (18.0)	3 (0.9)	37 (11.2)	1 (0.3)
Peripheral sensory neuropathy	57 (17.4)	6 (1.8)	36 (10.9)	3 (0.9)
Proteinuria	54 (16.5)	4 (1.2)	20 (6.1)	0
Malignant neoplasm progression	52 (15.9)	47 (14.4)	60 (18.2)	59 (17.9)
Neuropathy peripheral	47 (14.4)	10 (3.1)	30 (9.1)	7 (2.1)
Weight decreased	45 (13.8)	6 (1.8)	49 (14.9)	4 (1.2)
Thrombocytopenia	43 (13.1)	5 (1.5)	20 (6.1)	6 (1.8)
Dyspnoea	42 (12.8)	8 (2.4)	31 (9.4)	2 (0.6)
Cough	40 (12.2)	0	25 (7.6)	0
Back pain	39 (11.9)	4 (1.2)	40 (12.2)	5 (1.5)
Rash	35 (10.7)	0	26 (7.9)	0
Myalgia	34 (10.4)	0	33 (10.0)	1 (0.3)
Ascites	33 (10.1)	12 (3.7)	27 (8.2)	13 (4.0)
Abdominal pain upper	32 (9.8)	3 (0.9)	35 (10.6)	1 (0.3)

In RAINBOW study, adverse events with an incidence ≥10% higher in the ramucirumab/PTX group than in the placebo/PTX group were neutropenia, leukopenia, abdominal pain, epistaxis, oedema peripheral, hypertension, stomatitis, and proteinuria. Grade ≥3 adverse events with an incidence ≥5% higher in the ramucirumab/PTX group than in the placebo/PTX group were neutropenia, leukopenia, and hypertension. A serious adverse event with an incidence ≥2% higher in the ramucirumab/PTX group than in the placebo/PTX group was neutropenia (3.7% in the ramucirumab/PTX group, 0.9% in the placebo/PTX group). Adverse events leading to the discontinuation of ramucirumab or placebo with an incidence ≥2% higher in the ramucirumab/PTX group than in the placebo/PTX group were not reported. Adverse events leading to the discontinuation of PTX with an incidence ≥2% higher in the ramucirumab/PTX group than in the placebo/PTX group were neutropenia (4.0%, 0.3%) and thrombocytopenia (2.8%, 0%). Adverse events leading to the suspension, interruption, or reduction of ramucirumab or placebo with an incidence ≥2% higher in the ramucirumab/PTX group than in the placebo/PTX group were neutropenia (12.8%, 3.3%), proteinuria (8.9%, 1.8%), fatigue (4.9%, 1.8%), asthenia (3.1%, 0.6%), leukopenia (2.8%, 0%), and hypertension (2.4%, 0%). Adverse events leading to the suspension, interruption, or reduction of PTX with an incidence ≥2% higher in the ramucirumab/PTX group than in the placebo/PTX group were neutropenia (42.8%, 22.8%), leukopenia (12.8%, 6.4%), fatigue (7.0%, 3.0%), thrombocytopenia (5.8%, 1.5%), peripheral sensory neuropathy (4.9%, 1.2%), aspartate aminotransferase (AST) increased (3.4%, 1.2%), and asthenia (3.4%, 1.2%).

ii) REGARD study

In the REGARD study, adverse events with an incidence of ≥10% either in the ramucirumab group or in the placebo group were as shown in the following table.

Adverse events with an incidence of ≥10% in either group (REGARD study)

Preferred term (MedDRA/J ver.15.0)	Number of patients (%)			
	Ramucirumab N = 236		Placebo N = 115	
	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	223 (94.5)	134 (56.8)	101 (87.8)	67 (58.3)
Fatigue	58 (24.6)	10 (4.2)	28 (24.3)	4 (3.5)
Decreased appetite	57 (24.2)	8 (3.4)	26 (22.6)	4 (3.5)
Vomiting	47 (19.9)	6 (2.5)	29 (25.2)	5 (4.3)
Abdominal pain	45 (19.1)	12 (5.1)	29 (25.2)	3 (2.6)
Nausea	45 (19.1)	3 (1.3)	30 (26.1)	0
Constipation	36 (15.3)	1 (0.4)	26 (22.6)	3 (2.6)
Hypertension	36 (15.3)	17 (7.2)	9 (7.8)	3 (2.6)
Anaemia	35 (14.8)	15 (6.4)	17 (14.8)	9 (7.8)
Diarrhoea	34 (14.4)	2 (0.8)	10 (8.7)	2 (1.7)
Asthenia	28 (11.9)	5 (2.1)	19 (16.5)	8 (7.0)
Abdominal pain upper	27 (11.4)	3 (1.3)	5 (4.3)	0
Weight decreased	27 (11.4)	3 (1.3)	11 (9.6)	1 (0.9)
Dysphagia	25 (10.6)	5 (2.1)	12 (10.4)	5 (4.3)
Dyspnoea	22 (9.3)	4 (1.7)	15 (13.0)	7 (6.1)

In the REGARD study, adverse events with an incidence ≥5% higher in the ramucirumab group than in the placebo group were hypertension, diarrhoea, and abdominal pain upper. A Grade ≥3 adverse event with an incidence ≥3% higher in the ramucirumab group than in the placebo group was hypertension. Serious adverse events with an incidence ≥2% higher in the ramucirumab group than in the placebo group were anaemia (3.8% in the ramucirumab group, 1.7% in the placebo group), medication error (3.0%, 0.9%), and intestinal obstruction (2.1%, 0%). Adverse events leading to the discontinuation, suspension, interruption, or reduction of ramucirumab or placebo with an incidence ≥2% higher in the ramucirumab group than in the placebo group were not reported.

PMDA considers as follows:

The incidences of individual adverse events tended to be higher following ramucirumab/PTX therapy in the RAINBOW study than following ramucirumab monotherapy in the REGARD study. However, as compared with the occurrence of adverse events in the placebo/PTX group of the RAINBOW study, there was no obvious difference in observed events between ramucirumab/PTX therapy (the RAINBOW

study) and ramucirumab monotherapy (the REGARD study). Also, there was no trend toward clearly higher incidences of fatal or serious adverse events in the ramucirumab/PTX group (the RAINBOW study) or the ramucirumab group (the than in the control group of the respective study.

Taking account of the above, ramucirumab is considered tolerable provided appropriate measures are taken as needed, such as treatment interruption, dose reduction, or treatment discontinuation. However, the incidences of Grade ≥3 adverse events including hypertension, neutropenia, and leukopenia were higher than those in the control group. Therefore, it is necessary to provide a caution to healthcare professionals on the actual statues of these events, through the package insert, etc.

4.(iii).B.(3).2) Safety in Japanese patients

The applicant explained the difference in the safety profile of ramucirumab between Japanese and non-Japanese patients, based on the safety-related information obtained in the RAINBOW study, as follows: The outline of the safety in Japanese and non-Japanese patients in the RAINBOW study were as shown in the following table.

Outline of the difference in safety between Japanese and non-Japanese patients (RAINBOW study)

	Number of patients (%)			
	Ramucirumab/PTX		Placebo/PTX	
	Japanese patients N = 68	Non-Japanese patients N = 259	Japanese patients N = 71	Non-Japanese patients N = 258
All adverse events	68 (100)	256 (98.8)	70 (98.6)	252 (97.7)
Grade ≥3 adverse events	57 (83.8)	210 (81.1)	37 (52.1)	169 (65.5)
Adverse events resulting in death	1 (1.5)	38 (14.7)	2 (2.8)	49 (19.0)
Serious adverse events	15 (22.1)	138 (53.3)	19 (26.8)	120 (46.5)
Adverse events leading to treatment discontinuation				
Ramucirumab (or placebo)	8 (11.8)	60 (23.2)	8 (11.3)	60 (23.3)
PTX	15 (22.1)	76 (29.3)	11 (15.5)	65 (25.2)
Adverse events leading to treatment interruption or dose reduction				
Ramucirumab (or placebo)	8 (11.8)	8 (3.1)	1 (1.4)	2 (0.8)
PTX	31 (45.6)	47 (18.1)	8 (11.3)	16 (6.2)

Adverse events reported by ≥10% of Japanese or non-Japanese patients in the RAINBOW study were as shown in the following table.

Adverse events reported by ≥10% of Japanese or non-Japanese patients (RAINBOW study)

Preferred term (MedDRA/J ver.16.0)	Number of patients (%)							
	Ramucirumab/PTX				Placebo/PTX			
	Japanese patients N = 68		Non-Japanese patients N = 259		Japanese patients N = 71		Non-Japanese patients N = 258	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	68 (100)	57 (83.8)	256 (98.8)	210 (81.1)	70 (98.6)	37 (52.1)	252 (97.7)	169 (65.5)
Neutropenia	58 (85.3)	45 (66.2)	120 (46.3)	88 (34.0)	37 (52.1)	18 (25.4)	65 (25.2)	44 (17.1)
Alopecia	55 (80.9)	0	52 (20.1)	0	58 (81.7)	0	69 (26.7)	1 (0.4)*
Leukopenia	49 (72.1)	31 (45.6)	62 (23.9)	26 (10.0)	33 (46.5)	10 (14.1)	36 (14.0)	12 (4.7)
Peripheral sensory neuropathy	38 (55.9)	2 (2.9)	19 (7.3)	4 (1.5)	29 (40.8)	3 (4.2)	7 (2.7)	0
Decreased appetite	37 (54.4)	2 (2.9)	94 (36.3)	8 (3.1)	33 (46.5)	4 (5.6)	72 (27.9)	9 (3.5)
Epistaxis	37 (54.4)	0	63 (24.3)	0	10 (14.1)	0	13 (5.0)	0
Fatigue	32 (47.1)	1 (1.5)	98 (37.8)	22 (8.5)	28 (39.4)	2 (2.8)	78 (30.2)	11 (4.3)
Stomatitis	31 (45.6)	0	33 (12.7)	2 (0.8)	6 (8.5)	0	18 (7.0)	2 (0.8)
Diarrhoea	29 (42.6)	3 (4.4)	77 (29.7)	9 (3.5)	24 (33.8)	2 (2.8)	52 (20.2)	3 (1.2)
Nausea	26 (38.2)	0	89 (34.4)	6 (2.3)	25 (35.2)	1 (1.4)	83 (32.2)	7 (2.7)
Anaemia	23 (33.8)	7 (10.3)	88 (34.0)	23 (8.9)	20 (28.2)	9 (12.7)	97 (37.6)	25 (9.7)
Vomiting	21 (30.9)	1 (1.5)	67 (25.9)	9 (3.5)	14 (19.7)	1 (1.4)	54 (20.9)	11 (4.3)
Proteinuria	20 (29.4)	3 (4.4)	34 (13.1)	1 (0.4)	5 (7.0)	0	15 (5.8)	0
Oedema peripheral	19 (27.9)	0	63 (24.3)	5 (1.9)	10 (14.1)	1 (1.4)	35 (13.6)	1 (0.4)
Hypertension	16 (23.5)	3 (4.4)	62 (23.9)	43 (16.6)	1 (1.4)	0	15 (5.8)	8 (3.1)
Pyrexia	16 (23.5)	1 (1.5)	43 (16.6)	2 (0.8)	12 (16.9)	0	25 (9.7)	1 (0.4)
Dysgeusia	15 (22.1)	0	14 (5.4)	0	8 (11.3)	0	13 (5.0)	0
Thrombocytopenia	14 (20.6)	2 (2.9)	29 (11.2)	3 (1.2)	2 (2.8)	0	18 (7.0)	6 (2.3)
Arthralgia	14 (20.6)	1 (1.5)	15 (5.8)	0	11 (15.5)	1 (1.4)	9 (3.5)	0
Myalgia	14 (20.6)	0	20 (7.7)	0	16 (22.5)	1 (1.4)	17 (6.6)	0
Nasopharyngitis	13 (19.1)	0	10 (3.9)	0	11 (15.5)	0	8 (3.1)	0
Rash	13 (19.1)	0	22 (8.5)	0	6 (8.5)	0	20 (7.8)	0
Neuropathy peripheral	11 (16.2)	1 (1.5)	36 (13.9)	9 (3.5)	9 (12.7)	1 (1.4)	21 (8.1)	6 (2.3)
Constipation	11 (16.2)	0	59 (22.8)	0	12 (16.9)	0	59 (22.9)	2 (0.8)
Back pain	11 (16.2)	0	28 (10.8)	4 (1.5)	9 (12.7)	0	31 (12.0)	5 (1.9)
Malaise	11 (16.2)	0	5 (1.9)	0	13 (18.3)	0	0	0
Headache	10 (14.7)	0	22 (8.5)	0	8 (11.3)	0	14 (5.4)	1 (0.4)
Hypoalbuminaemia	10 (14.7)	0	21 (8.1)	4 (1.5)	4 (5.6)	0	9 (3.5)	2 (0.8)
AST increased	9 (13.2)	1 (1.5)	18 (6.9)	5 (1.9)	6 (8.5)	1 (1.4)	11 (4.3)	4 (1.6)
Weight decreased	9 (13.2)	0	36 (13.9)	6 (2.3)	11 (15.5)	0	38 (14.7)	4 (1.6)
Dry skin	9 (13.2)	0	16 (6.2)	0	6 (8.5)	0	4 (1.6)	1 (0.4)
γ-GTP increased	8 (11.8)	2 (2.9)	3 (1.2)	1 (0.4)	3 (4.2)	1 (1.4)	3 (1.2)	2 (0.8)
Insomnia	8 (11.8)	0	22 (8.5)	0	10 (14.1)	0	16 (6.2)	0
Haematuria	8 (11.8)	0	8 (3.1)	0	2 (2.8)	0	9 (3.5)	0
ALT increased	7 (10.3)	1 (1.5)	13 (5.0)	3 (1.2)	7 (9.9)	0	11 (4.3)	3 (1.2)
Blood ALP increased	7 (10.3)	0	8 (3.1)	4 (1.5)	6 (8.5)	1 (1.4)	9 (3.5)	5 (1.9)
Pruritus	7 (10.3)	0	14 (5.4)	1 (0.4)	4 (5.6)	0	7 (2.7)	0
Abdominal pain	5 (7.4)	0	96 (37.1)	18 (5.5)	6 (8.5)	0	61 (23.6)	11 (3.3)
Cough	3 (4.4)	0	37 (14.3)	0	1 (4.4)	0	24 (9.3)	0
Malignant neoplasm progression	3 (4.4)	3 (4.4)	49 (18.9)	44 (17.0)	7 (9.9)	7 (9.9)	53 (20.5)	52 (20.2)
Dyspnoea	2 (2.9)	1 (1.5)	40 (15.4)	7 (2.7)	0	0	31 (12.0)	8 (0.8)
Ascites	0	0	33 (12.7)	12 (4.6)	2 (2.8)	2 (2.8)	25 (9.7)	11 (4.3)

AST, Aspartate aminotransferase; ALT, Alanine aminotransferase; ALP, Alkaline phosphatase; γ-GTP, gamma-glutamyl transferase

* Although Grade 3 alopecia is not defined in the Common Terminology Criteria for Adverse Events (CTCAE) v. 4.02 used for calculation, this event was reported as Grade 3 alopecia by the investigator.

Adverse events with a ≥20% higher incidence in Japanese patients than in non-Japanese patients in the ramucirumab/PTX group of the RAINBOW study were neutropenia, alopecia, leukopenia, peripheral sensory neuropathy, epistaxis, and stomatitis. Grade ≥3 adverse events with a ≥5% higher incidence in Japanese patients than in non-Japanese patients were neutropenia and leukopenia. In contrast, the adverse event with a ≥20% higher incidence in non-Japanese patients than in Japanese patients was abdominal pain, and Grade ≥3 adverse events with a ≥5% higher incidence in non-Japanese patients than in Japanese patients were fatigue, hypertension, abdominal pain, and malignant neoplasm progression.

PMDA considers as follows:
In the RAINBOW study, there was no clear difference between Japanese and non-Japanese patients in the types of adverse events observed in the ramucirumab/PTX group. Also, there was no trend toward higher incidences of adverse events resulting in death, serious adverse events, or adverse events leading to the discontinuation of the study drug (ramucirumab, placebo, or PTX) in Japanese patients than in non-Japanese patients. However, attention should be paid to adverse events that tended to be seen more frequently in Japanese patients than in non-Japanese patients in the RAINBOW study. Information on these events should be provided to healthcare professionals appropriately through information materials, etc.

The following sections discuss (a) major adverse events with a higher incidence in the ramucirumab group than in the control group in the RAINBOW or REGARD study, and major adverse events with a higher incidence in Japanese patients than in non-Japanese patients, and (b) serious adverse events observed after the administration of ramucirumab or other antineoplastics with anti-angiogenic activity, such as IRR, gastrointestinal perforation, cardiac failure congestive, neutropenia/leukopenia, RPLS, fistula, and disturbance of wound healing.

4.(iii).B.(3).3) Hypertension
The applicant explained hypertension-related events after the administration of ramucirumab as follows:
As hypertension-related events, MedDRA preferred terms (PTs) categorized as Standardized MedDRA Query (SMQ) "hypertension" were tabulated except for hyperaldosteronism, maternal hypertension affecting foetus, pre-eclampsia, secondary aldosteronism, hypertension neonatal, metabolic syndrome, and renal artery ablation.

The incidences of hypertension-related adverse events in the RAINBOW and REGARD studies were as shown in the following table.

Incidences of hypertension-related adverse events (RAINBOW and REGARD studies)

Preferred term*	Number of patients (%)							
	RAINBOW study				REGARD study			
	Ramucirumab/PTX N = 327		Placebo/PTX N = 329		Ramucirumab N = 236		Placebo N = 115	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Hypertension-related events	82 (25.1)	48 (14.7)	19 (5.8)	9 (2.7)	38 (16.1)	18 (7.6)	9 (7.8)	3 (2.6)
Hypertension	78 (23.9)	46 (14.1)	16 (4.9)	8 (2.4)	36 (15.3)	17 (7.2)	9 (7.8)	3 (2.6)
Blood pressure increased	5 (1.5)	2 (0.6)	2 (0.6)	0	3 (1.3)	1 (0.4)	0	0
Hypertensive cardiomyopathy	0	0	1 (0.3)	0	0	0	0	0
Procedural hypertension	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)	0	0	0	0
Systolic hypertension	1 (0.3)	1 (0.3)	0	0	0	0	0	0

* MedDRA/J ver.16.0 in the RAINBOW study, MedDRA/J ver.15.0 in the REGARD study

In the RAINBOW and REGARD studies, antihypertensive treatment was initiated when Grade ≤3 hypertension-related events occurred. In asymptomatic patients, the administration of ramucirumab or placebo was continued (ramucirumab or placebo was discontinued if Grade 3 hypertension persisted for more than 2 weeks). In symptomatic patients, the administration of ramucirumab or placebo was interrupted until the symptom disappeared. In patients with Grade 4 hypertension or poorly controlled hypertension (systolic blood pressure ≥160 mm Hg or diastolic blood pressure ≥100 mm Hg persisting for more than 4 weeks) despite appropriate antihypertensive treatment (≥3 types of oral antihypertensive drugs at the maximum dose), the administration of ramucirumab or placebo was discontinued.

Antihypertensive drugs (diuretics, peripheral vasodilators, β-blockers, calcium channel blockers, renin-angiotensin system drugs) were concomitantly administered during the study period in 180 of 327 patients (55.0%) in the ramucirumab/PTX group and in 124 of 329 patients (37.7%) in the placebo/PTX group of the RAINBOW study, and in 101 of 236 patients (42.8%) in the ramucirumab group and in 46 of 115 patients (40.0%) in the placebo group of the REGARD study.

In the RAINBOW study, there were no hypertension-related events that were serious or resulted in death. Hypertension-related events leading to discontinuation of ramucirumab were reported by 2 of 327 patients (0.6%, hypertension in both patients) in the ramucirumab/PTX group.

In the REGARD study, a serious hypertension-related event was reported by 1 of 236 patients (0.4%, hypertension) in the ramucirumab group. A causal relationship of the event to ramucirumab could not be ruled out. There were no hypertension-related events that resulted in death or the discontinuation of ramucirumab.

PMDA considers as follows:
In both the RAINBOW and REGARD studies, the incidences of all grades and Grade ≥3 hypertension-related events were higher in the ramucirumab group than in the control group. Therefore, attention should be paid to these events in the use of ramucirumab, and information on the incidences of and how to respond to these events, etc. should be provided to healthcare professionals appropriately via the package insert, etc.

4.(iii).B.(3).4) Proteinuria
The applicant explained proteinuria-related events after the administration of ramucirumab as follows:
As proteinuria-related events, MedDRA PTs of albuminuria, nephrotic syndrome, protein urine, protein urine present, proteinuria, and "urine protein, quantitative" were tabulated.

In the RAINBOW and REGARD studies, the incidences of proteinuria-related events were as shown in the following table.

