Report on the Deliberation Results

May 16, 2016

Evaluation and Licensing Division, Pharmaceutical Safety and Environmental Health 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	May 26, 2015

Results of Deliberation
In its meeting held on April 25, 2016, the Second Committee on New Drugs concluded that the application for partial change for 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 for the present application is the remainder of the 8-year re-examination period for the initial approval of the product (until March 25, 2023).

Conditions of Approval
The applicant is required to design and appropriately implement a risk management plan.

**Japanese Accepted Name (modified INN)*

Review Report

April 11, 2016

Pharmaceuticals and Medical Devices Agency

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

Brand Name	Cyramza Injection 100 mg Cyramza Injection 500 mg
Non-proprietary Name	Ramucirumab (Genetical Recombination)
Applicant	Eli Lilly Japan K.K.
Date of Application	May 26, 2015
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, (4) Drugs with new indications, (6) Drugs with a new dosages
Reviewing Office	Office of New Drug V

Results of Review

The Pharmaceuticals and Medical Devices Agency (PMDA) has concluded that the data submitted demonstrate the efficacy of the product in the treatment of unresectable advanced/recurrent colorectal cancer and acceptable safety in view of the benefits indicated by the data submitted, as shown in Attachment.

As a result of its review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following conditions. Further investigations are needed through post-marketing surveillance, etc. regarding hypertension, proteinuria/nephrotic syndrome, haemorrhage, infusion-related reaction, thromboembolism, gastrointestinal perforation, congestive cardiac failure, neutropenia/leukopenia, posterior reversible encephalopathy syndrome, fistula, disturbance of wound healing, liver disorder, and interstitial lung disease.

Indications

Unresectable advanced/recurrent gastric cancer
Unresectable advanced/recurrent colorectal cancer

(Underline denotes additions.)

Dosage and Administration

1. Unresectable advanced/recurrent gastric cancer

The usual adult dosage is 8 mg/kg (body weight) of Ramucirumab (Genetical Recombination) administered as an intravenous infusion over approximately 60 minutes every 2 weeks. The dose may be adjusted according to on the condition of the patient.

2. Unresectable advanced/recurrent colorectal cancer

The usual adult dosage is 8 mg/kg (body weight) of Ramucirumab (Genetical Recombination) administered as an intravenous infusion over approximately 60 minutes every 2 weeks, in combination with irinotecan hydrochloride hydrate, levofolinate, and fluorouracil. The dose may be adjusted according to the condition of the patient.

(Underline denotes additions.)

Conditions for approval

The applicant is required to design and appropriately implement a risk management plan.

Attachment

Review Report (1)

February 26, 2016

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

Product Submitted for Approval

Brand name	Cyramza Injection 100 mg Cyramza Injection 500 mg
Non-proprietary Name	Ramucirumab (Genetical Recombination)
Applicant	Eli Lilly Japan K.K.
Date of Application	May 26, 2015
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(s)	Unresectable advanced/recurrent gastric cancer Unresectable advanced/recurrent colorectal cancer (Underline denotes additions.)

Proposed Dosage and Administration

1. Unresectable advanced/recurrent gastric cancer

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

2. Unresectable, advanced/recurrent colorectal cancer

The usual adult dosage is 8 mg/kg (body weight) of Ramucirumab (Genetical Recombination) administered as an intravenous infusion over approximately 60 minutes every 2 weeks, in combination with irinotecan hydrochloride hydrate, levofolinate, and fluorouracil. The dose may be adjusted according to the condition of the patient.

(Underline denotes additions.)

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List of Abbreviations

ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BQL	Below the quantification limit
BV	Bevacizumab (Genetical Recombination)
$C_{ave,ss}$	Average serum concentration at steady state
CI	Confidence interval
CLcr	Creatinine clearance
$C_{max,ss}$	Maximum serum concentration at steady state
C_{min}	Minimum serum concentration
$C_{min,1}$	Minimum serum concentration following first dose
$C_{min,ss}$	Minimum serum concentration at steady state
COPD	Chronic obstructive pulmonary disease
CPT-11	Irinotecan hydrochloride hydrate
CRC	Colorectal cancer
dl-LV	Folinate
DLT	Dose limiting toxicity
EGFR	Epidermal growth factor receptor
FOLFIRI	Combination of 5-FU + *dl*-LV (or *l*-LV) + CPT-11
FOLFOX	Combination of 5-FU + *dl*-LV (or *l*-LV) + L-OHP
GCP	Good Clinical Practice
icrucumab/mFOLFOX6	Combination of icrucumab (unapproved in Japan) and mFOLFOX6
Ig	Immunoglobulin
ILD	Interstitial lung disease
ITT	intent-to-treat
KRAS	Kirsten rat sarcoma viral oncogene homolog
l-LV	Levofolinate
L-OHP	Oxaliplatin
MedDRA	Medical Dictionary for Regulatory Activities
MedDRA/J	Medical Dictionary for Regulatory Activities Japanese version
mFOLFOX6	modified FOLFOX6
NCCN Guidelines (colon cancer)	National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Colon Cancer
NRAS	Neuroblastoma RAS viral (V-Ras) oncogene homolog
Nude mouse	Athymic mouse
OS	Overall survival
PFS	Progression-free survival
PK	Pharmacokinetics
Placebo/FOLFIRI	Combination of placebo and FOLFIRI
PMDA	Pharmaceuticals and Medical Devices Agency
Postdiscontinuation anticancer therapy	Therapy with systemic antineoplastic drugs performed after discontinuation of study drug
PPK	Population pharmacokinetics
PT	Preferred term
PTX	Paclitaxel
RAINBOW study	Study I4T-IE-JVBE
RAISE study	Study I4T-MC-JVBB
Ramucirumab	Ramucirumab (genetical recombination)
Ramucirumab/FOLFIRI	Combination of ramucirumab and FOLFIRI
Ramucirumab/mFOLFOX6	Combination of ramucirumab and mFOLFOX6
Ramucirumab/PTX	Combination of ramucirumab and PTX
REACH study	Study I4T-IE-JVBF
REGARD study	Study I4T-IE-JVBD
REVEL study	Study I4T-MC-JVBA

TE-ADA-positive	Treatment emergent anti-drug antibody positive
ULN	Upper limit of normal
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor
V_1	Central volume of distribution
V_2	Peripheral volume of distribution
5-FU	Fluorouracil

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

1.1 Overview of the product submitted for approval

Ramucirumab (genetical recombination) (hereinafter referred to as "ramucirumab") is a human IgG1 monoclonal antibody against human vascular endothelial growth factor (VEGF) receptor 2 (VEGFR-2). It was developed by ImClone Systems Incorporated. Ramucirumab binds to VEGFR-2 to block the binding of VEGF to VEGFR-2, thereby inhibiting the angiogenesis mediated through VEGFR-2 signaling pathway, leading to the inhibition of tumor growth.

In Japan, ramucirumab was approved in March 2015 for the indication for "unresectable advanced/recurrent gastric cancer."

1.2 Development history, etc.

Outside Japan, ImClone Systems initially undertook the clinical development of ramucirumab for unresectable advanced/recurrent colorectal cancer (CRC) and initiated a phase II study (Study I4T-IE-JVBH) involving the patient population in April 2009. After that, Eli Lilly and Company (United States) took over the clinical development. In August 2010, Eli Lilly started a phase II study (Study I4Y-IE-JCDB) involving patients with unresectable advanced/recurrent CRC with disease progression after chemotherapy including irinotecan hydrochloride hydrate (CPT-11), and in December 2010, a phase III study (RAISE study [I4T-MC-JVBB]) involving patients with unresectable advanced/recurrent CRC with disease progression after therapy with bevacizumab (BV), oxaliplatin (L-OHP), and a fluoropyrimidine.

In the US and the European Union, a marketing application for ramucirumab (Cyramza) was submitted for the indication of CRC in February 2015, based on the results of the pivotal RAISE study. Cyramza was approved in the US in April 2015 for the following indication: "CYRAMZA, in combination with FOLFIRI (irinotecan, folinic acid, and 5-fluorouracil), is indicated for the treatment of patients with metastatic colorectal cancer (mCRC) with disease progression on or after prior therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine," and in the EU in January 2016 for the following indication: "Cyramza, in combination with FOLFIRI (irinotecan, folinic acid, and 5-fluorouracil), is indicated for the treatment of adult patients with metastatic colorectal cancer (mCRC) with disease progression on or after prior therapy with bevacizumab, oxaliplatin and a fluoropyrimidine."

As of January 2016, ramucirumab has been approved in 5 countries and regions for the indication of CRC.

In Japan, the applicant started a phase I study (Study I4T-IE-JVBY) in February 2011, involving patients with unresectable advanced/recurrent CRC with disease progression after treatment with BV, L-OHP, and a fluoropyrimidine. Enrollment in the RAISE study began in [redacted] 20[redacted].

Recently, a partial change application was submitted for the additional indication of CRC and the dosage and administration for CRC, based on the results of the pivotal RAISE study.

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

Because the present application is intended for addition of the new indication and new dosage, quality-related data were omitted.

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

3.1 Primary pharmacodynamics

3.1.1 Growth-inhibitory effect on malignant tumor-derived cell lines

Because ramucirumab does not bind to murine VEGFR-2 (see "Review Report dated February 16, 2015: Cyramza Injection 100 mg, Cyramza Injection 500 mg"), DC101, a rat anti-murine VEGFR-2 antibody, was used in studies to investigate the tumor growth-inhibitory effect in mice. In this section, the dose of folinate (*dl*-LV) is expressed on the basis of calcium salt hydrate.

3.1.1.1 Human CRC-derived cell lines (CTD 4.2.1.1.1, 4.2.1.1.2, 4.2.1.1.3, 4.2.1.1.4)

The tumor growth-inhibitory effect of DC101 was investigated in nude mice with subcutaneously transplanted human CRC-derived cell line, HT-29. The administration of DC101 was started when the

tumor volume reached approximately 300 mm^3 (on post-transplantation day 8, which was defined as Day 1 of the study). DC101 (0.6, 6, and 60 mg/kg on Day 1, followed thereafter by 0.4, 4, and 40 mg/kg, respectively) was administered intraperitoneally 3 times weekly until Day 27, and the tumor volume was calculated. The inhibition of tumor growth in the DC101 40 mg/kg group was statistically significant as compared with the control (normal saline) group on Days 1 to 27 (Table 1).

Table 1. Tumor-growth inhibitory effect of DC101 on HT-29 cells

Treatment group	Tumor volume (mm^3)	T/C%	*P* value[*1]
Control (normal saline)	1501 ± 358	-	-
Human IgG 40 mg/kg (60 mg/kg[*2])	1382 ± 193	90	-
DC101 0.4 mg/kg (0.6 mg/kg[*2])	1552 ± 334	102	0.83
DC101 4 mg/kg (6 mg/kg[*2])	848 ± 108	60	0.16
DC101 40 mg/kg (60 mg/kg[*2])	618 ± 48	43	0.02

Mean ± standard error; n = 12; T/C%, the ratio of tumor volume in the DC101 or human IgG group (T) to that in the control group (C); -, not applicable; [*1] repeated measures analysis of variance; [*2] starting dose

The tumor growth inhibitory effect of DC101 was investigated in nude mice with subcutaneously transplanted human CRC-derived cell line, HCT-8 or HCT-116. The administration of DC101 was started when the tumor volume reached approximately 300 mm^3 (on post-transplantation day 13 or 15, which was defined as Day 1 of the study). DC101 (40 mg/kg) was administered intraperitoneally 3 times weekly until Day 44 or 22, and the tumor volume was calculated. In both cell lines, statistically significant inhibition of tumor growth was observed in the DC101 group as compared with the control (normal saline) group ($P < 0.0001$ [HCT-8, Days 1-41], [HCT-116, Days 1-24], repeated measures analysis of variance).

The tumor growth inhibitory effect of DC101 was investigated in nude mice with subcutaneously transplanted human CRC-derived cell line, Colo205. The administration of DC101 was started when the tumor volume reached approximately 320 mm^3 (on post-transplantation day 22, which was defined as Day 1 of the study). DC101 (40 mg/kg) was administered intraperitoneally 3 times weekly until Day 65, and tumor volumes were calculated. In a separate experiment, the administration of DC101 was started when the tumor volume reached approximately 800 mm^3 (on post-transplantation day 43, which was Day 22). DC101 (40 mg/kg) was administered intraperitoneally 3 times weekly until Day 65, and the tumor volume was calculated. In both experiments, statistically significant inhibition of tumor growth was observed in the DC101 group as compared with the control (normal saline) group ($P = 0.0003$ [baseline tumor volume, approximately 320 mm^3; Days 1-69], $P = 0.0010$ [baseline tumor volume, approximately 800 mm^3; Days 22-69]; repeated measures analysis of variance).

3.1.1.2 Cell line derived from human CRC resistant to L-OHP and anti-VEGF antibody (CTD 4.2.1.1.5, 4.2.1.1.6, 4.2.1.1.7)

The ability of DC101 to inhibit the growth of a tumor resistant to both oxaliplatin (L-OHP) and anti-VEGF antibody was studied in nude mice with subcutaneously transplanted HT-29 cells. The administration of DC101 was started when the tumor volume reached approximately 340 mm^3 (on post-transplantation 13 day, which was defined as Day 1 of the study). L-OHP (10 mg/kg) was administered intraperitoneally once weekly, and a humanized anti-human and mouse VEGF monoclonal antibody S12 (40 mg/kg) intraperitoneally 3 times weekly from Day 2 onward. The tumor growth inhibitory effect of DC101 was investigated in mice showing a ≥2-fold increase in tumor volume. On Day 37, animals intraperitoneally received (a) DC 101 (40 mg/kg 3 times weekly until Day 55) alone, (b) combination therapy with fluorouracil (5-FU) (40 mg/kg once weekly), *dl*-LV (20 mg/kg once weekly), and CPT-11 (100 mg/kg once weekly), or (c) combination therapy with DC101, 5-FU, *dl*-LV, and CPT-11, and tumor volume was calculated. A statistically significant inhibition of tumor growth was observed in the DC101 alone group, the 5-FU/*dl*-LV/CPT-11 group, and the DC101/5-FU/*dl*-LV/CPT-11 group as compared with the control (normal saline) group from Days 37 to 59 ($P < 0.0001$, 0.0009, and <0.0001, respectively; repeated measures analysis of variance). The inhibition of tumor growth in the DC101/5-FU/*dl*-LV/CPT-11 group was also statistically significant as compared with the DC101 alone group or the 5-FU/*dl*-LV/CPT-11 group ($P = 0.0032$ and <0.0001, respectively; repeated measures analysis of variance).

The tumor growth inhibitory effect of DC101 was investigated in mice bearing L-OHP- and S12-resistant tumor generated by the above-mentioned method. The day of starting L-OHP was defined as Day 0. On Day 33, animals received intraperitoneally (a) combination therapy with DC101 (40 mg/kg 3 times weekly up to Day 47), 5-FU, *dl*-LV, and CPT-11, (b) combination therapy with S12 (40 mg/kg 3 times weekly), 5-FU, *dl*-LV, and CPT-11, or (c) L-OHP and S12, and tumor volume was calculated. A statistically significant inhibition of tumor growth was observed in the DC101/5-FU/*dl*-LV/CPT-11 group as compared with the control (normal saline) group or the S12/5-FU/*dl*-LV/CPT-11 group from Days 32 to 49 ($P < 0.0001$ in both comparisons, repeated measures analysis of variance). The inhibition of tumor growth in the S12/5-FU/*dl*-LV/CPT-11 group was also statistically significant as compared with the control group ($P = 0.0206$, repeated measures analysis of variance).

3.R Outline of the review conducted by PMDA

PMDA's view:

The data submitted in support of the initial application has demonstrated the growth inhibitory activity of ramucirumab against malignant tumor (see "Review Report dated February 16, 2015: Cyramza Injection 100 mg, Cyramza Injection 500 mg"). In addition, the data submitted for the present application support the efficacy of ramucirumab for CRC.

