Report on the Deliberation Results

March 15, 2013

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

[Brand name]	Stivarga Tablets 40 mg
[Non-proprietary name]	Regorafenib Hydrate (JAN*)
[Applicant]	Bayer Yakuhin, Ltd.
[Date of application]	July 31, 2012

[Results of deliberation]
In the meeting held on March 13, 2013, the Second Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The product is not classified as a biological product or a specified biological product, the re-examination period is 8 years, and both the drug substance and drug product are classified as powerful drugs.

**Japanese Accepted Name (modified INN)*

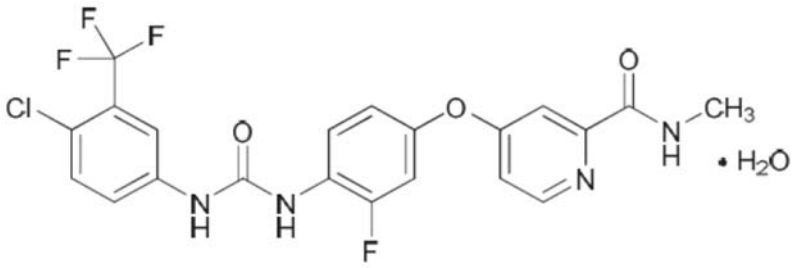
Review Report

March 4, 2013
Pharmaceuticals and Medical Devices Agency

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

[Brand name]	Stivarga Tablets 40 mg
[Non-proprietary name]	Regorafenib Hydrate
[Applicant]	Bayer Yakuhin, Ltd.
[Date of application]	July 31, 2012
[Dosage form/strength]	Each tablet contains 40 mg of regorafenib (41.49 mg as regorafenib hydrate).
[Application classification]	Prescription drugs (1) Drugs with a new active ingredient

[Chemical structure]



Molecular formula: $C_{21}H_{15}ClF_4N_4O_3 \cdot H_2O$
Molecular weight: 500.83
Chemical name:
4-[4-({[4-Chloro-3-(trifluoromethyl)phenyl]carbamoyl}amino)-3-fluorophenoxy]-*N*-methylpyridine-2-carboxamide monohydrate

[Items warranting special mention]
Priority Review (PFSB/ELD Notification No. 0830-8 dated August 30, 2012)

[Reviewing office] Office of New Drug V

Review Results

March 4, 2013

[Brand name]	Stivarga Tablets 40 mg
[Non-proprietary name]	Regorafenib Hydrate
[Applicant]	Bayer Yakuhin, Ltd.
[Date of application]	July 31, 2012

[Results of review]
Based on the submitted data, it is concluded that the efficacy of the product in patients with incurable, unresectable, advanced/recurrent colorectal cancer has been demonstrated, and its safety is acceptable in view of its observed benefits. In usage conditions of the product, the situations leading to dose interruption, dose reduction, and discontinuation of the product, time of onset of events, and safety of concomitant use with drugs having the pharmacokinetic interaction potential need to be further investigated via post-marketing surveillance.

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

[Indication]	Incurable, unresectable, advanced/recurrent colorectal cancer
[Dosage and administration]	The usual adult dosage is 160 mg of regorafenib orally administered once daily after a meal for 3 weeks followed by 1-week off therapy. The above regimen should be repeated in a 4-week cycle. The dose may be reduced according to the patient's condition.

Review Report (1)

December 28, 2012

I. Product Submitted for Registration

[Brand name]	Stivarga Tablets 40 mg
[Non-proprietary name]	Regorafenib Hydrate
[Applicant]	Bayer Yakuhin, Ltd.
[Date of application]	July 31, 2012
[Dosage form/strength]	Each tablet contains 40 mg of regorafenib (41.49 mg as regorafenib hydrate).
[Proposed indication]	Incurable, unresectable, advanced/recurrent colorectal cancer
[Proposed dosage and administration]	The usual adult dosage is 160 mg of regorafenib orally administered once daily for 3 weeks followed by 1-week off therapy. The above regimen should be repeated in a 4-week cycle. The dose may be reduced according to the patient's condition.

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

A summary of the submitted data and an outline of the review by the Pharmaceuticals and Medical Devices Agency (PMDA) are as shown below.

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

1.(1) Product Submitted for Registration

Regorafenib hydrate (hereinafter referred to as regorafenib) has a chemical structure similar to that of sorafenib tosilate, a biaryl urea substance, and was discovered by Bayer HealthCare as a chemical compound that inhibits multiple tyrosine kinases. Regorafenib is expected to suppress tumor growth by inhibiting phosphorylation mediated by kinases such as vascular endothelial growth factor receptor (VEGFR) and angiopoietin receptor (TIE2), which are potentially involved in tumor angiogenesis, platelet-derived growth factor receptor (PDGFR) and fibroblast growth factor receptor (FGFR), which are potentially involved in tumor extension in a microenvironment of the tumor tissue, and stem cell growth factor receptor (KIT), RET, and BRAF, etc., which are potentially involved in tumor growth.

1.(2) Development history etc.

A foreign phase I study (Study 11650) was conducted in patients with solid tumor, starting in [redacted] 20[redacted] by Bayer HealthCare. Then, multiple phase II studies were initiated in patients with non-colorectal solid tumor. In [redacted] 20[redacted], the phase III study (Study 14387) was initiated in 15 countries including Japan in patients with colorectal cancer who have progressed after standard chemotherapy (which includes fluoropyrimidine oxaliplatin, irinotecan hydrochloride, and bevacizumab [genetical recombination], and cetuximab [genetical recombination] or panitumumab [genetical recombination] for patients with wild-type Kirsten rat sarcoma 2 viral oncogene homolog [*KRAS*] gene in the tumor tissue).

In Japan, the applicant initiated the phase I study (Study 13172) in patients with solid tumor in [redacted] 20[redacted] after initiation of the above foreign phase II study. Around the time when Study 14387 was initiated overseas, patient enrollment in the phase III study was also started in Japan.

In the US and EU, the application for the approval of regorafenib was filed in April 2012 and [redacted], respectively, using data from Study 14387 as the pivotal study. In the US, regorafenib was

approved in September 2012 for the indication stating that "Stivarga is a kinase inhibitor indicated for the treatment of patients with metastatic colorectal cancer (CRC) who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF therapy, and, if KRAS wild type, an anti-EGFR therapy." In the EU, it was under review as of [redacted] 20[redacted].

In Japan, the application for the approval of regorafenib was filed in July 2012, using data from Study 14387 as the pivotal study.

2. Data relating to quality

2.A. Summary of the submitted data

2.A.(1) Drug substance

2.A.(1).1) Characterization

The drug substance occurs as a white to pale light red or pale brownish powder. The description, solubility, hygroscopicity, acid dissociation constant, partition coefficient, and crystalline polymorphism have been determined. While a total of 4 crystal forms including one hydrate form have been identified as polymorphism of the drug substance, only the monohydrate form is produced in the commercial manufacturing process. This form has been confirmed to be stable at room temperature.

The chemical structure of the drug substance has been determined by elemental analysis, mass spectrometry (MS), ultraviolet-visible spectrophotometry (UV/VIS), infrared spectrophotometry (IR), raman spectroscopy, nuclear magnetic resonance spectroscopy (^{1}H-, ^{13}C-NMR), and X-ray crystallography.

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

The drug substance is synthesized using [redacted], [redacted], and [redacted] as starting materials.

The [redacted] process of [redacted] and [redacted] process for [redacted] and [redacted] of [redacted] have been defined as critical process steps. In addition, [redacted] is controlled as a critical intermediate to consistently ensure the quality of the drug substance.

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

The proposed specifications for the drug substance include content, description, identification (IR, liquid chromatography [HPLC]), purity (related substance [Related Substance A (HPLC) and other related substances (HPLC)], residual solvents [gas chromatography (GC)]), water content, and assay (HPLC).

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

Stability studies of the drug substance are as shown in the table below. Photostability testing has shown that the drug substance is stable to light.

Stability studies of the drug substance

Tests	Primary batch	Temperature	Humidity	Storage form	Storage period
Long-term	Pilot scale, 3 lots	25°C	60%RH	Polypropylene bag or polyethylene bag	36 months
Accelerated	Pilot scale, 3 lots	40°C	75%RH		[redacted] months

Based on the above, a retest period of 36 months for the drug substance when stored in the polypropylene or polyethylene bag at room temperature has been proposed.

2.A.(2) Drug product

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

The drug product is a film-coated tablet containing 40 mg of regorafenib (41.49 mg as regorafenib hydrate). The drug product contains microcrystalline cellulose, croscarmellose sodium, magnesium stearate, povidone, light anhydrous silicic acid, and Opadry [redacted] as excipients.

Since the drug substance is practically insoluble in aqueous solvents, a focus was placed on improvement of dissolution characteristics during formulation development. Consequently, the formulation containing [redacted] regorafenib was shown to have improved *in vivo* dissolution characteristics compared with that containing [redacted] regorafenib. The [redacted] formulation was selected for clinical development.

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

The manufacturing process of the drug product consists of (1) Mixing step, (2) Granulation step, (3) [redacted] step, (4) Tableting step, (5) Coating and [redacted] step, and (6) Packaging and labeling step. As critical process steps, [redacted] step and [redacted] step have been defined. Process control parameters and process control values have been set for the [redacted] step, [redacted] step, [redacted] step, and [redacted] step.

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

The proposed specifications for the drug product include content, description, identification (near-infrared spectroscopy [NIR] [HPLC]), purity (related substance [Related Substance A (HPLC) and other related substances (HPLC)], residual solvents [GC]), uniformity of dosage units (content uniformity), microbial limit test, dissolution, and assay (HPLC).

The microbial limit test is included as skip-lot testing (at least every [redacted] lots or [redacted] lots annually) in accordance with the "Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances" (PMSB/ELD Notification No. 568 dated May 1, 2001).

2.A.(2).4) Stability of the drug product

Stability studies of the drug product are as shown in the table below. Photostability testing has shown that the drug product is stable to light.

Stability studies of the drug product

Tests	Primary batch	Temperature	Humidity	Storage form	Storage period
Long-term	Pilot scale, 3 lots	25°C	60%RH	PTP packaging	36 months
Under the intermediate conditions	Pilot scale, 3 lots	30°C	75%RH	PTP packaging	36 months
Accelerated	Pilot scale, 3 lots	40°C	75%RH	PTP packaging	6 months

In accelerated testing, non-conformance to the specification was found in [redacted] of 3 lots at 6 months (while the acceptance criteria for the purity [related substance (Related Substance A)] is ≤[redacted]%, the actual value measured was [redacted]%). Thus, a test under the intermediate conditions was conducted, and non-conformance to the specification (the actual value measured for the purity

[related substance (Related Substance A)] was [redacted]%) was found in [redacted] of 3 lots at 36 months. Based on the above, a shelf life of 30 months was proposed for the drug product when stored in a PTP package ([redacted] aluminum [redacted] and aluminum foil) at room temperature [see "2.B.(2) Shelf-life for the drug product"].

2.B. Outline of the review by PMDA

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

2.B.(1) Formulation and manufacturing process of the drug product

The applicant explained that povidone is used as [redacted] base to manufacture the drug product as [redacted] so that [redacted] regorafenib [redacted] to [redacted], and as a result, the drug product can be stably maintained while the dissolution rate is improved.

PMDA asked the applicant to explain why and how the company selected the manufacturing process in which the drug product is manufactured as [redacted] to ensure [redacted] [redacted] of regorafenib and maintenance of [redacted].

The applicant responded as follows:
Throughout the development period of the drug product, there was no ways to manufacture [redacted] regorafenib other than production of the drug product as [redacted]. The process in which the drug product is manufactured as [redacted] was thus selected. As to the [redacted] formulation manufactured using the drug substance and [redacted] base at an appropriate ratio, [redacted] base inhibits [redacted], allowing regorafenib to remain in [redacted] stably. Although the subsequent examinations made it possible to manufacture [redacted] regorafenib other than [redacted], the dissolution test showed that the [redacted] mixture of the synthesized [redacted] regorafenib and excipients of the drug product had lower dissolving speed and dissolution rate than the [redacted] formulation. Based on the previous findings, the applicant considers it difficult to maintain [redacted] regorafenib stably without [redacted] of [redacted], because the [redacted] mixture of [redacted] regorafenib and excipients are potentially less stable than the [redacted] formulation, and [redacted] is likely to occur in the manufacturing process steps after mixing, during the storage and in the body after administration.

Next, PMDA asked the applicant to explain why povidone with K-value of [redacted] (molecular mass of povidone is usually expressed as K-value) (povidone K[redacted]) was selected as [redacted] base, and how changes of the lots and variations of the molecular mass would affect the quality of the drug product.

The applicant responded as follows:
During the development phase of the [redacted] formulation, povidone K[redacted], K[redacted], and K[redacted] were used for comparison. As a result, with povidone at any K-value, regorafenib was completely [redacted]. However, povidone K[redacted] led to slightly lower dissolution rate of [redacted] than povidone K[redacted], and povidone K[redacted] led to slower [redacted] of povidone in [redacted], which made [redacted] [redacted], indicating that povidone K[redacted] was slightly inferior in [redacted]. Thus, povidone K[redacted] was selected as [redacted] base because it was considered to be most appropriate for manufacture of the [redacted] formulation, from viewpoints of dissolution and [redacted].

Although the drug product using povidone K[redacted] had lower dissolution rate of [redacted] than that using povidone K[redacted], the other quality attributes were hardly affected. In addition, the drug product using povidone K[redacted] provided comparable dissolution profile of [redacted] to that with povidone K[redacted], and no significant effects were observed for other quality attributes either. As described above, even apparent differences in molecular mass of povidone hardly affected the quality attributes. Although the dissolution rate was affected to some extent, all of the observed

differences fell within the range conforming to the specification. The applicant considers that the variations of the molecular mass of povidone K[redacted] due to reasons such as changes of the lots of povidone K would not affect the quality of the drug product. (In this drug product, povidone K[redacted] conforming to the corresponding monograph of the Japanese Pharmacopoeia [JP] is used. The JP specifies that the K-value is 90% to 108%. Thus, variations of the molecular mass at the K-values of [redacted] to [redacted] are acceptable).

Taking account of the applicant's response, PMDA concluded that manufacturing the [redacted] formulation using JP listed povidone K[redacted] causes no quality concerns.

2.B.(2) Shelf life for the drug product

A shelf life of 36 months has been proposed by the applicant because no significant quality changes were observed at 36 months under long-term storage conditions or at 12 months under intermediate conditions. Since non-conformance to the specification in Related Substance A, a related substance, was observed in [redacted] of 3 lots at 36 months in stability testing under intermediate conditions, PMDA asked the applicant to present their views on the risk associated with the establishment of a shelf life of 36 months at room temperature.

The applicant responded as follows:

Since the drug product is packaged in a humidity-protecting material that does not allow vapor to pass through, the increasing rate of the related substance is independent of the relative humidity but dependent on the temperature. The 36-month long-term testing and intermediate testing showed that the increase in Related Substance A was [redacted]. The [redacted] analysis on the data from the above 2 tests and 6-month accelerated testing also showed that the increasing rate was remarkably affected by the temperature (according to the [redacted] analysis performed by the applicant, the increasing rates in testing under intermediate conditions and accelerated testing were [redacted]-fold and [redacted]-fold that in long-term testing, respectively). Taking into account that the increasing rate of Related Substance A is thought to change in line with [redacted] reaction kinetics although it is affected by the temperature, the increase in the amount of Related Substance A was estimated at different temperatures for different storage periods, based on the increasing rate for each temperature. The estimates indicated that the amount of Related Substance A during the 36-month storage period may exceed the acceptance criteria under particular conditions such as storage at [redacted]°C for longer than [redacted] months. However, taking into account that the mean kinetic temperature estimated from the calculated activation energy is <[redacted]°C, and that the drug product is not expected to be stored under extreme conditions as described above because the climate in Japan is classified as climatic zone II, the applicant considers there is no risk in setting the shelf life of the drug product at 36 months under storage conditions at room temperature.

PMDA, however, concluded as follows:

Under intermediate storage conditions, significant change occurs and the increasing rate was notably affected by the temperature, that is, the increasing rate of Related Substance A substantially changed by the differences of + 5°C/+ 15% RH (differences in conditions between long-term testing and testing under intermediate conditions). Taking account of these findings, it is inappropriate to set the shelf life of 36 months for the drug product under storage conditions at room temperature (specified at 1°C-30°C in the JP) based on the discussions presented by the applicant. PMDA thus instructed the applicant to re-evaluate the shelf-life.

The applicant responded that the shelf-life of the drug product will be changed to 30 months under storage conditions at room temperature. PMDA accepted the applicant's response.

3. Non-clinical data

3.(i) Summary of pharmacology studies

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

In this section, doses and concentrations of the study drug and comparator are all expressed in a free-base basis and regorafenib hydrate is referred to as "regorafenib."

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

3.(i).A.(1).1) Tumor growth inhibitory effects

***in vitro*: (Report A58229)**

Tumor growth inhibitory effects of regorafenib (0.318-10,000 nmol/L) on human colorectal cancer cell lines were evaluated by 4',6-diamidino-2-phenylindole (DAPI) staining (the table below).

Tumor growth inhibitory effects of regorafenib on human colorectal cancer cell lines

Cell line	IC_{50} value (nmol/L)	Cell line	IC_{50} value (nmol/L)
SW1417	4020	HCT-116	2660
Colo320DM	> 10,000	HT-29	3890
SW403	> 10,000	LS-174T	5930
RKO-AS45-1	5930	LS1034	> 10,000
SW480	6670	RKOE6	5010
SW948	7020	RKO	5350
Colo201	6160	SW1116	> 10,000
Colo205	4590	SW48	6310
Colo320HSR	8480	SW620	9690
DLD-1	6760	SW837	8420
HCT-15	7610	T84	> 10,000
NCI-H508	> 10,000	WiDr	3900
NCI-H747	3590		

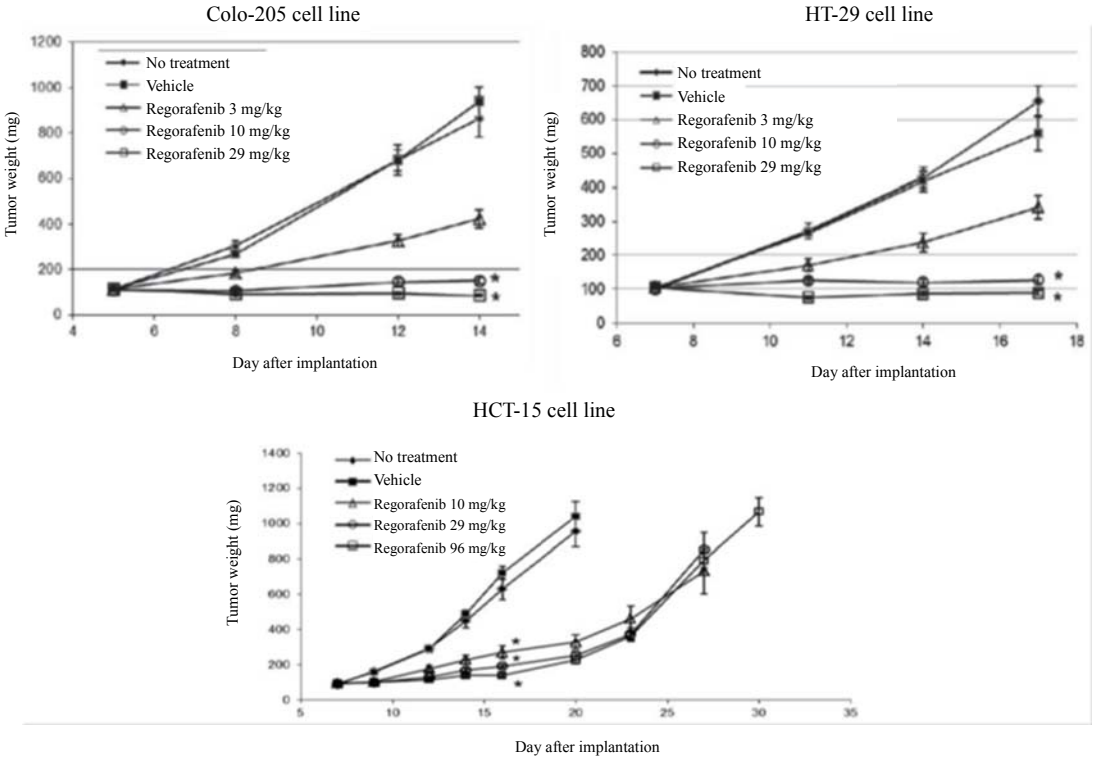
n = 1

The applicant explained that the relationship of presence or absence of Kirsten rat sarcoma 2 viral oncogene homolog (*KRAS*) and *BRAF* gene mutation in the above human colorectal cancer cell lines with the intensity of the tumor growth inhibitory effect of regorafenib was investigated, but no clear relationship was found.