Incidences of proteinuria-related events (RAINBOW and REGARD studies)

Preferred term*	Number of patients (%)							
	RAINBOW study				REGARD study			
	Ramucirumab/PTX N = 327		Placebo/PTX N = 329		Ramucirumab N = 236		Placebo N = 115	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Proteinuria-related events	55 (16.8)	4 (1.2)	20 (6.1)	0	7 (3.0)	1 (0.4)	3 (2.6)	0
Proteinuria	54 (16.5)	4 (1.2)	20 (6.1)	0	7 (3.0)	1 (0.4)	3 (2.6)	0
Protein urine	1 (0.3)	0	0	0	0	0	0	0

* MedDRA/J ver.16.0 in the RAINBOW study, MedDRA/J ver.15.0 in REGARD study

In the RAINBOW and REGARD studies, 24-hour urine was collected if urinalysis showed ≥2+ urine protein. If protein in the collected urine was ≥2 g/24 hours and <3 g/24 hours, the administration of ramucirumab or placebo was withdrawn for 1 week. If protein in the collected urine was ≥3 g/24 hours, if protein ≥2 g/24 hours and <3 g/24 hours was observed 3 times, or if protein increased to ≥2 g/24 hours and <3 g/24 hours and did not decrease to <2 g/24 hours within 2 weeks, the administration of ramucirumab or placebo was discontinued.

In the RAINBOW study, a Grade ≥3 proteinuria-related event was reported by 1 patient. This event had a temporal relationship with Grade 2 hypoalbuminaemia and Grade 1 face oedema, which suggested the possibility of nephrotic syndrome. There were no proteinuria-related events that were serious or resulted in death. Proteinuria-related events leading to the discontinuation of ramucirumab or placebo were reported by 4 of 327 patients (1.2%, proteinuria in 4 patients) in the ramucirumab/PTX group.

In REGARD study, there were no proteinuria-related events that were serious or resulted in death. Proteinuria-related events leading to the discontinuation of the study drug were reported by 2 of 236 patients (0.8%, proteinuria in both patients) in the ramucirumab group.

PMDA considers as follows:
In both the RAINBOW and REGARD studies, the incidences of all grades and Grade ≥3 proteinuria-related events were higher in the ramucirumab group than in the control group. In the ramucirumab/PTX group of the RAINBOW study, events suggesting the possibility of nephrotic syndrome were observed, and all grades and Grade ≥3 proteinuria-related events were observed more frequently in Japanese patients than in non-Japanese patients [see "4.(iii).B.(3).2) Safety in Japanese patients"]. Attention should be paid to these events in the use of ramucirumab, and information on the incidences of and how to respond to these events, etc. should be provided appropriately to healthcare professionals via the package insert, etc.

4.(iii).B.(3).5) Haemorrhage

The applicant explained haemorrhage-related events after the administration of ramucirumab as follows: As haemorrhage-related events, MedDRA PTs categorized as MedDRA SMQ "haemorrhage terms (excl laboratory terms)" other than arterial rupture and iliac artery rupture, MedDRA PTs categorized as MedDRA SMQ "haemorrhage laboratory terms (narrow)," and MedDRA PT skin neoplasm bleeding were tabulated. Also, MedDRA PTs categorized as MedDRA SMQ "gastrointestinal haemorrhage" were tabulated as gastrointestinal haemorrhage-related events.

The incidences of haemorrhage-related events and gastrointestinal haemorrhage-related events in the RAINBOW and REGARD studies were as shown in the following table.

Incidences of haemorrhage-related events and gastrointestinal haemorrhage-related events (RAINBOW and REGARD studies)

Preferred term*	Number of patients (%)							
	RAINBOW study				REGARD study			
	Ramucirumab/PTX N = 327		Placebo/PTX N = 329		Ramucirumab N = 236		Placebo N = 115	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Haemorrhage-related events	137 (41.9)	14 (4.3)	59 (17.9)	8 (2.4)	32 (13.6)	9 (3.8)	13 (11.3)	3 (2.6)
Gastrointestinal haemorrhage-related events among haemorrhage-related events	33 (10.1)	12 (3.7)	20 (6.1)	5 (1.5)	15 (6.4)	7 (3.0)	7 (6.1)	3 (2.6)
Epistaxis	100 (30.6)	0	23 (7.0)	0	11 (4.7)	0	1 (0.9)	0
Haematuria	16 (4.9)	0	11 (3.3)	0	3 (1.3)	1 (0.4)	2 (1.7)	0
Gingival bleeding	9 (2.8)	0	0	0	1 (0.4)	0	0	0
Haemoptysis	7 (2.1)	1 (0.3)	3 (0.9)	0	2 (0.8)	0	1 (0.9)	0
Melaena	6 (1.8)	2 (0.6)	3 (0.9)	0	1 (0.4)	0	0	0
Gastric haemorrhage	5 (1.5)	4 (1.2)	5 (1.5)	2 (0.6)	1 (0.4)	1 (0.4)	1 (0.9)	1 (0.9)
Gastrointestinal haemorrhage	5 (1.5)	5 (1.5)	4 (1.2)	2 (0.6)	3 (1.3)	3 (1.3)	2 (1.7)	1 (0.9)
Anal haemorrhage	5 (1.5)	0	3 (0.9)	0	0	0	0	0
Haemorrhoidal haemorrhage	5 (1.5)	0	3 (0.9)	0	1 (0.4)	0	0	0
Haematemesis	4 (1.2)	2 (0.6)	1 (0.3)	0	9 (3.8)	2 (0.8)	3 (2.6)	0
Rectal haemorrhage	4 (1.2)	0	1 (0.3)	0	1 (0.4)	0	0	0
Haematochezia	2 (0.6)	0	0	0	0	0	0	0
Oesophageal haemorrhage	1 (0.3)	1 (0.3)	0	0	0	0	0	0
Upper gastrointestinal haemorrhage	1 (0.3)	0	1 (0.3)	1 (0.3)	1 (0.4)	1 (0.4)	1 (0.9)	1 (0.9)
Diarrhoea haemorrhagic	1 (0.3)	0	0	0	0	0	0	0
Mallory-Weiss syndrome	0	0	1 (0.3)	0	0	0	0	0

* MedDRA/J ver.16.0 in the RAINBOW study, MedDRA/J ver.15.0 in the REGARD study

In the RAINBOW study, haemorrhage-related events resulting in death were reported by 1 of 327 patients (0.3%, gastrointestinal haemorrhage) in the ramucirumab/PTX group and 2 of 329 patients (0.6%, cerebral haemorrhage and gastrointestinal haemorrhage in 1 patient each) in the placebo/PTX group. Among them, a causal relationship to ramucirumab or placebo could not be ruled out for gastrointestinal haemorrhage (1 patient) in the ramucirumab/PTX group and cerebral haemorrhage (1 patient) in the placebo/PTX group. Serious haemorrhage-related events were reported by 15 of 327 patients (4.6%; gastric haemorrhage and haematemesis in 3 patients each, gastrointestinal haemorrhage, melaena, and haemoptysis in 2 patients each, gastrointestinal haemorrhage/oesophageal haemorrhage, upper gastrointestinal haemorrhage, and anal haemorrhage in 1 patient each) in the ramucirumab/PTX group, and 4 of 329 patients (1.2%; gastric haemorrhage in 2 patients, gastrointestinal haemorrhage and disseminated intravascular coagulation in 1 patient each) in the placebo/PTX group. A causal relationship to ramucirumab or placebo could not be ruled out for gastric haemorrhage and haemoptysis (2 patients each), gastrointestinal haemorrhage, melaena, and gastric haemorrhage/oesophageal haemorrhage (1 patient each) in the ramucirumab/PTX group and gastric haemorrhage (2 patients) in the placebo/PTX group. Haemorrhage-related events leading to the discontinuation of ramucirumab or placebo were reported by 3 of 327 patients (0.9%; gastrointestinal haemorrhage in 2 patients, gastric haemorrhage in 1 patient) in the ramucirumab/PTX group and 1 of 329 patients (0.3%, gastric haemorrhage) in the placebo/PTX group.

In the REGARD study, haemorrhage-related events resulting in death were reported by 2 of 236 patients (0.8%, gastric haemorrhage and gastrointestinal haemorrhage in 1 patient each) in the ramucirumab

group and 1 of 115 patients (0.8%, gastrointestinal haemorrhage) in the placebo group. A causal relationship to ramucirumab could not be ruled out for gastric haemorrhage (1 patient) in the ramucirumab group. Serious haemorrhage-related events were reported by 5 of 236 patients (2.1%; haematemesis in 2 patients, gastrointestinal haemorrhage, upper gastrointestinal haemorrhage, and disseminated intravascular coagulation in 1 patient each) in the ramucirumab group and 3 of 115 patients (2.6%; gastrointestinal haemorrhage, gastric haemorrhage, and upper gastrointestinal haemorrhage in 1 patient each) in the placebo group. A causal relationship to ramucirumab or placebo could not be ruled out for haematemesis, upper gastrointestinal haemorrhage, and disseminated intravascular coagulation (1 patient each) in the ramucirumab group and upper gastrointestinal haemorrhage (1 patient) in the placebo group. Haemorrhage-related events leading to the discontinuation of ramucirumab or placebo were reported by 3 of 236 patients (1.3%; haematemesis, upper gastrointestinal haemorrhage, and disseminated intravascular coagulation in 1 patient each) in the ramucirumab group and 2 of 115 patients (1.7%, gastric haemorrhage and upper gastrointestinal haemorrhage in 1 patient each) in the placebo group.

Details of patients who had fatal or serious haemorrhage-related events in the RAINBOW or REGARD study were as shown in the following table.

Patients who had fatal or serious haemorrhage-related events (RAINBOW and REGARD studies)

Treatment group	Age	Sex	Primary lesion	Primary tumor	Peritoneal dissemination	Preferred term*	Grade	Days to onset	Number of doses	Causal relationship to ramucirumab	Outcome
RAINBOW study											
Ramucirumab/ PTX	65	M	GEJ	Yes	No	Gastric haemorrhage	3	52	4	Yes	Recovered
Ramucirumab/ PTX	40	M	Stomach	Yes	Yes	Haematemesis	2	5	1	No	Recovered
Ramucirumab/ PTX	57	M	GEJ	No	No	Melaena	4	519	31	No	Recovered
Ramucirumab/ PTX	77	M	GEJ	Yes	No	Gastrointestinal haemorrhage	5	54	4	Yes	Death
Ramucirumab/ PTX	73	F	GEJ	No	Yes	Anal haemorrhage	2	26	2	No	Recovered
Ramucirumab/ PTX	47	M	GEJ	No	No	Gastrointestinal haemorrhage	3	68	5	Yes	Recovered
						Oesophageal haemorrhage	3	68	5	Yes	Recovered
Ramucirumab/ PTX	55	M	Stomach	No	No	Gastrointestinal haemorrhage	3	192	14	No	Recovered
Ramucirumab/ PTX	47	M	Stomach	Yes	Yes	Gastric haemorrhage	3	62	5	Yes	Recovered
Ramucirumab/ PTX	42	M	Stomach	Yes	Yes	Haemoptysis	1	175	13	Yes	Recovered
Ramucirumab/ PTX	66	M	Stomach	No	Yes	Haematemesis	3	99	6	No	Recovered
Ramucirumab/ PTX	71	M	GEJ	Yes	Yes	Haemoptysis	1	27	2	Yes	Recovered
Ramucirumab/ PTX	60	F	Stomach	Yes	Yes	Melaena	3	249	18	Yes	Recovered
Ramucirumab/ PTX	68	M	Stomach	Yes	Yes	Gastric haemorrhage	3	243	16	No	Recovered
Ramucirumab/ PTX	60	M	Stomach	No	Yes	Gastrointestinal haemorrhage	3	175	13	Yes	Recovered
Ramucirumab/ PTX	62	M	Stomach	No	Yes	Haematemesis	2	388	26	No	Recovered
Ramucirumab/ PTX	28	F	Stomach	Yes	Yes	Upper gastrointestinal haemorrhage	1	121	9	No	Recovered
Placebo/PTX	53	M	Stomach	Yes	No	Gastric haemorrhage	3	298	21	Yes	Unrecovered
Placebo/PTX	75	F	GEJ	Yes	No	Gastric haemorrhage	3	89	6	Yes	Unrecovered
Placebo/PTX	63	F	Stomach	Yes	No	Gastrointestinal haemorrhage	5	28	2	No	Death
Placebo/PTX	61	F	Stomach	Yes	Yes	Gastrointestinal haemorrhage	4	93	7	No	Recovered
Placebo/PTX	58	F	Stomach	No	Yes	Disseminated intravascular coagulation	4	22	2	No	Unrecovered

Treatment group	Age	Sex	Primary lesion	Primary tumor	Peritoneal dissemination	Preferred term*	Grade	Days to onset	Number of doses	Causal relationship to ramucirumab	Outcome
Placebo/PTX	64	F	Stomach	No	Yes	Cerebral haemorrhage	4	67	6	Yes	Death
						Cerebral haemorrhage	5	69	6	Yes	Death
REGARD study											
Ramucirumab	73	F	Stomach	Yes	No	Gastrointestinal haemorrhage	3	8	1	No	Recovered
Ramucirumab	66	M	GEJ	Yes	No	Gastric haemorrhage	5	44	4	Yes	Death
Ramucirumab	56	M	Stomach	Yes	No	Disseminated intravascular coagulation	3	7	1	Yes	Ongoing
Ramucirumab	68	M	GEJ	Yes	No	Upper gastrointestinal haemorrhage	3	3	1	Yes	Recovered
Ramucirumab	49	M	Stomach	Yes	No	Haematemesis	3	79	6	No	Recovered
Ramucirumab	49	M	GEJ	Yes	Yes	Haematemesis	4	20	2	Yes	Recovered
Ramucirumab	50	M	Stomach	Yes	No	Gastrointestinal haemorrhage	5	6	1	No	Death
Placebo	71	F	GEJ	Yes	No	Upper gastrointestinal haemorrhage	3	87	6	Yes	Recovered
Placebo	65	M	Stomach	Yes	Yes	Gastric haemorrhage	4	10	1	No	Death
Placebo	59	M	Stomach	Yes	Unknown	Gastrointestinal haemorrhage	1	53	4	No	Recovered
						Gastrointestinal haemorrhage	1	85	6	No	Recovered
Placebo	70	M	Stomach	No	Yes	Gastrointestinal haemorrhage	5	40	3	No	Death

GEJ, Gastroesophageal junction;
* MedDRA/J ver.16.0 in the RAINBOW study, MedDRA/J ver.15.0 in the REGARD study

The applicant explained that the following findings were observed in the RAINBOW and REGARD studies: (a) Gastrointestinal haemorrhage-related events were observed regardless of whether the primary tumor had been resected or not or the presence or absence of peritoneal metastasis, and (b) although there was a correlation between the onset of thrombocytopenia and the onset of gastrointestinal haemorrhage-related events regardless of whether ramucirumab was administered or not, there was no trend toward stronger correlation between the onset of thrombocytopenia and of gastrointestinal haemorrhage-related events in the ramucirumab group as compared with the control group.

PMDA considers as follows:
In both the RAINBOW and REGARD studies, the incidences of all grades and Grade ≥3 haemorrhage-related events were higher in the ramucirumab group than in the control group. Also, gastrointestinal haemorrhage-related events accounted for the majority of serious haemorrhage-related events including fatal cases. Therefore, attention should be paid to haemorrhage-related events, particularly to gastrointestinal haemorrhage-related events, in treatment with ramucirumab. Information on the incidences of and how to respond to these events, etc. should be provided appropriately to healthcare professionals via the package insert, etc.

4.(iii).B.(3).6) IRR
The applicant explained IRR-related events after the administration of ramucirumab as follows:
As IRR-related events, MedDRA PTs of anaphylactic reaction, anaphylactic shock, cytokine release syndrome, drug hypersensitivity, hypersensitivity, and infusion related reaction were tabulated.

The incidences of IRR-related events in the RAINBOW and REGARD studies were as shown in the following table.

Incidences of IRR-related events (RAINBOW and REGARD studies)

Preferred term*	Number of patients (%)							
	RAINBOW study				REGARD study			
	Ramucirumab/PTX N = 327		Placebo/PTX N = 329		Ramucirumab N = 236		Placebo N = 115	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
IRR-related events	19 (5.8)	2 (0.6)	12 (3.6)	0	1 (0.4)	0	2 (1.7)	0
Infusion related reaction	14 (4.3)	1 (0.3)	8 (2.4)	0	0	0	1 (0.9)	0
Drug hypersensitivity	4 (1.2)	1 (0.3)	3 (0.9)	0	0	0	1 (0.9)	0
Hypersensitivity	1 (0.3)	0	1 (0.3)	0	1 (0.4)	0	0	0

* MedDRA/J ver.16.0 in the RAINBOW study, MedDRA/J ver.15.0 in the REGARD study

In the JVBO study (a foreign phase II study in patients with malignant melanoma), the incidence of IRR was higher in the initial cohort (6 of 37 patients [16.2%], with Grade ≥3 events in 2 patients). Therefore, in all then-ongoing and scheduled clinical studies on ramucirumab, pretreatment before the administration of ramucirumab was encouraged. Thus, in the RAINBOW and REGARD studies, pretreatment with an antihistaminic drug (diphenhydramine), etc. was recommended before the administration of ramucirumab or placebo. RAINBOW study required pretreatment in accordance with the package insert of PTX before the administration of PTX. In case of a Grade 1 IRR-related event, the infusion rate of ramucirumab or placebo was to be reduced to 50% of the original rate. In case of a Grade 2 IRR-related event, the administration of ramucirumab or placebo was temporarily discontinued and, after the event improved to Grade ≤1, treatment was to be resumed with the infusion rate reduced to 50%. In both Grade 1 and 2 cases, pretreatment was mandated at every subsequent dose. In case of a Grade 3 or 4 IRR-related event, the administration of ramucirumab or placebo was to be discontinued. If a Grade 1 or 2 IRR-related event occurred twice, the patient was to be pretreated with an antihistaminic drug, acetaminophen, or dexamethasone sodium phosphate, etc. before the administration of the study drug at every subsequent dose. In case of a Grade ≥2 event, symptomatic therapy with antihistaminic drug, acetaminophen, and dexamethasone sodium phosphate, etc. was to be performed.

In the RAINBOW study, pretreatment was performed before the administration of ramucirumab or placebo in 78.9% (2865 of 3632 doses) in the ramucirumab/PTX group and in 79.9% (2125 of 2659 doses) in the placebo/PTX group. In the REGARD study, pretreatment was performed in 77.5% (183 of 236 patients) in the ramucirumab group and in 80.0% (92 of 115 patients) in the placebo group. In the RAINBOW study, pretreatment was performed before the administration of PTX in 99.9% (4492 of 4494 doses) in the ramucirumab/PTX group and in 99.8% (3707 of 3715 doses) in the placebo/PTX group.

In the RAINBOW study, there were no IRR-related events that were serious or resulted in death. An IRR-related event leading to the discontinuation of ramucirumab or placebo was reported by 1 of 329 patients (0.3%, drug hypersensitivity) in the placebo/PTX group. IRR-related events leading to the interruption of ramucirumab or placebo were reported by 4 of 327 patients (1.2%) in the ramucirumab/PTX group and 2 of 329 patients (0.6%) in the placebo/PTX group. An event that resulted in a change in the infusion rate was reported by 1 of 327 patients (0.3%) in the ramucirumab/PTX group and 1 of 329 patients (0.3%) in the placebo/PTX group.

In the REGARD study, there were no IRR-related events that were fatal, serious, or resulted in the discontinuation or interruption of ramucirumab or placebo, or a change in the infusion rate.

PMDA considers as follows:
In both the RAINBOW and REGARD studies, pretreatment was encouraged and IRR was controlled by changing the infusion rate or interrupting infusion depending on the severity of IRR. As a result, there was no serious IRR reported, and IRR is considered tolerable. Accordingly, the "Precautions for Dosage and Administration" section of the package insert should highlight the need of pretreatment before the administration of ramucirumab, as required in the RAINBOW and REGARD studies [see "4.(iii).B.(5) Dosage and administration"].

Also, the incidence of and how to respond to IRR, etc. should be provided appropriately to healthcare professionals via the package insert, etc.