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

The non-clinical pharmacokinetic data was evaluated in support of the initial application for ramucirumab. The data were considered applicable to the present application for the new indication and dosage. Therefore, no additional data were submitted under this section.

5. Toxicology and Outline of the Review Conducted by PMDA

The present application is intended for addition of the new indication and new dosage. No additional toxicity data were submitted.

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

The results of biopharmaceutic studies and associated analytical methods was evaluated in support of the initial application for ramucirumab. The results were considered applicable to the present application for the new indication and new dosage. Therefore, no additional data were submitted under this section.

6.1 Clinical pharmacology

The pharmacokinetics (PK) of ramucirumab in patients with malignant tumor was investigated after the administration of ramucirumab alone, ramucirumab in combination with 5-FU + *dl*-LV (or *l*-LV) + CPT-11 (FOLFIRI), and ramucirumab in combination with 5-FU + *dl*-LV (or *l*-LV) + L-OHP (modified FOLFOX6 [mFOLFOX6]).

Table 2 shows the dosing regimens of FOLFIRI and mFOLFOX6 in each study. *Dl*-LV was used in the RAISE study and Study I4T-IE-JVBH, and levofolinate (*l*-LV) was used in Study I4T-IE-JVBY. In Studies I4T-IE-JVCB and I4Y-IE-JCDB, *dl*-LV was the first option and *l*-LV was used when *dl*-LV was unavailable.

Table 2. Dosing regimens of FOLFIRI and mFOLFOX6 in each clinical study

	Dosing regimen
FOLFIRI	In each 2-week treatment cycle, patients received (a) CPT-11 (180 mg/m^2) intravenously over 90 minutes on Day 1, (b) *dl*-LV (400 mg/m^2) or *l*-LV (200 mg/m^2) intravenously over 2 hours (simultaneously with or immediately after administration of [a]) on Day 1, and (c) 5-FU (400 mg/m^2) by bolus intravenous injection on Day 1, followed by (d) continuous intravenous infusion of 5-FU (2400 mg/m^2) over 46 to 48 hours starting on Day 1.
mFOLFOX6	In each 2-week treatment cycle, patients received (a) L-OHP (85 mg/m^2) intravenously over 2 hours on Day 1, (b) *dl*-LV (400 mg/m^2) or *l*-LV (200 mg/m^2) intravenously over 2 hours (simultaneously with or immediately after administration of [a]) on Day 1, and (c) 5-FU (400 mg/m^2) by bolus intravenous injection on Day 1, followed by (d) continuous intravenous infusion of 5-FU (2400 mg/m^2) over 46 hours starting on Day 1.

6.1.1 Global phase III study (CTD 5.3.5.1.1, RAISE study [ongoing since December 2010 (data cut-off; July 17, 2014)])

A double-blind, randomized, comparative study was conducted to investigate the efficacy, safety, etc. of ramucirumab in combination with FOLFIRI in 1057 patients with unresectable advanced/recurrent CRC with disease progression after treatment with BV, L-OHP, and a fluoropyrimidine (529 in the ramucirumab/FOLFIRI group, 528 in the placebo/FOLFIRI group) (512 patients evaluable for PK analysis). The patients received ramucirumab (8 mg/kg) or placebo in combination with FOLFIRI intravenously every 2 weeks, and serum ramucirumab concentrations were determined.

Trough serum concentrations of ramucirumab (geometric mean [coefficient of variation]) in Cycle 2 and Cycle 4 were 46.3 (45%) and 65.1 (43%) μg/mL, respectively. In the ramucirumab/FOLFIRI group, 477 patients underwent anti-ramucirumab antibody testing after the start of treatment. Of the 477 patients, 15 (3.1%) were positive for anti-ramucirumab antibodies. Of the 15 patients, 6 (1.3%) were found to be treatment emergent anti-drug antibody positive (TE-ADA-positive)[1)] and 1 (0.2%) neutralizing antibody-positive.

6.1.2 Global phase III study (CTD 5.3.5.4.2, REACH study [November 2010 to March 2015])

A double-blind, randomized, comparative study was conducted to investigate the efficacy and safety of ramucirumab in 630 patients with advanced hepatocellular carcinoma resistant or intolerant to sorafenib tosilate (317 in the ramucirumab group, 313 in the placebo group) (315 patients evaluable for PK analysis [276 patients of Child-Pugh class A, 39 patients of Child-Pugh class B]). The patients received ramucirumab (8 mg/kg) or placebo intravenously every 2 weeks, and serum ramucirumab concentrations were determined.

Trough serum ramucirumab concentrations (geometric mean [coefficient of variation]) in Cycle 3 and Cycle 6 were 42.5 (60.9%) and 55.5 (63.5%) μg/mL, respectively, in patients of Child-Pugh class A and 45.4 (71.6%) and 53.3 (67.2%) μg/mL, respectively, in patients of Child-Pugh class B, showing no clear difference between the two patient subgroups. In the ramucirumab group, anti-ramucirumab antibody was detected in 23 of 241 patients (9.5%) in whom the antibody level was measured after the start of treatment. Of those patients positive for anti-ramucirumab antibody, 10 (4.1%) were found to be TE-ADA-positive and 1 (0.4%) neutralizing antibody-positive.

6.1.3 Foreign phase II study (CTD 5.3.5.4.1, Study I4Y-IE-JCDB [August 2010 to December 2013])

An open-label, randomized, comparative study was conducted to investigate the PK, etc. of ramucirumab in 153 patients with unresectable advanced/recurrent CRC with disease progression after CPT-11-based chemotherapy (49 in the mFOLFOX6 group, 52 in the ramucirumab/mFOLFOX6 group, 52 in the icrucumab/mFOLFOX6 group) (9 patients evaluable for PK analysis). The patients received intravenous doses of (a) mFOLFOX6, (b) ramucirumab 8 mg/kg plus mFOLFOX6 every 2 weeks, or (c) icrucumab (unapproved in Japan) 15 mg/kg plus mFOLFOX6 every 2 weeks, and serum ramucirumab concentrations were determined.

Trough serum ramucirumab concentrations (geometric mean [coefficient of variation]) in Cycles 1, 4, and 5 were 29.7 (66%), 53.6 (123%), and 73.3 (45%) μg/mL, respectively. No anti-ramucirumab antibody was detected in any of 36 patients in whom the antibody level was measured after the start of treatment with ramucirumab.

6.1.4 Study on drug interaction with CPT-11 (CTD 5.3.3.4.1, Study I4T-IE-JVCB [ongoing since October 2012 (data cut-off; August [redacted], 2013)])

An open-label study was conducted in 29 patients with advanced solid cancer (28 patients evaluable for PK analysis) to investigate the safety and PK of ramucirumab in combination with FOLFIRI and to evaluate the effect of ramucirumab on the PK of CPT-11 and its metabolite SN-38. The patients received

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1) Antibody titer >4 times the baseline titer, or antibody titer >1:20 when baseline anti-ramucirumab antibody was negative or baseline value was missing (see "Review Report dated February 16, 2015: Cyramza Injection 100 mg, Cyramza Injection 500 mg").

intravenously FOLFIRI on Day 1 and ramucirumab 8 mg/kg plus FOLFIRI every 2 weeks from Day 15 onward. Serum concentrations of ramucirumab, CPT-11, and SN-38 were determined.

The ratios of the least square geometric means (90% confidence interval [CI]) of C_{max} and AUC_{inf} of CPT-11 after ramucirumab/FOLFIRI treatment (Day 15) to the values after FOLFIRI treatment (Day 1) were 1.04 (0.97, 1.12) and 0.93 (0.83, 1.05), respectively, and the ratios of the least square geometric means (90% CI) of C_{max} and AUC_{inf} of SN-38 were 0.97 (0.85, 1.12) and 0.95 (0.88, 1.04), respectively. Table 3 shows the PK parameters of ramucirumab after ramucirumab/FOLFIRI treatment (Day 15). The PK parameters were similar to those of ramucirumab administered alone in the foreign phase II study (Study I4T-IE-JVCA) in patients with advanced solid cancer, which was conducted to investigate the pharmacokinetic interactions between ramucirumab and paclitaxel (PTX) (see "Review Report dated February 16, 2015: Cyramza Injection 100 mg, Cyramza Injection 500 mg").

Table 3. PK parameters of ramucirumab after administration of ramucirumab plus FOLFIRI (Day 15)

C_{max} (μg/mL)	t_{max}*1 (h)	$AUC_{0\text{-}168h}$ (μg·h/mL)	AUC_{inf} (μg·h/mL)	$t_{1/2}$*2 (h)	CL (L/h)	V_z (L)
201.6 (31%)	2.0 (1.0, 7.0)	15,500 (34%)	28,300 (35%)*3	144 (100, 212)*3	0.0226 (29%)*3	4.68 (28%)*3

n = 25; geometric mean (coefficient of variation); *1median (range); *2 geometric mean (range); *3 n = 18

The applicant's explanation:
The results suggested that ramucirumab does not affect the PK of CPT-11 or SN-38 and that FOLFIRI does not affect the PK of ramucirumab. Although the effect of ramucirumab on the PK of *dl*-LV, *l*-LV, or 5-FU was not investigated, ramucirumab is unlikely to affect the PK of the concomitant drugs because they are eliminated through different pathways (see "Review Report dated February 16, 2015: Cyramza Injection 100 mg, Cyramza Injection 500 mg," the package insert of 5-FU Injection 250 mg, 5-FU Injection 1000 mg, and *Semin Oncol*. 1992;19:16-25).

6.1.5 Population pharmacokinetics analysis

A population pharmacokinetics (PPK) analysis was performed using a non-linear mixed effect model (software, NONMEM ver.7.3), based on PK data (1639 patients, 6427 time points) obtained from the following 11 studies: Japanese phase I studies (Studies I4T-IE-JVBW, I4T-IE-JVBX, and I4T-IE-JVBY), global phase III studies (Studies I4T-IE-JVBE and I4T-IE-JVBF [RAINBOW and REACH, respectively], and RAISE study), foreign phase II studies (Studies I4T-IE-JVBJ, I4T-IE-JVCA, and I4T-IE-JVCC), and foreign phase III studies (Studies I4T-IE-JVBD and I4T-MC-JVBA [REGARD and REVEL,[2)] respectively]). The PK of ramucirumab was described by a 2-compartment model that included zero-order absorption and first-order elimination processes. The following parameters were evaluated as covariates for the PK parameters of ramucirumab (clearance [CL], central volume of distribution [V_1], and peripheral volume of distribution [V_2]): age, body weight, sex, race, ethnicity, creatinine clearance (CLcr), renal function,[3)] serum albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, total bilirubin, α-fetoprotein, hepatic function,[4)] Child-Pugh class, cancer type, absolute dose, and dose per body weight.

None of these covariates were selected as significant covariates for the PK parameters of ramucirumab (CL, V_1, and V_2).

6.1.6 Difference in the PK of ramucirumab between Japanese and non-Japanese patients

The applicant explained that there was no clear difference in the PK of ramucirumab between Japanese patients and non-Japanese patients, based on the following findings:

2) Foreign phase III study that investigated the efficacy and safety of ramucirumab in combination with docetaxel hydrate in patients with advanced/recurrent non-small cell lung cancer with disease progression after one prior first-line platinum-based therapy

3) Patients with normal renal function (CLcr ≥90 mL/min), patients with mild renal impairment (60 mL/min ≤ CLcr <90 mL/min), patients with moderate renal impairment (30 mL/min ≤ CLcr <60 mL/min), and patients with severe renal impairment (15 mL/min ≤ CLcr <30 mL/min)

4) Patients with normal hepatic function (total bilirubin ≤ upper limit of normal (ULN) and AST ≤ ULN), patients with mild hepatic impairment (total bilirubin ≤1.5 × ULN and AST > ULN, or ULN < total bilirubin ≤1.5 × ULN), and patients with moderate hepatic impairment (1.5 × ULN < total bilirubin ≤3 × ULN)

- In the Japanese phase I study (Study I4T-IE-JVBY) and the foreign phase II study (Study I4T-IE-JVCB), a single dose of ramucirumab 8 mg/kg was administered in combination with FOLFIRI (see "Review Report dated February 16, 2015: Cyramza Injection 100 mg, Cyramza Injection 500 mg" and 6.1.4 Study on drug interaction with CPT-11). The PK of ramucirumab was comparable between the 2 studies.
- In the PPK analysis, race was not selected as a significant covariate of PK parameters of ramucirumab [see 6.1.5 PKK analysis].

6.1.7 Relationship between exposure and efficacy or safety

6.1.7.1 Relationship between exposure and efficacy

The results of the RAISE study were analyzed to investigate a relationship between exposure to ramucirumab[5)] (minimum serum concentration following the first dose [$C_{min,1}$], minimum serum concentration at steady state [$C_{min,ss}$], maximum serum concentration at steady state [$C_{max,ss}$], and average serum concentration at steady state [$C_{ave,ss}$]) and overall survival (OS) or progression-free survival (PFS). There was a correlation between an increase in the exposure ($C_{min,1}$, $C_{min,ss}$, $C_{max,ss}$, and $C_{ave,ss}$) and improved OS or PFS.

6.1.7.2 Relationship between exposure and safety

The results of the RAISE study were analyzed to investigate (a) relationships between exposure to ramucirumab ($C_{min,1}$, $C_{min,ss}$, $C_{max,ss}$, and $C_{ave,ss}$) and Grade ≥3 neutropenia, hypertension, and fatigue (adverse events which occurred in ≥5% of patients in the ramucirumab/FOLFIRI group and which were reported ≥2% more frequently in the ramucirumab/FOLFIRI group than in the placebo/FOLFIRI group) and (b) a relationship between the exposure and Grade ≥3 diarrhoea, a major adverse event observed after FOLFIRI treatment (*J Clin Oncol.* 2005;23:4866-75). There was a correlation between an increase in the exposure ($C_{min,1}$, $C_{min,ss}$, $C_{max,ss}$, and $C_{ave,ss}$) and the increased incidence of Grade ≥3 neutropenia.

6.R Outline of the review conducted by PMDA

6.R.1 Effect of an anti-ramucirumab antibody on the PK of ramucirumab

The applicant's explanation on the expression of an anti-ramucirumab antibody and its effect on the PK of ramucirumab:

The expression of an anti-ramucirumab antibody was investigated based on the results of the following studies: 4 Japanese phase I studies (Studies I4T-IE-JVBI, I4T-IE-JVBW, I4T-IE-JVBX, and I4T-IE-JVBY), 2 foreign phase I studies (Studies I4T-IE-JVBM and I4T-IE-JVBN), 11 foreign phase II studies (Studies I4T-IE-JVBK, I4T-IE-JVBP, I4T-IE-JVBQ, I4T-IE-JVBR, I4T-IE-JVBH, I4T-IE-JVBJ, I4T-IE-JVBO, I4T-IE-JVBS, I4Y-IE-JCDB, I4T-IE-JVBL, and I4T-IE-JVCC), 3 foreign phase III studies (REGARD, REVEL, and I4T-IE-JVBC [ROSE]), and 3 global phase III studies (RAINBOW, RAISE, and REACH). Anti-ramucirumab antibodies were detected in 143 of 2890 patients (4.9%) from whom a blood sample was collected at least once after the start of treatment with ramucirumab. Of these, 86 patients (3.0%) were found to be TE-ADA-positive, and 14 patients (0.5%) positive for neutralizing antibodies.

The effect of the anti-ramucirumab antibody on the PK of ramucirumab was investigated in the RAISE and the REACH studies in which an anti-ramucirumab antibody was detected during the treatment period. Table 4 shows the range of serum ramucirumab concentrations obtained at the time when anti-ramucirumab antibody testing was performed. In both studies, serum ramucirumab concentrations at the time points of anti-ramucirumab antibody testing of antibody-positive patients were within the range of serum ramucirumab concentrations of antibody-negative patients at the same time points.