***in vivo*:**

i) Tumor growth inhibitory effects on human colorectal cancer cell lines (Report MRC-01307)

Tumor growth inhibitory effect of regorafenib was evaluated in athymic mice ("nude mice") by subcutaneous implantation of human colorectal cancer cell lines, Colo-205, HT-29, and HCT-15. After the implanted tumor weight reached 75 to 144 mg (5-7 days after implantation), regorafenib was orally administered once daily (QD) at the doses of 3, 10, 29, and 96 mg/kg for 9 days, and the tumor weight was measured (the figure below). In nude mice with Colo-205 and HT-29 cell lines, 10 and 29 mg/kg of regorafenib inhibited tumor growth with statistical significance compared with the control mice (vehicle) on the last day of tumor weight measurement. In nude mice with HCT-15 cell line, 10, 29, and 96 mg/kg of regorafenib inhibited tumor growth with statistical significance compared with the control mice (vehicle) after 16 days of implantation. Reproducibility of the inhibition against Colo-205 and HT-29 cell lines was confirmed, although that for HCT-15 cell line has not been evaluated.



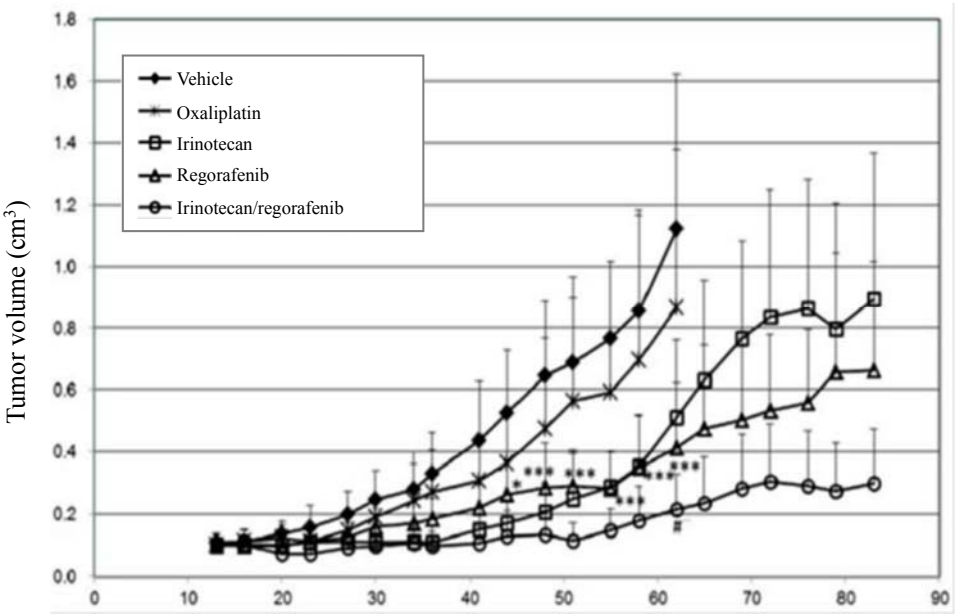
Tumor growth inhibitory effect of regorafenib
(Colo-205, HT-29, HCT-15 cell lines)

Mean ± standard error, n = 10,
*: $P < 0.05$ for control group (vehicle) (Kruskal-Wallis test, Dunn's method)
Of mice implanted with HCT-15cell line, 1 mouse in the 96 mg/kg group was euthanized due to toxicity development after 12 days of implantation. After completion of the administration, observation was continued until the tumor weight reached the specified level.

ii) Tumor growth inhibitory effects on patient-derived colorectal cancer (Report A57118)

Tumor growth inhibitory effect of regorafenib was evaluated in nude mice implanted subcutaneously with Co8183, one of the patient-derived oxaliplatin-resistant colorectal cancers passaged in mice. After the implanted tumor volume reached approximately 0.1 cm^3 (after 13 days of implantation), regorafenib (10 mg/kg QD, oral daily administration), irinotecan hydrochloride (irinotecan) (13 mg/kg QD, intraperitoneal administration for 5 days), and oxaliplatin (5 mg/kg QD, intraperitoneal administration for 5 days) were administered, and the tumor volume was calculated (the figure below). Regorafenib inhibited tumor growth with statistical significance compared with the control (vehicle) group. Similar results were obtained in mice implanted with other oxaliplatin-resistant patient-derived colorectal cancers (Co8434, Co8435, Co5896).

The applicant explained that it was suggested that regorafenib is effective even in oxaliplatin-resistant colorectal cancers.



Tumor growth inhibitory effect of regorafenib (mice implanted with Co8183)
Mean ± standard deviation, n = 8,
*: $P < 0.05$ against control (vehicle) group (after 44 days of implantation), ***: $P < 0.001$ against control (vehicle) group (after 48-62 days of implantation), #: $P < 0.01$ against irinotecan alone group (after 62 days of implantation) (repeated measures analysis of variance [ANOVA], Bonferroni method)

The applicant explained that the above *in vitro* and *in vivo* data demonstrated the tumor growth inhibitory effects of regorafenib on colorectal cancers.

3.(i).A.(1).2) Mechanism of action
i) Phosphorylation inhibitory activity
***in vitro*:**
(a) Evaluation at an enzymatic level (Reports A57121, A58277)
The inhibitory effect of regorafenib against phosphorylation by kinases (recombinant proteins) was determined using the consumption of the [γ-^{33}P]ATP by substrate peptides. In addition, the competitive inhibitory effect of regorafenib against ligands in kinase binding was determined using PCR-amplified products resulted from binding of a kinase to immobilized ligands [Note by PMDA: DNA is attached to kinases to determine their binding to ligands quantitatively, from which the inhibitory effect can be calculated] (the table below).

The applicant explained as follows:
The results in the table below suggested that regorafenib inhibits phosphorylation by kinases such as VEGFR and TIE2, which are involved in tumor angiogenesis, PDGFR and FGFR, which are involved in tumor progression in a microenvironment of the tumor tissue, and KIT, RET, and BRAF, which are involved in tumor growth, and that profiles of the kinase inhibition and ligand-binding inhibition by regorafenib are almost comparable.

Kinase inhibitory activity and ligand-binding inhibitory activity of regorafenib

Kinase	Kinase inhibition	Ligand-binding inhibition	Kinase	Kinase inhibition	Ligand-binding inhibition
	IC_{50} (nmol/L)	Kd (nmol/L)		IC_{50} (nmol/L)	Kd (nmol/L)
VEGFR-1	10, 16	27	c-Kit V560G	13	ND
VEGFR-2	10	28	c-Kit V654A	79	ND
TIE2	471	290	RET	1, 2	5.2
TIE2 R849W	43	ND	RAF-1	67	59
TIE2 Y897S	70	ND	BRAF	ND	52
PDGFRα	886	19	BRAF V600E	ND	42
PDGFRα D842V	50	ND	DDR2	29	9.7
PDGFRα V561D	6	ND	EPHA2	85	ND
PDGFRβ	> 1000	8.3	PTK5	8	ND
FGFR1	26	280	p38α	44	48
c-Kit	> 1000, 807	6.9	p38β	56	28
c-Kit D816H	329	ND	ABL	56	16
c-Kit D816V	> 1000	300			

n = 1 or 2 (for n = 2, values are indicated for each measurement), ND: Not detected

(b) Pharmacological effects of metabolites
(Reports A57121, A58277, A58230, A57101, A57105)

As major metabolites of regorafenib, pyridine N-oxide form (M-2) and pyridine *N*-oxideamide form (M-5) have been identified. The kinase inhibitory activity and kinase-ligand binding inhibitory activity of these metabolites were evaluated as done in "3.(i).A.(1).2).i).(a) Examination at an enzymatic level" (the table below). The kinase-ligand binding inhibitory activity was calculated from the inhibition observed at 1 μmol/L of a test compound as a percentage (% Control) using the inhibitions of the negative and positive controls as 100% and 0%, respectively.

Kinase inhibitory activity and ligand-binding inhibitory activity of metabolites

Kinase inhibitory activity				Ligand-binding inhibitory activity			
Kinase	IC_{50} value (nmol/L)			Kinase	% Control		
	Regorafenib	M-2	M-5		Regorafenib	M-2	M-5
VEGFR-1	10, 16	9	11	VEGFR-1	1, 1.4	0.7	0.95
PDGFRβ	> 1000	134	221	VEGFR-2	0.55, 0.85	0.35	0.55
FGFR-1	26	46	84	VEGFR-3	0.5, 0.95	0.25	0.7
FGFR-2	50	78	152	RAF-1	2.4, 3.5	3.2	2.4
c-Kit	> 1000, 807	715	684	BRAF	10, 9.4	5.1	5.7
RET	1, 2	1	1	BRAF V600E	5, 3.2	1.8	2.2
ABL	56	63	39	TIE2	26, 35	21	37
DDR2	29	36	35	c-Kit	0, 0	0	0
EPHA2	85	40	44	RET	0, 0	0	0
PTK5	8	6	5	FGFR-1	33, 22	49	60
p38α	44	41	56	PDGFRα	0.5, 1.2	0.1	0.3
p38β	56	51	54	PDGFRβ	0, 0.05	0	0
LYN	44	46	79	EGFR	69, 81	79	77
TrkA	74	16	16				
EGFR	> 1000	> 1000	> 1000				

n = 1 or 2 (for n = 2, values are indicated for each measurement.)

The inhibitory effects of regorafenib, M-2, and M-5 on the phosphorylation of TIE2, c-Kit, and BRAF V600E in response to ligand stimulation were measured in cell lines expressing each

kinase by enzyme-linked immunoassay (ELISA), and the obtained IC_{50} values are as shown in the table below.

Inhibitory activities of metabolites against phosphorylation in cell lines expressing each kinase

Cell line	Type of expressed kinase	Phosphorylation inducing substance	Test article	IC_{50} value (nmol/L)	n
TIE2/CHO*1	TIE2	Sodium orthovanadate	Regorafenib	41, 27, 24	3
			M-2	90, 41	2
			M-5	180, 180	2
M07e*2	c-Kit	SCF	Regorafenib	23	1
			M-2	13	1
			M-5	110	1
BRAF V600E/Rat1*3	BRAF V600E	Tamoxifen	Regorafenib	69	1
			M-2	21	1
			M-5	27	1

n = 1-3, *1: Chinese hamster ovary cell line with TIE2 forcedly expressed, *2: Human megakaryoblastic leukemic cell line, *3: Rat fibroblast cell line with BRAF V600E forcedly expressed

In addition, the 28-day once-daily repeated oral administration of regorafenib as well as M-2 and M-5 (3 and 10 mg/kg QD, respectively) suppressed the tumor growth in nude mice subcutaneously implanted with human breast cancer-derived cell lines, MDA-MB-231 and HT-29.

Based on the above data, the applicant explained that M-2 and M-5 contribute to the tumor growth suppression through their phosphorylation inhibitory effect similar to that of regorafenib.

ii) Effects on tumor blood vessels

In tumor tissues in patients with colorectal cancer, expression of VEGF was found, and it has been reported that expression of VEGFR-2 correlates to the increased number of blood vessels and the proliferation of tumor cells (percentage of cells stained positively with anti-proliferating cell nuclear antigen [PCNA] antibodies) (*Cancer Res.* 1995;55:3964-8), suggesting that colorectal cancer growth is dependent on angiogenesis.

(a) Antiangiogenesis (Report A58234 Revised version 1)

Regorafenib 10 mg/kg QD (single dose, or for 4 days) was orally administered to rats intramuscularly implanted with rat glioblastoma-derived GS9L cell line, and the effects on the blood volume and vascular permeability of the tumor site were evaluated by dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI). The applicant explained that exposure to the contrast medium decreased and tumor volume also decreased in the regorafenib group compared with the control (vehicle) group, suggesting that regorafenib suppresses tumor growth by decreasing the blood supply to the tumor.

In addition, the applicant explained that M-2 also has the effect on the blood vessels as with regorafenib because both single oral and intravenous administration of M-2 at the dose of 7.5 mg/kg decreased exposure to the contrast medium.

(b) Antiangiogenesis and signal transduction inhibition (Report MRC-01307)

Following oral administration of regorafenib 10 and 29 mg/kg QD for 5 days to nude mice implanted with Colo-205 cell line, MDA-MB-231 cell line, human pancreas cancer-derived BxPC-3 cell line, and human non-small-cell lung cancer-derived NCI-H460 cell line, the effects on the blood vessels (CD31 protein expression) and cell proliferation signal transduction cascade (phosphorylation of Erk1/2 protein) were evaluated by an immunohistochemical staining method.

In all implanted mice, administration of regorafenib resulted in a decreased percentage of the area stained with anti-CD31 antibody to the overall area of tumor tissue. The count of cells stained with anti-phosphorylated Erk1/2 antibody in the tumor tissue was decreased in mice implanted with MDA-MB-231 cell line and BxPC-3 cell line following administration of regorafenib, while no changes were observed in mice implanted with Colo-205 cell line and NCI-H460 cell line.

Based on the above results, the applicant explained that the tumor growth inhibitory effect of regorafenib involves two mechanisms: antiangiogenesis and suppression of cell proliferation signal transduction; and that the tumor growth inhibition mediated by the suppression of cell proliferation signal transduction differs depending on the tumor cells.

iii) Tumor growth inhibitory effects on various tumor cell lines (Reports A58229, MRC-01307, A58231, A58233)

***in vitro*:**

Tumor growth inhibitory effects of regorafenib on 8 types of human pancreas cancer-derived cell lines, AsPC-1, BxPC-3, CFPAC-1, Capan-1, HPAF-II, HuP-T4, MiaPaCa-2, and YAPC, were evaluated, and the IC_{50} values ranged from 4770 to >10,000 nmol/L.

***in vivo*:**

The following results were obtained from regorafenib treatment:

- Regorafenib suppressed the tumor growth in nude mice implanted with MDA-MB-231 cell line, NCI-H460 cell line, and BxPC-3 cell line in a dose-dependent manner.
- Regorafenib (10 mg/kg) prolonged the survival in mice orthotopically implanted with mouse hepatocellular carcinoma-derived H129 cell line.
- Regorafenib (10 mg/kg) suppressed the tumor growth of the primary lesion and also decreased the number of metastatic tumors in the lungs in mice orthotopically implanted with mouse breast cancer-derived 4T1 cell line.

3.(i).A.(2) Secondary pharmacodynamics (Report PH-36660)

Effects of regorafenib, M-2, and M-5 on blood pressure decrease induced by intravenous administration of vascular endothelial growth factor (VEGF) were evaluated in anesthetized rats (4-6 animals per group). Prior to VEGF (recombinant protein) administration at the dose of 9 μg/kg, regorafenib (0.1, 1 mg/kg), M-2 or M-5 (1 mg/kg for each) was intravenously administered to the rats. As a result, the blood pressure decrease induced by VEGF was suppressed.

The applicant explained that in addition to data on the primary pharmacodynamics, the above result also suggested that M-2 and M-5 have the effect as with regorafenib.

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

3.(i).A.(3).1) Effects on the central nervous system (Reports PH-33840, PH-33856, PH-35438, PH-35409)

Following single oral doses of 2, 10, or 50 mg/kg of regorafenib to male rats (6 animals per group), the effects on general symptoms, locomotor activity, and body temperature were evaluated. No effects of regorafenib were observed for any evaluation item. Following single oral doses of 2, 10, or 50 mg/kg of regorafenib to male rats (5-8 animals per group), the effects on hexobarbital-induced sleep, pentylenetetrazole-induced convulsion, and nociceptive reaction were evaluated. No effects of regorafenib were observed for any evaluation item.

Following single oral administration of metabolites (M-2, M-5) at doses of 1, 5, or 20 mg/kg to male rats (6 animals per group), the effects on general symptoms, locomotor activity, and body temperature were investigated. Except for findings such as prone position observed in 1 animal which received M-2 at the dose of 20 mg/kg, no findings that may raise concerns in clinical use were observed.

The applicant explained that M-2 is unlikely to raise toxicity concerns in clinical use because the abnormal behavior observed in 1 animal receiving M-2 in the safety pharmacology study was considered to be an accidental change for the following grounds: the mean C_{max} of plasma unbound M-2 in rats receiving M-2 at the dose of 20 mg/kg was estimated to be 53.1 μg/L based on the pharmacokinetic data, which was approximately 8 times higher than that of plasma unbound M-2 in clinical use (6.3 μg /L); and no findings suggesting abnormal behaviors were observed in mice receiving M-2 at the dose of 20 mg/kg/day in the mouse 4-week repeat-dose study [see "3.(iii).A.(7).2).(a) Four-week oral dose toxicity study in mice for M-2"].

3.(i).A.(3).2) Effects on the cardiovascular system

i) Effects on hERG current (Report PH-33109 [non-GLP study, reference data], Reports PH-35502, PH-35519)

In human embryonic kidney cell-derived HEK 293 cell line in which human *ether-a-go-go*-related gene (hERG) is transferred, effects of regorafenib on hERG potassium ion current were evaluated by whole-cell patch clamping. Regorafenib inhibited the hERG current dose-dependently, and the IC_{20} value and IC_{50} value were approximately 12 and 27 μmol/L, respectively.