4.(iii).B.(3).7) Thromboembolism

The applicant explained thromboembolism-related events after the administration of ramucirumab as follows:

The following events were tabulated as arterial thromboembolism-related events: (i) MedDRA PTs categorized as MedDRA SMQ "embolic and thrombotic events, arterial," except for visual acuity reduced transiently, blindness transient, thrombotic thrombocytopenic purpura, thrombotic microangiopathy, amaurosis, hypothenar hammer syndrome, aortogram abnormal, arteriogram abnormal, and capsular warning syndrome, (ii) MedDRA PTs categorized as MedDRA SMQ "myocardial infarction (narrow)" or "other ischaemic heart disease (narrow)," and (iii) MedDRA PTs coronary bypass thrombosis, thrombotic cerebral infarction, thrombotic stroke, thyroid infarction, embolic cerebral infarction, embolic stroke, thalamic infarction, haemorrhagic infarction, haemorrhagic stroke, haemorrhagic cerebral infarction, post procedural stroke, cerebellar infarction, renal infarct, testicular infarction, spinal cord infarction, haemorrhagic transformation stroke, basal ganglia stroke, brain stem thrombosis, brain stem infarction, brain stem stroke, cerebral ischaemia, cerebrovascular accident, cerebral infarction, peripheral revascularisation, retinal infarction, and splenic infarction, cardiac arrest, cardio-respiratory arrest, cerebral circulatory failure, ischaemia, peripheral vascular disorder, and retinal ischaemia. Also, the following events were tabulated as venous thromboembolism-related events: (i) MedDRA PTs categorized as MedDRA SMQ "embolic and thrombotic events, venous," except for SI QIII TIII pattern, Budd-Chiari syndrome, Homans' sign positive, compression stockings application, hepatic vein thrombosis, hepatic vein occlusion, venous thrombosis neonatal, catheterisation venous, intravenous catheter management, central venous catheterisation, postpartum venous thrombosis, portal vein thrombosis, and portal vein occlusion, and (ii) MedDRA PTs atrial thrombosis, thrombosis in device, embolism, and thrombosis.

The incidences of thromboembolism-related events in the RAINBOW and REGARD studies were as shown in the following table.

Incidences of thromboembolism-related events (RAINBOW and REGARD studies)

Preferred term*	Number of patients (%)							
	RAINBOW study				REGARD study			
	Ramucirumab/PTX N = 327		Placebo/PTX N = 329		Ramucirumab N = 236		Placebo N = 115	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Arterial thromboembolism-related events	6 (1.8)	3 (0.9)	5 (1.5)	3 (0.9)	4 (1.7)	3 (1.3)	0	0
Myocardial infarction	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.4)	1 (0.4)	0	0
Angina pectoris	1 (0.3)	0	1 (0.3)	1 (0.3)	1 (0.4)	0	0	0
Myocardial ischaemia	1 (0.3)	0	0	0	1 (0.4)	0	0	0
Acute coronary syndrome	0	0	1 (0.3)	1 (0.3)	0	0	0	0
Coronary artery disease	0	0	1 (0.3)	0	0	0	0	0
Stress cardiomyopathy	0	0	1 (0.3)	1 (0.3)	0	0	0	0
Cardiac arrest	0	0	0	0	1 (0.4)	1 (0.4)	0	0
Cerebrovascular accident	1 (0.3)	1 (0.3)	0	0	1 (0.4)	1 (0.4)	0	0
Ischaemic stroke	1 (0.3)	1 (0.3)	0	0	0	0	0	0
Cerebral infarction	1 (0.3)	0	1 (0.3)	0	0	0	0	0
Cerebral ischaemia	0	0	0	0	1 (0.4)	0	0	0
Intestinal ischaemia	0	0	1 (0.3)	1 (0.3)	0	0	0	0
Venous thromboembolism-related events	13 (4.0)	8 (2.4)	18 (5.5)	11 (3.3)	11 (4.7)	3 (1.3)	8 (7.0)	5 (4.3)
Atrial thrombosis	0	0	1 (0.3)	1 (0.3)	0	0	0	0
Deep vein thrombosis	5 (1.5)	3 (0.9)	3 (0.9)	1 (0.3)	3 (1.3)	0	3 (2.6)	2 (1.7)
Embolism	2 (0.6)	0	0	0	0	0	2 (1.7)	0
Embolism venous	1 (0.3)	0	0	0	0	0	0	0
Pulmonary embolism	4 (1.2)	4 (1.2)	11 (3.3)	10 (3.0)	4 (1.7)	3 (1.3)	3 (2.6)	3 (2.6)
Pulmonary thrombosis	1 (0.3)	1 (0.3)	0	0	0	0	0	0
Thrombophlebitis	0	0	1 (0.3)	0	2 (0.8)	0	0	0
Thrombosis	1 (0.3)	0	1 (0.3)	0	1 (0.4)	0	1 (0.9)	1 (0.9)
Vena cava thrombosis	0	0	2 (0.6)	2 (0.6)	0	0	0	0
Venous thrombosis	0	0	2 (0.6)	0	0	0	0	0
Venous thrombosis limb	0	0	0	0	1 (0.4)	0	0	0

* MedDRA/J ver.16.0 in the RAINBOW study, MedDRA/J ver.15.0 in the REGARD study

In the RAINBOW study, an arterial thromboembolism-related event resulting in death was reported by 1 of 329 patients (0.3%, myocardial infarction) in the placebo/PTX group, but its causal relationship to placebo was ruled out. Arterial thromboembolism-related serious events were reported by 3 of 327 patients (0.9%; cerebral infarction, cerebrovascular accident, and ischaemic stroke in 1 patient each) in the ramucirumab/PTX group and 3 of 329 patients (0.9%; cerebral infarction, acute coronary syndrome/angina pectoris, and intestinal ischaemia in 1 patient each) in the placebo/PTX group. A causal relationship to ramucirumab or placebo could not be ruled out for cerebral infarction (1 patient) in the ramucirumab/PTX group and intestinal ischaemia (1 patient) in the placebo/PTX group. There were no arterial thromboembolism-related events leading to the discontinuation of ramucirumab or placebo. Venous thromboembolism-related events resulting in death were reported by 1 of 327 patients (0.3%; pulmonary embolism) in the ramucirumab/PTX group and 2 of 329 patients (0.6%; pulmonary embolism in both patients) in the placebo/PTX group, and their causal relationship to ramucirumab or placebo could not be ruled out. Venous thromboembolism-related serious events were reported by 4 of 327 patients (1.2%, deep vein thrombosis and pulmonary embolism in 2 patients each) in the ramucirumab/PTX group and 11 of 329 patients (3.3%; pulmonary embolism in 5 patients, venous thrombosis in 2 patients, deep vein thrombosis, deep vein thrombosis/pulmonary embolism, atrial thrombosis, and vena cava thrombosis in 1 patient each) in the placebo/PTX group. A causal relationship to ramucirumab or placebo could not be ruled out for deep vein thrombosis and pulmonary embolism (2 patients each) in the ramucirumab/PTX group and pulmonary embolism (4 patients), deep vein thrombosis, deep vein thrombosis/pulmonary embolism, vena cava thrombosis, and atrial thrombosis (1 patient each) in the placebo/PTX group. Venous thromboembolism-related events leading to the discontinuation of ramucirumab or placebo were reported by 2 of 327 patients (0.6%; deep vein thrombosis in both patients) in the ramucirumab/PTX group and 6 of 329 patients (1.8%; pulmonary embolism in 3 patients, deep vein thrombosis, venous thrombosis, and atrial thrombosis in 1 patient each) in the placebo/PTX group.

In the REGARD study, arterial thromboembolism-related events resulting in death were reported by 2 of 236 patients (0.8%, myocardial infarction and cardiac arrest in 1 patient each) in the ramucirumab group. A causal relationship to ramucirumab could not be ruled out for myocardial infarction (1 patient). Arterial thromboembolism-related serious events were reported by 2 of 236 patients (0.8%, cerebral ischaemia and cerebrovascular accident in 1 patient each) in the ramucirumab group. A causal relationship to ramucirumab could not be ruled out for cerebrovascular accident (1 patient). An arterial thromboembolism-related event leading to the discontinuation of ramucirumab or placebo was reported by 1 of 236 patients (0.4%, cerebrovascular accident) in the ramucirumab group. Venous thromboembolism-related events resulting in death were reported by 2 of 115 patients (1.7%, pulmonary embolism in both patients) in the placebo group. A causal relationship to placebo could not be ruled out for pulmonary embolism (1 patient). Venous thromboembolism-related serious events were reported by 1 of 236 patients (0.4%; pulmonary embolism) in the ramucirumab group and 4 of 115 patients (3.5%; deep vein thrombosis in 3 patients, embolism in 1 patient) in the placebo group. A causal relationship to ramucirumab or placebo could not be ruled out for pulmonary embolism (1 patient) in the ramucirumab group and deep vein thrombosis (2 patients) and embolism (1 patient) in the placebo group. A venous thromboembolism-related event leading to the discontinuation of ramucirumab or placebo was reported by 1 of 115 patients (0.9%, pulmonary embolism) in the placebo group.

The following table shows the details of patients who had fatal or serious arterial or venous thromboembolism-related events in the RAINBOW and REGARD studies.

Patients who had fatal or serious arterial thromboembolism-related events (RAINBOW and REGARD studies)

Treatment group	Age	Sex	Preferred term*	Grade	Days to onset	Number of doses	Causal relationship to ramucirumab	Outcome
RAINBOW study								
Ramucirumab/PTX	57	M	Cerebrovascular accident	4	141	8	No	Unrecovered
Ramucirumab/PTX	63	M	Ischaemic stroke	4	35	3	No	Recovered
			Ischaemic stroke	4	64	4	No	Unrecovered
Ramucirumab/PTX	63	M	Cerebral infarction	2	312	21	Yes	Unrecovered
Placebo/PTX	73	M	Myocardial infarction	5	77	6	No	Death
Placebo/PTX	48	F	Intestinal ischaemia	3	173	12	Yes	Recovered
Placebo/PTX	59	M	Acute coronary syndrome	3	34	3	No	Unrecovered
			Angina pectoris	3	34	3	No	Unrecovered
Placebo/PTX	74	F	Cerebral infarction	2	34	3	No	Recovered
REGARD study								
Ramucirumab	54	M	Cerebral ischaemia	2	254	18	No	Recovered
Ramucirumab	65	M	Cardiac arrest	5	34	3	No	Death
Ramucirumab	63	M	Cerebrovascular accident	4	31	3	Yes	Ongoing
Ramucirumab	67	M	Myocardial infarction	5	85	6	Yes	Death

* MedDRA/J ver.16.0 in the RAINBOW study, MedDRA/J ver.15.0 in REGARD study

Patients who had fatal or serious venous thromboembolism-related events (RAINBOW and REGARD studies)

Treatment group	Age	Sex	Preferred term*	Grade	Days to onset	Number of doses	Causal relationship to ramucirumab	Outcome
RAINBOW study								
Ramucirumab/PTX group	63	M	Deep vein thrombosis	2	97	7	Yes	Unrecovered
Ramucirumab/PTX group	67	M	Pulmonary embolism	3	83	6	Yes	Unrecovered
			Pulmonary embolism	5	84	6	Yes	Death
Ramucirumab/PTX group	71	M	Pulmonary embolism	3	172	13	Yes	Recovered
Ramucirumab/PTX group	63	M	Deep vein thrombosis	3	310	21	Yes	Unrecovered
Placebo/PTX group	71	M	Atrial thrombosis	3	57	4	Yes	Unrecovered
Placebo/PTX group	63	M	Pulmonary embolism	3	127	10	Yes	Recovered
Placebo/PTX group	74	M	Pulmonary embolism	3	27	2	Yes	Unrecovered
Placebo/PTX group	44	M	Deep vein thrombosis	2	23	2	Yes	Unrecovered
Placebo/PTX group	45	M	Pulmonary embolism	2	29	2	No	Unrecovered
Placebo/PTX group	81	M	Venous thrombosis	2	13	1	No	Recovered
Placebo/PTX group	73	M	Deep vein thrombosis	3	169	11	Yes	Unrecovered
			Pulmonary embolism	4	168	11	Yes	Recovered
Placebo/PTX group	48	F	Venous thrombosis	2	120	9	No	Unrecovered
Placebo/PTX group	74	M	Pulmonary embolism	3	170	13	Yes	Unrecovered
			Pulmonary embolism	5	180	13	Yes	Death
Placebo/PTX group	71	M	Vena cava thrombosis	3	63	4	Yes	Unrecovered
Placebo/PTX group	72	M	Pulmonary embolism	4	11	1	Yes	Unrecovered
			Pulmonary embolism	5	12	1	Yes	Death
REGARD study								
Ramucirumab group	45	M	Pulmonary embolism	3	42	3	Yes	Ongoing
Placebo group	24	F	Deep vein thrombosis	2	16	1	Yes	Ongoing
Placebo group	51	M	Deep vein thrombosis	3	40	2	Yes	Ongoing
Placebo group	50	M	Deep vein thrombosis	3	16	2	No	Ongoing
Placebo group	64	M	Pulmonary embolism	5	11	1	No	Death
Placebo group	65	M	Embolism	2	45	2	Yes	Recovered
Placebo group	38	F	Pulmonary embolism	5	2	1	Yes	Death

* MedDRA/J ver.16.0 in RAINBOW study, MedDRA/J ver.15.0 in the REGARD study

PMDA considers as follows:

In the RAINBOW and REGARD studies, thromboembolism-related serious events occurred after treatment with ramucirumab, and some resulted in death. Caution should therefore be exercised against these events in treatment with ramucirumab. The incidences of these events should be provided appropriately to healthcare professionals via the package insert, etc.

4. (Iii).B. (3).8) Gastrointestinal perforation

The applicant explained gastrointestinal perforation-related events after the administration of ramucirumab as follows:

The following MedDRA PTs were tabulated: anastomotic ulcer perforation; appendicitis perforated; diverticular perforation; duodenal perforation; duodenal ulcer perforation; duodenal ulcer perforation, obstructive; gastric perforation; gastric ulcer perforation; gastric ulcer perforation, obstructive; gastrointestinal perforation; gastrointestinal ulcer perforation; large intestinal ulcer perforation; ileal perforation; ileal ulcer perforation; intestinal perforation; intestinal ulcer perforation; jejunal perforation; jejunal ulcer perforation; large intestine perforation; oesophageal perforation; oesophageal rupture; oesophageal ulcer perforation; peptic ulcer perforation; peptic ulcer perforation, obstructive; perforated peptic ulcer oversewing; perforated ulcer; rectal perforation; small intestinal perforation; and small intestinal ulcer perforation.

The following table shows details of patients who had gastrointestinal perforation-related events in the RAINBOW and REGARD studies.

Patients who had gastrointestinal perforation-related events (RAINBOW and REGARD studies)

Treatment group	Age	Sex	Primary lesion	Primary tumor	History of surgery/ operation	Peritoneal dissemination	Preferred term[*1]	Grade	Days to onset	Number of doses	Serious-ness	Causal relationship to ramucirumab	Outcome
RAINBOW study													
Ramucirumab/ PTX	50	M	Stomach	Yes	No	Yes	Diverticular perforation	4	308	20	Serious	No	Recovered
Ramucirumab/ PTX	83	M	Stomach	Yes	No	Yes	Intestinal perforation	4	3	1	Serious	No	Unrecovered[*2]
Ramucirumab/ PTX	69	F	Stomach	Yes	Gastrojejunostomy	No	Gastrointestinal perforation	3	152	9	Serious	Yes	Unknown[*3]
Ramucirumab/ PTX	64	F	Stomach	Yes	No	Yes	Gastrointestinal perforation	3	61	4	Serious	No	Death
							Gastrointestinal perforation	5	71	4	Serious	No	Death
Placebo/ PTX	67	M	GEJ	Yes	Esophageal stent	No	Oesophageal perforation	2	79	5	Serious	Yes	Recovered
REGARD study													
Ramucirumab	53	M	Stomach	No	Gastrectomy	No	Intestinal perforation	5	64	5	Serious	Yes	Death
Ramucirumab	69	M	Stomach	No	Total gastrectomy	Yes	Large intestine perforation	5	24	2	Serious	Yes	Death
Placebo	71	M	Stomach	No	Total gastrectomy + right hemicolectomy	No	Large intestine perforation	5	6	1	Serious	Yes	Death

GEJ, Gastrointestinal junction

[*1] MedDRA/J ver.16.0 in RAINBOW study, MedDRA/J ver.15.0 in the REGARD study

[*2] Died on the next day of the onset because of septic shock.

[*3] Died 56 days after the onset because of the progression of the primary disease.

In the RAINBOW study, gastrointestinal perforation-related events were reported by 4 of 327 patients (1.2%; gastrointestinal perforation in 2 patients, diverticular perforation and intestinal perforation in 1 patient each) in the ramucirumab/PTX group and 1 of 329 patients (0.3%, oesophageal perforation) in the placebo/PTX group. All gastrointestinal perforation-related events observed in the ramucirumab/PTX group were Grade ≥3. A gastrointestinal perforation-related fatal event was reported by 1 of 327 patients (0.3%, gastrointestinal perforation) in the ramucirumab/PTX group, and a causal relationship of the event to ramucirumab was ruled out. Gastrointestinal perforation-related serious events were reported by 3 of 327 patients (0.9%; gastrointestinal perforation, diverticular perforation, and intestinal perforation in 1 patient each) in the ramucirumab/PTX group and 1 of 329 patients (0.3%, oesophageal perforation) in the placebo/PTX group. A causal relationship to ramucirumab or placebo could not be ruled out for gastrointestinal perforation (1 patient) in the ramucirumab/PTX group and oesophageal perforation (1 patient) in the placebo/PTX group. A gastrointestinal perforation-related event leading to the discontinuation of ramucirumab or placebo was reported by 1 of 329 patients (0.3%,

oesophageal perforation) in the placebo/PTX group.

In the REGARD study, gastrointestinal perforation-related events were reported by 2 of 236 patients (0.8%, intestinal perforation and large intestine perforation in 1 patient each) in the ramucirumab group and 1 of 115 patients (0.9%, large intestine perforation) in the placebo group. All events were fatal, and their causal relationship to ramucirumab or placebo could not be ruled out.

Gastrointestinal perforation-related events following the administration of ramucirumab were observed regardless of whether the primary tumor had been resected or not or the presence or absence of peritoneal dissemination at baseline.

PMDA considers as follows:
In the RAINBOW and REGARD studies, gastrointestinal perforation-related events were infrequent but serious, and some were even fatal. Caution should therefore be exercised against these events during treatment with ramucirumab. Information on the incidences of these events, etc. should be provided appropriately to healthcare professionals via the package insert, etc.

4.(iii).B.(3).9) Congestive cardiac failure

The applicant explained congestive cardiac failure-related events after the administration of ramucirumab as follows:
As congestive cardiac failure-related events, the following MedDRA PTs were tabulated: acute left ventricular failure, acute pulmonary oedema, acute right ventricular failure, cardiac asthma, cardiac failure, cardiac failure acute, cardiac failure chronic, cardiac failure congestive, cardiac failure high output, cardiac index decreased, cardiac output decreased, cardiogenic shock, cardiopulmonary failure, cardiorenal syndrome, chronic left ventricular failure, chronic right ventricular failure, diastolic dysfunction, ejection fraction, ejection fraction decreased, left ventricular dysfunction, left ventricular failure, low cardiac output syndrome, multiple gated acquisition scan abnormal, oedema due to cardiac disease, pulmonary oedema, right ventricular dysfunction, right ventricular failure, scan myocardial perfusion abnormal, systolic dysfunction, ventricular dysfunction, and ventricular failure.

The following table shows the incidences of congestive cardiac failure-related events in the RAINBOW and REGARD studies.

Incidences of congestive cardiac failure-related events (RAINBOW and REGARD studies)

Preferred term*	Number of patients (%)							
	RAINBOW study				REGARD study			
	Ramucirumab/PTX N = 327		Placebo/PTX N = 329		Ramucirumab N = 236		Placebo N = 115	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Congestive cardiac failure-related events	8 (2.4)	2 (0.6)	4 (1.2)	2 (0.6)	2 (0.8)	1 (0.4)	0	0
Ejection fraction decreased	5 (1.5)	2 (0.6)	3 (0.9)	1 (0.3)	0	0	0	0
Pulmonary oedema	2 (0.6)	0	0	0	1 (0.4)	1 (0.4)	0	0
Cardiac failure	1 (0.3)	0	1 (0.3)	1 (0.3)	1 (0.4)	0	0	0

* MedDRA/J ver.16.0 in the RAINBOW study, MedDRA/J ver.15.0 in the REGARD study

In the RAINBOW study, a congestive cardiac failure-related fatal event occurred in 1 of 329 patients (0.3%, cardiac failure) in the placebo/PTX group, and its causal relationship to placebo could not be ruled out. There were no congestive cardiac failure-related serious events. Congestive cardiac failure-related events leading to the discontinuation of ramucirumab or placebo were reported by 1 of 327 patients (0.3%, ejection fraction decreased) in the ramucirumab/PTX group and 1 of 329 patients (0.3%, cardiac failure) in the placebo/PTX group.

In the REGARD study, serious congestive cardiac failure-related events were reported by 2 of 236 patients (0.8%, pulmonary oedema and cardiac failure in 1 patient each) in the ramucirumab group, and a causal relationship to ramucirumab could not be ruled out for cardiac failure (1 patient). There were no congestive cardiac failure-related events that resulted in death or the discontinuation of ramucirumab or placebo.