5) Individual values were estimated using PPK analysis [see 6.1.5 PPK analysis].

Table 4. Range of serum ramucirumab concentrations (μg/mL) following multiple doses of ramucirumab (8 mg/kg)

Study	Cycle	Patients who tested positive for anti-ramucirumab antibodies		Patients who tested negative for anti-ramucirumab antibodies	
		n	C_{min}	n	C_{min}
RAISE	2	4	18.3-96.0	247	BQL*-118.8
	4	3	35.4-104.3	153	BQL*-204.5
REACH	3	10	14.8-61.3	164	BQL*-163.5
	6	5	30.5-85.9	93	9.2-173.0

Min. to Max; * <1.9 or <2.5 μg/mL (see "Review Report dated February 16, 2015: Cyramza Injection 100 mg, Cyramza Injection 500 mg"); BQL, below the quantification limit; C_{min}, minimum serum concentration

The small number of patients investigated precludes a definitive conclusion on the effect of the anti-ramucirumab antibody on the PK of ramucirumab. Nevertheless, the anti-ramucirumab antibody is not considered to affect the PK of ramucirumab clearly.

PMDA's view:
The submitted data do not show any clear effect of the anti-ramucirumab antibody on the PK of ramucirumab. However, because of the limited study data, effects of the anti-ramucirumab antibody on the PK of ramucirumab should be further investigated through continuous data collection. Any new findings should be communicated to healthcare professionals appropriately.

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

The applicant submitted efficacy and safety evaluation data from 2 clinical studies (1 Japanese phase I study and 1 global phase III study), as shown in Table 5. Reference data submitted were the results of 4 clinical studies (1 global phase III study and 3 foreign phase II studies).

Table 5. List of clinical studies on efficacy and safety

Data category	Region	Study	Phase	Target patients	Number of enrolled subjects	Dosing regimen	Primary endpoints
Evaluation	Japan	I4T-IE-JVBY	I	Patients with unresectable advanced/recurrent CRC with disease progression after treatment with BV, L-OHP, and a fluoropyrimidine	6	Ramucirumab 8 mg/kg plus FOLFIRI was administered intravenously every 2 weeks.	Safety PK
	Global	I4T-MC-JVBB (RAISE)	III	Patients with unresectable advanced/recurrent CRC with disease progression after treatment with BV, L-OHP, and a fluoropyrimidine	1072 (a) 536 (b) 536	(a) Ramucirumab 8 mg/kg plus FOLFIRI or (b) placebo plus FOLFIRI was administered intravenously every 2 weeks.	Efficacy Safety
Reference	Global	I4T-IE-JVBF (REACH)	III	Patients with advanced hepatocellular carcinoma resistant or intolerant to sorafenib tosilate	Child-Pugh A: 565 (a) 283 (b) 282 Child-Pugh B: 79 (a) 41 (b) 38	(a) Ramucirumab 8 mg/kg or (b) placebo was administered intravenously every 2 weeks.	Safety
	Foreign	I4T-IE-JVCB	II	Patients with advanced solid cancer	29	Cycle 1: FOLFIRI Cycle 2+: ramucirumab 8 mg/kg plus FOLFIRI The above regimen was administered intravenously every 2 weeks.	Safety PK
		I4T-IE-JVBH	II	Chemotherapy-naïve patients with unresectable advanced/recurrent CRC	48	Ramucirumab 8 mg/kg plus mFOLFOX6 was administered intravenously every 2 weeks.	Efficacy Safety
		I4Y-IE-JCDB	II	Patients with unresectable advanced/recurrent CRC with disease progression after treatment with chemotherapy including CPT-11	158 (a) 54 (b) 52 (c) 52	(a) mFOLFOX6, (b) ramucirumab 8 mg/kg plus mFOLFOX6, or (c) icrucumab (unapproved in Japan) 15 mg/kg plus mFOLFOX6 The above regimens were administered intravenously every 2 weeks.	Efficacy Safety

The following sections outline each clinical study. Major non-fatal adverse events reported in each clinical study are summarized in "7.3 Adverse events, etc. reported in clinical studies" and PK study results in "6.1 Clinical pharmacology studies."

7.1 Evaluation data

7.1.1 Japanese clinical study

7.1.1.1 Japanese phase I study (CTD 5.3.3.2.1, Study I4T-IE-JVBY [February 2011 to March 2012])

An open-label, uncontrolled study in patients with unresectable advanced/recurrent CRC with disease progression after treatment with BV, L-OHP, and a fluoropyrimidine (target sample size, 6-9 patients) was conducted at 3 centers in Japan to investigate the safety, PK, etc. of ramucirumab/FOLFIRI.

The patients received ramucirumab 8 mg/kg plus FOLFIRI intravenously every 2 weeks until they met any of the criteria for treatment discontinuation.

All 6 patients enrolled in the study received the study drug and were included in the safety analysis.

The evaluation of dose limiting toxicity (DLT) was conducted from Cycle 1 through Day 1 of Cycle 3, and tolerability was evaluated during this period. Although 1 of 6 patients experienced DLT (Grade 2 proteinuria and Grade 4 neutropenia, for which a causal relationship to the study drug could not be ruled out. Due to the events, the Cycle 3 treatment was postponed to Day 44 after the start of treatment or later), the combination therapy with ramucirumab 8 mg/kg/dose plus FOLFIRI was considered well tolerated.

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

7.1.2 Global clinical study

7.1.2.1 Global phase III study (CTD 5.3.5.1.1, RAISE study [Ongoing since December 2010 (data cut-off; July 17, 2014)])

A double-blind, randomized, comparative study in patients with unresectable advanced/recurrent CRC with disease progression after treatment with BV, L-OHP, and a fluoropyrimidine (target sample size, 1050 patients) was conducted at 224 centers in 24 countries and regions including Japan to evaluate the efficacy and safety of ramucirumab/FOLFIRI relative to placebo/FOLFIRI.

The patients received ramucirumab 8 mg/kg every 2 weeks or placebo in combination with FOLFIRI intravenously until they met any of the criteria for treatment discontinuation.

All 1072 patients enrolled in the study (536 in the ramucirumab/FOLFIRI group, 536 in the placebo/FOLFIRI group) were included in the intent-to-treat (ITT) population and the efficacy analysis was based on this population. Of the patients included in the ITT population, 1057 patients were treated with the study drug (529 in the ramucirumab/FOLFIRI group, 528 in the placebo/FOLFIRI group[6)]) and were included the safety analysis.

The primary endpoint of this study was OS. The study was designed to have 2 interim analyses; the first interim analysis was performed when approximately 122 PFS events were reported, and the second interim analysis when 227 OS events (approximately 30% of the target number of events) were reported; to evaluate the futility of the study drug based on PFS and OS, respectively. Although no interim analysis was planned to evaluate the efficacy, the significance level at the final OS analysis was set at 4.998% (two-sided), taking account of the interim analyses to evaluate the futility of the study drug.

The efficacy of study drug presented as OS analysis results are shown in Table 6 and in the Kaplan-Meier curves in Figure 1.

Table 6. Final OS analysis results (ITT population; data cut-off, July 17, 2014)

	Ramucirumab/FOLFIRI	Placebo/FOLFIRI
Number of patients	536	536
Number of death (%)	372 (69.4)	397 (74.1)
Median (95% CI) (months)	13.3 (12.4, 14.5)	11.7 (10.8, 12.7)
Hazard ratio (95% CI)[*1]	0.844 (0.730, 0.976)	
P value (two-sided)[*2]	0.0219	

[*1] Cox proportional-hazards model adjusted for stratification factors (region, Kirsten rat sarcoma viral oncogene homolog [*KRAS*] gene mutation, and time to progression after the start of the first-line therapy [<6 months vs. ≥6 months])

[*2] Stratified log-rank test (stratified by region, *KRAS* gene mutation, and time to progression after the start of the first-line therapy [<6 months vs. ≥6 months]), significance level, 0.04998 (two-sided)

6) One patient assigned to the placebo/FOLFIRI group received ramucirumab at the first dose by mistake, and was therefore handled as a subject in the ramucirumab/FOLFIRI group in the safety analysis.

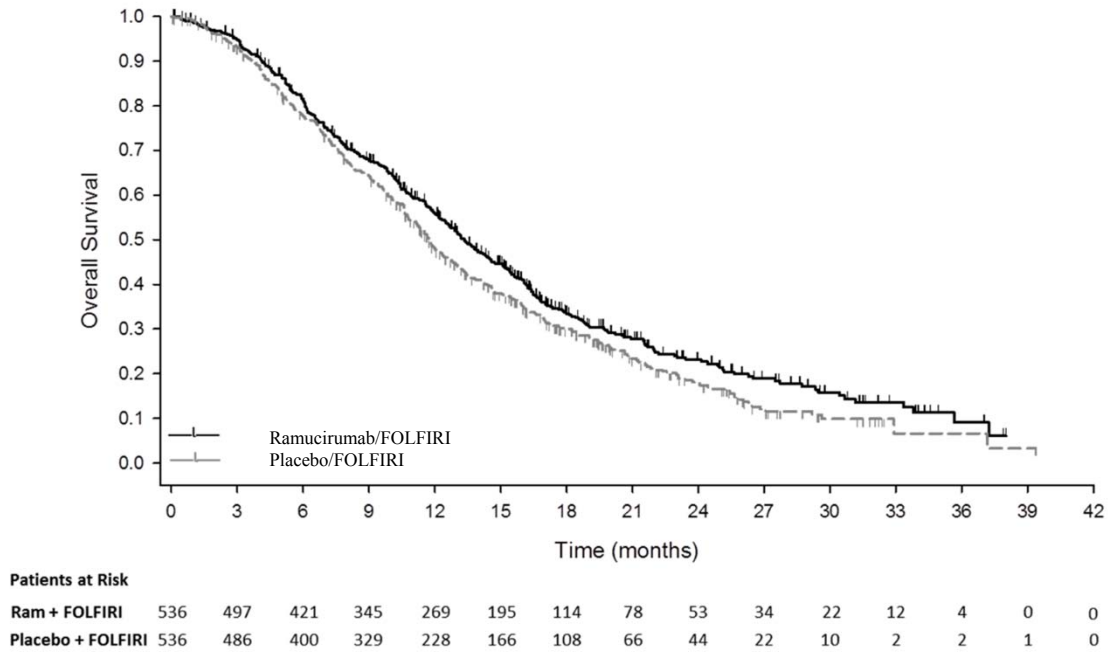

Figure 1. Kaplan-Meier curves in the final OS analysis (ITT population; data cut-off, July 17, 2014)

The safety analyses revealed deaths of 23 patients in the ramucirumab/FOLFIRI group and 29 patients in the placebo/FOLFIRI group during the treatment period or within 30 days after the last dose of the study drug. Ten patients in the ramucirumab/FOLFIRI group and 11 patients in the placebo/FOLFIRI group died due to disease progression. The causes of death other than disease progression in the ramucirumab/FOLFIRI group were sepsis in 2 patients, intestinal perforation, large intestine perforation, small intestinal perforation, gastric haemorrhage, large intestinal haemorrhage, haematemesis, septic shock, right ventricular failure, multi-organ failure, lung infiltration, and cerebral ischaemia in 1 patient each. Those in the placebo/FOLFIRI group were myocardial infarction in 2 patients, ileus, cerebrovascular accident/cardiac failure, large intestinal haemorrhage, respiratory arrest, bronchopulmonary aspergillosis, sepsis, Klebsiella sepsis, cardiac failure, intestinal obstruction, alcohol abuse, cardiac arrest, acute hepatic failure, cachexia, suicide attempt, multi-organ failure, and cardio-respiratory arrest in 1 patient each. Adverse events for which a causal relationship to the study drug could not be ruled out were intestinal perforation, large intestine perforation, small intestinal perforation, large intestinal haemorrhage, haematemesis, septic shock, right ventricular failure, and lung infiltration in 1 patient each in the ramucirumab/FOLFIRI group; and myocardial infarction, large intestinal haemorrhage, bronchopulmonary aspergillosis, Klebsiella sepsis, cardiac failure, acute hepatic failure, and suicide attempt in 1 patient each in the placebo/FOLFIRI group.

7.2 Reference data

7.2.1 Global study

7.2.1.1 Global phase III study (CTD 5.3.5.4.2, REACH study [November 2010 to March 2015])

A double-blind, randomized, comparative study in patients with advanced hepatocellular carcinoma resistant or intolerant to sorafenib tosilate (target sample size, 544 patients of Child-Pugh class A) was conducted at 154 centers in 27 countries and regions including Japan to evaluate the efficacy and safety of ramucirumab relative to placebo.

Of 644 patients enrolled and randomized (565 patients of Child-Pugh class A, 79 patients of Child-Pugh class B), 630 patients were treated with the study drug (553 [277 in the ramucirumab group, 276 in the placebo group], 77 [40 in the ramucirumab group, 37 in the placebo group]) and were included in the safety analysis.

The safety analysis revealed deaths of 26 patients of Child-Pugh class A in the ramucirumab group and 17 patients of Child-Pugh class A in the placebo group of during the treatment period or within 30 days after the last dose of the study drug. Twelve patients in the ramucirumab group and 10 in the placebo

group died due to disease progression. The causes of death other than disease progression in the ramucirumab group were hepatic failure in 3 patients, and hepatic failure/oesophageal varices haemorrhage, sepsis/urinary tract infection, sepsis, acute renal failure, multi-organ failure, shock haemorrhagic, acute hepatic failure, sudden death, cachexia, asthenia, and liver carcinoma ruptured in 1 patient each. Those in the placebo group were hepatic failure in 2 patients, pulmonary embolism, oesophageal varices haemorrhage, cachexia, acute respiratory distress syndrome, and pneumonia in 1 patient each. Adverse events for which a causal relationship to the study drug could not be ruled out were hepatic failure in 2 patients, sepsis/urinary tract infection, multi-organ failure, and acute hepatic failure in 1 patient each in the ramucirumab group; and pulmonary embolism, oesophageal varices haemorrhage, and acute respiratory distress syndrome in 1 patient each in the placebo group. Death occurred in 6 patients of Child-Pugh class B in the ramucirumab group and in 7 patients of Child-Pugh class B in the placebo group were reported during the treatment period or within 30 days after the last dose of the study drug. Four patients in the ramucirumab group and 7 in the placebo group died due to disease progression. The causes of death other than disease progression were general physical health deterioration and acute hepatic failure in 1 patient each in the ramucirumab group. A causal relationship to the study drug was ruled out for both adverse events.

7.2.2 Foreign clinical studies

7.2.2.1 Foreign phase II study (CTD 5.3.3.4.1, Study I4T-IE-JVCB [ongoing since October 2012 (data cut-off; August [redacted], 2013)])

An open-label, uncontrolled study in patients with advanced solid cancer (target sample size, 15 patients) was conducted at 6 centers overseas to investigate the safety, PK, etc. of ramucirumab/FOLFIRI.

All 29 patients enrolled and treated with the study drug were included in the safety analysis.

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

7.2.2.2 Foreign phase II study (CTD 5.3.5.2.1, Study I4T-IE-JVBH [April 2009 to August 2011])

An open-label, uncontrolled study in chemotherapy-naïve patients with unresectable advanced/recurrent CRC (target sample size, 45 patients) was conducted at 8 centers overseas to investigate the efficacy and safety of ramucirumab/mFOLFOX6.

All 48 patients enrolled and treated with the study drug were included in the safety analysis.

The safety analysis revealed deaths of 2 patients during the treatment period or within 30 days after the last dose of the study drug. The causes of death were acute myocardial infarction and cardio-respiratory arrest in 1 patient each. A causal relationship to the study drug could not be ruled out for either adverse event.