The effects of the metabolites (M-2, M-5) on the hERG current were evaluated by the same method. Both M-2 and M-5 inhibited the hERG current dose-dependently, and the IC_{20} values of both metabolites were approximately 0.4 μmol/L and the IC_{50} value was 1.1 μmol/L for M-2 and 1.8 μmol/L for M-5. The inhibitory effect of these metabolites persisted even after washout.

ii) Effects on action potential in Purkinje fibers (Report PH-33827 [non-GLP study, reference data])

In Purkinje fibers isolated from rabbit hearts, effects of regorafenib (0.2, 2, 20 μmol/L) on myocardial action potential were evaluated (n = 5) with stimulation at 0.2, 1, and 2.5 Hz, using the resting membrane potential, action potential amplitude, maximum depolarization rate, and action potential duration (APD_{20}, APD_{50}, APD_{90}). Following treatment with regorafenib at 20 μmol/L, the APD_{50} and APD_{90} decreased from their baseline values with statistical significances (decreased by 23% and 14%, respectively), and the plateau potential was shifted in the negative direction. The applicant explained that the above data suggested that regorafenib at concentrations close to the solubility limit inhibits calcium ion current.

iii) Effects on blood pressure, heart rate, and electrocardiogram (Reports PH-33963, PH-35619, PH-35628, PH-35620)

Following a single intraduodenal administration of regorafenib at doses of 10, 30, or 100 mg/kg in anesthetized male and female dogs (3 animals per group), the effects on blood pressure, heart rate, left ventricular pressure, dP/dt, left ventricular end-diastolic pressure, central venous pressure, stroke volume, total peripheral blood vessel resistance, electrocardiogram (ECG) (PR, QT interval, etc.), hematocrit, and plasma potassium/sodium were studied. No potentially clinically significant findings due to the administration of regorafenib were observed.

Regorafenib, M-2, and M-5 were intravenously administered to anesthetized male and female dogs (n = 4) at dose steps of 0.25, 0.75, and 2.25 mg/kg in cumulative manner, and the effects on the same parameters as those in the above study were investigated, but no potentially clinically significant findings due to the administration of regorafenib were observed.

Taking the above results into account, the applicant explained as follows:
Although *in vitro* studies suggested that regorafenib may affect the ECG, the IC_{20} values of regorafenib, M-2, and M-5 (approximately 12, 0.4, and 0.4 μmol/L, respectively) were at least 30 times higher than the mean C_{max} values of plasma unbound regorafenib, M-2, and M-5 in clinical use (40, 13, and 3.2 nmol/L, respectively). In the cumulative intravenous administration study in

dogs, no effects on ECG were observed even when the total dose reached 3.25 mg/kg, and the mean concentrations of plasma unbound regorafenib, M-2, and M-5 at that time were 92, 139, and 47 nmol/L, respectively, which were higher than their mean C_{max} values in clinical use. The applicant, therefore, considers that no concerns about the effects of regorafenib and its metabolites will be raised in clinical use.

3.(i).A.(3).3 Effects on respiratory system (Reports PH-33963, PH-35619, PH-35628, PH-35620)

Following single intraduodenal dose of 10, 30, or 100 mg/kg of regorafenib to anesthetized male and female dogs (3 animals per group), the effects on respiratory functions, such as respiratory rate and tidal volume, blood gas, and acid-base equilibrium, were investigated. No findings that would raise clinical concerns due to regorafenib treatment were observed.

Regorafenib, M-2, and M-5 were intravenously administered to anesthetized male and female dogs (n = 4) at dose steps of 0.25, 0.75, and 2.25 mg/kg in cumulative manner, and the effects on the same parameters as those in the above study were evaluated, but no findings that would raise concerns were observed.

3.(i).A.(3).4 Effects on blood glucose (Report PH-33925)

Following a single oral dose of 2, 10, or 50 mg/kg of regorafenib to fasted and freely fed male rats (6 animals per group), the effect on blood glucose was evaluated. In the fasted rats receiving regorafenib 2 and 50 mg/kg, statistically significant decreases in blood glucose levels were observed (decreased by up to 22%) compared with the control (vehicle) rats.

The applicant explained that in rats receiving regorafenib, the decrease in blood glucose levels was not dose-dependent, and the variation ranges of the blood glucose levels are approximated to those in the control (vehicle) group, thus, these changes are not physiologically significant and the decrease in blood glucose levels will not become a clinically relevant problem.

3.(i).A.(3).5 Effects on smooth muscle (Report PH-34043)

In ileum isolated from guinea pigs (n = 4), effects of regorafenib (0.2, 2 μmol/L) on resting tension as well as contraction induced by acetylcholine, serotonin, histamine, or barium chloride were evaluated, and no effects of the treatment were observed.

3.(i).A.(3).6 Effects on gastrointestinal tract (Report PH-33841)

Following a single oral dose of 2, 10, or 50 mg/kg of regorafenib to male rats (5 animals per group), the effects on gastrointestinal motility were monitored with barium sulfate. Regorafenib suppressed the motility dose-dependently. The gastrointestinal transit distance decreased in all regorafenib treatment groups compared with the control (vehicle) group with a statistical significance.

The applicant explained that although the relationship between gastrointestinal adverse events (diarrhoea, constipation, vomiting, etc.) observed in clinical studies and gastrointestinal motility suppression remain unclear, a caution about gastrointestinal related events will be provided based on the clinical data.

3.(i).A.(3).7 Effects on renal functions (Report PH-34006)

Following a single oral dose of 2, 10, or 50 mg/kg of regorafenib to male rats (9-10 animals per group), the urine output, urine electrolytes, blood count, blood coagulation, haematocrit, blood hemoglobin level, plasma triglycerides, and cholesterol level were determined. No effects of regorafenib were observed.

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

Based on the submitted data and the following evaluations, PMDA concluded that regorafenib is expected to have efficacy in the treatment of colorectal cancer.

Mechanism of action of regorafenib
The applicant explained based on the submitted data that the mechanism of action of regorafenib against colorectal cancer is related to inhibition of phosphorylation by various kinases such as (1) VEGFR and TIE2, which are involved in tumor angiogenesis; (2) PDGFR and FGFR, which are involved in tumor progression in a microenvironment of the tumor tissue; and (3) KIT, RET, BRAF, etc., which are involved in tumor growth.

PMDA considers as follows:
The mechanism of action of regorafenib described above (1) and (3) showed that the inhibitory effects of regorafenib against phosphorylation by the kinases such as VEGFR, TIE2, KIT, RET, and BRAF as well as the consequent inhibitory effects of regorafenib on tumor growth and tumor angiogenesis have been demonstrated [see "3.(i).A.(1).1) Tumor growth inhibitory effects" and "3.(i).A.(1).2).ii) Effects on tumor blood vessels"]. Thus, PMDA accepts the applicant's explanation. On the other hand, PMDA considers that the applicant's explanation in terms of (2) remains a matter for speculation at present because there are no evaluation data indicating that the suppression of phosphorylation mediated by the kinases such as PDGFR and FGFR in the microenvironment of the tumor tissue would result in suppression of tumor progression, although the inhibitory effects of regorafenib against phosphorylation by these kinases have been demonstrated.

3.(ii) Summary of pharmacokinetic studies

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

In this section, doses and concentrations of the study drug are all expressed on the free-base basis and regorafenib hydrate is referred to as "regorafenib."

Pharmacokinetics (PK) of regorafenib in animals were evaluated in mice, rats, dogs, and monkeys. Plasma protein binding, drug-metabolizing enzymes, transporters, etc. for regorafenib were evaluated with biological samples from humans or animals.

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

3.(ii).A.(1).1) Single-dose

After single intravenous or oral dosing of ^{14}C-labeled regorafenib (^{14}C-regorafenib) or unlabeled regorafenib to male rats, the plasma regorafenib concentration levels were determined (the table below). In the oral dose range of 0.5 to 8 mg/kg, the AUC increased dose-proportionally, while the C_{max} increased less than dose proportionally. Regarding the difference in linearity between these PK parameters, the applicant explained that regorafenib is practically insoluble, that is, the solubility in the gastrointestinal tract is low, and the absorption rate decreased at the high doses, resulting in less than a dose-proportional increase of the C_{max}, while the continuous absorption relatively independent of the solubility led to the linear increase in the AUC with the dose.

After single intravenous or oral dosing of ^{14}C-labeled or unlabeled regorafenib to female dogs, the plasma regorafenib concentration levels were determined (the table below). Following the oral administration, the AUC and C_{max} increased dose-proportionally between 1 mg/kg and 2.5 mg/kg, while their increases were less than dose-proportional between 2.5 mg/kg and 10 mg/kg, suggesting that the absorption of regorafenib is saturated at high doses.

Following single oral dose of 1 mg/kg of regorafenib to female monkeys, the plasma concentration levels of regorafenib and the metabolites (pyridine *N*-oxide form [M-2], *N*-hydroxymethyl form [M-3], amide form [M-4], pyridine *N*-oxideamide form [M-5]) were determined (the table below). The geometric mean AUC of regorafenib, M-2, M-3, and M-4 were

4.94, 0.206, 0.428, and 3.34 mg·h/L, respectively, and the geometric mean C_{max} were 0.324, 0.0430, 0.0320, and 0.0321 mg/L, respectively. The applicant explained that the measurement values were below the lower limit of quantitation (2.0 μg/L) at most of the time points, the PK parameters of M-5 were not calculated.

PK parameters of regorafenib
(by animal species, single intravenous or oral administration)

Animals species	Route of administration	Dose (mg/kg)	n	C_{max} (mg/L)	t_{max} (h)	AUC (mg·h/L)	$t_{1/2}$ (h)	CL (L/h/kg)	V_{ss} (L/kg)	BA (%)
Rat (male)	Intravenous*1	0.5	3*3	-	-	3.44	4.05	0.145	0.880	-
		2*2	3*3	-	-	13.3	6.28	0.150	0.924	-
	Oral*4	0.5	3*3	0.277	6.0	2.83	6.70	-	-	85.1*5
		2*2	3*3	0.682	4.0	10.2	5.91	-	-	76.6*5
		8	3*3	3.46	4.0	47.1	7.27	-	-	88.5*5
Dog (female)	Intravenous*6	1	3	1.72 (1.07)	-	3.67 (1.18)	7.67 (1.33)	0.272 (1.18)	1.89 (1.02)	-
		2.5*2	3	4.37 (1.17)	0.25 (1.00)	12.0 (1.16)	7.72 (1.06)	0.208 (1.16)	1.70 (1.15)	-
	Oral*7	1	3	0.369 (1.19)	2.67 (1.29)	2.46 (1.24)	6.10 (1.25)	-	-	67.1 (1.18)
		2.5*2	4	0.825 (1.37)	1.57 (1.92)	6.39 (1.27)	5.34 (1.19)	-	-	59.9*8 (1.16)
		10	3	1.15 (1.15)	1.89 (2.23)	10.6 (1.17)	8.12 (1.06)	-	-	28.8 (1.24)
Monkey (female)	Oral*7	1	3	0.324 (1.37)	2.62 (1.26)	4.94 (1.59)	32.6 (1.20)	-	-	-

Geometric mean value (standard deviation), BA: Bioavailability
*1: Rapid intravenous administration of regorafenib in 60% (v/v) PEG400 aqueous solution, *2: Administered as ^{14}C-regorafenib, *3: Number of animals included in the measurement at each time point (blood samples were taken from the different rats at each time point), *4: Administration of regorafenib in 10% (v/v/v) ethanol/40% (v/v/v) Solutol HS 15 aqueous solution, *5: Calculated using the AUC following intravenous administration of regorafenib 2 mg/kg and dose-corrected AUC following oral administration of regorafenib, *6: Continuous intravenous administration of regorafenib in 10% (v/v/v) ethanol/60% (v/v/v) PEG400 aqueous solution over 15 minutes, *7: Administration of regorafenib dissolved in 100% PEG400, *8: n = 3

3.(ii).A.(1).2) Repeat-dose

The PK of regorafenib was evaluated in repeat-dose studies in mouse (4-, 5-week), in rat (4-, 13-, 26-week), and in dog (4-, 13-, 52-week). The applicant explained that data from the 4-week repeat-dose study in each animal species were used for evaluation because the 4-week administration period was sufficient for the regorafenib concentration to reach the steady state.

Regorafenib was orally administered at the doses of 5 to 80 mg/kg/day for 4 weeks to male and female mice, and the plasma concentration levels of regorafenib and M-2 were determined (the table below). No gender-related differences were observed in exposures of regorafenib and M-2. At any blood collection time point, the C_{max} and AUC_{0-24} of regorafenib and M-2 increased with the dose. At all doses, the accumulation factors of the C_{max} and AUC_{0-24} were 0.724 to 1.06, and 0.805 to 1.19, respectively, for regorafenib, and 0.703 to 1.51 and 0.723 to 1.12, respectively, for M-2; no accumulation due to the repeated doses were noted.

PK parameters of regorafenib and M-2 (male and female mice, repeated oral doses)

	Time point	Dose (mg/kg)	C_{max} (mg/mL)		AUC_{0-24} (mg·h/L)	
			Male	Female	Male	Female
Regorafenib	Day 1	5	2.16	2.80	14.6	20.2
		20	7.27	8.58	51.1	64.7
		80	23.7	24.3	193	206
	Day 26	5	1.60	2.29	13.4	14.3
		20	8.77	8.01	60.9	77.3
		80	17.4	17.8	149	202
M-2	Day 1	5	0.231	0.281	2.18	3.60
		20	0.837	0.969	10.0	12.2
		80	5.76	4.16	54.1	53.1
	Day 26	5	0.205	0.284	1.80	2.40
		20	1.21	1.46	10.8	14.2
		80	3.18	3.71	35.1	42.6

Geometric mean value, 3 animals/time point (blood samples were taken from the different mice at each time point)

Regorafenib was orally administered at the doses of 1 to 16 mg/kg/day for 4 weeks to male and female rats, and the plasma regorafenib concentration levels were determined (the table below). At any dose, the C_{max} and AUC_{0-24} tended to be higher in females than in males. The C_{max} and AUC_{0-24} were proportional to the dose, and these values on Day 29 tended to be higher than those on Day 1. The applicant explained that definite causes of the gender-related difference in exposure of regorafenib in rats remain unknown, although it may be caused by the gender-related differences in CYP isoforms for the following backgrounds: CYP-mediated oxidation plays a substantial role in metabolism of regorafenib in rats; it has been reported that expression levels of CYP isoforms have gender-related differences in rats (*Biochem Pharmacol.* 1996;51:1041-50); and M-3 (hydroxylated metabolite) is the major metabolite of regorafenib in rat liver microsomes and hepatocytes [see "3.(ii).A.(3).1) *In vitro*"], but the CYP isoforms involved in generation of M-3 in rats have not been identified.

PK parameters of regorafenib (male and female rats, repeated oral doses)

Time point	Dose (mg/kg)	C_{max} (mg/mL)		AUC_{0-24} (mg·h/L)	
		Male	Female	Male	Female
Day 1	1	0.361	0.455	3.30	5.42
	4	1.17	1.87	11.4	19.6
	16	4.83	6.76	49.5	87.3
Day 29	1	0.454	0.542	4.96	6.80
	4	1.49	2.33	15.5	27.9
	16	4.71	5.96	60.0	111

Geometric mean value, 3 animals/time point (blood samples were taken from the different rats at each time point)

Regorafenib was orally administered at the doses of 5 to 80 mg/kg/day for 4 weeks to male and female dogs, and the plasma regorafenib concentration levels were determined (the table below). The C_{max} and AUC_{0-24} had no marked gender-related differences and increased less than dose-proportionally. The C_{max} and AUC_{0-24} on Day 26 were lower than those on Day 1. The applicant explained that the lower values may be caused by hepatic drug-metabolizing enzymes induced by the repeated doses, which are involved in metabolism of regorafenib, but the definite causes

remain unknown [Note by PMDA: 13- and 52-week repeat-dose studies did not show such significant decrease in exposure of regorafenib as observed in the 4-week repeat-dose study].

PK parameters of regorafenib (male and female dogs, repeated oral doses)

Time point	Dose (mg/kg)	C_{max} (mg/mL)		AUC_{0-24} (mg·h/L)	
		Male	Female	Male	Female
Day 1	5	2.68 ± 1.11	2.88 ± 1.10	12.9 ± 1.10	13.8 ± 1.16
	20	5.52 ± 1.13	5.55 ± 1.10	39.8 ± 1.21	31.8 ± 1.14
	80	14.8 ± 1.24	12.1 ± 1.19	94.1 ± 1.11	93.6 ± 1.19
Day 26	5	1.84 ± 1.04	1.43 ± 1.45	10.0 ± 1.05	8.70 ± 1.36
	20	3.57 ± 2.32	4.98 ± 1.88	24.1 ± 2.01	28.1 ± 1.39
	80	5.52 ± 2.43	9.41 ± 1.11	32.2 ± 1.93	60.1 ± 1.18

Geometric mean ± standard deviation, n = 3

3.(ii).A.(1).3) *In vitro* permeability

Permeability of regorafenib in the human gastrointestinal tract was evaluated in human colon cancer-derived Caco-2 cell line. At the regorafenib concentration of 0.3 μmol/L, the apparent permeability coefficient in the apical to basolateral direction ("$P_{app\ A\rightarrow B}$") was 124 ± 26.2 nm/sec (mean ± standard deviation [SD]), and the apparent permeability coefficient in the basolateral to apical direction ("$P_{app\ B\rightarrow A}$") was 104 ± 29.0 nm/sec (mean ± SD). Of the amount of regorafenib added to the apical and basolateral sides, 73.8% ± 21.2% and 21.0% ± 1.51%, respectively, remained in the cells. The elimination ratio ($P_{app\ B\rightarrow A}/P_{app\ A\rightarrow B}$) was 0.835 ± 0.344 (mean ± SD), indicating that the intracellular regorafenib concentrations were higher than extracellular ones. The applicant thus explained that the above data suggest active intracellular uptake or binding of regorafenib to cell membranes.

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

3.(ii).A.(2).1) Tissue distribution

Following a single intravenous or oral dose of 3 mg/kg of ^{14}C-regorafenib to male albino rats, and following a single oral dose of 3 mg/kg of ^{14}C-regorafenib to female albino rats and male pigmented rats, the tissue distributions of radioactivity were qualitatively evaluated. The radioactivity was extensively distributed across tissues, and no differences in radioactivity distribution were observed between the routes of administration or between males and females. However, the radioactivity concentrations in most of the tissues were found higher in females than in males at 24 hours after the administration. The applicant explained that the gender-related difference in tissue radioactivity concentration may be related to the gender-related difference in exposure of regorafenib in rats [see "3.(ii).A.(1).2) Repeat-dose].

Following single oral dose of 3 mg/kg of ^{14}C-regorafenib to male albino and male pigmented rats, the tissue distribution of the radioactivity was investigated by quantitative whole-body autoradiography. In albino rats, the tissue radioactivity concentration reached the maximum at 2 to 8 hours after administration in most of the tissues, which was found to be 2 to 4 times the maximum blood radioactivity concentration (1.63 mg eq/L). The radioactivity concentrations were found to be high in the liver (10.68 mg eq/L) and adrenal cortex (10.23 mg eq/L), while they were found to be low in the testis (0.597 mg eq/L) and brain (0.301 mg eq/L), suggesting that regorafenib or metabolite does not have a high permeability at the blood-testis barrier and blood-brain barrier. In albino rats, the apparent $t_{1/2}$ of the radioactivity in each tissue up to 72 hours after administration was 9 to 22 hours, and at 7 days after administration, 0.91% of the administered radioactivity was found mainly in the liver. The radioactivity distribution and elimination pattern in pigmented rats in the terminal phase were almost similar to those in albino rats, but in the ocular wall, which contained melanin, the radioactivity in pigmented rats was 3.8 to 5.6 times that in albino rats. The applicant explained that the concentrated distribution of regorafenib or metabolite

in the melanin-containing tissues is unlikely to raise safety concerns taking into account that the terminal phase $t_{1/2}$ of the radioactivity in the ocular wall in albino and pigmented rats was 93 and 82 hours, respectively, which is not remarkably different.