PMDA considers as follows:
In the RAINBOW and REGARD studies, the incidences of congestive cardiac failure-related events were generally low but tended to be higher in the ramucirumab group than in the control group. The events were serious in some patients. These events are also of concern in treatment with other antineoplastics with anti-angiogenic activity (see the Review Report "Avastin for Intravenous Infusion 100 mg/4 mL and 400 mg/16 mL" dated February 14, 2007). Therefore, caution should be exercised against congestive cardiac failure-related events during treatment with ramucirumab. The incidences, etc. of these events should be provided appropriately to healthcare professionals via the package insert, etc.

4.(iii).B.(3).10) Neutropenia/leukopenia
The applicant explained neutropenia (neutropenia and neutrophil count decreased in MedDRA PTs) and leukopenia (leukopenia and white blood cell count decreased in MedDRA PTs) after the administration of ramucirumab as follows:
In the RAINBOW study, neutropenia and leukopenia were reported by 178 of 327 patients (54.4%) and 111 of 327 patients (33.9%), respectively, in the ramucirumab/PTX group, and 102 of 329 patients (31.0%) and 69 of 329 patients (21.0%), respectively, in the placebo/PTX group. Grade ≥3 events were reported by 133 of 327 patients (40.7%) and 57 of 327 patients (17.4%), respectively, in the ramucirumab/PTX group, and 62 of 329 patients (18.8%) and 22 of 329 patients (6.7%), respectively, in the placebo/PTX group. There were no fatal events. Serious neutropenia and leukopenia were reported by 12 of 327 patients (3.7%) and 1 of 327 patients (0.3%), respectively, in the ramucirumab/PTX group, and 3 of 329 patients (0.9%) and 0 of 329 patients, respectively, in the placebo/PTX group. A causal relationship to ramucirumab could not be ruled out for neutropenia (3 patients) in the ramucirumab/PTX group. Neutropenia leading to the discontinuation of ramucirumab or placebo was reported by 1 of 327 patients (0.3%) in the ramucirumab/PTX group. There were no cases of leukopenia leading to the discontinuation of ramucirumab or placebo.

In the REGARD study, neutropenia and leukopenia were reported by 11 of 236 patients (4.7%) and 1 of 236 patients (0.4%), respectively, in the ramucirumab group and 1 of 115 patients (0.9%) and 2 of 115 patients (1.7%), respectively, in the placebo group. Grade ≥3 neutropenia was reported by 5 of 236 patients (2.1%) in the ramucirumab group, whereas Grade ≥3 leukopenia was not reported. There were no events that were fatal, serious, or resulted in the discontinuation of ramucirumab or placebo.

PMDA considers as follows:
In the RAINBOW and REGARD studies, the incidences of all grades and Grade ≥3 neutropenia and leukopenia were higher in the ramucirumab group than in the control group, and some events were serious. Therefore, caution should be exercised against these events in the use of ramucirumab. The incidences of these events, etc. should be provided appropriately to healthcare professionals via the package insert, etc.

4.(iii).B.(3).11) RPLS
The applicant explained ramucirumab-induced RPLS (posterior reversible encephalopathy syndrome in MedDRA PT) after the administration of ramucirumab as follows:
No RPLS was observed in the RAINBOW or REGARD study. However, in the ongoing double-blind, randomized, phase III study (Study I4T-MC-JVBB) that is aimed to investigate the efficacy and safety of ramucirumab in combination with FOLFIRI in patients with metastatic colorectal cancer with disease progression on or after prior chemotherapy with bevacizumab, oxaliplatin, and fluoropyrimidine-based antineoplastics in Japan and overseas, RPLS was reported by 2 of 1057 patients (1.9%). The event was serious in the both patients, and its causal relationship to ramucirumab or placebo could not be ruled out. Also, a case of RPLS was reported after the market launch overseas (data cut-off, September 15, 2014).

PMDA considers as follows:
A causal relationship to ramucirumab could not be ruled out for the reported RPLS. RPLS was also reported by patients receiving other antineoplastics with anti-angiogenic activity (see the Review Reports "Avastin for Intravenous Infusion 100 mg/4 mL and 400 mg/16 mL" dated February 14, 2007, "Stivarga Tablets 40 mg" dated March 4, 2013, etc.). Vascular endothelial impairment and rapid increase

in blood pressure are suspected to be involved in the mechanism of onset of RPLS (*Intern Med J.* 2009;39:826-34). Considering these facts, caution should be exercised against the occurrence of RPLS in treatment with ramucirumab. If RPLS is suspected, MRI and other examinations should promptly be performed for definitive diagnosis. Information on the incidence of and how to respond to RPLS should be provided appropriately to healthcare professionals using information materials, etc.

4.(iii).B.(3).12) Fistula

The applicant explained fistula after the administration of ramucirumab as follows:

As fistula, the following MedDRA PTs were tabulated: acquired tracheo-oesophageal fistula, anal fistula, anal fistula excision, anovulvar fistula, aorto-duodenal fistula, aorto-oesophageal fistula, colon fistula repair, colonic fistula, diverticular fistula, duodenal fistula, enterocolonic fistula, enterocutaneous fistula, enterovesical fistula, gastric fistula, gastric fistula repair, gastrointestinal fistula, gastrointestinal fistula repair, gastropleural fistula, gastrosplenic fistula, ileal fistula, intestinal fistula, intestinal fistula repair, jejunal fistula, oesophageal fistula, oesophageal fistula repair, oesophagobronchial fistula, rectal fistula repair, and rectourethral fistula.

No fistula was observed in the RAINBOW study. In the REGARD study, fistula was reported by 1 of 236 patients (0.4%, enterocutaneous fistula) in the ramucirumab group and 1 of 115 patients (0.9%, oesophageal fistula) in the placebo group. Both were Grade ≥3 events. Oesophageal fistula in 1 patient in the placebo group was serious, but its causal relationship to placebo was ruled out. There were no cases of fistula that resulted in death or treatment discontinuation.

Fistula was also reported by 4 of 1722 patients (0.2%), who received ramucirumab in other clinical studies on ramucirumab* (data cut-off, September 1, 2013; sample size, 1722). A fatal fistula was reported by 1 patient (oesophagobronchial fistula), and its causal relationship to ramucirumab could not be ruled out. Serious fistula was reported by 1 patient (female genital tract fistula), but its causal relationship to ramucirumab was ruled out.

* A total of 21 ongoing or completed clinical studies on ramucirumab as of September 1, 2013, excluding the RAINBOW, REGARD, JVBN, and JVBM studies.

PMDA considers as follows:

The incidence of fistula following the administration of ramucirumab was low, but 1 patient with fistula died. Fistula was also reported by patients receiving other antineoplastics with anti-angiogenic activity (see the Review Reports "Avastin for Intravenous Infusion 100 mg/4 mL and 400 mg/16 mL" dated September 27, 2013, "Stivarga Tablets 40 mg" dated March 4, 2013, etc.). Therefore, caution should be exercised against fistula in treatment with ramucirumab. The incidence, etc. of fistula should be provided appropriately to healthcare professionals via the package insert, etc.

4.(iii).B.(3).13) Disturbance of wound healing

The applicant explained disturbance of wound healing after the administration of ramucirumab as follows:

As disturbance of wound healing, the following MedDRA PTs were tabulated: impaired healing, open wound, postoperative wound complication, seroma, suture rupture, wound decomposition, and wound dehiscence.

In the RAINBOW and REGARD studies, disturbance of wound healing was not reported.

In other clinical studies on ramucirumab* (data cut-off, September 1, 2013; sample size, 1722 patients), disturbance of wound healing was reported by 14 of 1722 patients (0.8%) who received ramucirumab. Fatal wound healing disturbance occurred in 1 patient (suture rupture), but its causal relationship to ramucirumab was ruled out. Serious wound healing disturbance occurred in 2 patients (wound dehiscence in both patients), and its causal relationship to ramucirumab could not be ruled out in either case. No disturbance of wound healing has not been reported overseas since the market launch (data cut-off, September 15, 2014). However, since ramucirumab is considered to have anti-angiogenic activity, it may affect wound healing. Therefore, cautions should be provided in the package insert, etc., that (i) the use of ramucirumab should be refrained in patients scheduled to undergo surgical operation, (ii) the

use of ramucirumab, if appropriate, should be resumed after the surgical wound completely heals, and (iii) if disturbance of wound healing occurs during the treatment with ramucirumab, the treatment should be suspended until the wound completely heals.

* A total of 21 ongoing or completed clinical studies on ramucirumab as of September 1, 2013, excluding RAINBOW, REGARD, JVBN, and JVBM studies.

PMDA accepted the explanation of the applicant.

4.(iii).B.(3).14) Liver disorder

The applicant explained liver disorder occurring after the administration of ramucirumab as follows:

[redacted].

- Patients with Child-Pugh class B should be excluded.

- The inclusion/exclusion criteria should allow enrollment only to patients with Child-Pugh class A without a history of hepatic encephalopathy or clinically significant ascites. Clinically significant ascites is defined as hepatic cirrhosis-induced ascites requiring continuous treatment with diuretics and/or puncture.

- In patients with newly diagnosed hepatic encephalopathy or hepatorenal syndrome, the administration of the study drug (ramucirumab or placebo) should be discontinued. The administration of the study drug should not be resumed in patients who have discontinued the study drug for hepatic encephalopathy or hepatorenal syndrome.

As liver disorder-related events, the following events were tabulated: (i) MedDRA PTs categorized as MedDRA SMQ "cholestasis and jaundice of hepatic origin" except for deficiency of bile secretion, (ii) MedDRA PTs categorized as MedDRA SMQ "hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions (narrow)," except for Reye's syndrome, Reynold's syndrome, bacterascites, diabetic hepatopathy, ascites, portal vein dilatation, and peripancreatic varices, (iii) MedDRA PTs categorized as MedDRA SMQ "hepatitis, non-infectious," except for lupus hepatitis, chronic graft versus host disease in liver, and liver sarcoidosis, (iv) MedDRA PTs categorized as MedDRA SMQ "liver related investigations, signs and symptoms (narrow)," except for Kayser-Fleischer ring, galactose elimination capacity test abnormal, galactose elimination capacity test decreased, guanase increased, bromosulphthalein test abnormal, hepaplastin abnormal, hepaplastin decreased, hepatic mass, bacterascites, molar ratio of total branched-chain amino acid to tyrosine, and ascites, and (v) MedDRA PTs portal shunt, portal vein pressure increased, hypocoagulable state, ALT, AST, and liver function test.

The following table shows the incidences of liver disorder-related events in the RAINBOW and REGARD studies.

Incidences of liver disorder-related events (RAINBOW and REGARD studies)

Preferred term*	Number of patients (%)							
	RAINBOW study				REGARD study			
	Ramucirumab/PTX N = 327		Placebo/PTX N = 329		Ramucirumab N = 236		Placebo N = 115	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Liver disorder-related events	54 (16.5)	15 (4.6)	41 (12.5)	13 (4.0)	24 (10.2)	11 (4.7)	9 (7.8)	5 (4.3)
Clinical symptom-related								
Cholestasis	2 (0.6)	0	1 (0.3)	0	1 (0.4)	1 (0.4)	1 (0.9)	1 (0.9)
Hepatic function abnormal	0	0	2 (0.6)	0	1 (0.4)	0	0	0
Hepatocellular injury	0	0	1 (0.3)	0	0	0	0	0
Hepatomegaly	2 (0.6)	0	1 (0.3)	0	2 (0.8)	1 (0.4)	0	0
Jaundice	3 (0.9)	1 (0.3)	3 (0.9)	1 (0.3)	4 (1.7)	1 (0.4)	1 (0.9)	0
Jaundice cholestatic	0	0	2 (0.6)	1 (0.3)	1 (0.4)	1 (0.4)	1 (0.9)	0
Ocular icterus	1 (0.3)	0	0	0	0	0	0	0
Hepatic failure	0	0	0	0	1 (0.4)	1 (0.4)	0	0
Hepatic pain	0	0	0	0	0	0	1 (0.9)	0
Liver disorder	0	0	0	0	2 (0.8)	1 (0.4)	0	0
Laboratory value-related								
ALT increased	20 (6.1)	4 (1.2)	18 (5.5)	3 (0.9)	9 (3.8)	3 (1.3)	2 (1.7)	1 (0.9)
AST increased	27 (8.3)	6 (1.8)	17 (5.2)	5 (1.5)	9 (3.8)	3 (1.3)	2 (1.7)	2 (1.7)
Blood bilirubin increased	16 (4.9)	3 (0.9)	11 (3.3)	5 (1.5)	6 (2.5)	3 (1.3)	1 (0.9)	1 (0.9)
γ-GTP increased	11 (3.4)	3 (0.9)	6 (1.8)	3 (0.9)	1 (0.4)	0	1 (0.9)	1 (0.9)
Hepatic enzyme increased	3 (0.9)	3 (0.9)	1 (0.3)	0	2 (0.8)	1 (0.4)	0	0
Hyperammonaemia	1 (0.3)	0	0	0	1 (0.4)	0	0	0
Hyperbilirubinaemia	7 (2.1)	1 (0.3)	7 (2.1)	2 (0.6)	3 (1.3)	1 (0.4)	3 (2.6)	3 (2.6)
Hypertransaminasaemia	2 (0.6)	1 (0.3)	0	0	0	0	0	0
Liver function test abnormal	2 (0.6)	2 (0.6)	1 (0.3)	0	0	0	0	0
Transaminases increased	0	0	2 (0.6)	0	0	0	1 (0.9)	0
Bilirubin conjugated increased	0	0	0	0	1 (0.4)	1 (0.4)	0	0

ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; Bil, Bilirubin; γ-GTP, gamma-glutamyltransferase
* MedDRA/J ver.16.0 in the RAINBOW study, MedDRA/J ver.15.0 in the REGARD study

In the RAINBOW study, no liver disorder-related fatal events were observed. Liver disorder-related serious events were reported by 1 of 327 patients (0.3%, jaundice) in the ramucirumab/PTX group and 3 of 329 patients (0.9%; jaundice cholestatic, γ-GTP increased, and ALT increased/AST increased in 1 patient each) in the placebo/PTX group. A causal relationship to placebo could not be ruled out for ALT increased/AST increased (1 patient) in the placebo/PTX group. Liver disorder-related events leading to the discontinuation of ramucirumab or placebo were reported by 2 of 327 patients (0.6%, hyperbilirubinaemia and liver function test abnormal in 1 patient each) in the ramucirumab/PTX group and 2 of 329 patients (0.6%, liver function test abnormal and blood bilirubin increased in 1 patient each) in the placebo/PTX group.

In the REGARD study, a fatal liver disorder-related event was reported by 1 of 236 patients (0.4%, cholestasis) in the ramucirumab group, but its causal relationship to ramucirumab was ruled out. Liver disorder-related serious events were reported by 3 of 236 patients (1.3%; jaundice cholestatic, liver disorder, and ALT increased/AST increased/cholestasis in 1 patient each) in the ramucirumab group and 1 of 115 patients (0.9%, hyperbilirubinaemia) in the placebo group. A causal relationship to ramucirumab or placebo was ruled out for all events. A liver disorder-related event leading to the discontinuation of ramucirumab or placebo was reported by 1 of 236 patients (0.4%, cholestasis) in the ramucirumab group.

PMDA considers as follows:
In both the RAINBOW and REGARD studies, the incidences of all grades and Grade ≥3 liver disorder-related events tended to be higher in the ramucirumab group than in the control group. The JVBF study was conducted in patients with hepatocellular carcinoma, and the patient characteristics including concurrent liver disease were different from those in the RAINBOW and REGARD studies. Nevertheless, taking into account of the incidences of liver disorder-related events in the JVBF study, caution should be exercised against liver disorder-related events in treatment with ramucirumab. Information on the incidences, etc. of liver disorder-related events should be provided appropriately to healthcare professionals via the package insert, etc.

4.(iii).B.(4) Clinical positioning and indication

The proposed indication for ramucirumab was "unresectable advanced/recurrent gastric cancer." The following cautions were provided in the "Precautions for Indications" section of the package insert:

- The efficacy and safety of ramucirumab in post-operative adjuvant chemotherapy have not been established.

- The efficacy and safety of ramucirumab in primary chemotherapy have not been established.

- Eligibility of the patient for the treatment should be determined based on good understanding of the descriptions in the "Clinical Studies" section, of the characteristics of the patient, and of the efficacy and safety of ramucirumab.

Based on the results of reviews in "4.(iii).B.(2) Efficacy," "4.(iii).B.(3) Safety," and the following review, PMDA has concluded that the indication of ramucirumab "unresectable advanced/recurrent gastric cancer" as proposed by the applicant is acceptable. PMDA also concluded that the following precautionary statements should be included in the "Precautions for Indications" section of the package insert.

- The efficacy and safety of ramucirumab in post-operative adjuvant chemotherapy have not been established.

- The efficacy and safety of ramucirumab in primary chemotherapy have not been established.

- Eligibility of the patient for the treatment should be determined based on good understanding of the "Clinical Studies" section (particularly the information about primary lesions) and of the efficacy and safety of ramucirumab.

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

PMDA confirmed that ramucirumab is described as below in Japanese and foreign clinical practice guidelines and internationally recognized clinical oncology textbooks. As of now, ramucirumab is explained neither in the Japanese gastric cancer treatment guidelines 2014 (ver. 4), edited by the Japanese Gastric Cancer Association (Kanehara & Co., Ltd., 2014) nor in the Clinical oncology update, 3rd revised edition, edited by Japanese Society of Medical Oncology (Nankodo Co., Ltd. 2012), which is a leading textbook of clinical oncology in Japan.

Clinical practice guidelines

- NCCN Guidelines (Gastric Cancer, v.1.2014):
  The guidelines recommend ramucirumab monotherapy as Category 1 based on the REGARD study and the combination of ramucirumab with PTX as Category 2A based on the RAINBOW study in patients with unresectable advanced/recurrent gastric or gastro-esophageal junction cancer who received previously chemotherapy. A footnote states that the combination therapy of ramucirumab with PTX is preferable to the ramucirumab monotherapy, according to a scientific meeting abstract on the RAINBOW study (the study results had not been published as an article when the guidelines were edited).

  Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
  Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Textbooks

- DeVita, Hellman, and Rosenberg's Cancer: Principles & Practice of Oncology 9th edition (Lippincott Williams & Wilkins 2011, PA, USA) (updated on January 17, 2014):
  The REGARD study showed that ramucirumab monotherapy prolonged OS more than placebo did in patients with previously treated metastatic gastric or gastro-esophageal junction cancer.

The applicant explained the clinical positioning of ramucirumab as follows:
Based on the results of the RAINBOW and REGARD studies [see "4.(iii).B.(2) Efficacy" and 4.(iii).B.(3) Safety"], ramucirumab can be a new treatment option for patients with unresectable advanced/recurrent gastric or gastro-esophageal junction adenocarcinoma with disease progression on or after prior fluoropyrimidine- and platinum-containing chemotherapy.

PMDA accepted the explanation of the applicant.

4.(iii).B.(4).2) Target patients (site of primary lesion, histological type, treatment history)
In the RAINBOW and REGARD studies, eligible patients were those who had a diagnosis of gastric or gastro-esophageal junction adenocarcinoma. Therefore, PMDA asked the applicant to explain the reason for proposing the indication of "unresectable advanced/recurrent gastric cancer."

The applicant responded as follows:
In the RAINBOW and REGARD studies, eligible patients were those with advanced/recurrent gastric or gastro-esophageal junction adenocarcinoma. However, "gastric cancer" and "gastro-esophageal junction cancer" were not clearly defined. According to the protocols, gastric cancer included cardia tumor extending to the gastro-esophageal junction, while gastro-esophageal junction cancer was defined to include distal oesophageal tumour extending to the gastro-esophageal junction. A tumor of unknown primary lesion (organ) spreading to the gastro-esophageal junction was also included in gastro-esophageal junction cancer. In Japan, gastro-esophageal junction cancer is defined by the Japanese Gastric Cancer Association and the Japan Esophageal Society as cancer with the tumor center located in the area within 2 cm above or below the gastro-esophageal junction, regardless of histological type (Japanese Classification of Esophageal Cancer, 10th revised edition [Kanehara & Co., Ltd., 2008], Japanese Classification of Gastric Carcinoma, 14th edition [Kanehara & Co., Ltd., 2010]). In contrast, the NCCN Guidelines (Gastric Cancer, v.1.2014) explains that gastro-esophageal junction cancer is adenocarcinoma that develops in the area within 5 cm above or below the gastro-esophageal junction, based on the definition by Siewert (*Dis Esophagus.* 1996;9:173-82.).

Both the RAINBOW and REGARD studies have demonstrated the efficacy and safety of ramucirumab in the entire study population, indicating that treatment with ramucirumab is recommendable for patients with unresectable advanced/recurrent gastric or gastro-esophageal junction adenocarcinoma with disease progression on or after prior fluoropyrimidine- and platinum-containing chemotherapy. On the other hand, patients with gastric or gastro-esophageal junction cancer with a histological type other than adenocarcinoma were not included in these studies; hence, the efficacy and safety of ramucirumab in these patients are unknown.