7.2.2.3 Foreign phase II study (CTD 5.3.5.4.1, Study I4Y-IE-JCDB [August 2010 to December 2013])

An open-label, randomized, comparative study in patients with unresectable advanced/recurrent CRC with disease progression after CPT-11-based chemotherapy (target sample size, 150 patients) was conducted in 19 centers overseas to investigate the efficacy and safety of mFOLFOX6, ramucirumab/mFOLFOX6, and icrucumab/mFOLFOX6.

Of 158 patients enrolled for randomization in the study (54 in the mFOLFOX6 group, 52 in the ramucirumab/mFOLFOX6 group, 52 in the icrucumab/mFOLFOX6 group), 153 were treated with the study drug (49 in the mFOLFOX6 group, 52 in the ramucirumab/mFOLFOX6 group, 52 in the icrucumab/mFOLFOX6 group). The 153 patients were included in the safety analysis.

The safety analysis revealed 3 deaths occurring in the ramucirumab/mFOLFOX6 group during the treatment period or within 30 days after the last dose of the study drug. The causes of deaths other than disease progression (1 patient) were neoplasm progression and cerebrovascular accident in 1 patient each. A causal relationship to the study drug could not be ruled out for cerebrovascular accident.

7.R Outline of the review conducted by PMDA

7.R.1 Efficacy

PMDA's view:

The efficacy of ramucirumab has been demonstrated in patients with unresectable advanced/recurrent CRC with disease progression after treatment with BV, L-OHP, and a fluoropyrimidine. The following sections show the details of the reviews.

7.R.1.1 Setting of the control group

The applicant's justification for using placebo/FOLFIRI as the control in the RAISE study:

Patients with advanced/recurrent CRC with disease progression after first-line therapy who intended to receive second-line therapy were eligible for enrollment in the RAISE study. When the RAISE study was planned (2010), the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Colon Cancer (NCCN Guidelines [colon cancer]) (*J Natl Compre Canc Netw*. 2009;7:778-831) and the Japanese Society for Cancer of the Colon and Rectum Guidelines 2010 for the treatment of colon cancer for physicians (Kanehara & Co., Ltd., 2010) were available in the US and Japan, respectively. Both guidelines recommended that second-line therapy for this patient population should be either FOLFOX or FOLFIRI, whichever not chosen for the first-line therapy. Because the use of FOLFOX was assumed to be more common for first-line therapy than FOLFIRI, placebo/FOLFIRI was selected as the control in the RAISE study.

PMDA accepted the applicant's explanation.

7.R.1.2 Efficacy endpoints and evaluation results

PMDA's view:

Treatment of patients with unresectable advanced/recurrent CRC aims at survival improvement. OS was the appropriate primary endpoint of the RAISE study.

The RAISE study demonstrated the superiority of ramucirumab/FOLFIRI to placebo/FOLFIRI in OS [see 7.1.2 Global clinical study]. Ramucirumab/FOLFIRI was shown to be effective in the patients eligible for enrollment in the RAISE study.

7.R.1.3 Efficacy in Japanese patients

The results of OS in the Japanese population in the RAISE study are shown in Table 7 and the Kaplan-Meier curves in Figure 2.

Table 7. OS analysis results for Japanese population (data cut-off; July 17, 2014)

	Ramucirumab/FOLFIRI	Placebo/FOLFIRI
Number of patients	74	62
Number of death (%)	46 (62.2)	39 (62.9)
Median (95% CI) (months)	16.4 (13.4, 20.9)	19.4 (14.2, 25.3)
Hazard ratio (95% CI)[*1]	1.193 (0.762, 1.868)	
P value (two-sided)[*2]	0.4391	

[*1] Cox proportional hazards model adjusted for stratification factors (*KRAS* gene mutation, time to progression in the first-line therapy [<6 months vs. ≥6 months])

[*2] Stratified log-rank test (stratified by *KRAS* gene mutation, time to progression in the first-line therapy [<6 months vs. ≥6 months])

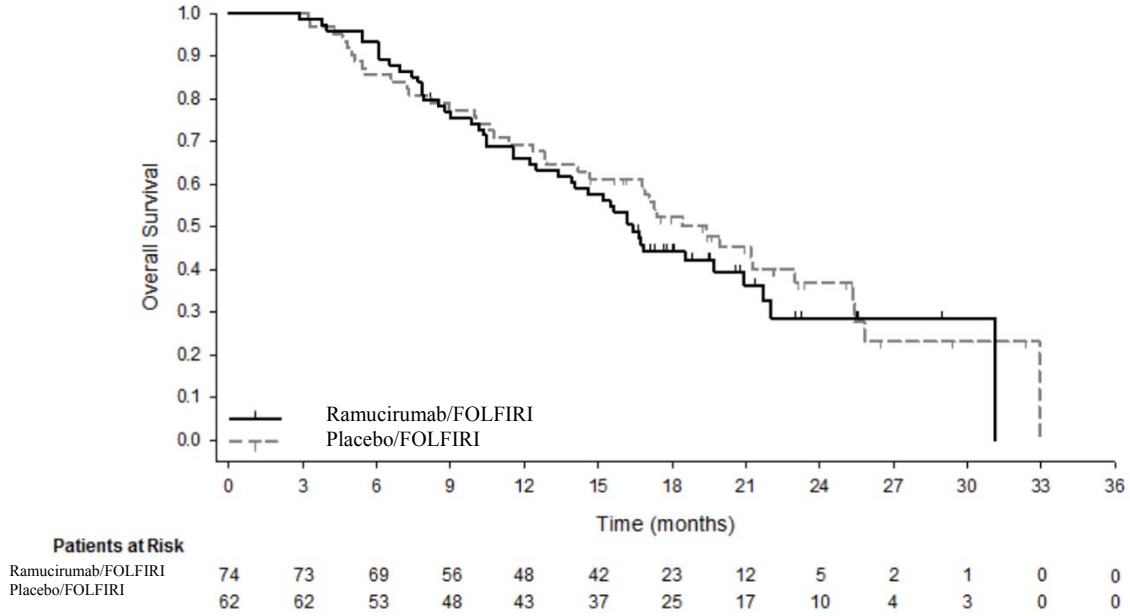

Figure 2. Kaplan-Meier curves of OS in Japanese population (data cut-off; July 17, 2014)

The results of the RAISE study showed inconsistency in the OS analysis results between the Japanese population and the entire study population. PMDA asked the applicant to explain the efficacy of ramucirumab in Japanese patients.

The applicant's response:
Prognostic factors were identified from the OS results for the entire population in the RAISE study, and possible effects of these factors on the OS in the Japanese population were investigated by a multivariate analysis, etc. The identified prognostic factors had no clear effect on the OS in the Japanese population.

At the same time, the applicant investigated whether the imbalance in the number of postdiscontinuation anticancer therapies between the entire study population and Japanese population had affected the OS analysis results for the Japanese population. The percentage of patients receiving any postdiscontinuation anticancer therapy was higher in the Japanese population than in the entire study population and was also higher in the placebo/FOLFIRI group than in the ramucirumab/FOLFIRI group (Table 8).

Table 8. Outline of postdiscontinuation anticancer therapy

Number of postdiscontinuation anticancer-therapies	Number of patients (%)			
	Entire study population		Japanese population	
	Ramucirumab/FOLFIRI (N = 536)	Placebo/FOLFIRI (N = 536)	Ramucirumab/FOLFIRI (N = 74)	Placebo/FOLFIRI (N = 62)
None	247 (46.1)	237 (44.2)	18 (24.3)	10 (16.1)
≥1 regimen	289 (53.9)	299 (55.8)	56 (75.7)	52 (83.9)
≥2 regimens	108 (20.1)	99 (18.5)	34 (45.9)	28 (45.2)
≥3 regimens	33 (6.2)	37 (6.9)	14 (18.9)	21 (33.9)

The analysis was therefore performed in light of a possible effect of postdiscontinuation anticancer therapies. The hazard ratio (95% CI) of OS in the Japanese population was 0.807 (0.488, 1.333) (median OS; 15.5 months in the ramucirumab/FOLFIRI group, 12.8 months in the placebo/FOLFIRI group) after the exclusion of patients receiving ≥3 postdiscontinuation anticancer therapies. Table 9 shows the hazard ratios of OS in the entire study population and the Japanese population at the data cut-off points, i.e., the starting days of the third and second postdiscontinuation anticancer therapies (fifth-line and fourth-line therapies, respectively). Hazard ratios were lower in the analysis with than without data censored at the starting days of postdiscontinuation anticancer therapies.

Table 9. Hazard ratio of OS based on the analysis without data censored at the starting days of postdiscontinuation anticancer therapies

Censoring date	Entire study population		Japanese population	
	(%)*	Hazard ratio (95% CI)	(%)*	Hazard ratio (95% CI)
Not censored at the starting day of postdiscontinuation anticancer therapy	28	0.844 (0.730, 0.976)	38	1.193 (0.762, 1.868)
Starting day of the third postdiscontinuation anticancer therapy	32	0.829 (0.714, 0.961)	51	1.152 (0.701, 1.893)
Starting day of the second postdiscontinuation anticancer therapy	42	0.809 (0.689, 0.950)	61	0.900 (0.519, 1.559)

* Percentage of censored patients relative to all patients

PFS is less likely to be affected by postdiscontinuation anticancer therapies and is a highly sensitive index for the therapeutic effect (*J Clin Oncol*. 2007;25:5153-4). Table 10 shows the investigator-assessed PFS in the entire study population and the Japanese population of the RAISE study, and Figure 3 presents the Kaplan-Meier curves of the PFS. There was consistency in the PFS between the entire study population and the Japanese population.

Table 10. PFS (ITT population, assessed by investigator, data cut-off on July 17, 2014)

	Entire study population		Japanese population	
	Ramucirumab/ FOLFIRI	Placebo/FOLFIRI	Ramucirumab/ FOLFIRI	Placebo/FOLFIRI
Number of patients	536	536	74	62
Number of death or disease progression (%)	476 (88.8)	494 (92.2)	70 (94.6)	62 (100)
Median (95% CI) (months)	5.7 (5.5, 6.2)	4.5 (4.2, 5.4)	5.7 (4.3, 7.1)	4.3 (3.7, 6.9)
Hazard ratio (95% CI)*1	0.793 (0.697, 0.903)		0.835 (0.584, 1.192)	
P value (two-sided)*2	0.0005		0.3212	

*1 Cox proportional-hazards model adjusted for stratification factors (region, *KRAS* gene mutation, and time to progression in the first-line therapy [<6 months vs. ≥6 months]) (region was not applied to the analysis of the Japanese population)
*2 Stratified log-rank test (stratified by region, *KRAS* gene mutation, and time to progression in the first-line therapy [<6 months vs. ≥6 months]) (region was not applied to the analysis of the Japanese population)

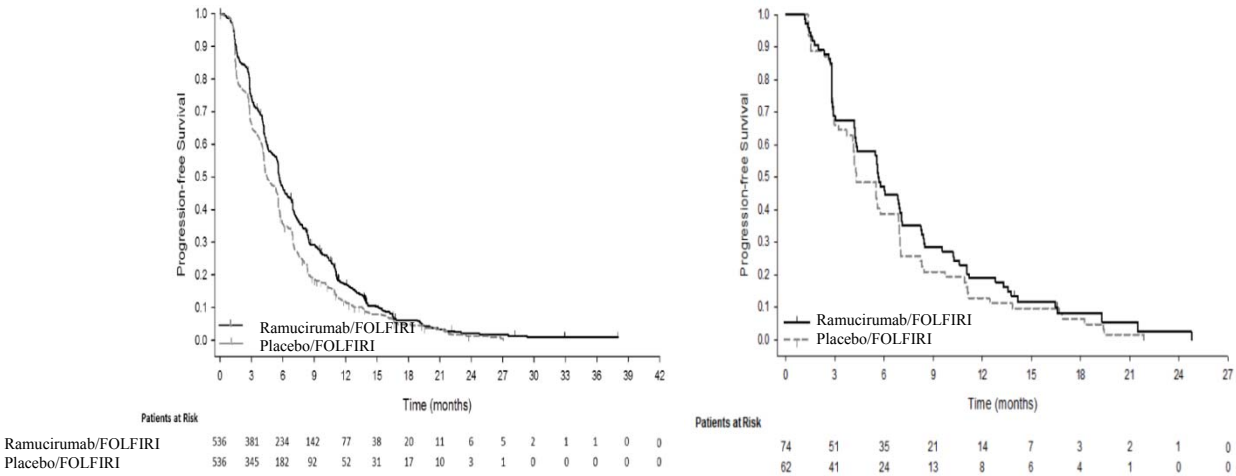

Figure 3. Kaplan-Meier curves of PFS in the entire study population (left) and the Japanese population (right) (ITT population, assessed by investigator, data cut off on July 17, 2014)

The OS analysis results for the Japanese population of the RAISE study was affected by the imbalance in the number of postdiscontinuation anticancer therapies between the entire study population and the Japanese population and that between the ramucirumab/FOLFIRI group and the placebo/FOLFIRI group. An analysis was performed to take the influential factor into account. Results showed that the hazard ratio of the ramucirumab/FOLFIRI group to the placebo/FOLFIRI group decreased in the

Japanese population. The PFS results were consistent between the entire study population and the Japanese population. Therefore, ramucirumab has promising efficacy in Japanese patients as well.

PMDA's view:
The applicant explained that the imbalance in postdiscontinuation anticancer therapy status possibly had an impact on the OS analysis results for the Japanese population in the RAISE study, and it is acceptable. However, the analysis of data adjusted for the above-mentioned imbalance suggests that post-randomization exclusion of a specific patient subgroup and the censoring of data from the patients receiving postdiscontinuation anticancer therapy raise concerns about biases in the analysis. Therefore, the analysis results do not adequately reflect the efficacy of ramucirumab in Japanese patients. Nevertheless, the applicant's claim on the expected efficacy of ramucirumab in Japanese patients is understandable to a certain extent for the reasons below. The OS analysis results for the Japanese population in the RAISE study are important information that helps determine the use of ramucirumab and should be therefore communicated to healthcare professionals appropriately through the package insert, etc.

- The PFS results assessed by the investigator, a secondary endpoint of the RAISE study, was consistent between the entire study population and the Japanese population, suggesting the efficacy of ramucirumab in Japanese patients as well.
- No clear difference is observed between Japanese and non-Japanese patients in the efficacy of ramucirumab in the treatment of gastric cancer, which is the approved indication.
- Cancer progression is caused by the accumulation of gene mutations. There is no clear difference between Japanese and non-Japanese patients in the genes involved in the progression of CRC.

7.R.2 Safety [see "7.3 Adverse events, etc. observed in clinical studies" for adverse events]
PMDA's view:
The safety reviews (presented in the sections below) revealed that the use of ramucirumab in patients with unresectable advanced/recurrent CRC requires close attention to nephrotic syndrome and interstitial lung disease (ILD) as well as the adverse events identified in the review of the initial application (hypertension, proteinuria, haemorrhage, infusion-related reaction, thromboembolism, gastrointestinal perforation, cardiac failure congestive, neutropenia/leukopenia, posterior reversible encephalopathy syndrome, fistula, disturbance of wound healing, and liver disorder) (see "Review Report dated February 16, 2015: Cyramza Injection 100 mg, Cyramza Injection 500 mg"). During treatment with ramucirumab, patients should be carefully monitored for these adverse events.

Despite these adverse events requiring close attention, ramucirumab is well tolerated when patients are managed by physicians with adequate knowledge of and experience with cancer chemotherapy through monitoring and controlling of adverse events, dose reduction, or interruption or discontinuation of treatment.

7.R.2.1 Safety profile of ramucirumab
The applicant explanation on the safety profile of ramucirumab based on the safety data obtained from the RAISE study:
In this section, events corresponding to the Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (PTs) of (a) "neutropenia" or "neutrophil count decreased," (b) "thrombocytopenia" or "platelet count decreased," and (c) "leukopenia" or "white blood cell count decreased" were tabulated as (a) neutropenia, (b) thrombocytopenia, and (c) leukopenia, respectively:

Table 11 outlines the safety of ramucirumab in the RAISE study.