The applicant further explained that a repeat-dose tissue distribution study was not conducted because the $t_{1/2}$ in the renal cortex from which the radioactivity was eliminated at the slowest rate in the single-dose tissue distribution study was 21.8 hours, which was shorter than the dosing interval (24 hours) of regorafenib in toxicity studies.

3.(ii).A.(2).2) Plasma protein binding and distribution in blood cells

^{14}C-regorafenib (approximately 0.5-18 mg/L), M-2 (approximately 0.5-7 mg/L, except for rabbit plasma), and M-5 (approximately 0.6-8 mg/L, except for rabbit and monkey plasma) were incubated with mouse, rat, rabbit, dog, monkey, and human plasma to evaluate the plasma protein binding using a solid-supported lipid membrane (Transil®).

The fraction of unbound regorafenib in plasma (f_u) in human, mouse, rat, dog, rabbit, and monkey plasma was 0.39% to 0.58%, 0.54% to 0.63%, 0.60% to 0.91%, 0.86% to 1.1%, 1.68% to 1.69%, and 1.92% to 2.45%, respectively; that is, the plasma protein binding rate of regorafenib did not show clear concentration-dependent changes in any animal species. In the range of pH 7.2 to 7.8, the plasma binding rate of regorafenib in human plasma did not show pH-dependent changes (f_u = 0.59%-0.71%), and the binding rate of regorafenib to human serum albumin exceeded 97%.

Regorafenib was incubated with the drugs with high plasma protein binding rates (warfarin, paclitaxel, salicylic acid, gefitinib, ibuprofen, digitoxin, cisplatin, furosemide, nifedipine, propranolol, docetaxel) at concentrations equivalent to their blood levels in patients. As a result, none of these drugs affected the f_u of regorafenib.

The f_u of M-2 in human, mouse, rat, dog, and monkey plasma was 0.185% to 0.190%, 0.865% to 0.912%, 0.670% to 0.702%, 1.18% to 1.26%, and 1.51% to 1.91%, respectively, and the f_u of M-5 in human, mouse, rat, and dog plasma was 0.053%, 0.412%, 0.286%, and 0.411%, respectively; the plasma protein binding rates of M-2 and M-5 did not show clear concentration-dependent changes in any animal species. In the range of pH 7.22 to 7.60, the plasma binding rate of M-2 in human plasma did not show pH-dependent changes (f_u = 0.149%-0.187%).

The applicant explained that regorafenib is mainly distributed in plasma because in a study of incubation of ^{14}C-regorafenib (1.21-46.0 ng/mL) with rat, dog, and human blood, the plasma/blood concentration ratios of the radioactivity were 1.50, 1.38, and 1.59, respectively.

3.(ii).A.(2).3) Placental permeability and maternal-fetal transfer

Following a single oral dose of 3 mg/kg of ^{14}C-regorafenib to pregnant rats (Gestation day 19), the placental permeability and maternal-fetal transfer of regorafenib were evaluated. The radioactivity concentrations in the maternal blood as well as maternal and fetal tissues reached the maxima at 8 hours after administration. The maximum radioactivity concentration ratios (fetus/dam) in major tissues except for the brain were 0.13 (liver) to 0.80 (skin), while the ratio (fetus/dam) in the brain was 2.1. The AUC_{0-24} of radioactivity in the fetal brain was approximately 1.6 times higher than that in the maternal brain. The applicant explained that the above data suggest that regorafenib is distributed in fetuses passing through the placenta, and the brain transfer rate in fetuses is higher than that in dams.

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

3.(ii).A.(3).1) *In vitro*

^{14}C-regorafenib (20 μmol/L) was incubated with mouse, rat, rabbit, dog, monkey, and human liver microsome at 37°C for 1 or 3 hours to evaluate the metabolites. In the mice, rabbits, monkeys,

and humans, M-2 and then M-3 were detected as the major primary metabolites, while in the dog and rat, M-3 and then M-2 were detected as the major ones. In any animal species, M-1/M-5 and M-4 were marginally generated.

^{14}C-regorafenib (2 μmol/L) was incubated with rat, dog, and human hepatocytes at 37°C for 2 hours to evaluate the metabolites. In the humans, the major metabolite was M-2, and M-3, M-4, M-5, M-6, M-7, and M-8 were also detected. In the rat, M-2 was generated only marginally, while M-3 was generated as the major metabolite, and M-4 and M-6 were also detected. In the dog, M-2 was not detected, while the major metabolite was M-3, and M-4 and M-6 were also detected. In the rat and dog hepatocytes, neither M-7 nor M-8 was detected.

The applicant explained that in the study with the rat, dog, and human hepatocytes, M-4 was generated at higher rates compared with the study with liver microsome, suggesting that M-4 was not the primary metabolite of regorafenib.

The applicant further explained that in the study in which M-3 was incubated with human liver microsome or liver cytosol in presence or absence of various coenzymes, M-4 and a small amount of M-6 were detected only in the liver cytosol in the presence of nicotinamide adenine dinucleotide (NAD), suggesting that alcohol dehydrogenase is involved in the metabolic reaction from M-3 to M-4 and M-6.

Regorafenib (2, 10 μmol/L) was incubated with human liver microsome in the presence of inhibitors such as CYP isoforms (CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 3A4) to identify CYP isozymes involved in metabolism of regorafenib. At 2 μmol/L of regorafenib, a CYP3A4 inhibitor inhibited the metabolism of regorafenib into M-2 and M-3 to 0% to 17.8% and 8.3% to 37.3%, respectively, and at 10 μmol/L, the metabolism was inhibited to 1.6% to 12.6% and 14.9% to 27.7%, respectively, by the CYP3A4 inhibitor. The other CYP inhibitors scarcely affected the metabolism of regorafenib. The applicant explained that the above results suggested that oxidative metabolism of regorafenib is mainly mediated by CYP3A4.

Regorafenib (2 μmol/L) and ^{14}C-regorafenib (10.6 μmol/L) were incubated with recombinant human CYP (CYP1A1, 1A2, 1B1, 2A6, 2B6, 2C8, 2C9, 2C18, 2C19, 2D6, 2E1, 2J2, 3A4, 3A5, 3A7, 4A11, 4F2, 4F3A, 4F3B, 4F12) to identify CYP isozymes involved in metabolism of regorafenib. The applicant explained that the results suggested that regorafenib was metabolized into M-2 by CYP3A4, and metabolism into M-3 was mediated by CYP3A4 and CYP2J2.

^{14}C-regorafenib (1.95 μmol/L, only for UDP glucuronosyltransferase [UGT] 1A9, 0.2-11 μmol/L) and M-2 (10 μmol/L) were incubated with recombinant human UGT (UGT1A1, 1A3, 1A4, 1A6, 1A7, 1A8, 1A9, 1A10, 2B4, 2B7, 2B15, 2B17) to identify UGT isozymes involved in metabolism of regorafenib and M-2. Only in the UGT1A9 and 1A7 expression systems, ^{14}C-regorafenib was metabolized into M-7 (12.2% and 0.8% of the administered dose, respectively), and the other UGT expression systems did not generate M-7. The Michaelis-Menten constant (K_m) and maximum velocity (V_{max}) in the incubation of ^{14}C-regorafenib with UGT1A9 were estimated to be approximately 2.1 μmol/L and 14.8 pmol/min/mg, respectively. M-2 was metabolized into M-8 (1.2% of the administered dose) only in the UGT1A9 expression system, and the other UGT expression systems did not generate M-8.

^{14}C-regorafenib (5 μmol/L) was incubated with human liver and kidney microsome in the presence of inhibitors such as UGT isoforms (UGT1A1, 1A4, 1A9, 2B7). As a result, in the liver and kidney microsome, a UGT1A9 inhibitor inhibited metabolism into M-7 to 10.9% and 11.1%, respectively. The other UGT inhibitors did not have significant effects on the metabolism into M-7. In the human liver microsome, the UGT1A9 inhibitor inhibited metabolism into M-8 to 9.6%.

The applicant explained that the above results suggested that glucuronidation of regorafenib is mainly mediated by UGT1A9.

Regorafenib was incubated with human liver microsome in the presence of various drugs (antineoplastic drugs, analgesics, antiviral drugs, antibacterial drugs, azole antifungal drugs, etc.) to evaluate their inhibitory effects against metabolism of regorafenib into M-2 and M-7. Ketoconazole, indinavir, ritonavir, and fluconazole inhibited the metabolism of regorafenib into M-2 with the IC_{50} values of 0.11, 0.9, 0.10, and >50 μmol/L, respectively. In addition, niflumic acid and mefenamic acid inhibited the metabolism of regorafenib into M-7 with the IC_{50} values of 1.6 and 19.3 μmol/L, respectively. The applicant explained that in consideration of the clinical blood concentrations of the above drugs, concomitant use with any of them may affect metabolism of regorafenib.

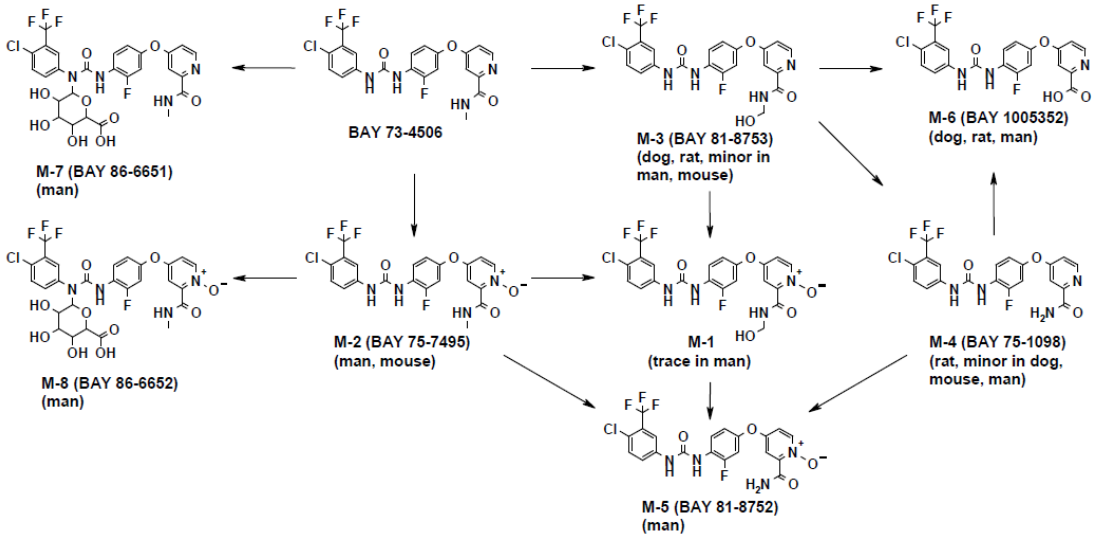
3.(ii).A.(3).2) *In vivo* metabolism

Following single oral dose of 2 mg/kg of ^{14}C-regorafenib to male mice, plasma metabolites were determined. Regorafenib was mainly found in an unchanged form in plasma (85.9%, % of AUC of plasma radioactivity), and M-2 (5.4%), M-3 (3.0%), and M-4 (4.3%) were detected as metabolites.

After single oral or intravenous administration of 2 mg/kg of ^{14}C-regorafenib to male rats and bile duct-cannulated male rats, the metabolites in plasma, urine, feces, and bile were determined. Following oral administration, the plasma regorafenib concentration reached the maximum at 0.25 hours (98.3% of total radioactivity), then decreased with time to 3.5% at 72 hours post-dose and found below the lower limit of quantitation at 96 hours post-dose. On the other hand, concentrations of M-3, M-4, and M-6, which are metabolites in plasma, increased with time. The structures of metabolites in urine have not been identified. The fecal excretion rate of radioactivity up to 96 hours after oral and intravenous administration was 80.1% and 82.9%, respectively. The major metabolites in feces were M-3 and M-6 (27.6%-28.6%, and 29.0%-29.1% of the administered radioactivity, respectively), and regorafenib and M-4 were also detected (8.1%-13.4% and 11.7%-14.7%, respectively). Following oral and intravenous administration, M-6 was mainly found in bile up to 24 hours post-dose (15.7%-23.3% of the administered radioactivity), and regorafenib, M-3, and M-4 were also detected (1.78%-1.89%, 7.61%-8.20%, and 1.11%, respectively).

After single oral or intravenous administration of 2.5 mg/kg of ^{14}C-regorafenib to female dogs, the metabolites in plasma, urine, and feces were determined. Following oral and intravenous administration, the AUC of plasma radioactivity for regorafenib was found the highest (61.6% and 68.7% of the total plasma radioactivity, respectively) among those for radioactive compounds, and metabolites M-3 (20.8% and 19.5%), M-4 (5.5% and 4.0%), and M-6 (11.3% and 6.9%) were detected. The structures of metabolites in urine have not been identified. As a major metabolite in feces, M-6 (70.9%-71.2%) was found, and regorafenib, M-3, and M-4 (1.31%-6.46%, 8.25%-8.35%, and 0.839%-3.75%, respectively) were also detected.

Based on the above *in vitro* and *in vivo* studies, and foreign phase I study (Study 12436) [see "4.(ii).A.(1) Healthy adult subjects"], the applicant explained that the metabolic pathways of regorafenib have been estimated as follows.



Possible metabolic pathways of regorafenib (BAY73-4506)

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

3.(ii).A.(4).1) Urinary, biliary, and fecal excretion

Following single oral or intravenous administration of ^{14}C-regorafenib to male rats at the dose of 2 mg/kg, the total recovery of radioactivity up to 168 hours post-dose (% of the administered dose) was 93.4% to 94.9%, and the urinary and fecal excretion rates were 5.51% to 6.09% and 86.0% to 88.2%, respectively.

Following single oral or intravenous administration of ^{14}C-regorafenib to female dogs at the dose of 2.5 mg/kg, the total recovery of radioactivity up to 168 hours post-dose (% of the administered dose) was 88.3% to 88.7%, and the urinary and fecal excretion rates were 0.746% to 0.817% and 87.4% to 87.6%, respectively.

Following single oral or intravenous administration of ^{14}C-regorafenib to bile duct-cannulated male rats at the dose of 2 mg/kg, the total recovery of radioactivity up to 24 hours post-dose (% of the administered dose) was 98.5% for oral dose and 90.9% for intravenous dose. Excretion rates after oral and intravenous administration were 33.6% and 43.4% in bile, respectively; 1.94% and 1.44% in urine, respectively; and 10.1% and 8.23% in feces, respectively. Based on the above data, the applicant explained that regorafenib is mainly excreted into bile/feces in rats; and into feces in dogs in which the biliary excretion has not been examined.

3.(ii).A.(4).2) Milk excretion

Following single oral dose of 2 mg/kg of ^{14}C-regorafenib to lactating female rats (8 days after delivery), the milk excretion of the radioactivity was determined. The milk excretion rate of radioactivity up to 48 hours post-dose (% of the administered dose) was 49.4%, and the AUC ratio of radioactivity in milk to that in plasma was 6.8. Based on the above data, the applicant explained that regorafenib is excreted into milk.

3.(ii).A.(5) Pharmacokinetic interaction

3.(ii).A.(5).1) Enzyme inhibition

Substrates of CYP isoforms (CYP1A2, 2B6, 2C8, 2C9, 2D6, 3A4) were incubated with human liver microsome in the presence of regorafenib (1.0-100 μmol/L, depending on CYP isoforms). Regorafenib inhibited metabolisms of CYP2B6, 2C8, 2C9, 2D6, and 3A4 substrates with the IC_{50} values of 8.1, 1.7, 2.7, 38, and 5.8-49 μmol/L, respectively. The K_i value of regorafenib against

metabolism of the CYP2B6 substrate was 5.2 μmol/L. On the other hand, regorafenib did not inhibit metabolism of the CYP1A2 substrate even at the highest concentration (50 μmol/L). Time-dependent inhibitory effects of regorafenib against CYP3A4 were examined; when regorafenib was incubated with human liver microsome in the presence of nicotinamide adenine dinucleotide phosphate (NADPH) for 15 minutes, it did not show time-dependent inhibition against CYP3A4.

Substrates of CYP isoforms (CYP2A6, 2C8, 2C9, 2C19, 2E1, 3A4) were incubated with recombinant CYP in the presence of regorafenib (0.59-250 μmol/L, depending on CYP isoforms). Regorafenib inhibited CYP2C8, 2C9, 2C19, and 3A4 with the K_i values of 0.6, 4.7, 16.4, and 11.1 μmol/L, respectively. On the other hand, regorafenib did not inhibit CYP2A6 and 2E1 even at the highest concentration (50 μmol/L for CYP2A6 substrate, 250 μmol/L for CYP2E1 substrate).

Substrates of CYP isoforms (CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 3A4) were incubated with human liver microsome in the presence of M-2 and M-5 (1.6-50 μmol/L for both) to evaluate inhibitory effects of the metabolites against CYP isoforms. M-2 inhibited metabolism of the CYP2B6, 2C8, 2C9, 2D6, and 3A4 substrates with the IC_{50} values of 20, 2.4, 6.1, 13, and 9.5 to 22 μmol/L, respectively. The K_i values of M-2 against metabolism of the CYP2C8, 2C9, 2D6, and 3A4 substrates were 1.0, 0.8, 7.8, and 4.0 μmol/L, respectively. On the other hand, M-2 did not inhibit metabolism of the CYP1A2, 2A6, 2C19, and 2E1 substrates even at the highest concentration (50 μmol/L). M-5 inhibited metabolism of the CYP2B6 and 2C8 substrates with the IC_{50} values of 47 and 2.5 μmol/L, respectively. The K_i value of M-5 against metabolism of the CYP2C8 substrate was 1.3 μmol/L. M-5 did not inhibit metabolism of the CYP1A2, 2A6, 2C9, 2C19, 2D6, 2E1, and 3A4 substrates even at the highest concentration (50 μmol/L). Time-dependent inhibitory effects of M-2 and M-5 against CYP3A4 were examined. When the metabolites were incubated with human liver microsome in the presence of NADPH for 30 minutes, both did not show time-dependent inhibitory effect against CYP3A4.

The CYP2J2 substrate was incubated with recombinant CYP in the presence of M-2 and M-5 (1.6-50 μmol/L for both). M-2 inhibited metabolism of the CYP2J2 substrate with the IC_{50} value of 32 μmol/L. On the other hand, M-5 did not inhibit metabolism of the CYP2J2 substrate even at the highest concentration (50 μmol/L).

The applicant explained that, in consideration of the mean C_{max} of regorafenib, M-2, and M-5 following multiple oral doses of regorafenib 160 mg to cancer patients (approximately 8, 6, and 6 μmol/L, respectively) and the K_i values of regorafenib, M-2, and M-5 against each CYP isoforms, it has been suggested that concomitant use of regorafenib with CYP2B6, 2C8, 2C9, or 3A4 substrate may cause pharmacokinetic interactions.