There are no established guidelines for chemotherapy of gastro-esophageal junction cancer as an independent disease entity either in Japan or elsewhere. In a meta-analysis of multiple clinical studies on gastric adenocarcinoma, gastro-esophageal junction adenocarcinoma, and lower oesophageal adenocarcinoma, the efficacy of chemotherapy was reported to be similar regardless of the site of the primary lesion (*Ann Oncol.* 2009;20:885-91.). Also, the NCCN Guidelines (Gastric Cancer, v.1.2014) state that chemotherapies recommended for advanced/recurrent oesophageal adenocarcinoma, gastro-esophageal junction adenocarcinoma, oesophageal squamous cell carcinoma, or gastric adenocarcinoma may be used indiscriminately for any of these cancers unless clearly specified otherwise. In addition, "Gastric cancer: ESMO–ESSO–ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up" (ESMO Guidelines) includes gastro-esophageal junction adenocarcinoma in gastric adenocarcinoma.

Based on the above, the applicant decided to propose the indication as "unresectable advanced/recurrent gastric cancer". In the "Clinical Studies" section of the package insert, the site of the primary lesion (stomach or gastro-esophageal junction) and the histological type (adenocarcinoma) of patients investigated in the RAINBOW and REGARD studies should be clearly mentioned. The package insert should also provide a precautionary statement that eligibility of the patient for the treatment should be determined based on good understanding of the descriptions in the "Clinical Studies" section, of the efficacy and safety of ramucirumab, and of characteristics of the patient

Also, the applicant explained that, since the RAINBOW and REGARD studies targeted only patients with a history of chemotherapy, the "Precautions for Indications" section of the package insert would note to the effect that the efficacy and safety of ramucirumab in primary chemotherapy have not been established.

PMDA considers as follows:
PMDA generally accepted the explanation of the applicant. However, the definition of gastro-esophageal junction cancer is not standardized between Japan and other countries, and gastro-esophageal junction cancer was not clearly defined in the RAINBOW or REGARD studies. Therefore, it is appropriate to indicate ramucirumab for "unresectable advanced/recurrent gastric cancer" as proposed by the applicant, but the descriptions in the "Precautions for Indications" section should be modified as shown below.

- The efficacy and safety of ramucirumab in primary chemotherapy have not been established.

- Eligibility of the patient for the treatment should be determined based on good understanding of the descriptions in the "Clinical Studies" section (particularly the information about primary lesions) and of the efficacy and safety of ramucirumab.

4.(iii).B.(4).3) Efficacy and safety as post-operative adjuvant chemotherapy
At present, there are no clinical data available on the efficacy and safety of ramucirumab as post-operative adjuvant chemotherapy. The applicant therefore considered the use of ramucirumab in post-operative adjuvant chemotherapy was not recommendable. The applicant explained that cautionary statements regarding post-operative adjuvant use of ramucirumab would be included in the "Precautions for Indications" section of the package insert.

PMDA accepted the explanation of the applicant.

4.(iii).B.(5) Dosage and administration
The proposed dosage and administration was "the usual adult dosage is 8 mg/kg (body weight) of Ramucirumab (Genetical Recombination) given as intravenous infusion over approximately 60 minutes every 2 weeks. The dose may be adjusted according to the condition of the patient." The "Precautions for Dosage and Administration" section of the package insert included cautionary statements regarding dose adjustment method etc.

Based on the reviews detailed in 4.(iii).B.(5).1) to 3), PMDA concluded that the dosage and administration of ramucirumab should be "the usual adult dosage is 8 mg/kg (body weight) of Ramucirumab (Genetical Recombination) given as intravenous infusion over approximately 60 minutes every 2 weeks, and the dose may be adjusted according to the condition of the patient," and that precautionary statements regarding the following points should be added to the "Precautions for Dosage and Administration" section of the package insert:

- The efficacy and safety of ramucirumab in combination with antineoplastics other than PTX have not been established.

- Premedication as specified in the RAINBOW and REGARD studies

- Guidelines for the reduction in infusion rate, treatment interruption, dose reduction, treatment discontinuation, and method for dose reduction of ramucirumab

- Reconstitution of the injection solution

4.(iii).B.(5).1) Dosage and administration of ramucirumab
The applicant explained the justification for the proposed dosage and administration as follows:
Based on the following results obtained from foreign phase I studies (the JVBM and JVBN studies), the dosage regimen in phase II and III studies was determined as ramucirumab 8 mg/kg at 2-week intervals or 10 mg/kg at 3-week intervals.

- In the JVBM study, when ramucirumab was administered intravenously at 1-week intervals, the serum ramucirumab concentration increased more than dose proportionally over the range from 2 to 6 mg/kg, and increased dose proportionally at ≥8 mg/kg, which suggested that the VEGFR-2-mediated elimination pathway had reached saturation at ramucirumab doses of ≥8 mg/kg.

- In the JVBN study, ramucirumab was well tolerated when administered intravenously at 6 to 10 mg/kg at 2-week intervals or at 15 to 20 mg/kg at 3-week intervals.

- In the JVBN study, the geometric mean (CV%) of trough serum concentrations of ramucirumab (before the second dose) in the intravenous administration of ramucirumab (8 mg/kg) at 2-week intervals was 21.9 (59) μg/mL, which was higher than the lowest serum concentration (18 μg/mL) of anti-mouse VEGFR-2 antibody (DC101) that exhibited a tumor growth-inhibitory effect in mice transplanted with a human pancreatic cancer-derived BxPC-3 cell line [see "3.(i).A.(1).6).(c).ii) Cell lines derived from tumors other than gastric cancer"]. Also, in the JVBN study, the geometric mean (CV%) of trough serum concentrations of ramucirumab (before the second dose) in intravenous administration of ramucirumab (15 mg/kg) at 3-week intervals was 44.8 (55) μg/mL. Accordingly, trough serum concentration of ramucirumab in intravenous administration at 10 mg/kg at 3-week intervals was estimated to be ≥18 μg/mL.

The dosage and administration of ramucirumab in the phase III studies on gastric cancer was determined based on the dosage regimen of the concomitant PTX in the RAINBOW study. Thus, in the RAINBOW study, ramucirumab (8 mg/kg) was scheduled to be administered at 2-week intervals in line with the PTX dosing schedule (administration on Days 1, 8, and 15 in each cycle of 28 days). The REGARD study also employed the same dose and dosing intervals.

The maximum infusion rate in phase I studies on ramucirumab was determined as 25 mg/min, based on experiences with other antibody drugs. The dosage and administration of ramucirumab in phase II and III studies were 6 mg/kg at 1-week intervals, 8 mg/kg at 2-week intervals, and 10 mg/kg at 3-week intervals. For all dosage regimens, ramucirumab was planned to be infused over 60 minutes or longer so that the maximum infusion rate would not exceed 25 mg/min, regardless of body weight.

The results of the RAINBOW and REGARD studies conducted with the above dosage regimens demonstrated the efficacy and safety of ramucirumab. Therefore, the intravenous infusion of ramucirumab (8 mg/kg) over 60 minutes at 2-week intervals was selected for the proposed dosage and administration.

PMDA considered as follows:
There is a limit to estimating the clinically effective serum ramucirumab concentration based solely on the serum DC101 concentration that exhibited a tumor growth-inhibitory effect. The lower limit of trough serum concentration in the intravenous administration of ramucirumab (8 mg/kg) at 2-week intervals was 11.3 μg/mL. In the JVBM study, the VEGFR-2-mediated elimination pathway was considered being saturated at doses of ≥8 mg/kg at 1-week intervals, whereas the dosing intervals in the phase II and III studies were 2 weeks and 3 weeks, respectively. Because of the difference in the dosing intervals, the phase II and III studies failed to provide sufficient clinical pharmacological evidence that supports the dosage regimens of ramucirumab used. Given that all dosage regimens investigated in the JVBN study were well-tolerated, there was room for further investigation of the dosage regimens of ramucirumab.

On the other hand, the efficacy and safety of intravenous infusion of ramucirumab (8 mg/kg) over 60 minutes at 2-week- intervals were confirmed in both the RAINBOW and REGARD studies. Therefore, it is appropriate to define the dosage and administration of ramucirumab as proposed by the applicant.

4.(iii).B.(5).2) Dose adjustment, etc.
The applicant justified the criteria established for infusion rate reduction, treatment interruption, dose reduction, and treatment discontinuation, and dose reduction method of ramucirumab that were specified in the proposed package insert, as follows:

In the RAINBOW and REGARD studies, specific rules were used for infusion rate reduction, treatment interruption, dose reduction, and treatment discontinuation in case of IRR, hypertension, or proteinuria depending on the event observed and its severity. Based on the rules set out and the incidences of IRR, hypertension, and proteinuria in the RAINBOW and REGARD studies, criteria for infusion rate reduction, treatment interruption, dose reduction, discontinuation of ramucirumab and dose reduction method were investigated. These criteria should be noted in the package insert.

IRR:
In the RAINBOW and REGARD studies, the infusion rate of ramucirumab or placebo was to be reduced to 50% in case of Grade 1 IRR. In case of Grade 2 IRR, the administration of ramucirumab or placebo was suspended and, after IRR improved to Grade ≤1, treatment was to be resumed at the infusion rate reduced to 50%. In case of Grade 3 or 4 IRR, the administration of ramucirumab or placebo was to be discontinued. The administration of ramucirumab or placebo was suspended only in 4 of 327 patients (1.2%) in the ramucirumab/PTX group and 2 of 329 patients (0.6%) in the placebo/PTX group in the RAINBOW study (a). In the REGARD study, there was no treatment discontinuation in either group, and IRR were controllable by the standard remedy and did not require interventional treatment in most patients (b). It is recommended that the infusion rate be reduced by 50% when resuming antibody drug infusion as post-IRR remedy (*Oncologist.* 2007;12:601-9) (c). In response to the findings (a) (b) and the recommendation (c), 50%-reduction of the infusion rate during infusion and in all subsequent infusion was to be advised in case of Grade 1 or 2 IRR.

Hypertension:
In the RAINBOW and REGARD studies, antihypertensive treatment was to be initiated in case of a Grade ≤3 hypertension-related event. In case of asymptomatic hypertension, the administration of ramucirumab or placebo was to be continued (if Grade 3 hypertension persisted for >2 weeks, the administration of ramucirumab or placebo was to be suspended). In case of symptomatic hypertension, the administration of ramucirumab or placebo was to be withdrawn until the symptom subsided. In case of Grade 4 or poorly controlled hypertension (systolic blood pressure of ≥160 mm Hg or diastolic blood pressure of ≥100 mm Hg persisting for >4 weeks) despite appropriate antihypertensive treatment (≥3 types of oral antihypertensive drugs each at the maximum dose), the administration of ramucirumab or placebo was to be discontinued. If ramucirumab or placebo was resumed after treatment interruption, the dose of ramucirumab or placebo was to be reduced to 6 mg/kg. If the treatment was resumed after the second interruption, the dose was to be reduced to 5 mg/kg. Treatment interruption or dose reduction of ramucirumab or placebo occurred only in 5 of 327 patients (1.5%) of the ramucirumab/PTX group in the RAINBOW study and in 4 of 236 patients (1.7%) of the ramucirumab group in the REGARD study, showing that ramucirumab-induced hypertension was controllable by regular antihypertensive treatment. Therefore, the applicant considered that determining dosing criteria for resumed ramucirumab was rather unpractical. Treatment with ramucirumab should be suspended until associated hypertension became controllable by the regular antihypertensive treatment. In the case of an uncontrollable condition, treatment with ramucirumab should be discontinued.

Proteinuria:
In the RAINBOW and REGARD studies, the administration of ramucirumab or placebo was to be withdrawn for 1 week if protein in pooled urine was ≥2 g/24 hours and <3 g/24 hours. If protein in pooled urine was ≥3 g/24 hours, or ≥2 g/24 hours and <3 g/24 hours at 3 measurements or did not decrease to <2 g/24 hours within 2 weeks following an increase to ≥2 g/24 hours and <3 g/24 hours, the administration of ramucirumab or placebo was to be discontinued. When ramucirumab or placebo was resumed after treatment interruption, the dose of ramucirumab or placebo was to be reduced to 6 mg/kg. When the treatment was resumed after the second interruption, the dose was to be reduced to 5 mg/kg. However, there was no patient in whom protein in pooled urine was ≥2 g/24 hours at 3 measurements, or did not decrease to <2 g/24 hours within 2 weeks in the RAINBOW and REGARD studies. Therefore, the applicant considered that determining dosing criteria was rather unpractical for patients in whom protein in pooled urine was ≥2 g/24 hours and <3 g/24 hours at 3 measurements or did not decrease to <2 g/24 hours within 2 weeks following an increase to ≥2 g/24 hours and <3 g/24 hours.

Based on the above explanation, the criteria for infusion rate reduction, treatment interruption, dose reduction, and discontinuation of ramucirumab, and dose reduction method were established as shown in the following table.

Adverse drug reaction		Measure to be taken
IRR	Grade 1 or 2	Reduce the infusion rate by 50% during the infusion and at all subsequent infusions.
	Grade 3 or 4	Discontinue ramucirumab immediately and never resume administration.
Severe hypertension		Suspend administration until hypertension is controlled by regular antihypertensive treatment and, if not controllable, discontinue administration.
Proteinuria	24-hour urine protein ≥2 g	First episode: Suspend administration. After 24-hour urine protein decreases to <2 g, resume administration at the reduced dose of 6 mg/kg.
		Second and subsequent episodes: Suspend administration. After 24-hour urine protein decreases to <2 g, resume administration at the reduced dose of 5 mg/kg.
	24-hour urine protein ≥3 g or an episode of nephrotic syndrome	Discontinue treatment.

PMDA accepted the explanation of the applicant.

4.(iii).B.(5).3) Concomitant use with other antineoplastics

The applicant explained the combination of ramucirumab with antineoplastics other than PTX as follows:

In patients with unresectable advanced/recurrent gastric cancer, the efficacy and safety of ramucirumab in combination with antineoplastics other than PTX have not been established. Therefore, the concomitant use of ramucirumab with antineoplastics other than PTX is not recommended.

PMDA considers as follows:

PMDA accepted the explanation of the applicant. In order to caution against treatment with ramucirumab in combination with antineoplastics other than PTX, the "Precautions for Dosage and Administration" section of the package insert should mention to the effect that the efficacy and safety of ramucirumab in combination with antineoplastics other than PTX have not been established.

4.(iii).B.(6) Post-marketing investigations

The applicant explained the plan for the post-marketing surveillance as follows:

In order to evaluate the safety, etc. of ramucirumab under routine use after the market launch, the applicant plans to conduct post-marketing surveillance in patients with unresectable advanced/recurrent gastric cancer treated with ramucirumab.

Based on the frequency, severity, and seriousness of adverse events occurring in the RAINBOW and REGARD studies, the priority investigation items for the surveillance were arterial thromboembolism, hypertension, IRR, proteinuria, gastrointestinal perforation, haemorrhage, and liver disorder/hepatic failure.

The target sample size was determined as 650, based on the incidences of the above-mentioned adverse events (which were selected as the priority investigation items) in the Japanese population in the RAINBOW study.

The observation period was determined as 1 year for the purpose of collecting safety information extensively under routine use in consideration of the following: (i) the median treatment duration was 154 days in the Japanese population in the RAINBOW study and was 56 days in the ramucirumab group in the REGARD study, and (ii) the last case of Grade ≥3 gastrointestinal perforation occurred 308 days after the start of treatment.

PMDA considers as follows:
In the data submitted for the present application, there were no new noteworthy characteristic events in patients treated with ramucirumab as compared with the safety profile on adverse events which were reported to be characteristic to other antineoplastics with anti-angiogenic activity. However, ramucirumab did cause adverse events requiring attention such as arterial thromboembolism. Also, the amount of accumulated safety information on ramucirumab in Japanese patients is not sufficient. Therefore, post-marketing surveillance should be conducted to investigate the safety, etc. of ramucirumab in clinical use in Japan.

The following adverse events should be included in the priority investigation items of the surveillance, in addition to the events selected by the applicant: venous thromboembolism, cardiac failure congestive, RPLS, fistula, and disturbance of wound healing, all of which are adverse events observed with other antineoplastics with anti-angiogenic activity and therefore require attention in treatment with ramucirumab. The proposed target sample size and follow-up period are acceptable.

4.(iv) Adverse events, etc. observed in clinical studies
Deaths reported in the clinical studies submitted as the safety evaluation data are described in "4.(iii) Summary of clinical efficacy and safety." Major adverse events other than death were as shown below.

4.(iv).(1) Japanese phase I study (Study I4T-IE-JVBI)
Adverse events were reported by 3 of 3 patients (100%) in the 6 mg/kg group, 6 of 6 patients (100%) in the 8 mg/kg group, and 6 of 6 patients (100%) in the 10 mg/kg group. Adverse events for which a causal relationship to the study drug could not be ruled out were reported by 3 of 3 patients (100%) in the 6 mg/kg group, 6 of 6 patients (100%) in the 8 mg/kg group, and 6 of 6 patients (100%) in the 10 mg/kg group. Adverse events reported by ≥3 patients in any group were as shown below.

Adverse events reported by ≥3 patients in any group

System organ class Preferred term (MedDRA/J ver.12.0)	Number of patients (%)					
	6 mg/kg N = 3		8 mg/kg N = 6		10 mg/kg N = 6	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	3 (100)	1 (33.3)	6 (100)	2 (33.3)	6 (100)	2 (33.3)
General disorders and administration site conditions						
Fatigue	1 (33.3)	0	1 (16.7)	0	3 (50.0)	0
Injection site rash	1 (33.3)	0	1 (16.7)	0	3 (50.0)	0
Pyrexia	1 (33.3)	0	2 (33.3)	0	4 (66.7)	0
Infections and infestations						
Nasopharyngitis	0	0	3 (50.0)	0	0	0
Nervous system disorders						
Headache	1 (33.3)	0	4 (66.7)	0	5 (83.3)	0
Renal and urinary disorders						
Proteinuria	0	0	3 (50.0)	0	0	0
Vascular disorders						
Hypertension	1 (33.3)	0	3 (50.0)	0	2 (33.3)	0

Serious adverse events were reported by 1 of 3 patients (33.3%) in the 6 mg/kg group, 2 of 6 patients (33.3%) in the 8 mg/kg group, and 2 of 6 patients (33.3%) in the 10 mg/kg group. These serious adverse events were hospitalisation* (1 patient [33.3%]) in the 6 mg/kg group, hospitalisation* (2 patients [33.3%]) in the 8 mg/kg group, and hospitalisation* and syncope (1 patient each [16.7%]) in the 10 mg/kg group. A causal relationship to the study drug could not be ruled out for syncope (1 patient) in the 10 mg/kg group.

There were no adverse events leading to study drug discontinuation.

* The patient was hospitalized to receive the study drug.

4.(iv).(2) Japanese phase I study (Study I4T-IE-JVBW)

Adverse events were reported by 6 of 6 patients (100%). Adverse events for which a causal relationship to the study drug could not be ruled out were reported by 6 of 6 patients (100%). Adverse events reported by ≥3 patients were shown below.

Adverse events reported by ≥3 patients

System organ class Preferred term (MedDRA/J ver.13.0)	Number of patients (%) N = 6	
	All Grades	Grade ≥3
All adverse events	6 (100)	5 (83.3)
Blood and lymphatic system disorders		
Neutropenia	4 (66.7)	1 (16.7)
Gastrointestinal disorders		
Nausea	3 (50.0)	0
General disorders and administration site conditions		
Pyrexia	3 (50.0)	0
Metabolism and nutrition disorders		
Decreased appetite	3 (50.0)	1 (16.7)
Renal and urinary disorders		
Proteinuria	3 (50.0)	1 (16.7)
Respiratory, thoracic and mediastinal disorders		
Epistaxis	5 (83.3)	0
Skin and subcutaneous tissue disorders		
Alopecia	3 (50.0)	0
Rash	4 (66.7)	0

Serious adverse events were reported by 4 of 6 patients (66.7%), which were pneumonia (2 patients [33.3%]), gastrointestinal haemorrhage, intestinal obstruction, decreased appetite, lymphangiosis carcinomatosa, and meningism (1 patient each [16.7%]). A causal relationship to the study drug could not be ruled out for pneumonia (2 patients) and gastrointestinal haemorrhage (1 patient).

An adverse event leading to the discontinuation of the study drug was reported by 1 of 6 patients (16.7%). The reported adverse event was meningism (1 patient [16.7%]), for which a causal relationship to the study drug was ruled out.

4.(iv).(3) Japanese phase I study (Study I4T-IE-JVBX)

Adverse events were reported by 7 of 7 patients (100%). Adverse events for which a causal relationship to the study drug could not be ruled out were reported by 7 of 7 patients (100%). Adverse events reported by ≥3 patients were shown below.