Table 11. Outline of safety (RAISE study)

	Number of patients (%)	
	Ramucirumab/FOLFIRI (N = 529)	Placebo/FOLFIRI (N = 528)
All adverse events	522 (98.7)	519 (98.3)
Grade ≥3 adverse events	418 (79.0)	329 (62.3)
Adverse events resulting in death	21 (4.0)	19 (3.6)
Serious adverse events	189 (35.7)	164 (31.1)
Adverse events leading to treatment discontinuation	197 (37.2)	89 (16.9)
Adverse events leading to interruption	182 (34.4)	123 (23.3)
Adverse events leading to dose reduction	309 (58.4)	213 (40.3)

In the RAISE study, adverse events of any grade that occurred at an incidence of ≥10% higher in the ramucirumab/FOLFIRI group than in the placebo/FOLFIRI group were neutropenia (311 of 529 patients [58.8%] in the ramucirumab/FOLFIRI group, 241 of 528 patients [45.6%] in the placebo/FOLFIRI group), decreased appetite (198 of 529 patients [37.4%], 144 of 528 patients [27.3%]), epistaxis (177 of 529 patients [33.5%], 79 of 528 patients [15.0%]), stomatitis (163 of 529 patients [30.8%], 110 of 528 patients [20.8%]), thrombocytopenia (150 of 529 patients [28.4%], 72 of 528 patients [13.6%]), hypertension (136 of 529 patients [25.7%], 45 of 528 patients [8.5%]), oedema peripheral (108 of 529 patients [20.4%], 48 of 528 patients [9.1%]), and proteinuria (89 of 529 patients [16.8%], 24 of 528 patients [4.5%]). Grade ≥3 adverse events occurring at an incidence of ≥5% higher in the former than in the latter were neutropenia (203 of 529 patients [38.4%], 123 of 528 patients [23.3%]) and hypertension (57 of 529 patients [10.8%], 15 of 528 patients [2.8%]). There were no fatal or serious adverse events occurring at an incidence of ≥2% higher in the ramucirumab/FOLFIRI group than in the placebo/FOLFIRI group.

Adverse events leading to treatment discontinuation that occurred at an incidence of ≥2% higher in the ramucirumab/FOLFIRI group than in the placebo/FOLFIRI group were neutropenia (67 of 529 patients [12.7%], 29 of 528 patients [5.5%]) and thrombocytopenia (29 of 529 patients [5.5%], 4 of 528 patients [0.8%]). Adverse events leading to interruption that occurred at an incidence of ≥2% higher in the former than in the latter were neutropenia (96 of 529 patients [18.1%], 61 of 528 patients [11.6%]) and thrombocytopenia (33 of 529 patients [6.2%], 6 of 528 patients [1.1%]). Adverse events leading to dose reduction that occurred at an incidence of ≥2% higher in the former than in the latter were neutropenia (173 of 529 patients [32.7%], 109 of 528 patients [20.6%]), stomatitis (35 of 529 patients [6.6%], 20 of 528 patients [3.8%]), mucosal inflammation (25 of 529 patients [4.7%], 8 of 528 patients [1.5%]), thrombocytopenia (23 of 529 patients [4.3%], 7 of 528 patients [1.3%]), and hypertension (13 of 529 patients [2.5%], 0 patients).

The applicant's explanation on the difference in the safety profile of ramucirumab between patients with unresectable advanced/recurrent CRC (RAISE study) and those with unresectable advanced/recurrent gastric cancer (RAINBOW study), which is the approved indication:
Table 12 outlines the safety of ramucirumab in the RAISE and RAINBOW studies.

Table 12. Outline of safety (RAISE and RAINBOW studies)

	Number of patients (%)			
	RAISE		RAINBOW	
	Ramucirumab/FOLFIRI (N = 529)	Placebo/FOLFIRI (N = 528)	Ramucirumab/PTX (N = 327)	Placebo/PTX (N = 329)
All adverse events	522 (98.7)	519 (98.3)	324 (99.1)	322 (97.9)
Grade ≥3 adverse events	418 (79.0)	329 (62.3)	267 (81.7)	206 (62.6)
Adverse events resulting in death	21 (4.0)	19 (3.6)	39 (11.9)	51 (15.5)
Serious adverse events	189 (35.7)	164 (31.1)	153 (46.8)	139 (42.2)
Adverse events leading to treatment discontinuation	197 (37.2)	89 (16.9)	102 (31.2)	80 (24.3)
Adverse events leading to interruption or dose reduction*	409 (77.3)	338 (64.0)	240 (73.4)	182 (55.3)

*Adverse events leading to treatment postponement dose interruption or dose reduction of study drug

Incidences of adverse events in the ramucirumab/FOLFIRI group of the RAISE study and the ramucirumab/PTX group of the RAINBOW study were compared. Adverse events of any grade that occurred at an incidence of ≥10% higher in the former than in the latter were diarrhoea (316 of 529 patients [59.7%] in the ramucirumab/FOLFIRI group of the RAISE study vs. 106 of 327 patients [32.4%] in the ramucirumab/PTX group of the RAINBOW study), nausea (262 of 529 patients [49.5%] vs. 115 of 327 patients [35.2%]), stomatitis (163 of 529 patients [30.8%] vs. 64 of 327 patients [19.6%]), thrombocytopenia (150 of 529 patients [28.4%] vs. 43 of 327 patients [13.1%]), mucosal inflammation (92 of 529 patients [17.4%] vs. 10 of 327 patients [3.1%]), and palmar-plantar erythrodysaesthesia syndrome (68 of 529 patients [12.9%] vs. 4 of 327 patients [1.2%]). A Grade ≥3 adverse event occurring at an incidence of ≥5% higher in the former than the latter was diarrhoea (57 of 529 patients [10.8%] vs. 12 of 327 patients [3.7%]).

There were some adverse events with a certain difference in the incidence between patients with CRC and patients with gastric cancer. However, they are the known adverse events related to individual concomitant drugs, and the differences in the types and incidence of adverse events are thus considered due to the use of different concomitant drugs.

PMDA's view:
In the RAISE study, some adverse events occurred more frequently in the ramucirumab/FOLFIRI group than in the placebo/FOLFIRI group. They were however the known adverse events related to the individual concomitant drugs used and most of the events were Grade ≤2 in severity. Accordingly, ramucirumab in combination with FOLFIRI is considered well tolerated in patients with CRC when they are managed by physicians with adequate knowledge of and experience with cancer chemotherapy, through appropriate measures such as monitoring and controlling of adverse events and interruption of treatment. The occurrence of the above-mentioned adverse events in the RAISE study should be appropriately communicated to healthcare professionals.

7.R.2.2 Difference in safety between Japanese and non-Japanese patients

The applicant's explanation on the difference in the safety of ramucirumab between Japanese and non-Japanese patients based on the safety data obtained from the RAISE study:
Table 13 outlines the safety results of Japanese and non-Japanese patients in the RAISE study.

Table 13. Outline of the difference in safety between Japanese and non-Japanese patients (RAISE study)

	Number of patients (%)			
	Japanese		Non-Japanese	
	Ramucirumab/FOLFIRI (N = 74)	Placebo/FOLFIRI (N = 62)	Ramucirumab/FOLFIRI (N = 455)	Placebo/FOLFIRI (N = 466)
All adverse events	74 (100)	62 (100)	448 (98.5)	457 (98.1)
Grade ≥3 adverse events	64 (86.5)	48 (77.4)	354 (77.8)	281 (60.3)
Adverse events resulting in death	2 (2.7)	1 (1.6)	19 (4.2)	18 (3.9)
Serious adverse events	23 (31.1)	14 (22.6)	166 (36.5)	150 (32.2)
Adverse events leading to treatment discontinuation	45 (60.8)	21 (33.9)	152 (33.4)	68 (14.6)
Adverse events leading to interruption	27 (36.5)	20 (32.3)	155 (34.1)	103 (22.1)
Adverse events leading to dose reduction	52 (70.3)	35 (56.5)	257 (56.5)	178 (38.2)

Incidences of adverse events were compared between Japanese and non-Japanese patients in the ramucirumab/FOLFIRI group of the RAISE study. Adverse events of any grade that occurred at an incidence of ≥20% higher in the former than in the latter were neutropenia (61 of 74 patients [82.4%] in Japanese patients vs. 250 of 455 patients [54.9%] in non-Japanese patients), stomatitis (44 of 74 patients [59.5%] vs. 119 of 455 patients [26.2%]), decreased appetite (43 of 74 patients [58.1%] vs. 155 of 455 patients [34.1%]), proteinuria (36 of 74 patients [48.6%] vs. 53 of 455 patients [11.6%]), alopecia (35 of 74 patients [47.3%] vs. 120 of 455 patients [26.4%]), hypertension (34 of 74 patients [45.9%] vs. 102 of 455 patients [22.4%]), leukopenia (27 of 74 patients [36.5%] vs. 42 of 455 patients [9.2%]), and malaise (23 of 74 patients [31.1%] vs. 16 of 455 patients [3.5%]). Grade ≥3 adverse events occurring at an incidence of ≥5% higher in the former than in the latter were neutropenia (44 of 74 patients [59.5%]

vs. 159 of 455 patients [34.9%]), hypertension (13 of 74 patients [17.6%] vs. 44 of 455 patients [9.7%]), leukopenia (8 of 74 patients [10.8%] vs. 6 of 455 patients [1.3%]), and proteinuria (6 of 74 patients [8.1%] vs. 9 of 455 patients [2.0%]).

Fatal adverse events occurring only in Japanese patients were septic shock and ILD in 1 patient each, and a causal relationship to the study drug could not be ruled out for either event. Serious adverse events observed only in Japanese patients were nephrotic syndrome in 3 of 74 patients (4.1%), ascites, cholecystitis, device related infection, gastrointestinal perforation, hyperglycaemia, ILD, jaundice cholestatic, lung infection, oesophageal varices haemorrhage, optic neuritis, pelvic infection, pneumothorax, pyelonephritis, septic shock, and wound infection in 1 of 74 patients (1.4%) each. A causal relationship to the study drug could not be ruled out for nephrotic syndrome in 3 patients, cholecystitis, device related infection, gastrointestinal perforation, ILD, lung infection, oesophageal varices haemorrhage, optic neuritis, pelvic infection, septic shock, and wound infection in 1 patient each.

In the ramucirumab/FOLFIRI group of the RAISE study, adverse events leading to study drug discontinuation that occurred at an incidence of ≥2% higher in Japanese patients than in non-Japanese patients were neutropenia (24 of 74 patients [32.4%] vs. 43 of 455 patients [9.5%]), proteinuria (5 of 74 patients [6.8%] vs. 6 of 455 patients [1.3%]), stomatitis (3 of 74 patients [4.1%] vs. 9 of 455 patients [2.0%]), and skin ulcer (2 of 74 patients [2.7%] vs. 0 patients). Adverse events leading to interruption that occurred at an incidence of ≥2% higher in the former than in the latter were neutropenia (22 of 74 patients [29.7%] vs. 74 of 455 patients [16.3%]) and hypertension (3 of 74 patients [4.1%] vs. 6 of 455 patients [1.3%]), and adverse events leading to dose reduction that occurred at an incidence of ≥2% higher in the former than in the latter were neutropenia (42 of 74 patients [56.8%], vs.131 of 455 patients [28.8%]), stomatitis (7 of 74 patients [9.5%] vs. 28 of 455 patients [6.2%]), and hypertension (5 of 74 patients [6.8%] vs. 8 of 455 patients [1.8%]).

PMDA's view:
Limited experience with the use of ramucirumab in Japanese patients with CRC precluded an accurate comparison of its safety between Japanese and non-Japanese patients. Nevertheless, the incidences of fatal or serious adverse events did not tend to be higher in Japanese patients than in non-Japanese patients. Ramucirumab in combination with FOLFIRI should be therefore well tolerated by Japanese patients as well when they are managed through appropriate measures such as dose reduction, interruption, and discontinuation. However, nephrotic syndrome, a serious adverse event, was observed in >1 patient in only Japanese patients, and it requires attention during the use of ramucirumab. Although all adverse events that occurred more frequently in Japanese patients than in non-Japanese patients are known to be caused by ramucirumab or the individual concomitant drugs, the occurrence of these events should be appropriately communicated to healthcare professionals.

In the RAISE study, serious nephrotic syndrome occurred only in Japanese patients and was experience by >1 patient. Nephrotic syndrome is one of disorders related to proteinuria, which was identified as an adverse event requiring attention in the initial application for ramucirumab. In the review presented in the section below, therefore, PMDA focused on nephrotic syndrome. Another focus of the review was placed on ILD, one of fatal adverse events noted in the ramucirumab/FOLFIRI group of the RAISE study. Although ILD was not identified as an adverse event requiring attention in the initial application, the number of cases of ILD reported as a post-marketing adverse drug reaction was taken into consideration (see "Review Report dated February 16, 2015: Cyramza Injection 100 mg, Cyramza Injection 500 mg").

7.R.2.3 Proteinuria and nephrotic syndrome
The applicant's explanation on proteinuria-related events caused by ramucirumab:
As proteinuria-related adverse events, events corresponding to the PTs "albuminuria," "nephrotic syndrome," "protein urine," "protein urine present," "proteinuria," or "urine protein, quantitative" in MedDRA (MedDRA/J ver.17.0) were tabulated.

In the RAISE study, proteinuria-related adverse events were observed in 90 of 529 patients (17.0%) in the ramucirumab/FOLFIRI group and in 24 of 528 patients (4.5%) in the placebo/FOLFIRI group. Grade ≥3 events were observed in 15 of 529 patients (2.8%) in the ramucirumab/FOLFIRI group and in 1 of 528 patients (0.2%) in the placebo/FOLFIRI group. There were no fatal adverse events. Serious adverse

events (nephrotic syndrome) were observed in 3 of 529 patients (0.6%) in the ramucirumab/FOLFIRI group (Grade 3 events in 2 patients and a Grade 4 event in 1 patient. A causal relationship to the study drug could not be ruled out for any of them. Adverse events led to treatment discontinuation in 12 of 529 patients (2.3%) in the ramucirumab/FOLFIRI group and in 2 of 528 patients (0.4%) in the placebo/FOLFIRI group, treatment interruption in 12 of 529 patients (2.3%) in the ramucirumab/FOLFIRI group and in 5 of 528 patients (0.9%) in the placebo/FOLFIRI group, and dose reduction in 2 of 529 patients (0.4%) in the ramucirumab/FOLFIRI group and in 1 of 528 patients (0.2%) in the placebo/FOLFIRI group.

Table 14 shows the particulars of patients who had nephrotic syndrome in all clinical studies submitted for the present application.

Table 14. List of patients who had nephrotic syndrome in the clinical studies (ramucirumab group)

Study	Regimen	Age	Sex	Complication	Grade	Seriousness	Time to onset (days)	Number of doses	Duration (days)	Causal relationship to ramucirumab	Action taken to ramucirumab	Outcome
RAISE	Ramucirumab/ FOLFIRI	70[*1]	M	Hypertension	3	Serious	42	2	6	Related	None[*2]	Recovered
					2	Non-serious	48	2	51	Related		
		52[*1]	M	Hypertension	3	Serious	33	1	11	Related	None[*3]	Recovered
		62[*1]	F	Hypertension	3	Serious	28	2	16	Related	Discontinued	Recovered
					4	Serious	44	2	4	Related		
					3	Serious	48	2	11	Related		
					1	Serious	59	2	-	Related		
I4T-IE-JVBH	Ramucirumab/ mFOLFOX6	68	M	Arteriosclerosis COPD Hydronephrosis	4	Serious	28	2	-	Related	Discontinued	Recovered
I4Y-IE-JCDB	Ramucirumab/ mFOLFOX6	50	M	Haemorrhoid Anxiety	4	Serious	36	2	28	Related	Discontinued	Improving
					3	Non-serious	63	2	14	Related		
					1	Non-serious	76	2	-	Related		

[*1] Japanese patient; [*2] Treatment was discontinued due to Grade 3 proteinuria before the onset of nephrotic syndrome; [*3] Treatment was discontinued after the onset of nephrotic syndrome at the request of the patient.