Substrates of UGT isoforms (UGT1A1, 1A6, 1A9, 2B7, etc.) were incubated with human liver microsome in the presence of regorafenib (0.1-200 μmol/L). Regorafenib inhibited metabolism of the UGT1A1 and 1A9 substrates with the K_i values of 0.7 to 3.1, and 2.1 μmol/L, respectively. On the other hand, regorafenib did not inhibit metabolism of the UGT1A6 and 2B7 substrates even at the highest concentration (100 μmol/L). The applicant explained that regorafenib does not affect glucuronidation of acetaminophen and estradiol 17-glucuronide because the IC_{50} values of regorafenib against conjugation of these substrates by various UGT were >100 and 45.6μmol/L, respectively.

When the UGT1A4 substrate was incubated with recombinant UGT1A4 in the presence of regorafenib (10-100 μmol/L), regorafenib did not inhibit UGT1A4.

Substrates of UGT isoforms (UGT1A1, 1A4, 1A6, 1A9, 2B7, etc.) were incubated with human liver microsome in the presence of M-2 and M-5 (0.05-50 μmol/L for both) to evaluate inhibitory effects of the metabolites against UGT isoforms. Both M-2 and M-5 inhibited metabolism of the

UGT1A1 and 1A9 substrates. The IC_{50} values of M-2 were 1.6 to 1.9 and 8.3 μmol/L, respectively, and those of M-5 were 1.8 to 2.0 and 15.8 μmol/L, respectively. The K_i values of M-2 against metabolism of UGT1A1 and 1A9 substrates were 0.6 and 4.3 μmol/L, respectively, and that of M-5 against metabolism of UGT1A1 substrate was 1.1 μmol/L. The IC_{50} values of M-2 and M-5 against UGT1A4, 1A6, and 2B7 substrates were all >25 μmol/L. The applicant explained that M-2 and M-5 do not affect glucuronidation of estradiol 17-glucuronide because the IC_{50} values of these metabolites against conjugation of the substrate by various UGT were all >5 μmol/L.

The applicant further explained that in consideration of the mean C_{max} of regorafenib, M-2 and M-5 following multiple oral doses of regorafenib 160 mg to cancer patients (approximately 8, 6, and 6 μmol/L, respectively) and the K_i values of regorafenib, M-2, and M-5 against each UGT isoforms, it has been suggested that concomitant use of regorafenib with either UGT1A1 or UGT1A9 substrate may cause pharmacokinetic interactions.

In the presence of regorafenib, M-2, M-3, M-4, and M-5 (1.0-20 μmol/L), ^{14}C-labeled fluorouracil (5-FU) was incubated with human liver cytosol, the inhibitory effects of regorafenib and the metabolites against metabolism of 5-FU by dihydropyrimidine dehydrogenase (DPD) were investigated. As a result, any of regorafenib, M-2, M-3, M-4, or M-5 did not inhibit DPD even at the highest concentration. Based on the finding, the applicant explained that in the case of concomitant use of regorafenib with 5-FU, regorafenib and the metabolites are unlikely to affect the PK of 5-FU.

3.(ii).A.(5).2) Enzyme induction

Human hepatocytes were treated with regorafenib (5-1000 ng/mL) for 5 days to evaluate enzyme activities of CYP1A2, 2B6, 2C19, and 3A4. Treatment of regorafenib did not increase the enzyme activities of any CYP isoforms.

Based on the above data, the applicant explained about the enzyme induction of regorafenib as follows:

Available data suggest that regorafenib does not induce CYP1A2, 2B6, 2C19, and 3A4 at up to approximately 1000 ng/mL. *In vitro* analysis showed that the f_u of regorafenib in hepatocyte culture medium (10% fetal bovine serum) used in this study was 41.2%, therefore, the concentration of unbound regorafenib in a medium at the nominal concentration of 1000 ng/mL was considered to be 412 ng/mL. In consideration of the f_u of regorafenib in human plasma [see "3.(ii).A.(2).2) Plasma protein binding and distribution in blood cells"], regorafenib 1000 ng/mL used in this study is comparable to human plasma containing regorafenib at the total concentration of approximately 84 mg/L. The concentration is at least 20 times higher than the mean C_{max} (3.9 mg/L) of regorafenib following multiple oral doses to cancer patients at the dose of 160 mg. Based on the above grounds, regorafenib is unlikely to cause pharmacokinetic interactions through induction of CYP isoforms studied.

3.(ii).A.(5).3) Transporters

The transport of regorafenib (0.2, 2, and 10 μmol/L) via P-glycoprotein (P-gp) in pig kidney cell-derived LLC-PK1 cell line expressing human P-gp (L-MDR1 cell line) was investigated. The apparent elimination ratios ($P_{app\ B\rightarrow A}/P_{app\ A\rightarrow B}$) of regorafenib at 10 μmol/L in LLC-PK1 and L-MDR1 cell lines were 0.093 and 0.30, respectively. The applicant explained that the apparent elimination ratios of regorafenib at 0.2 and 2 μmol/L could not be calculated because the concentration of permeated regorafenib was below the lower limit of quantitation (2.0 μg/L) in some samples. In the absence and presence of ivermectin, which is known to inhibit P-gp, the $P_{app\ A\rightarrow B}$ values of regorafenib at 2 μmol/L in L-MDR1 cell line were 67 and 40 nm/sec, respectively; that is, inhibition of P-gp did not result in major changes.

The transport of regorafenib (0.2, 2, 10 μmol/L) via human breast cancer resistance protein (BCRP) in dog kidney cell-derived MDCK II cell line expressing human BCRP (MDCK II-BCRP cell line) was investigated. The apparent elimination ratios ($P_{app\ B\rightarrow A}/P_{app\ A\rightarrow B}$) of regorafenib at 10 μmol/L in MDCK II and MDCK II-BCRP cell lines were 0.030 and 0.036, respectively. The applicant explained that the concentration of permeated regorafenib was below the lower limit of quantitation in some samples, and the apparent elimination ratios of regorafenib at 0.2 and 2 μmol/L could not be calculated. In the absence and presence of Ko143, which is known to inhibit BCRP, the $P_{app\ A\rightarrow B}$ values of regorafenib at 2 μmol/L in MDCK II-BCRP cell line were 209 and 156 nm/sec, respectively; that is, inhibition of BCRP did not result in major changes.

The transportation of regorafenib (0.2-10 μmol/L) via human organic anion transport polypeptide (OATP) in human embryonic kidney cell-derived HEK293 cell line expressing OATP1B1 (HEK-OATP1B1 cell line) and in HEK293 cell line expressing OATP1B3 (HEK-OATP1B3 cell line) were investigated. The active OATP1B1-mediated uptake rate, which was calculated from differences of the uptake rate of regorafenib between HEK-OATP1B1 and HEK293 cell lines, was -77.5 to -0.767 pmol/min/mg protein at 1.5 minutes after addition of regorafenib (0.2-10 μmol/L). The active OATP1B3-mediated uptake rate was -3.92 to 14.1 pmol/min/mg protein at 2.5 minutes after addition of regorafenib (0.5-10 μmol/L).

Based on the above data, the applicant explained that regorafenib is not a substrate of P-gp, BCRP, and OATP1B1 and 1B3.

The inhibitory effects of regorafenib (0.03-30 μmol/L) against the transport of digoxin and dipyridamole via P-gp in L-MDR1 cell line were investigated. Regorafenib inhibited apparent outputs of digoxin and dipyridamole with IC_{50} values of 0.78 or 3.4 and 2.3 μmol/L, respectively.

The inhibitory effects of regorafenib (0.01-1 μmol/L) against the transport of 2-amino-1-methyl-6-phenylimidazo [4,5-*b*] pyridine (PhIP) via nogitecan and BCRP in MDCK II-BCRP cell line were investigated. Regorafenib inhibited apparent outputs of nogitecan and PhIP with IC_{50} values of 44.8 and 67.7 nmol/L, respectively.

The inhibitory effects of regorafenib (1, 10 μmol/L) against the transport of pravastatin via OATP1B1 and 1B3 in HEK-OATP1B1 and HEK-OATP1B3 cell lines were investigated. The applicant explained that regorafenib at 1 and 10 μmol/L did not affect the active uptake rates via OATP1B1 and OATP1B3; that is, it did not inhibit OATP1B1 or 1B3.

The inhibitory effects of regorafenib (0.5, 10 μmol/L) against the transport of ^{3}H-labeled p-aminohippurate (human organic anion transporter [OAT] 1 substrate), estrone sulfate (OAT3 substrate) and 1-Methyl-4-phenylpyridinium iodide (MPP, an organic cation transporter [OCT] 2 substrate) via OAT and OCT in HEK293 cell line expressing OAT1 and OAT3 or OCT were determined. The applicant explained that in the presence of regorafenib at 0.5 and 10 μmol/L, the transport of the respective substrates via OAT1, OAT3, or OCT2 were 107% to 140%, 93% to 112%, and 98% to 109% of that of the vehicle control; that is, it did not inhibit OAT1, OAT3, or OCT2.

Based on the above, the applicant explained that concomitant use of regorafenib with a substrate of P-gp or BCRP may cause pharmacokinetic interactions in clinical settings in consideration of the finding of its inhibitory effects against P-gp and BCRP and its plasma concentration following multiple oral doses to cancer patients at the dose of 160 mg.

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

Based on the submitted data and the following evaluations, PMDA concluded that the explanations of the applicant about the absorption, distribution, metabolism, excretion, and pharmacokinetic interactions of regorafenib are acceptable except for a part of the pharmacokinetic interactions described below.

Pharmacokinetic interaction

Based on the non-clinical study data, the applicant explained about the pharmacokinetic interactions of regorafenib and the metabolites (M-2, M-5) as follows:

- Concomitant use of regorafenib with substrates of CYP2B6, 2C8, 2C9, and 3A4 may cause pharmacokinetic interactions [see "3.(ii).A.(5).1) Enzyme inhibition"].
- Concomitant use of regorafenib with substrates of UGT1A1 and 1A9 may cause pharmacokinetic interactions [see "3.(ii).A.(5).1) Enzyme inhibition"].
- Concomitant use of regorafenib with substrates of P-gp and BCRP may cause pharmacokinetic interactions [see "3.(ii)A.(5).3) Transporters"].

Based on the clinical study data, the applicant explained about the pharmacokinetic interactions of regorafenib and metabolites (M-2, M-5) as follows:

- Study 12434, in which various CYP probe substrates were concomitantly administered, suggests that regorafenib may have an inhibitory action against CYP2C9, while its inhibitory actions against CYP2C8, 2C19, and 3A4 were mild enough to be clinically insignificant or absent [see "4.(ii).A.(3).2) Concomitant administration study of various CYP probe substrates"].
- In Study 11656 in which regorafenib was concomitantly administered with the combination chemotherapy regimen of 5-FU, calcium folinate, and oxaliplatin (mFOLFOX6) or of 5-FU, calcium folinate, and irinotecan (FOLFIRI), the AUC value of SN-38, a substrate of UGT1A1, increased, suggesting that regorafenib may inhibit glucuronidation of SN-38 [see "4.(ii).A.(3).1) Drug interaction study with mFOLFOX6 or FOLFIRI"].

PMDA asked the applicant to explain a clinical study plan evaluating the pharmacokinetic interactions of regorafenib and transporters.

The applicant responded as follows:

By the time of regulatory submission in Japan, a clinical study evaluating pharmacokinetic interactions of regorafenib via P-gp and BCRP had not been conducted. However, based on the discussion with foreign regulatory authorities, the applicant is preparing a plan of the clinical study evaluating pharmacokinetic interactions of regorafenib and P-gp or BCRP substrate.

PMDA considers as follows:

Taking account of the K_i value of M-2 against CYP2D6 [see "3.(ii).A.(5).1) Enzyme inhibition"] as well as the plasma concentrations of regorafenib and the metabolites (M-2, M-5) following multiple oral doses of regorafenib 160 mg to cancer patients, it cannot be ruled out that regorafenib and the metabolites may cause pharmacokinetic interactions by inhibiting CYP2D6. In addition to the above, in consideration of *in vitro* study data [see "3.(ii).A.(5).1) Enzyme inhibition" and "3.(ii).A.(5).3) Transporters"], Study 12434 data [see "4.(ii).A.(3).2) Concomitant administration study of various CYP probe substrates"], and Study 11656 data [see "4.(ii).A.(3).1) Drug interaction study with mFOLFOX6 or FOLFIRI"], it is necessary to appropriately provide information about possibilities that regorafenib and the metabolites may cause pharmacokinetic interactions by inhibiting CYP2B6, 2C9, 2D6 and 3A4, UGT1A1 and 1A9 as well as P-gp and BCRP, based on the non-clinical and clinical data currently available.

PMDA considers that information on the pharmacokinetic interactions of regorafenib are important, and it is necessary to continuously collect information including data from the planned

study on the pharmacokinetic interactions with P-gp and BCRP substrates and to appropriately provide useful information when they become available.

3.(iii) Summary of toxicology studies

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

In *in vitro* studies, regorafenib anhydride was used. In *in vivo* studies, povidone-based [redacted] containing 10 % regorafenib was used unless otherwise specified.

In this section, doses and concentrations of the study drug and comparator are all expressed on the anhydride basis unless otherwise specified and regorafenib hydrate is referred to as "regorafenib." A part of the studies were conducted under non-GLP application, and the corresponding data are submitted as reference data.

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

3.(iii).A.(1).1) Rodent

Following oral administration of regorafenib to female NMRI mice and female Wistar rats at the dose of 250 mg/kg, which was the maximum dose for these animals, no toxicity findings were observed, and the approximate lethal dose was thus judged to be >250 mg/kg.

3.(iii).A.(1).2) Non-rodent

Although any single dose toxicity study in non-rodent animals have not been conducted, in the 4-week and 13-week repeated oral dose studies, regorafenib was administered to male and female beagles at the doses of 5, 20, and 80 mg/kg/day to evaluate acute toxicity of regorafenib. Increased incidences of loose stool and diarrhea were observed at the maximum dose of 80 mg/kg/day, but no animals died at any dose, and the approximate lethal dose was thus judged to be >80 mg/kg.

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

3.(iii).A.(2).1) Four-week oral dose study in mice

Regorafenib was orally administered at the doses of 0 (placebo control), 5, 20, and 80 mg/kg/day for 4 weeks to male and female ICR mice. At the doses of ≥20 mg/kg/day, reduction in body weight gain was observed, and in males at the doses of ≥20 mg/kg/day and in females at the dose of 80 mg/kg/day, some animals died or were sacrificed moribund in association with regorafenib treatment.

Hematological findings included increases in hemoglobin level and haematocrit (males at 80 mg/kg/day), and clinical chemistry findings included increases in aspartate aminotransferase (AST) (males at 80 mg/kg/day, females at ≥5mg/kg/day), alanine aminotransferase (ALT) (≥20 mg/kg/day), and total protein level (80 mg/kg/day). Gross pathological and histopathological findings included forestomach hyperkeratosis, alternation of incisor dentin (≥5 mg/kg/day), discolored incisor, degeneration of ameloblast (≥20 mg/kg/day), slight to mild glomerulonephropathy (females at ≥20 mg/kg/day), and thickening of femoral growth plate (males at ≥5 mg/kg/day, females at ≥20 mg/kg/day) as well as chondrodysplasia of knee joints (males at ≥5 mg/kg/day, females at 80 mg/kg/day) and sternal joints (males at ≥5 mg/kg/day, females at ≥20 mg/kg/day). VEGF plays an important role in dentinogenesis and calcification, and it has been reported that inhibition of VEGF results in dental lesions such as inflammation, degeneration, and necrosis (*Toxicol Pathol.* 2010;38:267-79). The applicant thus explained that the dental changes observed in this study were attributable to pharmacological effects of regorafenib. However, these effects are limited to teeth that continue to grow rapidly such as those in rodents, and human adult teeth that have stopped growing are unlikely to be affected. Similarly, the applicant explained that findings such as thickening of growth plates and chondrodysplasia are not considered to cause a risk in adult patients whose bones have stopped growing.

3.(iii).A.(2).2) Five-week oral dose study in mice

Regorafenib was orally administered at the doses of 0 (vehicle control), 1, 5, and 20 mg/kg/day for 5 weeks to male and female ICR mice. In the 20 mg/kg/day group, a mild reduction in body weight gain was observed.

Hematological findings included increases in hemoglobin level (males at ≥5 mg/kg/day, females at 20 mg/kg/day) and haematocrit (males at ≥5 mg/kg/day), and clinical chemistry findings included increases in ALT (males at ≥5 mg/kg/day, females at 20 mg/kg/day), AST, and total protein level (20 mg/kg/day). Histopathological findings included decreased eosinophilic corpora lutea and uterus edema (females at ≥5 mg/kg/day), forestomach hyperkeratosis (males at 20 mg/kg/day, females at ≥5 mg/kg/day), increased maturing follicles, and increased incidence of vaginal keratinization (females at 20 mg/kg/day). Findings related to effects on the bones and teeth included alternation of incisor dentin (≥5 mg/kg/day), discolored white incisor, degeneration of ameloblast and odontoblast (20 mg/kg/day), and thickening of epiphyseal growth plate in the sternum (females at 20 mg/kg/day). Development and functions of the corpora lutea are associated with angiogenesis actions of VEGF (*Reprod Biol Endocrinol.* 2003;1:88-95), and inhibition of VEGF results in impaired development and functions of the corpora lutea (*Am J Physiol Cell Physiol.* 2001;280:C1358-66, *Reprod Biol Endocrinol.* 2003;1:88-95). Taking account of the above publication data, the applicant explained that the findings in female reproductive organs, similarly to the effect on bones and teeth, are attributable to the inhibitory actions of regorafenib against VEGFR-related kinases, which impair the luteinization, and development and functions of the corpora lutea, reflecting the consequence of hormonal balance disruption.

Based on the above, the no-observed-adverse-effect level (NOAEL) in this study was determined to be 1 mg/kg/day.

3.(iii).A.(2).3) Four-week oral dose study in rats

Regorafenib was orally administered at the doses of 0 (placebo control), 1, 4, and 16 mg/kg/day for 4 weeks to male and female Wistar rats. Stained fur was observed in males at the doses of ≥4 mg/kg/day and in females at the dose of 16 mg/kg/day. Reduction in body weight gain was observed at the dose of 16 mg/kg/day. Five animals for recovery at the dose of 16 mg/kg/day were sacrificed moribund due to poor general condition approximately 3 weeks after the final dose. The poor general condition was considered as a consequence of decreased food consumption, which was caused by effects of regorafenib on the teeth (growth or fracture).