Adverse events reported by ≥3 patients

System organ class Preferred term (MedDRA/J ver.12.0)	Number of patients (%) N = 7	
	All Grades	Grade ≥3
All adverse events	7 (100)	7 (100)
Blood and lymphatic system disorders		
Febrile neutropenia	4 (57.1)	4 (57.1)
Eye disorders		
Lacrimation increased	3 (42.9)	0
Gastrointestinal disorders		
Stomatitis	3 (42.9)	0
General disorders and administration site conditions		
Face oedema	4 (57.1)	0
Malaise	4 (57.1)	1 (14.3)
Mucosal inflammation	4 (57.1)	0
Oedema peripheral	7 (100)	0
Infections and infestations		
Nasopharyngitis	5 (71.4)	0
Investigations		
Neutrophil count decreased	6 (85.7)	6 (85.7)
Metabolism and nutrition disorders		
Inappetence	3 (42.9)	0
Nervous system disorders		
Dysgeusia	4 (57.1)	0
Peripheral sensory neuropathy	3 (42.9)	0
Renal and urinary disorders		
Proteinuria	3 (42.9)	0
Respiratory, thoracic and mediastinal disorders		
Epistaxis	5 (71.4)	0
Pleural effusion	3 (42.9)	0
Skin and subcutaneous tissue disorders		
Alopecia	6 (85.7)	0
Nail disorder	5 (71.4)	0

Serious adverse events were reported by 7 of 7 patients (100%). These events were febrile neutropenia (3 patients [42.9%]), pleural effusion (2 patients [28.6%]), cardiac failure, neutrophil count decreased, epistaxis, and interstitial lung disease (1 patient each [14.3%]). A causal relationship to the study drug could not be ruled out for febrile neutropenia (2 patients) and epistaxis, cardiac failure, and interstitial lung disease (1 patient each).

Adverse events leading to the discontinuation of the study drug were reported by 4 of 7 patients (57.1%). These events were face oedema, oedema peripheral, platelet count decreased, interstitial lung disease, and pleural effusion (1 patient each [14.3%]). A causal relationship to the study drug could not be ruled out for face oedema, oedema peripheral, platelet count decreased, and interstitial lung disease (1 patient each).

4.(iv).(4) Japanese phase I study (Study I4T-IE-JVBY)

Adverse events were reported by 6 of 6 patients (100%), and adverse events for which a causal relationship to the study drug could not be ruled out were reported by 6 of 6 patients (100%). Adverse events reported by ≥3 patients were as shown below.

Adverse events reported by ≥3 patients

System organ class Preferred term (MedDRA/J ver.13.1)	Number of patients (%) N = 6	
	All Grades	Grade ≥3
All adverse events	6 (100)	6 (100)
Blood and lymphatic system disorders		
Neutropenia	5 (83.3)	5 (83.3)
Thrombocytopenia	4 (66.7)	1 (16.7)
Gastrointestinal disorders		
Diarrhoea	5 (83.3)	0
Nausea	3 (50.0)	0
Stomatitis	5 (83.3)	0
Vomiting	4 (66.7)	0
General disorders and administration site conditions		
Fatigue	3 (50.0)	0
Metabolism and nutrition disorders		
Decreased appetite	4 (66.7)	0
Respiratory, thoracic and mediastinal disorders		
Epistaxis	3 (50.0)	0

There were no serious adverse events.

Adverse events leading to the discontinuation of the study drug were reported by 3 of 6 patients (50.0%). The reported adverse events were proteinuria (2 patients [33.3%]) and neutropenia (1 patient [16.7%]). A causal relationship to the study drug could not be ruled out for all these adverse events.

4.(iv).(5) Global phase III study (Study I4T-IE-JVBE [RAINBOW study])

Adverse events were reported by 324 of 327 patients (99.1%) in the ramucirumab/PTX group and 322 of 329 patients (97.9%) in the placebo/PTX group. Adverse events for which a causal relationship to the study drug could not be ruled out were reported by 308 of 327 patients (94.2%) in the ramucirumab/PTX group and 283 of 329 patients (86.0%) in the placebo/PTX group. Adverse events with an incidence of ≥20% in either group were as shown in the following table.

Adverse events with an incidence of ≥20% in either group

System organ class Preferred term (MedDRA/J ver.16.0)	Number of patients (%)			
	Ramucirumab/PTX N = 327		Placebo/PTX N = 329	
	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	324 (99.1)	267 (81.7)	322 (97.9)	206 (62.6)
Blood and lymphatic system disorders				
Neutropenia	178 (54.4)	133 (40.7)	102 (31.0)	62 (18.8)
Anaemia	111 (33.9)	30 (9.2)	117 (35.6)	34 (10.3)
Leukopenia	111 (33.9)	57 (17.4)	69 (21.0)	22 (6.7)
Gastrointestinal disorders				
Nausea	115 (35.2)	6 (1.8)	108 (32.8)	8 (2.4)
Diarrhoea	106 (32.4)	12 (3.7)	76 (23.1)	5 (1.5)
Abdominal pain	101 (30.9)	18 (5.5)	67 (20.4)	11 (3.3)
Vomiting	88 (26.9)	10 (3.1)	68 (20.7)	12 (3.6)
Constipation	70 (21.4)	0	71 (21.6)	2 (0.6)
General disorders and administration site conditions				
Fatigue	130 (39.8)	23 (7.0)	106 (32.2)	13 (4.0)
Oedema peripheral	82 (25.1)	5 (1.5)	45 (13.7)	2 (0.6)
Asthenia	69 (21.1)	18 (5.5)	45 (13.7)	6 (1.8)
Metabolism and nutrition disorders				
Decreased appetite	131 (40.1)	10 (3.1)	105 (31.9)	13 (4.0)
Respiratory, thoracic and mediastinal disorders				
Epistaxis	100 (30.6)	0	23 (7.0)	0
Skin and subcutaneous tissue disorders				
Alopecia	107 (32.7)	0	127 (38.6)	1 (0.3)
Vascular disorders				
Hypertension	78 (23.9)	46 (14.1)	16 (4.9)	8(2.4)

Serious adverse events were reported by 153 of 327 patients (46.8%) in the ramucirumab/PTX group and 139 of 329 patients (42.2%) in the placebo/PTX group. Serious adverse events with an incidence of ≥2% were malignant neoplasm progression (40 patients [12.2%]), neutropenia (12 patients [3.7%]), abdominal pain, febrile neutropenia, and general physical health deterioration (8 patients each [2.4%]), anaemia, pyrexia, and vomiting (7 patients each [2.1%]) in the ramucirumab/PTX group, and malignant neoplasm progression (45 patients [13.7%]), abdominal pain (10 patients [3.0%]), vomiting and general physical health deterioration (9 patients each [2.7%]) in the placebo/PTX group. A causal relationship to the study drug could not be ruled out for neutropenia (12 patients), febrile neutropenia (8 patients), anaemia (5 patients), pyrexia (2 patients), vomiting, abdominal pain, and general physical health deterioration (1 patient each) in the ramucirumab/PTX group, and vomiting (3 patients) and general physical health deterioration (1 patient) in the placebo/PTX group.

Adverse events leading to the discontinuation of the study drug were reported by 102 of 327 patients (31.2%) in the ramucirumab/PTX group and 80 of 329 patients (24.3%) in the placebo/PTX group. Adverse events leading to the discontinuation of the study drug with an incidence of ≥2% were malignant neoplasm progression and neutropenia (13 patients each [4.0%]), thrombocytopenia (9 patients [2.8%]), and neuropathy peripheral (7 patients [2.1%]) in the ramucirumab/PTX group, and malignant neoplasm progression (16 patients [4.9%]) in the placebo/PTX group. A causal relationship to the study drug could not be ruled out for neutropenia (13 patients), neuropathy peripheral (7 patients), and thrombocytopenia (6 patients) in the ramucirumab/PTX.

4.(iv).(6) Foreign phase I study (Study I4T-IE-JVBM)

Adverse events were reported by 6 of 6 patients (100%) in the 2 mg/kg group, 4 of 4 patients (100%) in the 4 mg/kg group, 4 of 4 patients (100%) in the 6 mg/kg group, 5 of 5 patients (100%) in the 8 mg/kg group, 7 of 7 patients (100%) in the 10 mg/kg group, 5 of 5 patients (100%) in the 13 mg/kg group, and 6 of 6 patients (100%) in the 16 mg/kg group. Adverse events for which a causal relationship to the study drug could not be ruled out were reported by 4 of 6 patients (66.7%) in the 2 mg/kg group, 4 of 4 patients (100%) in the 4 mg/kg group, 4 of 4 patients (100%) in the 6 mg/kg group, 5 of 5 patients (100%) in the 8 mg/kg group, 6 of 7 patients (85.7%) in the 10 mg/kg group, 5 of 5 patients (100%) in the 13 mg/kg group, and 4 of 6 patients (66.7%) in the 16 mg/kg group.

Adverse events reported by ≥3 patients were constipation, oedema peripheral, and inappetence (3 patients each [50.0%]) in the 2 mg/kg group, fatigue (4 patients [100%]), diarrhoea, nausea, vomiting, and headache (3 patients each [75.0%]) in the 4 mg/kg group, upper respiratory tract infection (3 patients [75.0%]) in the 6 mg/kg group, headache (4 patients [80.0%]) and diarrhoea (3 patients [60.0%]) in the 8 mg/kg group, headache (4 patients [57.1%]), constipation, nausea, and fatigue (3 patients each [42.9%]) in the 10 mg/kg group, fatigue, oedema peripheral, pyrexia, dizziness, and headache (3 patients each [60.0%]) in the 13 mg/kg group, and fatigue, oedema peripheral, headache, proteinuria, cough, epistaxis, and sinus congestion (3 patients each [50.0%]) in the 16 mg/kg group. Among these, Grade 3 adverse events were inappetence (1 patient) in the 2 mg/kg group, headache (1 patient) in the 8 mg/kg group, headache (1 patient) in the 13 mg/kg group, and fatigue (1 patient) in the 16 mg/kg group.

Serious adverse events were reported by 2 of 6 patients (33.3%) in the 2 mg/kg group, 3 of 4 patients (75.0%) in the 4 mg/kg group, 1 of 4 patients (25.0%) in the 6 mg/kg group, 1 of 5 patients (20.0%) in the 8 mg/kg group, 2 of 7 patients (28.6%) in the 10 mg/kg group, 2 of 5 patients (40.0%) in the 13 mg/kg group, and 4 of 6 patients (66.7%) in the 16 mg/kg group. Serious adverse events observed were inappetence, ascites, dehydration, dyspnoea, malnutrition, pulmonary embolism, vomiting, and weight decreased (1 patient each [16.7%]) in the 2 mg/kg group, dyspnoea, fatigue, hypoglycaemia, mental status changes, pleuritic pain, and proteinuria (1 patient each [25.0%]) in the 4 mg/kg group, abdominal pain, nausea, small intestinal obstruction, and vomiting (1 patient each [25.0%]) in the 6 mg/kg group, headache and hypertension (1 patient each [20.0%]) in the 8 mg/kg group, dyspnoea, pleuritic pain, and syncope (1 patient each [14.3%]) in the 10 mg/kg group, abdominal pain, meningitis aseptic, pyrexia, and small intestinal obstruction (1 patient each [20.0%]) in the 13 mg/kg group, and deep vein thrombosis (2 patients [33.3%]), cerebral haemorrhage, hydronephrosis, hypertension, and pain (1 patient each [16.7%]) in the 16 mg/kg group. A causal relationship to the study drug could not be ruled out for inappetence and vomiting (1 patient each) in the 2 mg/kg group, proteinuria (1 patient) in the 4 mg/kg group, headache and hypertension (1 patient each) in the 8 mg/kg group, pleuritic pain (1 patient)

in the 10 mg/kg group, and deep vein thrombosis and hypertension (1 patient each) in the 16 mg/kg group.

Adverse events leading to the discontinuation of the study drug were reported by 3 of 6 patients (50.0%) in the 2 mg/kg group, 2 of 4 patients (50.0%) in the 4 mg/kg group, 1 of 5 patients (20.0%) in the 8 mg/kg group, and 2 of 6 patients (33.3%) in the 16 mg/kg group. These events were vena cava thrombosis, anal fistula, and vomiting (1 patient each [16.7%]) in the 2 mg/kg group; proteinuria and embolism (1 patient each [25.0%]) in the 4 mg/kg group, hypertension (1 patient [20.0%]) in the 8 mg/kg group, and cerebral haemorrhage and hypertension (1 patient each [16.7%]) in the 16 mg/kg group. A causal relationship to the study drug could not be ruled out for vomiting (1 patient) in the 2 mg/kg group, proteinuria and embolism (1 patient each) in the 4 mg/kg group, hypertension (1 patient) in the 8 mg/kg group, and hypertension (1 patient) in the 16 mg/kg group.

4.(iv).(7) Foreign phase I study (Study I4T-IE-JVBN)

Adverse events were reported by 4 of 4 patients (100%) in the 6 mg/kg group, 5 of 5 patients (100%) in the 8 mg/kg group, 4 of 4 patients (100%) in the 10 mg/kg group, 6 of 6 patients (100%) in the 15 mg/kg group, and 6 of 6 patients (100%) in the 20 mg/kg group. Adverse events for which a causal relationship to the study drug could not be ruled out were reported by 1 of 4 patients (25.0%) in the 6 mg/kg group, 3 of 5 patients (60.0%) in the 8 mg/kg group, 4 of 4 patients (100%) in the 10 mg/kg group, 5 of 6 patients (83.3%) in the 15 mg/kg group, and 5 of 6 patients (83.3%) in the 20 mg/kg group.

Adverse events reported by ≥3 patients were oedema peripheral (3 patients [60.0%]) in the 8 mg/kg group; constipation, vomiting, fatigue, and proteinuria (3 patients each [75.0%]) in the 10 mg/kg group; fatigue (3 patients [50.0%]) in the 15 mg/kg group; and headache (5 patients [83.3%]), diarrhoea, fatigue, and hypertension (3 patients each [50.0%]) in the 20 mg/kg group. Grade 3 events were diarrhoea, fatigue, and hypertension (1 patient each) in the 20 mg/kg group.

Serious adverse events were reported by 1 of 4 patients (25.0%) in the 6 mg/kg group, 1 of 5 patients (20.0%) in the 8 mg/kg group, 3 of 4 patients (75.0%) in the 10 mg/kg group, 3 of 6 patients (50.0%) in the 15 mg/kg group, and 1 of 6 patients (16.7%) in the 20 mg/kg group. Serious adverse events observed were dyspnoea exacerbated and pulmonary embolism (1 patient each [25.0%]) in the 6 mg/kg group, duodenal ulcer haemorrhage (1 patient [20.0%]) in the 8 mg/kg group, dysphagia, cellulitis, pneumonia, and thrombosis (1 patient each [25.0%]) in the 10 mg/kg group, atrial flutter, ileus, acute kidney injury, acute respiratory failure, and dyspnoea (1 patient each [16.7%]) in the 15 mg/kg group, and tachycardia, pyrexia, dyspnoea, and pneumothorax (1 patient each [16.7%]) in the 20 mg/kg group. A causal relationship to the study drug could not be ruled out for duodenal ulcer haemorrhage (1 patient) in the 8 mg/kg group, atrial flutter (1 patient) in the 15 mg/kg group, and pneumothorax (1 patient) in the 20 mg/kg group.

Adverse events leading to the discontinuation of the study drug were reported by 2 of 5 patients (40.0%) in the 8 mg/kg group, 1 of 4 patients (25.0%) in the 10 mg/kg group, and 2 of 6 patients (33.3%) in the 20 mg/kg group. The reported adverse events were hypertension, transient ischaemic attack, and duodenal ulcer haemorrhage (1 patient each [20.0%]) in the 8 mg/kg group, proteinuria (1 patient [25.0%]) in the 10 mg/kg group, and myocardial infarction, dyspnoea, and pneumothorax (1 patient each [16.7%]) in the 20 mg/kg group. A causal relationship to the study drug could not be ruled out for duodenal ulcer haemorrhage (1 patient) in the 8 mg/kg group, proteinuria (1 patient) in the 10 mg/kg group, and pneumothorax (1 patient) in the 20 mg/kg group.

4.(iv).(8) Foreign phase II study (Study I4T-IE-JVBK)

Adverse events were reported by 65 of 66 patients (98.5%). Adverse events for which a causal relationship to the study drug could not be ruled out were reported by 42 of 66 patients (63.6%). Adverse events with an incidence of ≥30% were as shown in the following table.

Adverse events with an incidence of ≥30%

System organ class Preferred term (MedDRA/J ver.15.0)	Number of patients (%) N = 66	
	All Grades	Grade ≥3
All adverse events	65 (98.5)	39 (59.1)
Gastrointestinal disorders		
Nausea	21 (31.8)	1 (1.5)
General disorders and administration site conditions		
Fatigue	21 (31.8)	2 (3.0)
Metabolism and nutrition disorders		
Decreased appetite	21 (31.8)	1 (1.5)
Respiratory, thoracic and mediastinal disorders		
Dyspnoea	20 (30.3)	3 (4.5)

Serious adverse events were reported by 32 of 66 patients (48.5%). These serious adverse events were disease progression and dyspnoea (6 patients each [9.1%]), abdominal pain and dehydration (4 patients each [6.1%]), neoplasm malignant (3 patients [4.5%]), nausea, vomiting, hyponatraemia, pleural effusion, pulmonary embolism, and deep vein thrombosis (2 patients each [3.0%]), anaemia, anaemia megaloblastic, atrial fibrillation, cardiac arrest, ascites, diarrhoea, gastrointestinal obstruction, ileus, pancreatitis, upper gastrointestinal haemorrhage, infusion related reaction, oedema peripheral, bile duct obstruction, hepatic failure, Clostridial infection, diverticulitis, pneumonia, urinary tract infection, hyperkalaemia, metabolic acidosis, intracranial tumour haemorrhage, neoplasm progression, tumour necrosis, headache, agitation, mental status changes, calculus urinary, haematuria, acute kidney injury, respiratory arrest, respiratory failure, and hypertension (1 patient each [1.5%]). A causal relationship to the study drug could not be ruled out for deep vein thrombosis (2 patients), ascites, upper gastrointestinal haemorrhage, infusion related reaction, hepatic failure, diverticulitis, dehydration, metabolic acidosis, intracranial tumour haemorrhage, tumour necrosis, mental status changes, haematuria, dyspnoea, pulmonary embolism, respiratory failure, and hypertension (1 patient each).

Adverse events leading to the discontinuation of the study drug were reported by 6 of 66 patients (9.1%). The reported adverse events were disease progression, intracranial tumour haemorrhage, neoplasm malignant, neoplasm progression, proteinuria, pulmonary embolism, and deep vein thrombosis (1 patient each [1.5%]). A causal relationship to the study drug could not be ruled out for proteinuria, deep vein thrombosis, and pulmonary embolism (1 patient each).

4.(iv).(9) Foreign phase II study (Study I4T-IE-JVCA)

Adverse events were reported by 24 of 24 patients (100%) in Part A and 11 of 16 patients (68.8%) in Part B. Adverse events for which a causal relationship to the study drug could not be ruled out were reported by 22 of 24 patients (91.7%) in Part A and 9 of 16 patients (56.3%) in Part B. Adverse events with an incidence of ≥30% in either part were fatigue (12 patients [50.0%]) and anaemia (10 patients [41.7%]) in Part A. Anaemia (1 patient) in Part A was Grade 3.

Serious adverse events were observed in 5 of 24 patients (20.8%) in Part A and none in Part B. Serious adverse events observed in Part A were non-cardiac chest pain, pyrexia, acute hepatic failure, influenza, fall, hepatic enzyme increased, depressed level of consciousness, acute kidney injury, cough, dyspnoea, pulmonary embolism, and hypoaesthesia facial (1 patient each [4.2%]). A causal relationship to the study drug could not be ruled out for hepatic enzyme increased, non-cardiac chest pain, pyrexia, cough, dyspnoea, and pulmonary embolism (1 patient each).

Adverse events leading to the discontinuation of the study drug were observed in 3 of 24 patients (12.5%) in Part A and none in Part B. These adverse events observed in Part A were anaemia, infusion related reaction, and hepatic enzyme increased (1 patient each [4.2%]), and a causal relationship to the study drug could not be ruled out for all events.

4.(iv).(10) Foreign phase II study (Study I4T-IE-JVCC)

Adverse events were reported by 21 of 22 patients (95.5%). Adverse events for which a causal relationship to the study drug could not be ruled out were reported by 19 of 24 patients (86.4%). Adverse events with an incidence of ≥30% were as shown in the following table.

Adverse events with an incidence of ≥30%

System organ class Preferred term (MedDRA/J ver.14.1)	Number of patients (%) N = 22	
	All Grades	Grade ≥3
All adverse events	21 (95.5)	14 (63.6)
Gastrointestinal disorders		
Nausea	12 (54.5)	0
General disorders and administration site conditions		
Fatigue	9 (40.9)	2 (9.1)
Investigations		
White blood cell count decreased	9 (40.9)	7 (31.8)
Respiratory, thoracic and mediastinal disorders		
Dyspnoea	7 (31.8)	2 (9.1)

Serious adverse events were reported by 9 of 22 patients (40.9%). These serious adverse events were febrile neutropenia, abdominal pain, pyrexia, and dyspnoea (2 patients each [9.1%]), and neutropenia, vision blurred, diarrhoea, fatigue, cellulitis, wound infection, dehydration, muscular weakness, and nervous system disorder (1 patient each [4.5%]). A causal relationship to the study drug could not be ruled out for febrile neutropenia and pyrexia (2 patients each) and neutropenia, vision blurred, fatigue, muscular weakness, and nervous system disorder (1 patient each).