According to the post-marketing safety data obtained in Japan (data cut-off, [redacted], 20[redacted]), serious proteinuria was reported in 4 patients (proteinuria in 3 patients, nephrotic syndrome in 1 patient). The outcomes of the events were "recovering/resolving" or "recovered/resolved" after the discontinuation of ramucirumab in 3 patients (proteinuria in 2 patients, nephrotic syndrome in 1 patient) and "not recovered/not resolved" in 1 patient (proteinuria).

PMDA's view:
In the RAISE study, the incidences of proteinuria-related adverse events of any grade and Grade ≥3 events were higher in the ramucirumab/FOLFIRI group than in the placebo/FOLFIRI group. Patients in the ramucirumab/FOLFIRI group experienced serious nephrotic syndrome, and a causal relationship to the study drug could not be ruled out for the events. Therefore, patients treated with ramucirumab should be closely monitored for nephrotic syndrome. The occurrence of nephrotic syndrome in the clinical studies should be appropriately communicated to healthcare professionals through the package insert, etc. to raise caution.

7.R.2.4 ILD
The applicant's explanation on ILD-related events caused by ramucirumab:
PTs categorized as "Interstitial lung disease" of Standardized MedDRA Query (MedDRA/J ver.17.0) were tabulated.

In the RAISE study, ILD-related events were observed in 4 of 529 patients (0.8%) in the ramucirumab/FOLFIRI group and in 4 of 528 patients (0.8%) in the placebo/ FOLFIRI group. Grade ≥3 events were observed in 3 of 529 patients (0.6%) in the ramucirumab/FOLFIRI group and in 1 of 528 patients (0.2%) in the placebo/FOLFIRI group. ILD-related events led to discontinuation of the study drug in 2 of 529 patients (0.4%) in the ramucirumab/FOLFIRI group and in 2 of 529 patients (0.4%) in the placebo/FOLFIRI group. No events led to treatment interruption or dose reduction.

Table 15 shows the particulars of patients who had ILD-related events in all clinical studies submitted in the present application.

Table 15. List of patients who had ILD-related events in the clinical studies (ramucirumab group)

Study	Regimen	Age	Sex	Smoking history	PT (MedDRA/J ver.17.0)	Grade	Seriousness	Time to onset (days)	Number of doses	Duration (days)	Causal relationship to ramucirumab	Action taken to ramucirumab	Outcome
RAISE	Ramucirumab/ FOLFIRI	83	M	Yes	Pneumonitis	2	Non-serious	22	1	-	Related	None	Not recovered
		50*	M	Yes	ILD	3	Serious	164	11	8	Related	Discontinued	Death
						1	Non-serious	172	11	27	Related		
						2	Non-serious	199	11	32	Related		
						3	Serious	231	11	5	Related		
						5	Serious	236	11	1	Related		
		52	M	Yes	Pneumonitis	3	Non-serious	121	8	23	Unrelated	None	Recovered
		59	M	Yes	Lung infiltration	5	Serious	15	1	17	Related	Discontinued	Death
REACH	Ramucirumab	63	M	Unknown	Lung infiltration	1	Non-serious	42	3	-	Unrelated	None	Not recovered
		59	M	Unknown	ILD	3	Non-serious	86	6	-	Unrelated	Discontinued	Not recovered

* Japanese patient

According to the safety data obtained in Japan for the approved indication of gastric cancer (data cut-off, [redacted], 20[redacted]), 9 patients experienced serious ILD-related events (all were ILD). The outcomes of the events were "recovered/resolved" in 5 patients, death in 3 patients, and "unknown" in 1 patient. All these patients received ramucirumab and PTX.

PMDA's view:
The ILD-related events are known to be caused by the drugs used concomitantly with ramucirumab. The RAISE study did not show any clear difference in the incidence of ILD-related events between the ramucirumab/FOLFIRI group and the placebo/FOLFIRI group. Given these observations, it is difficult to clearly determine a relationship between ramucirumab and ILD at present. However, some patients in the ramucirumab/FOLFIRI group of the RAISE study, including 1 Japanese patient, suffered fatal ILD-related events, and a causal relationship to ramucirumab could not be ruled out for the events. The occurrence of ILD-related events should be appropriately communicated to healthcare professionals through the package insert, etc., and the collection of relevant information/data should be continued.

7.R.3 Clinical positioning and indication

The proposed indication of ramucirumab was "unresectable advanced/recurrent colorectal cancer." Also, the "Precautions for Indications" section included the following precautionary advice:

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

PMDA's view:
Based on the reviews and in "7.R.1 Efficacy" and "7.R.2 Safety" as well as the sections below, the proposed indication "unresectable advanced/recurrent colorectal cancer" should be appropriate. Precautionary advice in the "Precautions for Indications" section should be given as follows:

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

- The efficacy and safety of ramucirumab in the first-line therapy 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 and of the efficacy and safety of ramucirumab.

7.R.3.1 Clinical positioning, target patient population, and indication of ramucirumab

Japanese or foreign clinical practice guidelines or internationally recognized clinical oncology textbooks describe ramucirumab for the treatment of unresectable advanced/recurrent CRC as follows:

Clinical practice guidelines

- The NCCN Guidelines (colon cancer, v.2.2016): The use of ramucirumab in combination with FOLFIRI or CPT-11 is recommended as a second-line treatment option for patients with unresectable advanced/recurrent CRC with disease progression after first-line therapy with BV, L-OHP, and a fluoropyrimidine. There are no clinical data suggesting the efficacy or safety of ramucirumab in patients with disease progression after the combination therapy with BV plus FOLFIRI. Ramucirumab should not be used for post-operative adjuvant chemotherapy.

PMDA asked the applicant to explain the clinical positioning of ramucirumab in treatment of unresectable advanced/recurrent CRC, patient population, and indication of ramucirumab.

The applicant's response:

In Japan, patients with unresectable advanced/recurrent CRC who have received FOLFOX or any other non-FOLFIRI chemotherapy as a first-line therapy can have the option of receiving FOLFIRI as a second-line therapy. In this case, the recommended therapy is FOLFIRI in combination with BV or an anti-epidermal growth factor receptor (EGFR) antibody drug (cetuximab [genetical recombination], panitumumab [genetical recombination]). In the RAISE study in patients with unresectable advanced/recurrent CRC with disease progression after treatment with BV, L-OHP, and a fluoropyrimidine, ramucirumab plus FOLFIRI improved OS [see 7.R.1 Efficacy and 7.R.2 Safety]. These results suggest that ramucirumab can be one of therapeutic options for this patient population, as with BV and anti-EGFR antibody drugs.

Based on the above, the proposed indication was "unresectable advanced/recurrent colorectal cancer." Because the RAISE study was conducted in patients with disease progression after the first-line therapy, the "Precautions for Indications" section will include precautionary advice that the efficacy and safety of ramucirumab in first-line therapy have not been established. In the RAISE study, a difference in the primary site of colorectal cancer did not obviously affect the efficacy or safety of ramucirumab. Nevertheless, healthcare professionals should be reminded that the patients enrolled in the study had the primary tumor in the colon or rectum. Precautionary advice on the primary tumor site will be added in the "Precautions for Indications" section.

PMDA's view:

The applicant's explanation was generally acceptable. However, the precautionary advice on the primary tumor site in the "Precautions for Indications" section is unnecessary because this issue has been clearly defined in the indication. On the other hand, first-line therapies used in patients in the RAISE study should be specifically communicated to healthcare professionals. Relevant information should be included in the "Clinical Studies" section of the package insert, along with the following precautionary advice in the "Precautions for Indications" section.

- The efficacy and safety of ramucirumab in first-line therapy 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 and of the efficacy and safety of ramucirumab.

7.R.3.2 Efficacy and safety as a post-operative adjuvant chemotherapy

The applicant explained that no clinical data are available currently on the efficacy or safety of ramucirumab as a post-operative adjuvant chemotherapy, and this will be indicated in the "Precautions for Indications" section.

PMDA accepted the applicant's explanation.

7.R.4 Dosage and administration

The proposed dosage and administration was "The usual adult dosage is 8 mg/kg (body weight) of Ramucirumab (Genetical Recombination) administered as an intravenous infusion over approximately 60 minutes every 2 weeks, in combination with irinotecan hydrochloride hydrate, levofolinate, and fluorouracil. The dose may be adjusted according to the condition of the patient." The "Precautions for Dosage and Administration" section included the following:

- Advice that antineoplastic drugs to be used concomitantly with ramucirumab should be selected by physicians with a good understanding of the descriptions of the "Clinical Studies" section.
- Advice that the package inserts of the concomitant antineoplastic drugs should be read carefully before use.
- Premedication
- Guidelines for infusion rate reduction, treatment interruption, dose reduction, and discontinuation of ramucirumab, and the method of dose reduction
- Preparation method for the injection solution

PMDA's view:

Based on the reviews below and in "7.R.1 Efficacy" and "7.R.2 Safety," the proposed dosage and administration ("The usual adult dosage is 8 mg/kg [body weight] of Ramucirumab [Genetical Recombination] administered as an intravenous infusion over approximately 60 minutes every 2 weeks, in combination with irinotecan hydrochloride hydrate, levofolinate, and fluorouracil. The dose may be adjusted according to the condition of the patient") is acceptable. However, the following precautionary advice should be given in the "Precautions for Dosage and Administration" section.

- Advice that antineoplastic drugs to be used concomitantly with ramucirumab should be selected by physicians with a good understanding of the descriptions of the "Clinical Studies" section.
- Advice that the package inserts of the concomitant antineoplastic drugs should be read carefully before use.
- Premedication
- Guidelines for infusion rate reduction, treatment interruption, dose reduction, and discontinuation of ramucirumab, and the method of dose reduction
- Preparation method for the injection solution

7.R.4.1 Dosage and administration of ramucirumab

The applicant's justification for the dosage and administration of ramucirumab for unresectable advanced/recurrent CRC:

The RAISE study employed the dosage determined based on the results of clinical studies, etc. as mentioned below. The results of the RAISE study demonstrated the clinical benefits of ramucirumab in patients with unresectable advanced/recurrent CRC. Therefore, the dosing regimen employed in the study was proposed as the dosage and administration for ramucirumab.

- In the foreign phase I study (Study I4T-IE-JVBM) in patients with solid cancer, ramucirumab was administered at doses ranging from 2 to 16 mg/kg every 2 weeks. Ramucirumab was well tolerated at all doses below 13 mg/kg, the maximum tolerated dose.
- In Study I4T-IE-JVBM, the exposure to ramucirumab increased more than dose-proportionally within the range from 2 to 6 mg/kg and tended to increase dose-proportionally at ≥8 mg/kg. The results suggested that the VEGFR-2-mediated elimination pathway is saturated at doses of ≥8 mg/kg. Also, the preliminary PK data from in the Japanese phase I study (Study I4T-IE-JVBI) and the foreign phase I study (Study I4T-IE-JVBN) in patients with solid cancer indicated that the trough serum concentration of ramucirumab administered at 8 mg/kg every 2 weeks is estimated to exceed 20 μg/mL, the target trough serum concentration.
- In the phase II and III studies in patients with CRC, FOLFIRI components used concomitantly with ramucirumab were administered every 2 weeks.

PMDA's view:
The proposed dosage and administration of ramucirumab for CRC seems to have room for further investigation, as with the approved dosage and administration for gastric cancer (see "Review Report dated February 16, 2015: Cyramza Injection 100 mg, Cyramza Injection 500 mg"). Nevertheless, in the light of the clinical benefits of ramucirumab observed in the RAISE study that used the above dosage, the proposed dosage and administration is acceptable.

7.R.4.2 Dose adjustment
The applicant's explanation on criteria for infusion rate and dose adjustment for ramucirumab:
The RAISE study demonstrated clinical benefits of ramucirumab with the same infusion rate and dose adjustment criteria as those used in the RAINBOW study in patients with gastric cancer, the approved indication. Therefore, the infusion rate and dose adjustment criteria for gastric cancer were employed also for CRC.

PMDA accepted the applicant's explanation.

7.R.4.3 Concomitant use of antineoplastic drugs other than FOLFIRI
The applicant's explanation on the concomitant use of ramucirumab with antineoplastic drugs other than FOLFIRI:
The concomitant use of ramucirumab with other antineoplastic drugs or therapies than FOLFIRI is not recommended for treatment of patients with unresectable advanced/recurrent CRC, because of no established efficacy or safety of the drug combination. Ramucirumab should be used with FOLFIRI, and this will be included in the "Dosage and Administration" section. Furthermore, the "Precautions for Dosage and Administration" section will advise that antineoplastic drugs to be used concomitantly with ramucirumab should be selected by physicians with a good understanding of the descriptions of the "Clinical Studies" section and that the package inserts of the concomitant antineoplastic drugs should be read carefully before use.

PMDA accepted the applicant's explanation.

7.R.5 Post-marketing investigations
The applicant's explanation on their post-marketing surveillance plan:
In order to evaluate the safety, etc. of ramucirumab in post-marketing clinical use, post-marketing surveillance will be conducted in patients with unresectable advanced/recurrent CRC treated with ramucirumab.

In the plan, the following important identified or potential risks defined in the initial application for ramucirumab (Cyramza) were selected as the key survey items: hypertension, proteinuria, haemorrhage, infusion reaction, arterial thromboembolism, venous thromboembolism, gastrointestinal perforation, cardiac failure congestive, posterior reversible encephalopathy syndrome, fistula, disturbance of wound healing, and liver disorder/hepatic failure.

The planned sample size is 350 patients. It was determined based on the incidence, etc. of gastrointestinal perforation, one of the relevant complications in patients with CRC, in the RAISE study. Given the incidence of each key survey item in the entire population of the RAISE study, the sample size of 350 patients will also allow collecting enough data on key survey items other than gastrointestinal perforation.

The proposed follow-up period is 1 year. It was determined based on the following findings in the RAISE study: (a) most adverse events selected as the key survey items were observed within 1 year after the start of treatment with ramucirumab, and (b) the median treatment duration (range) in the Japanese population was 20.5 (2-106) weeks.

PMDA's view:
(a) There is only limited safety information available on the use of ramucirumab in Japanese patients with CRC. (b) The post-marketing surveillance in patients with unresectable advanced/recurrent gastric cancer, the approved indication, is still underway, and safety data, etc. have not been available yet. (c) Adverse events reported included nephrotic syndrome and ILD, which are known adverse events

requiring particular attention during the treatment with ramucirumab. Given this situation, the post-marketing surveillance should aim to evaluate the safety, etc. of ramucirumab in patients with unresectable, advanced/recurrent CRC in clinical settings in Japan. The outcomes of the surveillance including the safety profile should be communicated to healthcare professionals in an appropriate manner.

Nephrotic syndrome and ILD should be added to the key survey items determined by the applicant. The target sample size and the follow-up period should be reconsidered by taking account of the incidences of these additional key survey items.

7.3 Adverse events, etc. reported in clinical studies

Based on the clinical study data submitted for safety evaluation, deaths reported are summarized in "7.1 Evaluation data" and "7.2 Reference data." The subsections below summarize major adverse events other than death. Because the data of Studies I4T-IE-JVBY and I4T-IE-JVBH were evaluated in support of the initial application (see "Review Report dated February 16, 2015: Cyramza Injection 100 mg, Cyramza Injection 500 mg"), they are omitted from the summaries in this section.