Hematological findings included increases in red blood cell count, hemoglobin level (≥1 mg/kg/day), and haematocrit (≥4 mg/kg/day) in males and decreases in red blood cell count, hemoglobin level, and haematocrit (16 mg/kg/day) in females. Clinical chemistry findings included increases in ALT (≥1 mg/kg/day), AST (males at ≥4 mg/kg/day, females at 16 mg/kg/day), bilirubin level (males at 4 mg/kg/day, females at ≥4 mg/kg/day), cholesterol level, and thyroid-stimulating hormone (TSH) level (16 mg/kg/day) as well as decreases in total protein, albumin, and thyroxine (T4) level (16 mg/kg/day). Findings related to effects on the kidney included an increase in urine protein excretion (16 mg/kg/day) and glomerulonephropathy (≥4 mg/kg/day) as well as degeneration, regeneration, and dilation of renal tubular (males at ≥1 mg/kg/day, females at 16 mg/kg/day). Findings related to effects on the bones and teeth included alternation of incisor dentin (≥4 mg/kg/day), thickening of femoral growth plate (males at ≥4 mg/kg/day, females at 16 mg/kg/day) as well as chondrodysplasia of knee joint (16 mg/kg/day) and sternal joint (males at 16 mg/kg/day, females at ≥4 mg/kg/day). The other findings included bone marrow hypocellularity in femur (males at ≥4 mg/kg/day, females at 16 mg/kg/day) and sternum (females at ≥4 mg/kg/day), Kupffer cell activation (≥4 mg/kg/day), biliary hyperplasia, forestomach hyperkeratosis, inflammation, degeneration, and regeneration in duodenum, pancreatic atrophy as well as adrenal necrosis and peliosis (16 mg/kg/day). Of the above gross and histopathological findings, Kupffer cell activation as well as those in the duodenum, pancreas,

and adrenal gland were reversible, but the other findings remained even after the recovery period. Findings in the kidney at the dose of 16 mg/kg/day remained even after a 4-week recovery period at the same or significant severity compared to those at the end of administration, and in addition, renal interstitial fibrosis was observed later.

3.(iii).A.(2).4) Thirteen-week oral dose study in rats

Regorafenib was orally administered at the doses of 0 (placebo control), 0.5, 2, and 8 mg/kg/day for 13 weeks to male and female Wistar rats. Reductions in body weight gain were observed in males at the doses of ≥0.5 mg/kg/day and in females at the dose of 8 mg/kg/day, and stained fur was observed in males at the doses of ≥2 mg/kg/day and in females at the dose of 8 mg/kg/day. Some females at the dose of 8 mg/kg/day died or were sacrificed moribund in association with regorafenib treatment.

Hematological findings included increases in hemoglobin level and haematocrit (8 mg/kg/day) in males and decreases in red blood cell count, hemoglobin level, and haematocrit (8 mg/kg/day) in females. Clinical chemistry findings included increases in ALT (≥0.5 mg/kg/day), cholesterol level, triglyceride level, and TSH level (8 mg/kg/day) as well as decreases in total protein, albumin, and T4 level (8 mg/kg/day). Findings related to effects on the kidney included increases in plasma creatinine and urea level (males at 8 mg/kg/day), decreases in urinary creatinine excretion (males at ≥0.5 mg/kg/day, females at 8 mg/kg/day) and urea excretion (males at ≥2 mg/kg/day, females at 8 mg/kg/day), and glomerulonephropathy as well as degeneration, regeneration, and dilatation of renal tubular (males at ≥0.5 mg/kg/day, females at ≥2 mg/kg/day). Findings related to effects on the bones and teeth included alternation of incisor dentin and ameloblast, thickening of femoral growth plate as well as chondrodysplasia of knee joint and sternal joint (8 mg/kg/day). The other findings included Kupffer cell activation (males at ≥0.5 mg/kg/day, females at ≥2 mg/kg/day), periportal cytoplasmic basophilia (males at ≥2 mg/kg/day, females at 8 mg/kg/day), forestomach hyperkeratosis, biliary hyperplasia, adrenal necrosis and peliosis (females at 8 mg/kg/day), and inflammation, degeneration, and regeneration in duodenum as well as pancreatic atrophy (8 mg/kg/day).

Of clinical chemistry findings after a 4-week recovery period, increases in hepatic enzyme levels resolved but the other changes remained unchanged. Histopathological findings included glomerulonephropathy and degeneration and regeneration of renal tubular (males at 2 mg/kg/day, females at ≥2 mg/kg/day) as well as changes in the duodenum, bones, and teeth (8 mg/kg/day).

3.(iii).A.(2).5) Twenty-six-week oral dose study in rats

Regorafenib was orally administered at the doses of 0 (placebo control), 0.1, 0.5, and 2 mg/kg/day for 26 weeks to male and female Wistar rats. Slight reduction in body weight gain in males at the dose of 2 mg/kg/day and stained fur at the dose of 2 mg/kg/day were observed, but no animals died in association with regorafenib treatment.

Hematological findings included increases in red blood cell count, hemoglobin level (males at 2 mg/kg/day, females at ≥0.5 mg/kg/day), and haematocrit (males at 2 mg/kg, females at ≥0.5 mg/kg/day). Histopathological findings included mild glomerulonephropathy, rounded hepatocytes (males at ≥0.5 mg/kg/day, females at 2 mg/kg/day), increased number of corpora lutea (females at ≥0.5 mg/kg/day), periportal cytoplasmic basophilia (2 mg/kg/day) and decreased ovarian follicular cyst (females at 2 mg/kg/day). In addition, non-degenerative thickening of atrioventricular valve (2 mg/kg/day) was observed in the heart. The applicant explained that this finding is "endocardial myxomatous change" in rats (Non-proliferative lesions of the heart and vasculature in rats [*Society of Toxicologic Pathologists*, 2000], *Toxicol Pathol.* 2002;30:483-91, *Ultrasound in Med & Biol.* 2009;35:558-65), which is a spontaneous age-related change; and regorafenib is considered to have intensified the change.

Based on the above, the NOAEL in this study was determined to be 0.1 mg/kg/day.

3.(iii).A.(2).6) Four-week oral dose study in dogs

Regorafenib was orally administered at the doses of 0 (placebo control), 5, 20, and 80 mg/kg/day for 4 weeks to male and female beagle dogs (23-27 weeks of age at the baseline). Mild decrease in body weight gain at the doses of ≥20 mg/kg/day, increased frequency of loose stools or liquid feces in females at the dose of 80 mg/kg/day, and aggravated clinical conditions in 1 female at the same dose at the end of administration (diarrhea with bloody particles and alveolar bleeding) were observed.

Clinical chemistry findings included increases in AST, ALT, glutamate dehydrogenase (GLDH), and γ-glutamyl transferase (GGT) (mainly at 80 mg/kg/day). Histopathological findings included enhanced extramedullary haemopoiesis in the spleen (males at ≥20 mg/kg/day, females at ≥5 mg/kg/day), slight to mild centrilobular hepatocyte hypertrophy (males at 80 mg/kg/day, females at ≥20 mg/kg/day), and pancreatic and thymic atrophy (mainly at 80 mg/kg/day). Glomerulonephropathy associated with hyaline casts in the renal tubules, renal tubular dilatation, mononuclear cell infiltration, and basophilic renal tubules were observed in females at the dose of 80 mg/kg/day. Findings related to effects on the bones and teeth included alternation of incisor and canine dentin (males at ≥5 mg/kg/day, females at ≥20 mg/kg/day), chondrodysplasia of sternal joint (≥20 mg/kg/day), and thickening of epiphyseal growth plate in the femur (80 mg/kg/day). After a 4-week recovery period, biliary hyperplasia in the liver, slight thickening of epiphyseal growth plate in the femur (females at 80 mg/kg/day), and alternation of dental dentin (80 mg/kg/day) were observed. The NOAEL in this study was determined to be 5 mg/kg/day based on the following considerations: the enhanced extramedullary haemopoiesis in the spleen observed in females at the dose of 5 mg/kg/day did not indicate degeneration or necrosis of the cells or tissues; and the alternation of dental dentin observed in males at the dose of 5 mg/kg/day was the effect specific to growing teeth; and the above two findings, therefore, have little toxicological significance.

3.(iii).A.(2).7) Thirteen-week oral dose study in dogs

Regorafenib was orally administered at the doses of 0 (placebo control), 5, 20, and 80 mg/kg/day for 13 weeks to male and female beagles (23-27 weeks of age at the baseline). Reduction in body weight gain, and white mucous stool or bloody stool at the doses of ≥20 mg/kg/day, and loose stool or liquid feces and increased frequency of vomiting at the dose of 80 mg/kg/day were observed, but no animals died.

Clinical chemistry findings included increases in ALT and GLDH (mainly at ≥20 mg/kg/day) as well as bilirubin level (females at 80 mg/kg/day), AST, and alkaline phosphatase (ALP) (80 mg/kg/day). At the doses of ≥5 mg/kg/day, hairless and haircoat sparse conditions were observed, and the histopathological findings included hair growth arrest correlational to these conditions and inflammatory or degenerative lesions in males. The applicant explained that these dermal changes were considered attributable to the pharmacological effects of regorafenib since they had been reported as toxicity findings of anti-VEGF antibody (*J Clin Invest.* 2001;107:409-17). The other findings included degeneration and regeneration of renal tubular, glomerulonephropathy, atrophy, degeneration, and necrosis of the lymphoid tissues, biliary hyperplasia, centrilobular cell hypertrophy, and cytoplasmic changes in the liver, retarded maturation of the male and female reproductive organs, epididymal oligospermia or aspermia (≥20 mg/kg/day), acinar atrophy or degeneration in the pancreas (males at 80 mg/kg/day, females at ≥20 mg/kg/day) as well as increased triglyceride content, centrilobular fat accumulation, and single cell necrosis in the liver (80 mg/kg/day). Findings related to effects on the bones and teeth included alternation of incisor and canine dentin (≥20 mg/kg/day) and persistent femoral epiphyseal growth plate with partial thickening (80 mg/kg/day).

3.(iii).A.(2).8) Fifty-two-week oral dose study in dogs

Regorafenib was orally administered at the doses of 0 (placebo control), 1, 4, and 16 mg/kg/day for 52 weeks to male and female beagle dogs (11-12 months of age at the baseline). At the doses of ≥4 mg/kg/day, deterioration of clinical conditions such as debility, atrophy of skeletal muscle, decreased locomotor activity, and reduction in body weight gain were observed, but no animals died. Scab, loss of hair, and abscess-like lesions (mainly at ≥4 mg/kg/day) were observed. The applicant explained that these findings were mainly caused by hair growth arrest.

Findings related to effects on the kidney included increased urine N-acetyl-β-D-glucosaminidase excretion (16 mg/kg/day), focal segmental glomerulosclerosis (≥4 mg/kg/day), glomerulosclerosis (males at ≥4 mg/kg/day, females at 16 mg/kg/day), reactive epithelial hyperplasia in Bowman's capsule (males at 16 mg/kg/day, females at ≥4 mg/kg/day), and degeneration and regeneration of renal tubular (≥4 mg/kg/day). Findings related to effects on the liver included increases in serum ALT, AST, and GLDH suggesting hepatocyte damage (16 mg/kg/day) as well as increases in serum ALP (≥4 mg/kg/day) and GGT (16 mg/kg/day) suggesting cholestasis. Histopathological findings included microgranuloma and increased frequency or severity of perivascular mononuclear cell infiltration (≥4 mg/kg/day). Findings in male and female reproductive organs included epithelial vacuolar degeneration in the epididymis (1 mg/kg/day, 16 mg/kg/day) as well as slightly to mildly increased multinucleated giant cells (≥1 mg/kg/day) and slight to mild atrophy in the seminiferous tubules (1, 16 mg/kg/day) in males, and included slight to severe cystic glandular dilatation with or without lumenal dilatation in the uterus (≥4 mg/kg/day) as well as mildly increased follicular degeneration (≥4 mg/kg/day), moderately reduced follicular development, cystic corpora lutea, and mild follicular cyst in the ovaries (16 mg/kg/day) in females. In addition, mineralization was observed in the epididymis (≥1 mg/kg/day) and ovaries (1, 4 mg/kg/day). The other findings included inflammatory and degenerative lesions in the gallbladder (increased mucosal lymphoid follicles, concentrated bile, calculus, and epithelial hyperplasia potentially attributable to the inflammatory process in the gallbladder) (mainly at ≥4 mg/kg/day), enhanced extramedullary haemopoiesis in the spleen (≥4 mg/kg/day), mild hyperplasia in the lymphoid tissues, thymic atrophy (16 mg/kg/day), and mineralization in the thyroid gland (males at ≥4 mg/kg/day, females at 1 and 16 mg/kg/day). In this study, which included adult animals, no effects on the bones or teeth were observed.

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

As genotoxity studies, a bacterial reverse mutation assay, a chromosomal aberration assay using cultured mammalian cells (Chinese hamster ovary V79 cells), and an intraperitoneal mouse bone marrow micronucleus assay were conducted. In any assay, regorafenib did not show genotoxicity.

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

Regorafenib is an antineoplastic drug for treatment of advanced cancers. No carcinogenicity test has been conducted.

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

For regorafenib, neither studies for fertility and early embryonic development nor ones for pre- and postnatal development have been conducted, because the mechanism of action and general toxicity data of the drug indicate that it can affect the male and female fertility and pre- and postnatal development as it is an antineoplastic drug for treatment of advanced cancers. To investigate the reproductive and developmental toxicity, studies for effects on embryo-fetal development were conducted in rats and rabbits. In the study in rabbits, the ratio of exposure at the NOAEL (0.4 mg/kg/day) on the embryo-fetal development to the clinical exposure* was ≤1. In rats, the placental permeability and milk excretion of regorafenib were observed [see "3.(ii).A.(2).3) Placental permeability and fetal transfer and "3.(ii).A.(4).2) Milk excretion"].

*: In the Japanese phase I study (Study 13172) in Japanese patients with solid tumor, the mean AUC_{0-24} following once daily oral administration of regorafenib 160 mg for 3 weeks (Day 21) was 33.0 mg·h/L.

3.(iii).A.(5).1) Pilot study for effects on embryo-fetal development in rats (Reference data)

Regorafenib was orally administered at the doses of 0 (placebo control), 0.1, 0.3, 0.5, 0.8, 1.0, 1.6, and 2.0 mg/kg/day to pregnant Wistar rats from Gestation day 6 to 17. Findings in dams included mild signs of toxicity in the 1.6 mg/kg/day group as well as reddish vaginal discharge, mild decrease in body weight, and reduction in body weight gain in the 2.0 mg/kg/day group. Findings in embryos and fetuses included delayed ossification in the ≥0.5 mg/kg/day group as well as increased frequencies of skeletal variation and skeletal malformation such as additional lumbar in the ≥1.0 mg/kg/day group. In the ≥1.6 mg/kg/day group, increased postimplantation loss, decreases in placental and fetal weights, and increased incidence of visceral malformations such as ventricular septal defect, right aortic arch, and diaphragmatic hernia were observed.

Based on the above, the NOAEL in this study was determined to be 1.0 mg/kg/day on general toxicity in dams and 0.3 mg/kg/day on embryo-fetal development.

3.(iii).A. (5).2) Pilot study for effects on embryo-fetal development in rabbits (Reference data)

Regorafenib was orally administered at the doses of 0 (placebo control), 0.5, 1.0, 1.6, and 2.0 mg/kg/day to pregnant Himalayan rabbits from Gestation day 6 to 20. In dams, decreased food consumption, decrease in body weight, decreased pregnancy rate due to total embryonic resorption, and increased postimplantation loss were observed in the 2.0 mg/kg/day group. Evaluation on the embryos and fetuses in the 1.6 and 2.0 mg/kg/day groups included only 1 dam with 5 live fetuses in the 2.0 mg/kg/day group and 3 dams with one live fetus in the 1.6 mg/kg/day group. Visceral findings in the fetuses included renal pelvis dilatation in 1 fetus in the 0.5 mg/kg/day group and kidney malformation in 4 of 5 fetuses in the 2.0 mg/kg/day group. The NOAEL in this study was determined to be 1.6 mg/kg/day for general toxicity in dams.

3.(iii).A. (5).3) Study for effects on embryo-fetal development in rabbits

Regorafenib was orally administered at the doses of 0 (placebo control), 0.4, 0.8, and 1.6 mg/kg/day to pregnant Himalaya rabbits from Gestation day 6 to 20. In dams, total embryonic resorption (4 of 20 dams) and increased postimplantation loss were observed in the 1.6 mg/kg/day group. Of dams with total embryonic resorption, 2 dams showed slight to mild decrease in body weight. Findings in embryos and fetuses included ventricular septal defect in the ≥0.4 mg/kg/day group as well as cardiovascular and urinary malformations such as tricuspid atresia and hydronephrosis and skeletal anomalies in the ≥0.8 mg/kg/day group. The applicant explained that the ventricular septal defect may be caused by the kinase inhibitory activity of regorafenib against VEGFR, as it has been reported that VEGF is involved in the heart development, and changes in VEGF expression etc. result in heart malformation (*Development.* 2000;127:3941-46, *Development.* 2001;128:1531-38, *Nat Med.* 2003;9:173-82). However, the finding was not dose-dependent, and the incidence at the dose of 0.4 mg/kg/day fell within historical control data range, thus, ventricular septal defect observed in the 0.4 mg/kg/day group was considered to be unrelated to regorafenib.

Based on the above, the NOAEL was determined to be 0.8 mg/kg/day in dams and 0.4 mg/kg/day in embryos and fetuses.

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

No local tolerance studies have been conducted, but local tolerance of regorafenib was evaluated in repeat dose studies in rodents and dogs. The esophagus and forestomach hyperkeratosis observed in mice and rats were considered as findings related to local tolerance of regorafenib.

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

3.(iii).A.(7).1) Photosafety testing

Since regorafenib, M-2 (BAY 75-7495), and M-5 (BAY 81-8752), which are major metabolites in humans, absorb near-ultraviolet light, their phototoxicity were evaluated in *in vitro* and *in vivo* studies. An *in vitro* study in mouse 3T3 fibroblasts (Study 3T3 NRU) suggested that regorafenib, M-2, and M-5 may have phototoxicity. To elucidate phototoxicity of regorafenib and M-5 further, a local lymph node assay (LLNA) was performed following oral administrations of regorafenib and M-5 to NMRI mice, but no phototoxicity was detected.

As M-2 showed a weak relative reaction in Study 3T3 NRU, LLNA for M-2 was not performed. However the incidences of adverse events related to phototoxicity were low in clinical studies with no difference between regorafenib and placebo groups. In addition, events related to phototoxicity were all at Grade 1, and no serious adverse events were reported.

Based on the phototoxicity and clinical data, regorafenib, M-2, and M-5 are considered unlikely to cause phototoxicity.

3.(iii).A.(7).2) Toxicity of metabolites

Although the exposures of M-2 and M-5 reached the same levels as that of unchanged form after multiple oral dose of regorafenib in cancer patients [see "4.(ii).A.(2) Cancer patients"], M-2 and M-5 are detected at limited levels or not detected in animal plasma [see "3.(ii).A.(1) Absorption," and "3.(ii).A.(3).2) *In vivo* metabolism"], and both metabolites have pharmacological activities [see "3.(i).A.(1).2).i).(b) Pharmacological effects of metabolites," and "3.(i).A.(2) Secondary pharmacodynamics"]. Therefore, for each of M-2 and M-5, mouse 4-week repeat dose, genotoxicity, and phototoxicity studies were conducted.