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

4.(iv).(11) Foreign phase II study (Study I4T-IE-JVBP)

Adverse events were reported by 39 of 39 patients (100%). Adverse events for which a causal relationship to the study drug could not be ruled out were reported by 37 of 39 patients (94.9%). Adverse events with an incidence of ≥30% were as shown in the following table.

Adverse events with an incidence of ≥30%

System organ class Preferred term (MedDRA/J ver.10.0)	Number of patients (%) N = 39	
	All Grades	Grade ≥3
All adverse events	39 (100)	19 (48.7)
General disorders and administration site conditions		
Fatigue	19 (48.7)	3 (7.7)
Oedema peripheral	14 (35.9)	0
Musculoskeletal and connective tissue disorders		
Arthralgia	12 (30.8)	0
Nervous system disorders		
Headache	14 (35.9)	1 (2.6)
Respiratory, thoracic and mediastinal disorders		
Epistaxis	13 (33.3)	0

Serious adverse events were reported by 12 of 39 patients (30.8%). These serious adverse events were cardio-respiratory arrest, myocardial infarction, fatigue, multi-organ failure, urinary tract infection, inappetence, back pain, altered state of consciousness, cerebral ischaemia, neuropathy peripheral, spinal cord compression, haematuria, proteinuria, acute kidney injury, haemoptysis, spinal laminectomy, and hypertensive crisis (1 patient each [2.6%]). A causal relationship to the study drug could not be ruled out for cardio-respiratory arrest, myocardial infarction, cerebral ischaemia, proteinuria, haemoptysis, and hypertensive crisis (1 patient each).

Adverse events leading to the discontinuation of the study drug were reported by 10 of 39 patients (25.6%). These adverse events were acute coronary syndrome, myocardial infarction, liver function test abnormal, cerebral ischaemia, neuropathy peripheral, spinal cord compression, proteinuria, acute kidney injury, haemoptysis, obstructive airways disorder, and hypertensive crisis (1 patient each [2.6%]). A causal relationship to the study drug could not be ruled out for acute coronary syndrome, myocardial infarction, liver function test abnormal, cerebral ischaemia, proteinuria, acute kidney injury, haemoptysis, and hypertensive crisis (1 patient each).

4.(iv).(12) Foreign phase II study (Study I4T-IE-JVBQ)

Adverse events were reported by 42 of 42 patients (100%). Adverse events for which a causal relationship to the study drug could not be ruled out were reported by 41 of 42 patients (97.6%). Adverse events with an incidence of ≥30% were as shown in the following table.

Adverse events with an incidence of ≥30%

System organ class Preferred term (MedDRA/J ver.11.0)	Number of patients (%) N = 42	
	All Grades	Grade ≥3
All adverse events	42 (100)	29 (69.0)
Gastrointestinal disorders		
Nausea	15 (35.7)	0
Diarrhoea	14 (33.3)	1 (2.4)
General disorders and administration site conditions		
Fatigue	28 (66.7)	4 (9.5)
Oedema peripheral	14 (33.3)	0
Nervous system disorders		
Headache	16 (38.1)	1 (2.4)
Vascular disorders		
Hypertension	17 (40.5)	6 (14.3)

Serious adverse events were reported by 24 of 42 patients (57.1%). These serious adverse events were gastrointestinal haemorrhage, hypertension (3 patients each [7.1%]), ascites, fatigue, infusion related reaction, pyrexia, pneumonia, confusional state, and hypoxia (2 patients each [4.8%]), adrenal insufficiency, abdominal pain, constipation, intestinal obstruction, chills, disease progression, hepatic failure, hepatorenal syndrome, hypersensitivity, bronchitis, cellulitis, Escherichia bacteraemia, Staphylococcal infection, inappetence, failure to thrive, hyponatraemia, arthralgia, musculoskeletal pain, pain in extremity, hepatic neoplasm malignant, encephalopathy, hepatic encephalopathy, syncope, mental status changes, pneumonia aspiration, hospitalisation,* liver transplant, arteriosclerosis, femoral artery occlusion, and hypotension (1 patient each [2.4%]). A causal relationship to the study drug could not be ruled out for gastrointestinal haemorrhage and hypertension (3 patients each), infusion related reaction (2 patients), fatigue, pyrexia, inappetence, hyponatraemia, and hospitalisation (1 patient each).

Adverse events leading to the discontinuation of the study drug were reported by 11 of 42 patients (26.2%). These adverse events were infusion related reaction, gastrointestinal haemorrhage (2 patients each [4.8%]), cellulitis, pneumonia, hypertension, cholecystitis acute, abdominal pain, arthralgia, back pain, musculoskeletal chest pain, fatigue, ascites, and hepatorenal syndrome (1 patient each [2.4%]). A causal relationship to the study drug could not be ruled out for infusion related reaction, gastrointestinal haemorrhage (2 patients each), hypertension, back pain, and musculoskeletal chest pain (1 patient each).

* Unspecified

4.(iv).(13) Foreign phase II study (Study I4T-IE-JVBR)

Adverse events were reported by 59 of 60 patients (98.3%). Adverse events for which a causal relationship to the study drug could not be ruled out were reported by 56 of 60 patients (93.3%). Adverse events with an incidence of ≥30% were as shown in the following table.

Adverse events with an incidence of ≥30%

System organ class Preferred term (MedDRA/J ver.15.1)	Number of patients (%) N = 60	
	All Grades	Grade ≥3
All adverse events	59 (98.3)	33 (55.0)
Gastrointestinal disorders		
Diarrhoea	21 (35.0)	1 (1.7)
Nausea	26 (43.3)	3 (5.0)
Vomiting	20 (33.3)	2 (3.3)
General disorders and administration site conditions		
Fatigue	41 (68.3)	5 (8.3)
Nervous system disorders		
Headache	43 (71.7)	6 (10.0)

Serious adverse events were reported by 22 of 60 patients (36.7%). These serious adverse events were neoplasm progression (4 patients [6.7%]), small intestinal obstruction (3 patients [5.0%]), intestinal perforation, expired drug administered, and ALT increased (2 patients each [3.3%]), thrombocytopenia, mitral valve incompetence, ascites, nausea, rectal haemorrhage, vomiting, abscess sterile, hernia obstructive, oedema peripheral, pyrexia, peritonitis, postoperative wound infection, sepsis, AST increased, hepatic enzyme increased, hypercalcaemia, hypokalaemia, neuralgia, acute kidney injury, female genital tract fistula, dyspnoea, pleural effusion, and deep vein thrombosis (1 patient each [1.7%]). A causal relationship to the study drug could not be ruled out for expired drug administered (2 patients), thrombocytopenia, mitral valve incompetence, intestinal perforation, oedema peripheral, ALT increased, hepatic enzyme increased, neuralgia, acute kidney injury, and deep vein thrombosis (1 patient each).

Adverse events leading to the discontinuation of the study drug were reported by 7 of 60 patients (11.7%). These adverse events were intestinal perforation and blood creatinine increased (2 patients each [3.3%]), proteinuria, ALT increased, AST increased, and neoplasm progression (1 patient each [1.7%]). A causal relationship to the study drug could not be ruled out for intestinal perforation, proteinuria, blood creatinine increased, ALT increased, and AST increased (1 patient each).

4.(iv).(14) Foreign phase II study (Study I4T-IE-JVBH)

Adverse events were reported by 48 of 48 patients (100%). Adverse events for which a causal relationship to the study drug could not be ruled out were reported by 45 of 48 patients (93.8%). Adverse events with an incidence of ≥30% were as shown in the following table.

Adverse events with an incidence of ≥30%

System organ class Preferred term (MedDRA/J ver.12.0)	Number of patients (%) N = 48	
	All Grades	Grade ≥3
All adverse events	48 (100)	45 (93.8)
Blood and lymphatic system disorders		
Neutropenia	27 (56.3)	20 (41.7)
Thrombocytopenia	17 (35.4)	1 (2.1)
Gastrointestinal disorders		
Diarrhoea	32 (66.7)	4 (8.3)
Nausea	21 (43.8)	0
General disorders and administration site conditions		
Asthenia	35 (72.9)	6 (12.5)
Mucosal inflammation	26 (54.2)	0
Nervous system disorders		
Dysaesthesia	23 (47.9)	4 (8.3)
Neurotoxicity	32 (66.7)	7 (14.6)
Respiratory, thoracic and mediastinal disorders		
Epistaxis	15 (31.3)	0
Vascular disorders		
Hypertension	27 (56.3)	8 (16.7)

Serious adverse events were reported by 17 of 48 patients (35.4%). Serious adverse events reported by ≥2 patients were pyrexia and pulmonary embolism (2 patients each [4.2%]). A causal relationship to the study drug could not be ruled out for pulmonary embolism (2 patients) and pyrexia (1 patient).

Adverse events leading to the discontinuation of the study drug were reported by 24 of 48 patients (50.0%). Adverse events leading to study drug discontinuation reported by ≥2 patients were dysaesthesia, neuropathy peripheral, and neurotoxicity (4 patients each [8.3%]), abdominal pain, pyrexia, pulmonary embolism, and hypertension (2 patients each [4.2%]). A causal relationship to the study drug could not be ruled out for dysaesthesia, neuropathy peripheral, and neurotoxicity (4 patients each), pulmonary embolism and hypertension (2 patients each), and abdominal pain and pyrexia (1 patient each).

4.(iv).(15) Foreign phase II study (Study I4T-IE-JVBJ)

Adverse events were reported by 40 of 40 patients (100%). Adverse events for which a causal relationship to the study drug could not be ruled out were reported by 34 of 40 patients (85.0%). Adverse events with an incidence of ≥30% were as shown in the following table.

Adverse events with an incidence of ≥30%

System organ class Preferred term (MedDRA/J ver.11.0)	Number of patients (%) N = 40	
	All Grades	Grade ≥3
All adverse events	40 (100)	31 (77.5)
Blood and lymphatic system disorders		
Neutropenia	14 (35.0)	9 (22.5)
Thrombocytopenia	13 (32.5)	8 (20.0)
Gastrointestinal disorders		
Constipation	16 (40.0)	1 (2.5)
Diarrhoea	14 (35.0)	0
Nausea	23 (57.5)	1 (2.5)
Vomiting	14 (35.0)	1 (2.5)
General disorders and administration site conditions		
Fatigue	30 (75.0)	7 (17.5)
Musculoskeletal and connective tissue disorders		
Arthralgia	16 (40.0)	0
Nervous system disorders		
Neuropathy peripheral	27 (67.5)	3 (7.5)
Respiratory, thoracic and mediastinal disorders		
Epistaxis	12 (30.0)	0
Skin and subcutaneous tissue disorders		
Alopecia	23 (57.5)	0

Serious adverse events were reported by 19 of 40 patients (47.5%). Serious adverse events reported by ≥2 patients were febrile neutropenia (4 patients [10.0%]), and neutropenia and catheter sepsis (2 patients each [5.0%]). A causal relationship to the study drug could not be ruled out for febrile neutropenia (2 patients) and neutropenia (1 patient).

Adverse events leading to the discontinuation of the study drug were reported by 13 of 40 patients (32.5%). Adverse events leading to study drug discontinuation reported by ≥2 patients were neutropenia, infusion related reaction, and fatigue (2 patients each [5.0%]). A causal relationship to the study drug could not be ruled out for fatigue (2 patients) and neutropenia (1 patient).

4.(iv).(16) Foreign phase II study (Study I4T-IE-JVBO)

Adverse events were reported by 52 of 52 patients (100%) in the ramucirumab/DTIC group and 49 of 50 patients (98.0%) in the ramucirumab group. Adverse events for which a causal relationship to the study drug could not be ruled out were reported by 47 of 52 patients (90.4%) in the ramucirumab/DTIC group and 40 of 50 patients (80.0%) in the ramucirumab group. Adverse events with an incidence of ≥30% in either group were as shown in the following table.

Adverse events with an incidence of ≥30% in either group

System organ class Preferred term (MedDRA/J ver.10.0)	Number of patients (%)			
	Ramucirumab/DTIC N = 52		Ramucirumab N = 50	
	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	52 (100)	30 (57.7)	49 (98.0)	24 (48.0)
Blood and lymphatic system disorders				
Thrombocytopenia	20 (38.5)	8 (15.4)	4 (8.0)	1 (2.0)
Neutropenia	18 (34.6)	15 (28.8)	0	0
Gastrointestinal disorders				
Nausea	20 (38.5)	0	14 (28.0)	0
Constipation	16 (30.8)	0	10 (20.0)	0
General disorders and administration site conditions				
Fatigue	33 (63.5)	4 (7.7)	28 (56.0)	2 (4.0)
Nervous system disorders				
Headache	9 (17.3)	1 (1.9)	16 (32.0)	1 (2.0)

Serious adverse events were reported by 13 of 52 patients (25.0%) in the ramucirumab/DTIC group and 15 of 50 patients (30.0%) in the ramucirumab group. These serious adverse events were syncope, febrile neutropenia, cardiac arrest, intestinal obstruction, proctalgia, chest pain, diverticulitis, infection, pneumonia, rib fracture, spinal compression fracture, metastatic malignant melanoma, tumour haemorrhage, cerebral haemorrhage, acute kidney injury, epistaxis, hypoxia, hypertension, and pelvic venous thrombosis (1 patient each [1.9%]) in the ramucirumab/DTIC group, and, infusion related reaction (3 patients [6.0%]), hepatic failure (2 patients [4.0%]), syncope, coronary artery disease, myocardial infarction, supraventricular tachycardia, abdominal pain, vomiting, jaundice, dehydration, back pain, pain in extremity, convulsion, psychotic disorder, proteinuria, bronchospasm, pulmonary embolism, flushing, and hypotension (1 patient each [2.0%]) in the ramucirumab group. A causal relationship to the study drug could not be ruled out for febrile neutropenia, cardiac arrest, proctalgia, tumour haemorrhage, cerebral haemorrhage, acute kidney injury, epistaxis, syncope, hypertension, and pelvic venous thrombosis (1 patient each) in the ramucirumab/DTIC group and infusion related reaction (3 patients), supraventricular tachycardia, hepatic failure, proteinuria, bronchospasm, flushing, and hypotension (1 patient each) in the ramucirumab group.

Adverse events leading to the discontinuation of the study drug were reported by 6 of 52 patients (11.5%) in the ramucirumab/DTIC group and 5 of 50 patients (10.0%) in the ramucirumab group. These adverse events were thrombocytopenia, diarrhoea, fatigue, blood creatinine increased, metastatic malignant melanoma, and epistaxis (1 patient each [1.9%]) in the ramucirumab/DTIC group and infusion related reaction (3 patients [6.0%]), supraventricular tachycardia, tachycardia, disease progression, proteinuria, bronchospasm, flushing, and hypotension (1 patient each [2.0%]) in the ramucirumab group. A causal relationship to the study drug could not be ruled out for thrombocytopenia, epistaxis, diarrhoea, fatigue, and blood creatinine increased (1 patient each) in the ramucirumab/DTIC group and infusion related reaction (3 patients), bronchospasm, flushing, hypotension, supraventricular tachycardia, and proteinuria (1 patient each) in the ramucirumab group.

4.(iv).(17) Foreign phase II study (Study I4T-IE-JVBS)

Adverse events were reported by 66 of 66 patients (100%) in the cixutumumab group and 66 of 66 patients (100%) in the ramucirumab group. Adverse events for which a causal relationship to the study drug could not be ruled out were reported by 64 of 66 patients (97.0%) in the cixutumumab group and 63 of 66 patients (95.5%) in the ramucirumab group. Adverse events with an incidence of ≥30% in either group were as shown in the following table.

Adverse events with an incidence of ≥30% in either group

System organ class Preferred term (MedDRA/J ver.12.0)	Number of patients (%)			
	Cixutumumab N = 66		Ramucirumab N = 66	
	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	66 (100)	51 (77.3)	66 (100)	55 (83.3)
Blood and lymphatic system disorders				
Neutropenia	28 (42.4)	21 (31.8)	25 (37.9)	21 (31.8)
Anaemia	23 (34.8)	2 (3.0)	24 (36.4)	7 (10.6)
Leukopenia	21 (31.8)	15 (22.7)	17 (25.8)	11 (16.7)
Thrombocytopenia	12 (18.2)	3 (4.5)	23 (34.8)	5 (7.6)
Gastrointestinal disorders				
Nausea	35 (53.0)	1 (1.5)	31 (47.0)	3 (4.5)
Diarrhoea	29 (43.9)	5 (7.6)	30 (45.5)	1 (1.5)
Constipation	27 (40.9)	0	25 (37.9)	1 (1.5)
General disorders and administration site conditions				
Fatigue	49 (74.2)	11 (16.7)	47 (71.2)	5 (7.6)
Investigations				
Weight decreased	43 (65.2)	3 (4.5)	40 (60.6)	1 (1.5)
Metabolism and nutrition disorders				
Inappetence	35 (53.0)	0	31 (47.0)	2 (3.0)
Hyperglycaemia	31 (47.0)	6 (9.1)	8 (12.1)	2 (3.0)
Respiratory, thoracic and mediastinal disorders				
Dyspnoea	12 (18.2)	2 (3.0)	21 (31.8)	5 (7.6)
Vascular disorders				
Hypertension	5 (7.6)	1 (1.5)	23 (34.8)	6 (9.1)

Serious adverse events were reported by 39 of 66 patients (59.1%) in the cixutumumab group and 35 of 66 patients (53.0%) in the ramucirumab group. These serious adverse events were disease progression (6 patients [9.1%]), dehydration, back pain (4 patients each [6.1%]), diarrhoea, syncope (3 patients each [4.5%]), febrile neutropenia, nausea, neutropenia, abdominal pain, pyrexia, pneumonia, deep vein thrombosis, myocardial infarction, asthenia, fatigue, haematuria, acute kidney injury, and respiratory distress (2 patients each [3.0%]), leukopenia, vomiting (1 patient each [1.5%]) in the cixutumumab group, and expired drug administered, medication error (3 patients each [4.5%]), disease progression, febrile neutropenia, nausea, leukopenia, vomiting, atrial fibrillation, left ventricular dysfunction, infusion related reaction, pain in extremity, and dyspnoea (2 patients each [3.0%]), dehydration, back pain, diarrhoea, neutropenia, abdominal pain, pyrexia, pneumonia, and deep vein thrombosis (1 patient each [1.5%]) in the ramucirumab group. A causal relationship to the study drug could not be ruled out for syncope (3 patients), febrile neutropenia, neutropenia, pyrexia, deep vein thrombosis, fatigue, acute kidney injury (2 patients each), and leukopenia (1 patient) in the cixutumumab group, and leukopenia, left ventricular dysfunction, infusion related reaction (2 patients each), and febrile neutropenia (1 patient) in the ramucirumab group.

Adverse events leading to the discontinuation of the study drug were reported by 18 of 66 patients (27.3%) in the cixutumumab group and 25 of 66 patients (37.9%) in the ramucirumab group. Adverse events leading to the discontinuation of the study drug reported by ≥2 patients were fatigue (3 patients [4.5%]), ejection fraction decreased and disease progression (2 patients each [3.0%]) in the cixutumumab group, and ejection fraction decreased, left ventricular dysfunction (3 patients each [4.5%]), fatigue, and infusion related reaction (2 patients each [3.0%]) in the ramucirumab group. A causal relationship to the study drug could not be ruled out for fatigue (3 patients) and ejection fraction decreased (2 patients) in the cixutumumab group and ejection fraction decreased, left ventricular dysfunction, fatigue, and infusion related reaction (2 patients each) in the ramucirumab group.

4.(iv).(18) Foreign phase III study (Study I4T-IE-JVBD [REGARD study])

Adverse events were reported by 223 of 236 patients (94.5%) in the ramucirumab group and 101 of 115 patients (87.8%) in the placebo group. Adverse events for which a causal relationship to the study drug could not be ruled out were reported by 125 of 236 patients (53.0%) in the ramucirumab group and 58 of 115 patients (50.4%) in the placebo group. Adverse events with an incidence of ≥20% in either group were as shown in the following table.