7.3.1 Global phase III study (RAISE study)

Adverse events were observed in 522 of 529 patients (98.7%) in the ramucirumab/FOLFIRI group and in 519 of 528 patients (98.3%) in the placebo/FOLFIRI group. Adverse events for which a causal relationship to the study drug could not be ruled out were observed in 505 of 529 patients (95.5%) in the ramucirumab/FOLFIRI group and in 501 of 528 patients (94.9%) in the placebo/FOLFIRI group. Table 16 shows adverse events with an incidence of ≥20% in either group.

Table 16. Adverse events with an incidence of ≥20% in either group

System organ class Preferred term (MedDRA/J ver.17.0)	Number of patients (%)			
	Ramucirumab/FOLFIRI (N = 529)		Placebo/FOLFIRI (N = 528)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	522 (98.7)	418 (79.0)	519 (98.3)	329 (62.3)
Gastrointestinal disorders				
Diarrhoea	316 (59.7)	57 (10.8)	271 (51.3)	51 (9.7)
Nausea	262 (49.5)	13 (2.5)	271 (51.3)	14 (2.7)
Stomatitis	163 (30.8)	20 (3.8)	110 (20.8)	12 (2.3)
Vomiting	154 (29.1)	15 (2.8)	144 (27.3)	13 (2.5)
Constipation	151 (28.5)	5 (0.9)	120 (22.7)	8 (1.5)
Abdominal pain	118 (22.3)	16 (3.0)	112 (21.2)	18 (3.4)
General disorders and administration site conditions				
Fatigue	247 (46.7)	42 (7.9)	219 (41.5)	27 (5.1)
Oedema peripheral	108 (20.4)	1 (0.2)	48 (9.1)	0
Respiratory, thoracic and mediastinal disorders				
Epistaxis	177 (33.5)	0	79 (15.0)	0
Skin and subcutaneous tissue disorders				
Alopecia	155 (29.3)	0	165 (31.3)	0
Investigations				
Neutrophil count decreased	137 (25.9)	92 (17.4)	115 (21.8)	64 (12.1)
Blood and lymphatic system disorders				
Neutropenia	188 (35.5)	115 (21.7)	131 (24.8)	59 (11.2)
Anaemia	84 (15.9)	8 (1.5)	109 (20.6)	18 (3.4)
Metabolism and nutrition disorders				
Decreased appetite	198 (37.4)	13 (2.5)	144 (27.3)	10 (1.9)
Vascular disorders				
Hypertension	136 (25.7)	57 (10.8)	45 (8.5)	15 (2.8)

Serious adverse events were observed in 189 of 529 patients (35.7%) in the ramucirumab/FOLFIRI group and 164 of 528 patients (31.1%) in the placebo/FOLFIRI group. Serious adverse events with an incidence of ≥1% in the ramucirumab/FOLFIRI group were diarrhoea in 19 patients (3.6%), febrile neutropenia in 15 patients (2.8%), vomiting in 12 patients (2.3%), pulmonary embolism in 10 patients (1.9%), abdominal pain, decreased appetite, and intestinal obstruction in 7 patients (1.3%) each, nausea, neutropenia, pneumonia, and small intestinal obstruction in 6 patients (1.1%) each; and those in the

placebo/FOLFIRI group were diarrhoea in 17 patients (3.2%), abdominal pain in 12 patients (2.3%), intestinal obstruction in 9 patients (1.7%), febrile neutropenia in 8 patients (1.5%), sepsis in 7 patients (1.3%), vomiting, pulmonary embolism, pneumonia, pyrexia, and dehydration in 6 patients (1.1%) each. A causal relationship to the study drug could not be ruled out for diarrhoea in 16 patients, febrile neutropenia in 13 patients, vomiting in 9 patients, pulmonary embolism in 7 patients, neutropenia in 6 patients, decreased appetite and nausea in 4 patients each, pneumonia in 3 patients, and intestinal obstruction in 1 patient in the ramucirumab/FOLFIRI group; and diarrhoea in 16 patients, febrile neutropenia in 7 patients, vomiting in 5 patients, pulmonary embolism and sepsis in 4 patients each, pyrexia in 3 patients, pneumonia and dehydration in 2 patients each, and abdominal pain in 1 patient in the placebo/FOLFIRI group.

Adverse events led to the discontinuation of the study drug in 197 of 529 patients (37.2%) in the ramucirumab/FOLFIRI group and 89 of 528 patients (16.9%) in the placebo/FOLFIRI group. Adverse events leading to discontinuation with an incidence of ≥1% in the ramucirumab/FOLFIRI group were neutrophil count decreased in 37 patients (7.0%), neutropenia in 30 patients (5.7%), thrombocytopenia in 16 patients (3.0%), diarrhoea and platelet count decreased in 13 patients (2.5%) each, stomatitis in 12 patients (2.3%), proteinuria in 11 patients (2.1%), mucosal inflammation in 10 patients (1.9%), and fatigue in 8 patients (1.5%); and those in the placebo/FOLFIRI group were neutrophil count decreased in 18 patients (3.4%), neutropenia in 11 patients (2.1%), diarrhoea in 9 patients (1.7%), and stomatitis in 6 patients (1.1%). A causal relationship to the study drug could not be ruled out for all these events except for neutrophil count decreased and proteinuria in 1 patient each in the ramucirumab/FOLFIRI group.

7.3.2 Global phase III study (REACH study)

7.3.2.1 Patients of Child-Pugh class A

Adverse events were observed in 270 of 277 patients (97.5%) in the ramucirumab group and 260 of 276 patients (94.2%) in the placebo group. Adverse events for which a causal relationship to the study drug could not be ruled out were observed in 238 of 277 patients (85.9%) in the ramucirumab group and 209 of 276 patients (75.7%) in the placebo group. Table 17 shows adverse events with an incidence of ≥20% in either group.

Table 17. Adverse events with an incidence of ≥20% in either group

System organ class Preferred term (MedDRA/J ver.16.1)	Number of patients (%)			
	Ramucirumab (N = 277)		Placebo (N = 276)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	270 (97.5)	172 (62.1)	260 (94.2)	132 (47.8)
Gastrointestinal disorders				
Abdominal pain	47 (17.0)	5 (1.8)	62 (22.5)	12 (4.3)
Ascites	74 (26.7)	13 (4.7)	40 (14.5)	11 (4.0)
General disorders and administration site conditions				
Fatigue	64 (23.1)	6 (2.2)	58 (21.0)	8 (2.9)
Oedema peripheral	101 (36.5)	1 (0.4)	50 (18.1)	1 (0.4)
Metabolism and nutrition disorders				
Decreased appetite	61 (22.0)	5 (1.8)	50 (18.1)	2 (0.7)

Serious adverse events were observed in 122 of 277 patients (44.0%) in the ramucirumab group and 89 of 276 patients (32.2%) in the placebo group. Serious adverse events with an incidence of ≥1% in the ramucirumab group were malignant neoplasm progression in 19 patients (6.9%), hepatic encephalopathy in 12 patients (4.3%), general physical health deterioration in 8 patients (2.9%), gastrointestinal haemorrhage and pyrexia in 7 patients (2.5%) each, ascites in 6 patients (2.2%), cholangitis and hepatic failure in 5 patients (1.8%) each, abdominal pain and asthenia in 4 patients (1.4%) each, decreased appetite, hepatorenal syndrome, oesophageal varices haemorrhage, pneumonia, acute renal failure, sepsis, and urinary tract infection in 3 patients (1.1%) each; and those in the placebo group were malignant neoplasm progression in 12 patients (4.3%), oesophageal varices haemorrhage in 10 patients (3.6%), abdominal pain in 9 patients (3.3%), hepatic failure in 5 patients (1.8%), tumour pain in 4 patients (1.4%), general physical health deterioration, pyrexia, ascites, pneumonia, pleural effusion, and back pain in 3 patients (1.1%) each. A causal relationship to the study drug could not be ruled out for

hepatic encephalopathy in 7 patients, gastrointestinal haemorrhage in 5 patients, hepatic failure in 4 patients, general physical health deterioration and pyrexia in 3 patients each, abdominal pain, asthenia, oesophageal varices haemorrhage, acute renal failure, and urinary tract infection in 2 patients each, malignant neoplasm progression, ascites, cholangitis, decreased appetite, hepatorenal syndrome, pneumonia, and sepsis in 1 patient each in the ramucirumab group; and oesophageal varices haemorrhage in 5 patients, pneumonia in 3 patients, malignant neoplasm progression, abdominal pain, and ascites in 2 patients each, hepatic failure, general physical health deterioration, pyrexia, and pleural effusion in 1 patient each in the placebo group.

Adverse events led to the discontinuation of the study drug in 59 of 277 patients (21.3%) in the ramucirumab group and 26 of 276 patients (9.4%) in the placebo group. Adverse events leading to study drug discontinuation with an incidence of ≥1% in the ramucirumab group were proteinuria in 7 patients (2.5%), hepatic encephalopathy in 6 patients (2.2%), malignant neoplasm progression in 5 patients (1.8%), and asthenia in 3 patients (1.1%); and those in the placebo group were oesophageal varices haemorrhage in 7 patients (2.5%) and fatigue in 3 patients (1.1%). A causal relationship to the study drug could not be ruled out for proteinuria in 7 patients, hepatic encephalopathy in 6 patients, and asthenia in 2 patients in the ramucirumab group; and oesophageal varices haemorrhage in 4 patients and fatigue in 1 patient in the placebo group.

7.3.2.2 Patients of Child-Pugh class B

Adverse events were observed in 40 of 40 patients (100%) in the ramucirumab group and 36 of 37 patients (97.3%) in the placebo group. Adverse events for which a causal relationship to the study drug could not be ruled out were observed in 35 of 40 patients (87.5%) in the ramucirumab group and 26 of 37 patients (70.3%) in the placebo group.

Adverse events with an incidence of ≥20% in the ramucirumab group were decreased appetite in 18 patients (45.0%), oedema peripheral in 17 patients (42.5%), nausea in 16 patients (40.0%), ascites and epistaxis in 12 patients (30.0%) each, vomiting in 11 patients (27.5%), diarrhoea, asthenia, and fatigue in 10 patients (25.0%) each, thrombocytopenia, abdominal pain, pyrexia, and hypoalbuminaemia in 8 patients (20.0%) each; and those in the placebo group were ascites in 9 patients (24.3%), nausea and malignant neoplasm progression in 8 patients (21.6%) each. Grade ≥3 events were ascites in 6 patients, asthenia in 4 patients, decreased appetite, fatigue, and hypoalbuminaemia in 3 patients each, and thrombocytopenia and abdominal pain in 2 patients each in the ramucirumab group; and malignant neoplasm progression in 8 patients and ascites in 7 patients in the placebo group.

Serious adverse events were observed in 27 of 40 patients (67.5%) in the ramucirumab group and 16 of 37 patients (43.2%) in the placebo group. Serious adverse events reported by ≥2 patients in the ramucirumab group were malignant neoplasm progression in 7 patients (17.5%), general physical health deterioration in 4 patients (10.0%), hepatic encephalopathy in 3 patients (7.5%), ascites, asthenia, and oesophageal varices haemorrhage in 2 patients (5.0%) each; and those in the placebo group were malignant neoplasm progression in 8 patients (21.6%) and sepsis in 3 patients (8.1%). A causal relationship to the study drug could not be ruled out for malignant neoplasm progression in 2 patients, general physical health deterioration, hepatic encephalopathy, and oesophageal varices haemorrhage in 1 patient each in the ramucirumab group; and malignant neoplasm progression and sepsis in 1 patient each in the placebo group.

Adverse events led to the discontinuation of the study drug in 10 of 40 patients (25.0%) in the ramucirumab group and 9 of 37 patients (24.3%) in the placebo group. Adverse events leading to study drug discontinuation reported by ≥2 patients in the ramucirumab group were general physical health deterioration, hepatic encephalopathy, malignant neoplasm progression, and oesophageal varices haemorrhage in 2 patients (5.0%) each. A causal relationship to the study drug could not be ruled out for general physical health deterioration and oesophageal varices haemorrhage in 1 patient each in the ramucirumab group.

7.3.3 Foreign phase II study (Study I4T-IE-JVCB)

Adverse events were observed in all patients, and those for which a causal relationship to the study drug could not be ruled out were observed in 28 of 29 patients (96.6%). Table 18 shows adverse events with

an incidence of ≥20%.

Table 18. Adverse events with an incidence of ≥20%

System organ class Preferred term (MedDRA/J ver.15.0)	Number of patients (%) (N = 29)	
	All Grades	Grade ≥3
All adverse events	29 (100)	13 (44.8)
Blood and lymphatic system disorders		
Anaemia	13 (44.8)	1 (3.4)
Neutropenia	13 (44.8)	5 (17.2)
Gastrointestinal disorders		
Abdominal pain	9 (31.0)	0
Constipation	9 (31.0)	0
Diarrhoea	16 (55.2)	1 (3.4)
Nausea	14 (48.3)	0
Vomiting	7 (24.1)	0
General disorders and administration site conditions		
Fatigue	19 (65.5)	0
Mucosal inflammation	7 (24.1)	0
Investigations		
Blood alkaline phosphatase increased	7 (24.1)	0
Metabolism and nutrition disorders		
Decreased appetite	13 (44.8)	0
Hyperglycaemia	6 (20.7)	1 (3.4)
Hypoalbuminaemia	10 (34.5)	0
Respiratory, thoracic and mediastinal disorders		
Cough	7 (24.1)	0
Epistaxis	6 (20.7)	0

Serious adverse events were observed in 4 of 29 patients (13.8%). They were diarrhoea, large intestinal obstruction, pneumonia, dehydration, metastases to central nervous system, hallucination, dyspnoea, and respiratory failure in 1 patient (3.4%) each. A causal relationship to the study drug could not be ruled out for diarrhoea, pneumonia, dehydration, and respiratory failure in 1 patient each.

Adverse events led to the discontinuation of the study drug in 6 of 29 patients (20.7%). They were platelet count decreased, infusion related reaction, respiratory failure, palmar-plantar erythrodysaesthesia syndrome, large intestinal obstruction, and diarrhoea in 1 patient (3.4%) each. A causal relationship to the study drug could not be ruled out for infusion related reaction, respiratory failure, palmar-plantar erythrodysaesthesia syndrome, and diarrhoea in 1 patient each.

7.3.4 Foreign phase II study (Study I4Y-IE-JCDB)

Adverse events were observed in all patients in both the mFOLFOX6 group and the ramucirumab/mFOLFOX6 group. Adverse events for which a causal relationship to the study drug could not be ruled out were observed in 48 of 49 patients (98.0%) in the mFOLFOX6 group and in all patients in the ramucirumab/mFOLFOX6 group. Table 19 shows adverse events with an incidence of ≥20% in either group.