(a) Four-week oral dose toxicity study in mice for M-2

M-2 was orally administered at the doses of 0 (vehicle control), 1, 5, and 20 mg/kg/day for 4 weeks to male and female ICR mice. No animals died in association with M-2. Histopathological findings included alternation of incisor dentin (20 mg/kg/day) and slightly enhanced extramedullary haemopoiesis in the liver (in females at 20 mg/kg/day). The NOAEL of M-2 in this study was determined to be 5 mg/kg/day. The mean $AUC_{0\text{-}24,ss}$ of M-2 at the NOAEL (11.5 mg･h/L) was almost comparable to that of M-2 at the clinical dose in humans (160 mg QD) (15.6 mg･h/L) (the $AUC_{0\text{-}24}$ at the steady state [$AUC_{0\text{-}24,ss}$] for unbound M-2 at the NOAEL in this study was approximately 3 times higher than that at the clinical dose in humans). In addition, due to biotransformation from M-2 to regorafenib, the exposure of regorafenib reached 0.7 times that of M-2 in mice. The applicant explained that the toxicity of M-2 is lower than that of regorafenib, and contribution of M-2 to the toxicity profile of regorafenib may be limited.

(b) Four-week oral dose toxicity study in mice for M-5

M-5 was orally administered at the doses of 0 (vehicle control), 1, 5, and 20 mg/kg/day for 4 weeks to male and female ICR mice. No animals died in association with M-5. Decreased lymphocyte count, increased segmented neutrophil count, and mild hypocellularity in bone marrow (males at 20 mg/kg/day), and alternation of incisor dentin (females at 20 mg/kg/day) were observed. The NOAEL of M-5 in this study was determined to be 5 mg/kg/day. The mean $AUC_{0\text{-}24,ss}$ of M-5 at the NOAEL (15.0 mg･h/L) was approximately 2 times higher than that at the clinical dose in humans (160 mg QD) (7.12 mg･h/L) (the $AUC_{0\text{-}24,ss}$ of unbound M-5 at the NOAEL in this study was approximately 16 times higher than that at the clinical dose in humans). The applicant explained that the toxicity of M-5 is lower than that of regorafenib, and contribution of M-5 to the toxicity profile of regorafenib may be limited.

(c) Genotoxicity of M-2

As genotoxity studies of M-2, a bacterial reverse mutation assay and a chromosomal aberration assay using cultured mammalian cells (Chinese hamster ovary V79 cells) were conducted. The reverse mutation assay produced a negative result. The chromosomal aberration assay using cultured mammalian cells showed an increased incidence of chromosomal aberrations. The concentration at which the increased incidence of chromosomal aberrations was observed is the level at which the cytotoxicity is clearly observed and which is approximately 27 times (without metabolism activation) or 72 times (with metabolism activation) higher than the plasma concentration of M-2 in clinical studies of regorafenib. In the micronucleus assay of regorafenib, the drug was intraperitoneally administered up to 2000 mg/kg to the mice that had demonstrated M-2 generation in the repeat-dose toxicity test, which produced negative results.

(d) Genotoxicity of M-5

As genotoxity studies of M-5, a bacterial reverse mutation assay and a chromosomal aberration assay using cultured mammalian cells (Chinese hamster ovary V79 cells) were conducted. In any assay, M-5 did not show genotoxicity.

3.(iii).A.(7).3) Toxicity studies of impurities

(a) Impurity B

The safety of Impurity B was evaluated in a bacterial reverse mutation assay; no mutagenicity was observed. The safety of Impurity B contained in the drug substance at the level above the qualification threshold was discussed based on the toxicity data of regorafenib obtained from the lots containing the impurity and genotoxicity data of the impurity [see "3.(iii).B.(2) Impurity B"].

(b) Impurity A

Impurity A is a process-related impurity contained in the drug substance, and was also detected in the drug product as a degradation product during the manufacturing and storage. The safety of the impurity was evaluated in the bacterial reverse mutation assay as well as micronucleus assay and liver comet assay in rats.

In the micronucleus assay, the impurity did not induce mutations up to the maximum dose of 500 mg/kg, but in the reverse mutation assay, mutations were observed, and the comet assay indicated that it may induce early DNA damage in hepatocytes at the doses of ≥125 mg/kg.

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

PMDA concluded that clinical use of regorafenib is acceptable in consideration of the seriousness of the disease for which it is intended to be indicated, although the drug has no safety margin as most of the toxicity findings in animals occurred at levels comparable to clinical exposure in humans or lower. However, PMDA considers that pregnant women and women who may be possibly pregnant should not receive regorafenib, since teratogenicity was observed in the studies for effects of regorafenib on embryo-fetal development.

3.(iii).B.(1) Use of regorafenib in pregnant women and women who may be possibly pregnant

PMDA asked the applicant to explain the reasons for proposing the use of regorafenib in pregnant women and women who may be possibly pregnant as "only if the expected therapeutic benefits outweigh the possible risks associated with treatment" in the package insert.

The applicant responded as follows:

If regorafenib is given to pregnant women and women who may be possibly pregnant, the effects on the embryos and fetuses cannot be ruled out, because reproductive and developmental toxicity studies of regorafenib showed that regorafenib has a teratogenic potential and embryonic lethal action, and non-clinical pharmacokinetic studies indicated that the drug can cross the blood-

placenta barrier. However, as poor prognosis is predicted in the patients for whom regorafenib is indicated, the applicant considered that drugs which were confirmed to extend the overall survival significantly were medically important, and that it would be therefore desirable to provide regorafenib as a treatment option to patients who are pregnant or may be possibly pregnant under conditions where the safety information and precautions are provided in the package insert. The package insert would thus include findings in the embryo-fetal development studies such as postimplantation loss and fetal malformations. The applicant therefore described the above in the package insert.

PMDA considers as follows:
In the embryo-fetal development studies, fetal malformations involving critical organs such as heart malformation were observed due to administration of regorafenib even at low dose levels, and thus the risk at the clinical dose could be high. For this reason, regorafenib should be contraindicated in pregnant women and women who may be possibly pregnant.

3.(iii).B.(2) Impurity B
The applicant explained about the safety of Impurity B contained in the drug substance at the level above the qualification threshold as follows:
The applicant considered that lots containing Impurity B at a concentration up to the upper limit of the acceptance criterion may be used, based on the following evaluation of the toxicity data of regorafenib obtained from the lots containing the impurity.

- In a mouse 4-week repeat dose study of regorafenib in which the impurity was administered at a dose ([redacted]μg/kg/day) equivalent to approximately 20 times the maximum clinical dose, no distinct toxicity findings were observed except for those attributable to the actions of regorafenib.
- The toxicity findings observed at the maximum tolerated dose ([redacted]μg/kg/day as the impurity) in the mouse 4-week repeat dose study (alternation of dental dentin, thickening of bone growth plate) are unlikely to occur in adult patients for whom regorafenib is indicated.
- Data comparison between the rat 13-week repeat dose toxicity study using the drug product lot with the impurity undetectable and the rat 26-week repeat dose toxicity study using the lot containing it ([redacted]μg and [redacted]μg/kg/day as the impurity) indicated that the findings in the latter study were mostly caused by the actions of regorafenib, and the impurity hardly contributed to development of the toxicities.

PMDA considers as follows:
With respect to the findings which were not observed in the rat 13-week repeat dose toxicity study but were observed in the rat 26-week repeat dose study (mild increases in white blood cell count and lymphocyte count, increased frequency of atrioventricular valve thickening, etc.), the causality with the impurity cannot be ruled out, but in consideration of the severity and toxicological significance, the toxicity of the impurity will not substantially outweigh that of regorafenib. In consideration that mutagenicity was not indicated in the genotixicty study of the impurity, drug products that contain the impurity even at a level up to the upper limit of the acceptance criterion are unlikely to raise safety concerns related to this impurity.

3.(iii).B.(3) Impurity A
PMDA asked the applicant to explain the carcinogenicity risk of the impurity as the bacterial reverse mutation assay of the impurity indicated mutagenicity.

The applicant responded as follows:
As Impurity A has an aromatic primary amine, aryl nitrenium ion, which may bind to DNA as with the other aromatic amines, is considered to be a final mutagen. However, the carcinogenicity

risk of the impurity is considered insignificant for the following reasons: based on the carcinogenicity data of Chloramben (CAS 133-90-4), which is an aromatic amine with the mutagenicity comparable to that of the impurity or higher (*National Cancer Institute, Carcinogenesis Technical Report Series*, No.25, 1977). The virtually safe dose of Chloramben is 0.0[redacted] mg/kg/day provided that 10^{-5} is set at the acceptable risk; and this safe dose is 19 times the maximum clinical dose estimated from the acceptance criteria of the impurity (0.0[redacted] mg/kg/day). In addition to the above discussion, the applicant also considered that the safety concern may be insignificant even if the impurity is contained at the upper limit of the acceptance criteria, in consideration that the exposure at the no-observed-effect-dose of rat-liver comet assay is 22,000 times the clinical exposure, and that regorafenib is indicated for serious disease.

PMDA accepted the applicant's response.

4. Clinical data

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

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

Oral preparations of regorafenib hydrate (hereinafter referred to as regorafenib) include 2% (w/v) liquid preparation, immediate-release tablets containing [redacted] regorafenib (conventional tablets) (20 mg tablets) and [redacted] ([redacted]) tablets film-coated per Bayer's standard (Bayer's standard film coated [redacted] tablets) (20, 100 mg tablets) as well as [redacted] tablets film-coated with commercially available Opadry [redacted] (Opadry [redacted] film-coated [redacted] tablets) (20, 40 mg tablets). In the foreign phase I study (Study 11650), the liquid preparation, conventional tablets, and Bayer's standard film coated [redacted] tablets were used. In the mass balance study (Study 12436), the liquid preparation was used to examine pharmacokinetics (PK) of regorafenib and metabolites (M-2, M-5). In some of the early clinical studies such as foreign phase I study (Study 11651) and foreign phase II study (Study 11726) etc., Bayer's standard film coated [redacted]tablets were used, while in many clinical studies including the global phase III study (Study 14387), Opadry [redacted] film-coated [redacted] tablets (40 mg tablets), the drug product for marketing, were used.

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

Assay of regorafenib and metabolites (pyridine *N*-oxide form [M-2], *N*-hydroxymethyl form [M-3], amide form [M-4], pyridine *N*-oxideamide form [M-5]) in human plasma was performed by LC-MS/MS method and the lower limit of quantification was 2 to 5 μg/mL.

Assay of regorafenib and M-2 in human urine was performed by LC-MS/MS method. Assay of *N*-glucuronate conjugates of regorafenib and M-2 (M-7 and M-8, respectively) was performed indirectly as regorafenib and M-2, which were released by enzymatic hydrolysis of these *N*-glucuronate conjugates. The lower limit of quantification regorafenib and M-2 in urine was approximately 10 μg/mL, and that of M-7 and M-8 was approximately 14 μg/mL.

4.(i).A.(2) Bioavailability study

4.(i).A.(2).1) Foreign phase I study (5.3.3.2.1, Study 11650 [[redacted] 20[redacted] - ongoing (Data cut-off; [redacted], 20[redacted])])

In the phase I study (Study 11650) in patients with solid cancer, single oral dose of regorafenib 60 mg (conventional tablets 20 mg × 3 tablets or Bayer's standard film coated [redacted] tablets 20 mg × 3 tablets) for Cohort 4 (6 subjects) and 100 mg (Bayer's standard film coated [redacted] tablets 100 mg) for Cohort 6 (7 subjects) were administered in a cross-over manner to examine relative bioavailability (BA) of the tablets to the liquid preparation [for cohorts in the study other than the above ones, see "4.(ii).A.(2).1) Foreign phase I study"].

In Cohort 4, the geometric mean AUC_{last} of the conventional tablets 60 mg and [redacted] tablets 60 mg were 2.16 and 18.4 mg·h/L, respectively, and the relative values to AUC_{last} of the liquid

preparation 60 mg (26.5 mg･h/L) were 8.15% and 69.5%, respectively. In Cohort 6, the geometric mean AUC_{last} of [redacted] tablets 100 mg was 33.8 mg･h/L, and the relative value to AUC_{last} of the liquid preparation 100 mg (40.6 mg･h/L) was 83.2%.

The applicant explained that based on the above data, the development of the conventional tablets was discontinued and [redacted] tablets were used in Study 11650 and the subsequent clinical studies.

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

Foreign phase I study (5.3.1.2.1, Study 12437 [[redacted] 20[redacted] to [redacted] 20[redacted]])

After single oral dose of regorafenib 160 mg (Bayer's standard film coated [redacted] tablets 100 mg tablet × 1, and 20 mg tablet × 3, or Opadry [redacted] film-coated [redacted] tablets 40 mg tablet × 4) to 46 healthy adult subjects in a cross-over manner to examine the relative BA of both drug formulations. The ratios of the AUC and C_{max} of regorafenib and the metabolites (M-2, M-5) (Opadry [redacted] film-coated [redacted] tablets/Bayer's standard film coated [redacted] tablets) are as shown in the table below. The 90% confidence interval (CI) of the ratios of the AUC and C_{max} of regorafenib fell within the range of acceptance criteria for bioequivalence (80%-125%). The AUC and C_{max} of metabolites (M-2, M-5) in Opadry [redacted] film-coated [redacted] tablets were slightly higher than the AUC and C_{max} in Bayer's standard film coated [redacted] tablets.

PK parameter ratios of regorafenib and the metabolites (M-2, M-5)

Compound	Estimated percentage*(%)	
	AUC	C_{max}
Regorafenib	99.73 [92.97, 106.98]	110.88 [100.59, 122.22]
M-2	116.49 [105.01, 129.22]	124.18 [110.16, 139.97]
M-5	124.11 [109.51, 140.66]	116.66 [104.13, 130.71]

Ratio of the geometric mean [90% CI], n = 46, *: PK parameter ratio of Opadry [redacted] film-coated [redacted] tablets to Bayer's standard film coated [redacted] tablets

4.(i).A.(3) Effects of food on PK of regorafenib

Foreign phase I study (5.3.1.1.1, Study 14656 [[redacted] 20[redacted] to [redacted] 20[redacted]])

A cross-over study was conducted in 24 healthy adult subjects to evaluate the effects of food on the PK of regorafenib and the metabolites (M-2, M-5). Subjects were fasted overnight (fasted), had a low-fat breakfast (approximately 319 kcal; fat content, 8.2 g), or had a high-fat breakfast (approximately 945 kcal, fat content 54.6 g), then, single oral dose of regorafenib 160 mg was administered (the table below). The exposure (AUC, C_{max}) of regorafenib was higher in the fed than in the fasted subjects. No clear differences were observed in change rates of the exposure of regorafenib between the two types of breakfast. On the other hand, exposure (AUC, C_{max}) of the metabolites (M-2, M-5) was higher in the low-fat fed than in the fasted subjects, and lower in the high-fat fed than in the fasted subjects.

The applicant explained that the above data suggested that the total exposure of regorafenib and the metabolites following administration of regorafenib to low-fat fed patients was higher than the total exposure following administration to fasted and high-fat fed patients.

PK parameters of regorafenib and the metabolites (M-2, M-5) in fasted, low-fat fed and high-fat fed subjects

Compound		AUC (mg·h/L)	C_{max} (mg/L)	t_{max}* (h)	$t_{1/2}$ (h)
Regorafenib	Fasted	45.39 (36.9)	1.25 (36.9)	4.0 (2.0, 24.0)	37.94 (28.7)
	Low-fat fed	61.75 (31.4)	1.93 (28.0)	4.0 (2.0, 16.0)	34.95 (20.9)
	High-fat fed	67.27 (35.6)	2.16 (31.8)	6.0 (3.0, 6.0)	35.0 (21.7)
M-2	Fasted	27.43 (52.8)	0.89 (45.7)	4.0 (2.0, 24.0)	28.05 (21.6)
	Low-fat fed	38.28 (37.2)	1.17 (34.6)	6.0 (3.0, 16.0)	26.22 (21.5)
	High-fat fed	21.94 (70.2)	0.65 (66.3)	6.0 (3.0, 12.0)	27.51 (23.0)
M-5	Fasted	12.77 (68.6)	0.12 (64.0)	24.0 (4.0, 48.0)	64.08 (28.0)
	Low-fat fed	15.67 (41.5)	0.14 (41.0)	48.0 (12.0, 96.0)	56.75 (17.3)
	High-fat fed	6.22 (71.6)	0.05 (78.2)	48.0 (12.0, 96.0)	65.46 (36.6)

Geometric mean value (coefficient of variation [CV] %), n = 24, *: Median (range)

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

Effects of food

The applicant explained the mechanism of the effects of food on PK of regorafenib as follows:
The exposure of regorafenib was higher in the fed than in the fasted subjects; the difference was caused by the insolubility of regorafenib, and the food could bring the following situations: (1) the solubility of regorafenib was increased by the detergent action of bile acid in the bile secreted in response to the food intake, resulting in increased absorption of regorafenib in the gastrointestinal tract; and (2) the food intake simulated peristaltic movements of the gastrointestinal tract. With respect to the decreased exposure of the metabolites (M-2, M-5) observed only in the high-fat fed patients, the decreased exposure of M-5, a metabolite of M-2, may be directly related to the decreased exposure of M-2, while why the exposure of M-2 decreased remains unknown.

PMDA asked the applicant to explain their view on whether or not to specify dosing timing of regorafenib in the Dosage and Administration section of the package insert.

The applicant responded as follows:
The dosing timing of regorafenib will be specified to be after meals in Dosage and Administration section to ensure that patients take the drug in compliance with the timing for the following reasons: (1) the exposure of regorafenib in fed subjects was higher than that in fasted subjects irrespective of contents of the meal; and (2) in the global phase III study (Study 14387), which demonstrated the efficacy and safety of regorafenib, the dosing timing of regorafenib was specified to be after low-fat meals. The applicant will provide the information about details of the meal specified in Study 14387 and effects of the meal contents on the PK of regorafenib and the metabolites (M-2, M-5).

PMDA accepted the applicant's response.

4.(ii) Summary of clinical pharmacology studies

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

The PK of regorafenib in healthy adult subjects and cancer patients was evaluated following administration of the drug alone, following combination regimen of the drug with antineoplastic drug (mFOLFOX6*[1] regimen consisting of fluorouracil [5-FU], calcium folinate, and oxaliplatin; FOLFIRI*[2] regimen consisting of 5-FU, calcium folinate, and irinotecan hydrochloride [irinotecan]), and following concomitant use of the drug with CYP probe substrates, ketoconazole or rifampicin.

*1: Rapid intravenous administration of oxaliplatin 85 mg/m^2, calcium folinate 400 mg/m^2, and 5-FU 400 mg/m^2 as well as continuous intravenous infusion of 5-FU 2400 mg/m^2 (for 46 hours)
*2: Rapid intravenous administration of irinotecan 180 mg/m^2, calcium folinate 400 mg/m^2, and 5-FU 400 mg/m^2 as well as continuous intravenous infusion of 5-FU 2400 mg/m^2 (for 46 hours)

4.(ii).A.(1) Healthy adult subjects

Foreign phase I study (5.3.3.1.1, Study 12436 [[redacted] to [redacted]])

A single oral dose of a liquid preparation of ^{14}C-labeled regorafenib 120 mg was administered to 4 healthy adult subjects to investigate the mass balance. Of the AUC values of total plasma radioactivity up to 144 hours after administration of regorafenib, AUC of regorafenib, M-2, M-5, and M-7 accounted for 57.4%, 28.7%, 6.3%, and 3.1%, respectively, and M-1, M-3, M-4, and M-8 were also detected as the other metabolites. The fecal and urinary excretion of radioactivity up to 288 hours after administration of regorafenib was 71.2% and 19.3% of the radioactivity dose, respectively. Identifiable compounds in the feces included regorafenib (47.1% of the administered dose), M-3 (1.8%), M-4 (2.2%), M-6 (14.7%), and M-7 (5.1%), while such compounds in urine included M-7 (13.0%) and M-8 (4.7%).