Adverse events with an incidence of ≥20% in either group

System organ class Preferred term (MedDRA/J ver.15.0)	Number of patients (%)			
	Ramucirumab N = 236		Placebo N = 115	
	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	223 (94.5)	134 (56.8)	101 (87.8)	67 (58.3)
Gastrointestinal disorders				
Abdominal pain	45 (19.1)	12 (5.1)	29 (25.2)	3 (2.6)
Constipation	36 (15.3)	1 (0.4)	26 (22.6)	3 (2.6)
Nausea	45 (19.1)	3 (1.3)	30 (26.1)	0
Vomiting	47 (19.9)	6 (2.5)	29 (25.2)	5 (4.3)
General disorders and administration site conditions				
Fatigue	58 (24.6)	10 (4.2)	28 (24.3)	4 (3.5)
Metabolism and nutrition disorders				
Decreased appetite	57 (24.2)	8 (3.4)	26 (22.6)	4 (3.5)

Serious adverse events were reported by 106 of 236 patients (44.9%) in the ramucirumab group and 51 of 115 patients (44.3%) in the placebo group. Serious adverse events with an incidence of ≥2% were disease progression, abdominal pain (10 patients each [4.2%]), anaemia (9 patients [3.8%]), medication error (7 patients [3.0%]), ascites, vomiting, multi-organ failure (6 patients each [2.5%]), dysphagia, and intestinal obstruction (5 patients each [2.1%]) in the ramucirumab group, and disease progression (7 patients [6.1%]), vomiting (5 patients [4.3%]), asthenia (4 patients [3.5%]), abdominal pain, ascites, dysphagia, dehydration, and deep vein thrombosis (3 patients each [2.6%]) in the placebo group. A causal relationship to the study drug could not be ruled out for vomiting, medication error (3 patients each), abdominal pain, dehydration (2 patients each), and disease progression, anaemia (1 patient each) in the ramucirumab group and deep vein thrombosis (2 patients), disease progression, vomiting, dysphagia, and asthenia (1 patient each) in the placebo group.

Adverse events leading to the discontinuation of the study drug were reported by 32 of 236 patients (13.6%) in the ramucirumab group and 8 of 115 patients (7.0%) in the placebo group. Adverse events leading to the discontinuation of the study drug reported by ≥2 patients were disease progression (4 patients [1.7%]), fatigue, and proteinuria (2 patients each [0.8%]) in the ramucirumab group and disease progression (2 patients [0.8%]) in the placebo group. A causal relationship to the study drug could not be ruled out for proteinuria (2 patients) and disease progression (1 patient) in the ramucirumab group and disease progression (1 patient) in the placebo group.

4.(iv).(19) Foreign phase III study (Study I4T-IE-JVBC)

Adverse events were reported by 742 of 752 patients (98.7%) in the ramucirumab group and 375 of 382 patients (98.2%) in the placebo group. Adverse events for which a causal relationship to the study drug could not be ruled out were reported by 731 of 752 patients (97.2%) in the ramucirumab group and 365 of 382 patients (95.5%) in the placebo group. Adverse events with an incidence of ≥30% in either group were as shown in the following table.

Adverse events with an incidence of ≥30% in either group

System organ class Preferred term (MedDRA/J ver.16.0)	Number of patients (%)			
	Ramucirumab N = 752		Placebo N = 382	
	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	742 (98.7)	464 (61.7)	375 (98.2)	200 (52.4)
Eye disorders				
Lacrimation increased	234 (31.1)	6 (0.8)	65 (17.0)	2 (0.5)
Gastrointestinal disorders				
Stomatitis	381 (50.7)	46 (6.1)	117 (30.6)	4 (1.0)
Diarrhoea	326 (43.4)	28 (3.7)	151 (39.5)	9 (2.4)
Nausea	279 (37.1)	10 (1.3)	157 (41.1)	5 (1.3)
General disorders and administration site conditions				
Fatigue	273 (36.3)	74 (9.8)	136 (35.6)	20 (5.2)
Asthenia	271 (36.0)	52 (6.9)	128 (33.5)	18 (4.7)
Skin and subcutaneous tissue disorders				
Alopecia	536 (71.3)	0	279 (73.0)	0
Nail disorder	231 (30.7)	16 (2.1)	105 (27.5)	6 (1.6)
Vascular disorders				
Epistaxis	300 (39.9)	1 (0.1)	64 (16.8)	0

Serious adverse events were reported by 279 of 752 patients (37.1%) in the ramucirumab group and 111 of 382 patients (29.1%) in the placebo group. Serious adverse events with an incidence of ≥2% in either group were febrile neutropenia (51 patients [6.8%]), neutropenia (47 patients [6.3%]), and neutropenic infection (19 patients [2.5%]) in the ramucirumab group, and neutropenia (20 patients [5.2%]), febrile neutropenia (11 patients [2.9%]), underdose (11 patients [2.9%]), and neutropenic infection (9 patients [2.4%]) in the placebo group. A causal relationship to the study drug could not be ruled out for febrile neutropenia (51 patients), neutropenia (47 patients), and neutropenic infection (18 patients) in the ramucirumab group and neutropenia (20 patients), febrile neutropenia (11 patients), and neutropenic infection (9 patients) in the placebo group.

Adverse events leading to the discontinuation of the study drug were reported by 268 of 752 patients (35.6%) in the ramucirumab group and 103 of 382 patients (27.0%) in the placebo group. Adverse events leading to the discontinuation of the study drug with an incidence of ≥2% in either group were fatigue (43 patients [5.7%]), asthenia (19 patients [2.5%]), pleural effusion (18 patients [2.4%]), oedema peripheral (15 patients [2.0%]), and peripheral sensory neuropathy (15 patients [2.0%]) in the ramucirumab group, and asthenia (13 patients [3.4%]), fatigue (10 patients [2.6%]), and neuropathy peripheral (8 patients [2.1%]) in the placebo group. A causal relationship to the study drug could not be ruled out for fatigue (42 patients), asthenia (19 patients), pleural effusion (17 patients), oedema peripheral (15 patients), and peripheral sensory neuropathy (15 patients) in the ramucirumab group and asthenia (12 patients), fatigue (10 patients), and neuropathy peripheral (8 patients) in the placebo group.

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

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

The assessment is ongoing. The results and PMDA's conclusion are to be reported in the Review Report (2).

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

The assessment is ongoing. The results and PMDA's conclusion are to be reported in the Review Report (2).

IV. Overall Evaluation

The submitted data show the efficacy of ramucirumab in the treatment of patients with unresectable advanced/recurrent gastric cancer and its safety is acceptable in view of its observed benefits.

Ramucirumab is a human monoclonal antibody against vascular endothelial growth factor receptor (VEGFR)-2, and is considered to be of clinical significance as a treatment option for unresectable advanced/recurrent gastric cancer. Clinical positioning, indication, dosage and administration, post-marketing investigations, etc. are to be further discussed at the Expert Discussion.

PMDA considers that ramucirumab may be approved if the drug is not considered to have any particular problems based on comments from the Expert Discussion.

Review Report (2)

February 12, 2015

I. Product Submitted for Registration

[Brand name]	Cyramza Injection 100 mg
	Cyramza Injection 500 mg
[Non-proprietary name]	Ramucirumab (Genetical Recombination)
[Name of applicant]	Eli Lilly Japan K.K.
[Date of application]	July 25, 2014

II. Content of the Review

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

(1) Efficacy

As a result of the review described in the "4.(iii).B.(2) Efficacy" of the Review Report (1), PMDA concluded that Ramucirumab (Genetical Recombination) (hereinafter referred to as ramucirumab) is effective for target patients, based on the results of the following 2 phase III studies, which demonstrated a statistically significant prolongation of overall survival, the primary endpoint, in the ramucirumab group as compared with the control group.

- A global phase III study, which compared the efficacy and safety between ramucirumab and placebo in combination with paclitaxel (PTX) in patients with unresectable gastric or gastro-esophageal junction adenocarcinoma with disease progression on or after prior fluoropyrimidine- and platinum-containing chemotherapy (Study I4T-IE-JVBE [the RAINBOW study]).

- A global phase III study, which compared the efficacy and safety between ramucirumab and placebo in patients with unresectable gastric or gastro-esophageal junction adenocarcinoma with disease progression on or after prior fluoropyrimidine- and platinum-containing chemotherapy (Study I4T-IE-JVBD [the REGARD study]).

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

(2) Safety

As a result of the review described in the "4.(iii).B.(3) Safety" of the Review Report (1), PMDA determined that adverse events requiring attention during treatment with ramucirumab were hypertension, proteinuria, haemorrhage, infusion-related reaction (IRR), thromboembolism, gastrointestinal perforation, cardiac failure congestive, neutropenia/leukopenia, posterior reversible encephalopathy syndrome (RPLS), fistula, disturbance of wound healing, and liver disorder, and that attention should be paid to the onset of these adverse events during treatment with ramucirumab.

PMDA concluded that ramucirumab is tolerable for patients, provided monitoring and managing of adverse events as well as appropriate measures such as the interruption, dose reduction, and discontinuation of both ramucirumab and concomitant drugs are taken by physicians with sufficient knowledge and experience in cancer chemotherapy, although attention should be paid to the occurrence of adverse events described above when using ramucirumab.

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

(3) Clinical positioning and indication

As a result of the review described in the "4.(iii).B.(4) Clinical positioning and indication" of the Review Report (1), PMDA concluded that ramucirumab is positioned as a treatment option for the patient groups investigated in the RAINBOW and REGARD studies, and therefore ramucirumab should be indicated for "unresectable advanced/recurrent gastric cancer," as proposed by the applicant. Since the term 'gastro-esophageal junction cancer' was not precisely defined in the RAINBOW and REGARD studies, the following should be noted in the "Precautions for Indications" section of the package insert.

- The efficacy and safety of ramucirumab in post-operative adjuvant chemotherapy have not been established.

- The efficacy and safety of ramucirumab in primary chemotherapy have not been established.

- Eligibility of the patient for the treatment should be determined based on good understanding of the descriptions in the "Clinical Studies" section (particularly the information about primary lesions) and of the efficacy and safety of ramucirumab.

The above conclusion of the PMDA was supported by the expert advisors at the Expert Discussion.

Accordingly, PMDA instructed the applicant to use the above wording for the "Indications" and Precautions for Indications" sections, and the applicant agreed.

(4) Dosage and administration

As a result of the review described in the "4.(iii).B.(5) Dosage and administration" of the Review Report (1), the dosage and administration of ramucirumab should be defined as follows: The usual adult dosage is 8 mg/kg (body weight) of Ramucirumab (Genetical Recombination) given as an intravenous infusion over approximately 60 minutes every 2 weeks. The dose may be adjusted according to the condition of the patient. PMDA also concluded that the following cautionary statements should be included in the "Precautions for Dosage and Administration" section of the package insert.

- The efficacy and safety of ramucirumab in combination with antineoplastics other than PTX have not been established.

- For the purpose of mitigating infusion reactions associated with ramucirumab, pretreatment with an antihistaminic drug (e.g., diphenhydramine) should be considered. If a Grade 1 or 2 infusion reaction occurs, the patient should be treated with an antihistaminic drug before all subsequent infusion of ramucirumab. If a Grade 1 or 2 infusion reaction recurs even with the pretreatment, an antipyretic analgesic (e.g., acetaminophen) and a corticosteroid (e.g., dexamethasone) should be administered in addition to the antihistaminic drug before ramucirumab.

- In case of a Grade 3 or 4 infusion reaction, ramucirumab should be discontinued immediately and should not be resumed. In case of a Grade 1 or 2 infusion reaction, the infusion rate should be reduced by 50%, and the reduced infusion rate should be maintained with all subsequent doses.

- In case of hypertension or proteinuria, the administration of ramucirumab should be interrupted or discontinued, or the dose of ramucirumab should be reduced according to the criteria below.

Adverse drug reaction		Measures to be taken
Hypertension	Symptomatic Grade 2, or Grade ≥3	Give anti-hypertensive treatment. Interrupt treatment with ramucirumab until blood pressure is appropriately controllable. If the anti-hypertensive treatment fails to control blood pressure, discontinue ramucirumab.
Proteinuria	24-hour urine protein ≥2 g	First episode: Interrupt treatment until 24-hour urine protein decreases to <2 g. Then resume the treatment at the reduced dose of 6 mg/kg.
		Second and subsequent episodes: Interrupt the treatment until 24-hour urine protein decreases to <2 g. Then resume the treatment at the reduced dose of 5 mg/kg.
	24-hour urine protein ≥3 g, or an episodes of nephrotic syndrome	Discontinue treatment.

- The preparation method for the injection solution

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

Based on the above, PMDA instructed the applicant to define the "Dosage and Administration" and "Precautions for Dosage and Administration" sections as described above, and the applicant agreed.

(5) Risk management plan (draft)

In order to evaluate the safety, etc. of ramucirumab under routine use after the market launch, the applicant plans to conduct post-marketing surveillance on patients with unresectable advanced/recurrent gastric cancer treated with ramucirumab (650 patients; 1-year observation period; priority investigation items are arterial thromboembolism, hypertension, IRR, proteinuria, gastrointestinal perforation, haemorrhage, and liver disorder/hepatic failure).

As a result of the review described in the "4.(iii).B.(6) Post-marketing investigations" of the Review Report (1), PMDA concluded that post-marketing surveillance should be conducted to collect safety information under routine use of ramucirumab in Japan. PMDA also concluded that priority investigation items in the surveillance should include the following adverse events in addition to those selected by the applicant: venous thromboembolism, cardiac failure congestive, RPLS, fistula, and disturbance of wound healing, all of which were observed with other antineoplastics with anti-angiogenic activity and require attention also in treatment with ramucirumab. The target sample size and the observation period proposed by the applicant are acceptable.

The above conclusion of the PMDA was supported by the expert advisors at the Expert Discussion. The following comment was made by expert advisors:

- Neutropenia/leukopenia occurred frequently when ramucirumab was administered in combination with PTX, and the incidence was higher in Japanese patients than in non-Japanese patients. Therefore, due caution should be used against the possible adverse events that require attention in combination of ramucirumab with PTX and those seen more frequently in Japanese patients than in non-Japanese patients.

Accordingly, PMDA gave the following instructions to the applicant, and the applicant agreed.

- Venous thromboembolism, cardiac failure congestive, RPLS, fistula, and disturbance of wound healing should be added to the priority investigation items in the surveillance.

- Information materials for healthcare professionals should highlight the adverse events requiring attention in combination of ramucirumab with PTX and those seen more frequently in Japanese patients than in non-Japanese patients, and the information should be provided to healthcare professionals.

Based on the above discussions, PMDA concluded that the draft risk management plan should include safety and efficacy investigation items as shown in the following table and that additional pharmacovigilance and risk minimization actions should be taken.

Safety and efficacy investigations in risk management plan (draft)

Safety specifications		
Important identified risks	Important potential risks	Important missing information
• Arterial thromboembolism • Hypertension • Proteinuria • Haemorrhage • Infusion reaction • Venous thromboembolism • Gastrointestinal perforation • Cardiac failure congestive • Neutropenia/leukopenia • Posterior reversible encephalopathy syndrome • Fistula • Disturbance of wound healing	• Liver disorder/hepatic failure	None
Efficacy specifications		
• Efficacy under routine clinical use		

Outline of additional pharmacovigilance and risk minimization in the risk management plan (draft)

Additional pharmacovigilance	Additional risk minimization actions
• Early post-marketing phase vigilance • Specified use-results survey (see the following table for the outline of the plan)	• Information provision obtained from early post-marketing phase vigilance • Preparation and supply of information materials for healthcare professionals

Outline of the post-marketing surveillance plan (draft)

Objective	To evaluate the safety, etc. of ramucirumab under routine clinical use
Survey method	Continuous registration
Population	Patients with unresectable advanced/recurrent gastric cancer
Observation period	1 year from treatment start
Planned sample size	650
Main investigation items	Priority investigation items: arterial thromboembolism, hypertension, infusion reaction, proteinuria, gastrointestinal perforation, haemorrhage, liver disorder/hepatic failure, venous thromboembolism, cardiac failure congestive, posterior reversible encephalopathy syndrome, fistula, and disturbance of wound healing Other main investigation items: patient characteristics (history, stage), treatment history, adverse events, etc.

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

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

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

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

A GCP on-site inspection was conducted in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the new drug application (5.3.5.1.1). PMDA concluded that there should be no problem with conducting a regulatory review based on the submitted application documents.

IV. Overall Evaluation

After the above review, PMDA has come to the conclusion as follows:

The product may be approved with the conditions for approval, the indication as well as the dosage and administration as written below. However, it must be ensured that necessary cautions are added to the package insert and information on the proper use of ramucirumab is provided appropriately after the market launch so that ramucirumab is properly used by physicians with sufficient knowledge and experience in cancer chemotherapy and at medical institutions that are able to properly respond to

emergencies. Since the product is a drug with a new active ingredient, the re-examination period is 8 years. The drug substance and the drug product are both classified as powerful drugs, and the product is classified as a biological product.

[Indication] Unresectable advanced/recurrent gastric cancer

[Dosage and administration] The usual adult dosage is 8 mg/kg (body weight) of Ramucirumab (Genetical Recombination) given as an intravenous infusion over approximately 60 minutes every 2 weeks. The dose may be adjusted according to the conditions of the patient.

[Conditions for approval] The applicant is required to design and appropriately implement a risk management plan.

[Warnings]

1. Ramucirumab should be administered only to patients considered to be eligible for ramucirumab therapy by a physician with sufficient knowledge and experience with cancer chemotherapy and at a medical institution that is able to properly respond to emergencies. The benefits and risks of the therapy should be thoroughly explained to the patient or their family member, and consent should be obtained prior to treatment.

2. Serious arterial thromboembolism such as myocardial infarction and cerebrovascular disorder has been reported with some fatal cases. Patients should be carefully monitored and, in case of any abnormality, ramucirumab should be discontinued and appropriate measures should be taken. If severe arterial thromboembolism occurs, treatment with ramucirumab should not be resumed.

3. Severe gastrointestinal haemorrhage has been reported with some fatal cases. Patients should be carefully monitored and, in case of any abnormality, ramucirumab should be discontinued and appropriate measures should be taken. If severe haemorrhage occurs, treatment with ramucirumab should not be resumed.

4. Gastrointestinal perforation has been reported with some fatal cases. Patients should be carefully monitored and, if any abnormalities are observed, treatment with ramucirumab should be discontinued and appropriate measures should be taken. If gastrointestinal perforation occurs, treatment with ramucirumab should not be resumed.

[Contraindication]

1. Patients with a history of serious hypersensitivity to any ingredient in ramucirumab

2. Pregnant women or women who may be pregnant

[Precautions for indications]

1. The efficacy and safety of ramucirumab in post-operative adjuvant chemotherapy have not been established.

2. The efficacy and safety of ramucirumab in primary chemotherapy have not been established.

3. Eligibility of the patient for the treatment should be determined based on good understanding of the descriptions in the “Clinical Studies” section (particularly the information about primary lesions) and of the efficacy and safety of ramucirumab.

[Precautions for dosage and administration]

1. The efficacy and safety of ramucirumab in combination with antineoplastics other than paclitaxel have not been established.

2. For the purpose of mitigating infusion reactions associated with ramucirumab, pretreatment with an antihistaminic drug (e.g., diphenhydramine) should be considered. If a Grade[Note 1)] 1 or 2 infusion reaction occurs, the patient should be treated with an antihistaminic drug before all subsequent infusion of ramucirumab. If a Grade[Note 1)] 1 or 2 infusion reaction recurs even with the pretreatment, an antipyretic analgesic (e.g., acetaminophen) and a corticosteroid (e.g., dexamethasone) should be administered in addition to the antihistaminic drug before ramucirumab.

3. In case of a Grade[Note 1)] 3 or 4 infusion reaction, the administration of ramucirumab should be discontinued immediately and should not be resumed. In case of Grade[Note 1)] 1 or 2 infusion reaction, the infusion rate should be reduced by 50%, and the reduced infusion rate should be maintained with all subsequent doses.

4. In case of hypertension or proteinuria, the administration of ramucirumab should be interrupted or discontinued, or the dose of ramucirumab should be reduced according to the criteria below.

Adverse drug reaction		Measure to be taken
Hypertension	Symptomatic Grade[Note 1)] 2, or Grade [Note 1)] ≥3	Give anti-hypertensive treatment. Interrupt treatment with ramucirumab until blood pressure is appropriately controllable. If the anti-hypertensive treatment fails to control blood pressure, discontinue ramucirumab.
Proteinuria	24-hour urine protein ≥2 g[Note 2)]	First episode: Interrupt the treatment until 24-hour urine protein decreases to <2 g[Note 2)], then resume the treatment at the reduced dose of 6 mg/kg.
		Second and subsequent episodes: Interrupt the treatment until 24-hour urine protein decreases to <2 g[Note 2)], then resume the treatment at the reduced dose of 5 mg/kg.
	24-hour urine protein ≥3 g[Note 2)] or an episode of nephrotic syndrome	Discontinue treatment.

Note 1) Common Terminology Criteria for Adverse Events (CTCAE ver.4.0)

Note 2) An all-urine test with 24-hour urine collection is desirable. If unfeasible, protein/creatinine ratio in urine should be determined.

5. Preparation method for the injection solution
Prior to administration, the required volume of ramucirumab is calculated and is withdrawn with a syringe. It is then mixed with normal saline (JP) so that the total volume of 250 mL of solution is made in a container for intravenous infusion. The infusion solution should be thoroughly mixed.