Table 19. Adverse events with an incidence of ≥20% in either group

System organ class Preferred term (MedDRA/J ver.12.0)	Number of patients (%)			
	mFOLFOX6 (N = 49)		Ramucirumab/mFOLFOX6 (N = 52)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	49 (100)	30 (61.2)	52 (100)	37 (71.2)
Blood and lymphatic system disorders				
Neutropenia	16 (32.7)	9 (18.4)	16 (30.8)	9 (17.3)
Thrombocytopenia	12 (24.5)	0	9 (17.3)	3 (5.8)
Gastrointestinal disorders				
Nausea	31 (63.3)	2 (4.1)	24 (46.2)	0
Vomiting	18 (36.7)	3 (6.1)	13 (25.0)	0
Diarrhoea	19 (38.8)	0	30 (57.7)	4 (7.7)
Abdominal pain	14 (28.6)	3 (6.1)	16 (30.8)	1 (1.9)
Constipation	12 (24.5)	0	18 (34.6)	0
Stomatitis	12 (24.5)	0	19 (36.5)	0
General disorders and administration site conditions				
Fatigue	35 (71.4)	6 (12.2)	45 (86.5)	12 (23.1)
Oedema peripheral	5 (10.2)	0	15 (28.8)	1 (1.9)
Temperature intolerance	21 (42.9)	0	13 (25.0)	0
Pyrexia	11 (22.4)	0	9 (17.3)	0
Investigations				
Weight decreased	7 (14.3)	0	14 (26.9)	0
Metabolism and nutrition disorders				
Anorexia	16 (32.7)	2 (4.1)	20 (38.5)	0
Nervous system disorders				
Peripheral sensory neuropathy	27 (55.1)	3 (6.1)	25 (48.1)	4 (7.7)
Neuropathy peripheral	12 (24.5)	1 (2.0)	12 (23.1)	2 (3.8)
Headache	8 (16.3)	0	16 (30.8)	0
Respiratory, thoracic and mediastinal disorders				
Dyspnoea	4 (8.2)	0	11 (21.2)	2 (3.8)
Cough	9 (18.4)	0	16 (30.8)	0
Epistaxis	5 (10.2)	0	14 (26.9)	0
Skin and subcutaneous tissue disorders				
Rash	3 (6.1)	0	15 (28.8)	0
Vascular disorders				
Hypertension	1 (2.0)	1 (2.0)	15 (28.8)	7 (13.5)

Serious adverse events were observed in 11 of 49 patients (22.4%) in the mFOLFOX6 group and 17 of 52 patients (32.7%) in the ramucirumab/mFOLFOX6 group. Serious adverse events reported in the mFOLFOX6 group were vomiting and sepsis in 2 patients (4.1%) each, febrile neutropenia, cataract, nausea, abdominal pain, large intestine perforation, small intestinal obstruction, infusion related reaction, bile duct stenosis, neutropenic infection, hydronephrosis, and ureteric obstruction in 1 patient (2.0%) each; and those in the ramucirumab/mFOLFOX6 group were fatigue and bile duct obstruction in 2 patients (3.8%) each, febrile neutropenia, acute myocardial infarction, abdominal pain, constipation, diarrhoea, hepatic failure, cystitis, device related infection, enterocolitis infectious, urinary tract infection, medication error, hyponatraemia, neoplasm progression, cerebrovascular accident, nephrotic syndrome, acute renal failure, urinary retention, pleural effusion, pulmonary embolism, dyspnoea, and embolism in 1 patient (1.9%) each. A causal relationship to the study drug could not be ruled out for vomiting and sepsis in 2 patients each, febrile neutropenia, nausea, infusion related reaction, and neutropenic infection in 1 patient each in the mFOLFOX6 group; and fatigue in 2 patients, bile duct obstruction, febrile neutropenia, acute myocardial infarction, abdominal pain, constipation, diarrhoea, cystitis, enterocolitis infectious, urinary tract infection, hyponatraemia, cerebrovascular accident, nephrotic syndrome, urinary retention, pleural effusion, pulmonary embolism, and embolism in 1 patient each in the ramucirumab/mFOLFOX6 group.

Adverse events led to the discontinuation of the study drug in 6 of 49 patients (12.2%) in the mFOLFOX6 group and 18 of 52 patients (34.6%) in the ramucirumab/mFOLFOX6 group. Adverse events leading to discontinuation in the mFOLFOX6 group were fatigue, infusion related reaction, blood bilirubin increased, platelet count decreased, neuropathy peripheral, and neurotoxicity in 1 patient

(2.0%) each; and those in the ramucirumab/mFOLFOX6 group were neutropenia and fatigue in 2 patients (3.8%) each, anaemia, thrombocytopenia, acute myocardial infarction, vitreous haemorrhage, diarrhoea, asthenia, non-cardiac chest pain, device related infection, eye infection, cerebrovascular accident, neuropathy peripheral, peripheral sensory neuropathy, nephrotic syndrome, proteinuria, dyspnoea, pleural effusion, skin ulcer, and hypertension in 1 patient (1.9%) each. A causal relationship to the study drug could not be ruled out for fatigue, infusion related reaction, blood bilirubin increased, platelet count decreased, neuropathy peripheral, and neurotoxicity in 1 patient each in the mFOLFOX6 group; and neutropenia and fatigue in 2 patients each, anaemia, thrombocytopenia, acute myocardial infarction, vitreous haemorrhage, diarrhoea, asthenia, non-cardiac chest pain, cerebrovascular accident, neuropathy peripheral, peripheral sensory neuropathy, nephrotic syndrome, proteinuria, and hypertension in 1 patient each in the ramucirumab/mFOLFOX6 group.

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

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

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

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

The new drug application data (CTD 5.3.5.1.1) were subjected to an on-site Good Clinical Practice (GCP) inspection in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. PMDA concluded that the clinical studies as a whole were conducted in compliance with GCP and that there should be no obstacles to conducting its review based on the application documents submitted. The inspection revealed a finding (as mentioned below) at a study site (medical institution) although it did not significantly affect the overall evaluation of the study. The matter was notified to the head of the pertinent medical institution for improvement.

Matters to be improved

Medical institution

- Protocol deviation (incompliance with the requirements for reporting serious adverse events)

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

PMDA has concluded that the data submitted demonstrate the efficacy of ramucirumab (Cyramza) in the treatment of patients with unresectable advanced/recurrent CRC and acceptable safety in view of the benefits indicated. Ramucirumab is of clinical significance and can be a therapeutic option for unresectable advanced/recurrent CRC. Also, the efficacy of the product and post-marketing investigations should be further discussed.

This application may be approved if ramucirumab is not considered to have particular problems based on comments from the Expert Discussion.

Review Report (2)

April 8, 2016

Product Submitted for Approval

Brand Name	Cyramza Injection 100 mg
	Cyramza Injection 500 mg
Non-proprietary Name	Ramucirumab (Genetical Recombination)
Applicant	Eli Lilly Japan K.K.
Date of Application	May 26, 2015

1. Content of the Review

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

1.1 Efficacy

PMDA's conclusions:

As reviewed in "7.R.1 Efficacy" of the Review Report (1), overall survival (OS) was assessed as the primary endpoint of the global phase III study (Study I4T-MC-JVBB [RAISE study]) in patients with unresectable advanced/recurrent colorectal cancer (CRC) with disease progression after treatment with bevacizumab (genetical recombination), oxaliplatin, and a fluoropyrimidine. Ramucirumab (Genetical Recombination) (hereinafter referred to as "ramucirumab") plus FOLFIRI (folinate, fluorouracil, and irinotecan hydrochloride hydrate) (ramucirumab/FOLFIRI) achieved a significant improvement in OS as compared with placebo plus FOLFIRI (placebo/FOLFIRI) used as the control. Thus, the study demonstrated the efficacy of ramucirumab in this patient population, and the applicant's view on the efficacy of ramucirumab in Japanese patients with unresectable advanced/recurrent CRC is generally acceptable.

The above conclusions of PMDA were supported by the expert advisors at the Expert Discussion. The following comment was raised by expert advisors:

- Preferably, the use of postdiscontinuation anticancer therapies in the RAISE study in Japan and foreign countries should be clarified in detail and appropriately communicated to healthcare professionals.

PMDA's view:

Information on the use of postdiscontinuation anticancer therapies in the RAISE study in Japan and foreign countries should be appropriately provided to healthcare professionals through written materials, etc.

Accordingly, PMDA advised the applicant to take appropriate actions on this matter, and the applicant agreed.

1.2 Safety

PMDA's conclusions:

As reviewed in "7.R.2 Safety" of the Review Report (1), nephrotic syndrome and interstitial lung disease (ILD) are adverse events requiring particular attention during the treatment with ramucirumab, in addition to those identified at the review of the initial application (hypertension, proteinuria, haemorrhage, infusion-related reaction, thromboembolism, gastrointestinal perforation, cardiac failure congestive, neutropenia/leukopenia, posterior reversible encephalopathy syndrome, fistula, disturbance of wound healing, and liver disorder).

Ramucirumab is well tolerated when patients are followed by physicians with sufficient knowledge of and experience with cancer chemotherapy, through monitoring and control of adverse events as well as appropriate measures such as treatment interruption, dose reduction, and discontinuation of treatment.

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

1.3 Clinical positioning and indication

PMDA's conclusions:

As reviewed in "7.R.3 Clinical positioning and indication" of the Review Report (1), ramucirumab is a therapeutic option for patients eligible for enrollment in the RAISE study. Ramucirumab should be indicated for "unresectable advanced/recurrent colorectal cancer," as proposed by the applicant. The types of first-line therapies given to patients enrolled in the RAISE study should be specifically mentioned in the "Clinical Studies" section of the package insert. The following precautionary advice should be given in the "Precautions for Indications" section.

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

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

Accordingly, PMDA advised the applicant to describe the "Indication" and "Precautions for Indication" sections as above, and the applicant agreed.

1.4 Dosage and administration

PMDA's conclusions:

As reviewed in "7.R.4 Dosage and administration" of the Review Report (1), the following proposed descriptions of the "Dosage and Administration" and "Precautions for Dosage and Administration" sections are acceptable.

[Dosage and Administration]

The usual adult dosage is 8 mg/kg (body weight) of Ramucirumab (Genetical Recombination) administered as an intravenous infusion over approximately 60 minutes every 2 weeks, in combination with irinotecan hydrochloride hydrate, levofolinate, and fluorouracil. The dose may be adjusted according to the condition of the patient.

[Precautions for Dosage and Administration]

- Advice that antineoplastic drugs to be used concomitantly with ramucirumab should be selected by physicians with a good understanding of the descriptions of the "Clinical Studies" section.
- Advice that the package inserts of the concomitant antineoplastic drugs should be read carefully before use.
- Premedication
- Guidelines for infusion rate reduction, dose interruption, dose reduction, and discontinuation of ramucirumab, and the method of dose reduction
- Preparation method for the injection solution

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

Accordingly, PMDA advised the applicant to describe the "Dosage and Administration" and "Precautions for Dosage and Administration" sections as above, and the applicant agreed.

1.5 Risk management plan (draft)

In order to investigate the safety of ramucirumab in post-marketing clinical use, the applicant plans to conduct post-marketing surveillance targeting patients with CRC who are treated with ramucirumab.

PMDA's conclusions:

As reviewed in "7.R.5 Post-marketing investigations" of the Review Report (1), post-marketing surveillance should be conducted to evaluate the safety, etc. of ramucirumab in clinical use. Any safety findings should be appropriately communicated to healthcare professionals.

The following should be noted in planning of the surveillance:

- Nephrotic syndrome and ILD should be added to the key survey items identified by the applicant.
- The target sample size and the follow-up period should be reconsidered taking account of the occurrence, etc. of the adverse events identified additionally as the key survey items.

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

Accordingly, PMDA advised the applicant to reconsider the surveillance plan.

The applicant's response:

- Nephrotic syndrome and ILD will be added to the key survey items.
- The target sample size of 350 patients and the follow-up period of 1 year will be employed, taking account of the incidence and time to onset of the adverse events added to the key survey items.

PMDA accepted the response of the applicant.

In view of the discussion above, PMDA has concluded that the risk management plan (draft) for ramucirumab should include safety and efficacy specifications presented in Table 20, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Table 21.

Table 20. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Hypertension • Proteinuria/nephrotic syndrome • Haemorrhage • Infusion reaction • Arterial thromboembolism • Venous thromboembolism • Gastrointestinal perforation • Congestive cardiac failure • Neutropenia/leukopenia • Posterior reversible encephalopathy syndrome • Fistula • Disturbance of wound healing	• Liver disorder/hepatic failure • ILD	• N/A
Efficacy specification (matters related to the present application for partial change)		
• Efficacy in patients with unresectable advanced/recurrent CRC in routine clinical use		

Table 21. Summary of additional pharmacovigilance activities and risk minimization activities under the risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimization activities
• Specified use-results survey in patients with unresectable advanced/recurrent CRC • Specified use-results survey in patients with unresectable advanced/recurrent gastric cancer	• Preparation and supply of materials for healthcare professionals

Underlines denote planned activities for the additional indication in the present application.

Table 22. Outline of use-results survey (draft)

Objective	To evaluate safety, etc., of ramucirumab in clinical use
Survey method	Continuous registration
Population	Patients with unresectable advanced/recurrent CRC
Observation period	1 year after the start of treatment
Planned sample size	350 patients
Main survey items	Key survey items: Hypertension, proteinuria/nephrotic syndrome, haemorrhage, infusion reaction, arterial thromboembolism, venous thromboembolism, gastrointestinal perforation, congestive cardiac failure, posterior reversible encephalopathy syndrome, fistula, disturbance of wound healing, liver disorder/hepatic failure, and ILD Other main survey items: Patient characteristics (body weight, medical history, complications, presence/absence of the primary lesion and the site of the primary lesion, clinical stage, presence/absence of metastatic lesions/recurrent lesions and the site of lesions, etc.), treatment history, use of ramucirumab, concomitant drugs and therapies, postdiscontinuation anticancer therapy, survival status, adverse events, etc.

2. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the indication and dosage and administration modified as below, with the following conditions for approval. However, (i) the package insert should include appropriate precautionary advice and information on the proper use of the product should be adequately communicated to healthcare professionals in the post-marketing setting, and (ii) the product should be properly used by physicians with adequate knowledge of and experience with cancer chemotherapy at medical institutions well-prepared for emergencies. The re-examination period for the present application is the remainder of the 8-year re-examination period for the initial approval of the product (until March 25, 2023).

[Indications] (Underline denotes addition.)
Unresectable advanced/recurrent gastric cancer
Unresectable advanced/recurrent colorectal cancer

[Dosage and administration] (Underline denotes addition.)
1. Unresectable advanced/recurrent gastric cancer
The usual adult dosage is 8 mg/kg (body weight) of Ramucirumab (Genetical Recombination) administered as an intravenous infusion over approximately 60 minutes every 2 weeks. The dose may be adjusted according to the condition of the patient.

2. Unresectable advanced/recurrent colorectal cancer
The usual adult dosage is 8 mg/kg (body weight) of Ramucirumab (Genetical Recombination) administered as an intravenous infusion over approximately 60 minutes every 2 weeks, in combination with irinotecan hydrochloride hydrate, levofolinate, and fluorouracil. The dose may be adjusted according to the condition of the patient.

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

[Warnings] (Unchanged)
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.

[Contraindications] (Unchanged)
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] (Underline denotes addition.)
1. The efficacy and safety of ramucirumab in post-operative adjuvant chemotherapy have not been established.

2. The efficacy and safety of ramucirumab in the first-line chemotherapy have not been established.

3. For unresectable advanced/recurrent gastric cancer, 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. For unresectable advanced/recurrent colorectal cancer, eligibility of the patient for the treatment should be determined based on good understanding of the description in the "Clinical Studies" section and of the efficacy and safety of ramucirumab.

[Precautions for dosage and administration] (Underline denotes addition, and strike-through denotes deletion.)
1. For unresectable advanced/recurrent gastric cancer, the efficacy and safety of ramucirumab in combination with antineoplastic drugs other than paclitaxel have not been established.

2. For unresectable advanced/recurrent colorectal cancer, antineoplastic drugs to be used with ramucirumab should be selected by physicians with a good understanding of the descriptions of the "Clinical Studies" section.

3. The package inserts of the concomitant antineoplastic drugs should be read carefully before use.

~~2~~4. For the purpose of mitigating infusion reactions associated with ramucirumab, premedication 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 reactions recurs even with the premedication, an antipyretic analgesic (e.g., acetaminophen) and a corticosteroid (e.g., dexamethasone) should be administered in addition to the antihistaminic drug before ramucirumab.

~~3~~5. 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 a 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~~6. 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 ≥3	Give anti-hypertensive treatment. Interrupt treatment with ramucirumab until blood pressure is appropriately controlled. 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 (ver.4.0)
[Note 2)]: An all-urine test with 24-hour urine collection is desirable. If infeasible, protein/creatinine ratio in urine should be determined.

~~5~~7. 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.