4.(ii).A.(2) Cancer patients

4.(ii).A.(2).1) Foreign phase I study (5.3.3.2.1, Study 11650 [[redacted] - ongoing (Data cut-off; [redacted])])

An open-label study was conducted in 76 patients with solid tumor (74 patients included in the PK analysis) to evaluate the PK of regorafenib and the metabolites (M-2, M-5) after multiple oral doses of regorafenib (liquid preparation, conventional tablets or [redacted] tablets) (the table below). To Cohort 4 and Cohort 6, each drug product was administered after at least 8 hours of fasting, and to those other than the above Cohort, regorafenib was administered after low-fat meals.

Following administration of the liquid preparation, the exposure of regorafenib ($AUC_{0\text{-}24}$ at the steady state [$AUC_{0\text{-}24,ss}$], C_{max} at the steady state [$C_{max,ss}$]) increased dose-proportionally in the dose range of 10 to 60 mg. Following administration of [redacted] tablets, the $AUC_{0\text{-}24}$ increased less than dose-proportionally in the dose range of 120 to 220 mg, while the C_{max} did not increase with the dose. The applicant explained that regorafenib is practically insoluble, thus, the absorption process is saturated due to the low solubility, but the continuous absorption led to the dose-dependent increase of the $AUC_{0\text{-}24}$ value.

PK parameters of regorafenib and the metabolites (M-2, M-5) after multiple-dose

	Cohort *1	Dosage form	Dose (mg)	Day of measurement (number of days after the initiation of the multiple dose)	n	$AUC_{0\text{-}24,ss}$ (mg·h/L)	$C_{max,ss}$ (mg/L)	$t_{max,ss}$ *2 (h)	$t_{1/2}$ (h)
Regorafenib	1*3	Liquid preparation	10	Day 14	3	5.67 (52.2)	0.534 (53.8)	2.92 (2.92, 3.17)	27.28 (6.7)
	3*4		30	Day 21	3	18.6 (11.6)	1.58 (38.1)	6.00 (2.00, 6.00)	20.06 (23.7)
	4*5		60	Day 21	6	48.3 (45.7)	4.14 (28.4)	2.03 (0.550, 3.97)	32.87*6 (69.1)
	5*4		120	Day 21	6	46.0 (95.6)	4.32 (51.6)	3.09 (0.517, 5.83)	41.73*7 (45.2)
	6*8	[redacted] tablet	120	Day 21	7	50.9 (81.2)	4.42 (74.1)	2.17 (1.90, 3.47)	30.52*7 (55.1)
	7*4		160	Day 21	10	58.3 (43.3)	3.90 (43.8)	5.03 (0.567, 8.75)	22.23 (45.4)
	8*4		220	Day 21	10	63.7 (40.6)	4.46 (41.9)	3.05 (0.417, 8.00)	35.43*7 (30.4)
	9*4		160	Day 21 (Cycle 1)	19	50.3 (85.5)	3.45 (62.8)	2.85 (0.500, 10.3)	28.39*9 (35.2)
	9*4		160	Day 21 (Cycle 2)	14	45.2 (87.9)	3.23 (72.6)	5.68 (0.483, 11.8)	26.21*10 (35.5)
M-2	3*4	Liquid preparation	30	Day 21	3	4.23 (38.9)	0.340 (74.6)	6.00 (2.00, 6.00)	19.10 (34.8)
	4*5		60	Day 21	6	20.8 (56.3)	1.67 (56.0)	2.57 (1.00, 3.97)	25.86*6 (40.7)
	5*4		120	Day 21	4	30.3 (101.6)	2.69 (51.6)	2.04 (0.517, 23.5)	-
	6*8	[redacted] tablet	120	Day 21	7	33.9 (57.1)	2.51 (54.0)	2.77 (1.13, 4.05)	25.96*7 (42.0)
	7*4		160	Day 21	10	53.7 (69.3)	3.34 (78.2)	8.25 (0.567, 23.7)	21.02*9 (28.2)
	8*4		220	Day 21	10	60.4 (51.5)	3.86 (48.3)	4.93 (0.417, 23.8)	31.82*11 (23.4)
	9*4		160	Day 21 (Cycle 1)	19	48.1 (88.5)	3.17 (72.4)	4.08 (0.500, 23.9)	24.96*12 (24.0)
	9*4		160	Day 21 (Cycle 2)	14	47.7 (77.8)	3.27 (61.9)	2.50 (0.483, 12.0)	25.48*13 (42.4)
M-5	4*5	Liquid preparation	60	Day 21	6	6.86 (121.2)	0.470 (123.8)	2.10 (1.00, 24.0)	-
	5*4		120	Day 21	6	29.7 (99.9)	1.96 (89.0)	12.8 (0.517, 23.5)	-
	6*8	[redacted] tablet	120	Day 21	7	20.3 (127.2)	1.29 (127.8)	1.90 (0.633, 4.05)	-
	7*4		160	Day 21	10	48.7 (82.9)	2.93 (88.9)	10.4 (1.02, 23.7)	-
	8*4		220	Day 21	10	59.7 (80.6)	3.74 (77.8)	2.93 (0.417, 23.8)	-
	9*4		160	Day 21 (Cycle 1)	19	64.6 (182.4)	3.99 (173.5)	3.03 (0.500, 24.0)	50.88*7 (31.4)
	9*4		160	Day 21 (Cycle 2)	14	79.4 (138.7)	5.15 (141.0)	2.48 (0.483, 23.9)	64.02*7 (68.1)

Geometric mean value (CV %), *1: Data for the following measurements are omitted due to limited data, which were obtained only from less than 3 samples, regorafenib and the metabolites (M-2, M-5) in Cohort 2, M-2 and M-5 in Cohort 1, and M-5 in Cohort 3, *2: Median (range), *3: After single dose of regorafenib, regorafenib was administered once daily for 7 days followed by a 14-day washout period (patients who had completed Cohort 1 were then included in Cohort 2), *4: the schedule of a 3-week multiple-dose period followed by a 1-week washout period was repeated, *5: single dose of regorafenib 60 mg in each dosage form of conventional tablets, [redacted] tablets, and liquid preparation, and then regorafenib in the liquid preparation was administered at the dose of 60 mg for 3 weeks followed by a 1-week washout period, *6: n = 3, *7: n = 5, *8: single dose of regorafenib 100 mg in each dosage form of conventional tablets, [redacted] tablets, and liquid preparation, and then regorafenib in [redacted] was administered at the dose of 120 mg for 3 weeks followed by a 1-week washout period, and the above dosing schedule was repeated, *9: n = 16, *10: n = 9, *11: n = 4, *12: n = 12, *13: n = 8

In Cohorts 6 to 9, patients were divided into groups based on the renal function according to the estimated glomerular filtration rate (in unit of mL/min/1.73 m^2) (eGFR: calculated by Cockroft Gault [CG] equation or Modification of Diet in Renal Disease [MDRD] equation). The PK following multiple doses of 160 mg of regorafenib once daily (QD) was investigated in patients with normal renal function (≥90), mild renal impairment (≥60, <90), or moderate renal impairment (≥30, <60) (the table below).

Exposure level of regorafenib and metabolites (M-2, M-5) estimated using MDRD Study equation ($AUC_{0\text{-}24,ss}$, $C_{max,ss}$) showed no marked differences between patients with normal renal function and patients with mild renal impairment. On the other hand, when the CG equation was used, the estimated exposure parameter values of regorafenib and metabolites (M-2, M-5) in patients with mild renal impairment tended to be lower than patients with normal renal function. The applicant explained that the decreasing trend in exposure parameter values of regorafenib and metabolites (M-2, M-5) in patients with mild renal impairment shown by the calculation using CG equation may not be attributable to the condition of their renal function, because such values would increase in patients with renal impairment if the condition of their renal function affected the PK of regorafenib. Regarding the reason why the results obtained using the MDRD equation were different from those obtained using the CG equation, the applicant explained that the concerned study included subjects with a wide age range (29-89 years old); and the biased distribution of eGFR values calculated using the CG equation may be reflected in the estimated exposure parameter values. Although 1 patient was found to have moderate renal impairment, the exposure parameter values of regorafenib in this patient fell within a range of the values found in patients with normal renal function and patients with mild renal impairment.

The applicant explained that mild or moderate renal impairment do not affect the PK of regorafenib based on the above results and absence of the unchanged regorafenib in urine in Study 12436.

PK parameters of regorafenib and the metabolites (M-2, M-5) by renal function

eGFR calculation method		CG equation			MDRD equation		
Severity of renal impairment		Normal renal function	Mild	Moderate	Normal renal function	Mild	Moderate
n		18	10	1	18	10	1
Regorafenib	$AUC_{0\text{-}24,ss}$ (mg·h/L)	59.4 (69.4)	39.2 (62.2)	129.4	53.0 (72.2)	48.1 (69.6)	129.4
	$C_{max,ss}$ (mg/L)	4.04 (50.3)	2.72 (54.4)	7.21	3.74 (52.6)	3.14 (60.6)	7.21
M-2	$AUC_{0\text{-}24,ss}$ (mg·h/L)	59.8 (69.8)	36.7 (94.2)	42.6	49.4 (99.3)	51.8 (54.2)	42.6
	$C_{max,ss}$ (mg/L)	3.84 (62.2)	2.42 (85.2)	2.53	3.23 (87.1)	3.30 (53.3)	2.53
M-5	$AUC_{0\text{-}24,ss}$ (mg·h/L)	69.1 (129)	49.5 (175)	16.3	55.9 (196)	72.5 (59.2)	16.3
	$C_{max,ss}$ (mg/L)	4.11 (138)	3.21 (149)	0.957	3.44 (185)	4.41 (68.0)	0.957

Geometric mean value (CV %)

4.(ii).A.(2).2) Foreign phase I study (5.3.3.2.2, 5.3.3.2.3; Study 11651 [[redacted] 20[redacted] - ongoing (Data cut-off; [redacted], 20[redacted])])

An open-label study was conducted in 84 patients with solid tumor (81 patients included in the PK analysis) to evaluate the PK of regorafenib and the metabolites (M-2, M-5) after single oral doses of 20 to 140 mg of regorafenib on Day 1 followed by multiple oral doses of regorafenib QD from Day 3. Regorafenib was administered to fasted subjects. This study consisted of the

dose-escalation cohort, and the extended cohort in which patients with hepatocellular carcinoma and patients with non-small cell lung cancer received regorafenib at the maximum tolerated dose (MTD) (100 mg/day) in the dose-escalation cohort.

The PK parameters of regorafenib and the metabolites (M-2, M-5) following single oral dose of regorafenib 100 mg (Day 1) in cancer patients with normal hepatic function in the dose-escalation cohort and patients with hepatic impairment (hepatocellular carcinoma) in the extended cohort are shown in the table below. No significant differences were observed in AUC_{last} or C_{max} between these patient sub-groups. Of patients with hepatic impairment, only 1 could be evaluated for PK at the steady state, not allowing comparison with patients with normal hepatic function.

Based on the above results, the applicant explained that hepatic impairment (Child-Pugh classification A and B) have no marked effect on the PK of regorafenib.

PK parameters of regorafenib and the metabolites (M-2, M-5) by hepatic function

	Hepatic function	n	AUC_{last} (mg·h/L)	AUC (mg·h/L)	C_{max} (mg/L)	t_{max} *1 (h)	$t_{1/2}$ (h)
Regorafenib	Normal hepatic function	10	32.7 (38)	43.7 (35)*2	1.25 (31)	5 (2, 48)	31.6 (32)*2
	Hepatocellular carcinoma Child-Pugh A	14	26.8 (68)	45.2 (84)*3	1.38 (98)	3 (2, 24)	25.2 (52)*3
	Hepatocellular carcinoma Child-Pugh B	4	33.0 (112)	57.7 (31)*4	1.42 (76)	3 (2, 10)	45.3 (80)*4
M-2	Normal hepatic function	10	11.3 (47)	12.8 (37)*2	0.40 (51)	10 (2, 48)	24.8 (29)*2
	Hepatocellular carcinoma Child-Pugh A	14	8.8 (122)	15.3 (70)*5	0.42 (154)	3 (2, 24)	24.0 (56)*5
	Hepatocellular carcinoma Child-Pugh B	4	13.4 (194)	27.2 (74.6)*6	0.54 (129)	10 (8, 24)	19.2 (16)*6
M-5	Normal hepatic function	10	0.98 (111)	-	0.030 (118)	48 (24, 48)	-
	Hepatocellular carcinoma Child-Pugh A	13	1.02 (122)	1.58*7	0.036 (110)	47 (4, 49)	68.7*7
	Hepatocellular carcinoma Child-Pugh B	4	0.82 (587)	-	0.035 (352)	35 (24, 47)	-

Geometric mean value (CV %), *1: median (range), *2: n = 5, *3: n = 9, *4: n = 3, *5: n = 10, *6: n = 2, *7: n = 1

4.(ii).A.(2).3) Japanese phase I study (5.3.3.2.4, Study 13172 [[redacted] 20[redacted] - ongoing (Data cut-off; [redacted], 20[redacted])])

An open-label study was conducted in 15 patients with solid tumor to evaluate the PK of regorafenib and the metabolites (M-2, M-5) following multiple oral dose of regorafenib. In the study, patients received single oral dose of regorafenib 160 mg followed by a 6-day washout period (Cycle 0) and then underwent the 28-day cycles in which regorafenib 160 mg QD was orally administered for 3 weeks followed by a 1-week washout period (3/1 schedule) (the table below). Regorafenib was administered to low-fat fed patients.

The plasma concentration-time curve of single dose of regorafenib was bimodal (peaked at 4 and 8 hours after administration). The $C_{max,ss}$ of regorafenib , M-2, and M-5 were 2.01, 4.76, and 36.0 times higher, respectively, than the C_{max} following the single dose, and the $AUC_{0-24,ss}$ were 2.14, 5.15, and 37.3 times higher, respectively, than the AUC_{0-24} following the single dose. The ratios

of $AUC_{0-24,ss}$/AUC (single dose) of regorafenib, M-2, and M-5 were 1.02, 2.43, and 3.95, respectively. The applicant explained that the above results showed that following the multiple administration, the increase in exposures of metabolites (M-2, M-5) tended to be greater than that in exposures of regorafenib.

The large inter-individual variability was observed in exposures of regorafenib and the metabolites (M-2, M-5): following the multiple administration, 2 patients showed significantly lower plasma concentrations compared with the other patients. The applicant explained that one of the potential causes for the large variations was that both patients had pancreatic cancer as the primary lesion and solubility of regorafenib in the gastrointestinal tract decreased due to the bile secretion decreased, thereby, gastrointestinal absorption may have decreased.

PK parameters of regorafenib and the metabolites (M-2, M-5)

	Day of measurement	n	AUC_{0-24} (mg·h/L)	C_{max} (mg/L)	t_{max}* (h)	$t_{1/2}$ (h)
Regorafenib	Cycle 0, Day 1	15	16.4 (86.1)	1.37 (108)	4 (2, 8)	27.4 (29.9)
	Cycle 1, Day 21	12	33.0 (68.5)	2.52 (77.0)	4 (1, 48)	30.4 (26.2)
M-2	Cycle 0, Day 1	15	3.70 (341)	0.273 (389)	4 (3, 24)	24.8 (27.7)
	Cycle 1, Day 21	12	15.6 (213)	1.04 (214)	4 (1, 48)	29.5 (24.1)
M-5	Cycle 0, Day 1	13	0.380 (164)	0.0311 (167)	24 (3, 71)	60.8 (78.2)
	Cycle 1, Day 21	12	7.12 (459)	0.515 (414)	36 (1, 73)	57.5 (33.7)

Geometric mean value (CV %), *: Median (range)

4.(ii).A.(2).4) Foreign phase I study (5.3.3.2.5, Study 14996 [[redacted] 20[redacted] - ongoing (Data cut-off; [redacted], 20[redacted])])

Following single oral dose of regorafenib 160 mg and multiple oral dose of regorafenib 160 mg on the 3/1 schedule to 12 patients with solid tumor (9 patients included in the PK analysis), plasma concentrations of regorafenib and the metabolites (M-2, M-5) were investigated. The PK parameters of regorafenib and the metabolites (M-2, M-5) following the single dose are as shown in the table below. Regorafenib was administered to low-fat fed patients.

Of 9 patients included in the PK analysis, 7 patients resulted in discontinuation or dose-reduction during Cycle 1. In 2 patients who continued the multiple dose of regorafenib without discontinuation or dose-reduction, the $AUC_{0-24,ss}$ of regorafenib, M-2, and M-5 were 1.29 and 3.33 times, 3.19 and 11.5 times, and 96.0 and 192 times, respectively, higher than the AUC_{0-24} following the single dose; and the $C_{max,ss}$ were 0.77 and 3.43 times, 2.42 and 10.3 times, and 32.8 and 114 times, respectively, higher than the C_{max} following the single dose.

PK parameters of regorafenib and the metabolites (M-2, M-5) following single dose of regorafenib 160 mg

	n	AUC (mg·h/L)	AUC_{0-24} (mg·h/L)	C_{max} (mg/L)	t_{max}*1 (h)	$t_{1/2}$ (h)
Regorafenib	9	117.41*2 (64.73)	35.45 (35.87)	2.98 (36.86)	3.08 (2.00, 12.00)	43.52*2 (43.82)
M-2	9	62.44 (92.31)	17.93 (49.96)	1.24 (61.36)	8.00 (2.00, 4.00)	44.36 (69.52)
M-5	9	12.12*3 (44.35)	1.59 (82.55)	0.18 (65.32)	48.00 (23.28, 97.00)	72.18*3 (31.18)

Geometric mean value (CV %), *1: Median (range), *2: n = 8, *3: n = 3

4.(ii).A.(2).5) Foreign phase II study (5.3.5.2.1, Study 14596 [20 - ongonig (Data cut-off; , 20)])

An open-label study was conducted in 28 Caucasian and 8 Korean patients with hepatocellular carcinoma to evaluate the PK of regorafenib and the metabolites (M-2, M-5) after multiple oral dose of regorafenib 160 mg QD on the 3/1 schedule. Regorafenib was administered to low-fat fed patients.

The applicant explained that the plasma concentration-time curves of regorafenib and the metabolites (M-2, M-5) were multimodal in Korean patients, suggesting the possibility of enterohepatic circulation of regorafenib or the metabolite. The geometric mean $AUC_{0\text{-}24,ss}$ (mg•h/L) of regorafenib, M-2, and M-5 (coefficient of variation [CV] %) on Day 21 in Cycle 1 were 27.0 (38), 8.64 (106), and 3.08 (193), respectively, and the corresponding geometric mean $C_{max,ss}$ (mg/L) (CV %) were 2.51 (41), 0.862 (76), and 0.336 (150), respectively, having large inter-individual variability. In 20 Caucasian patients who received regorafenib for 14 days, the geometric mean values of plasma trough concentrations (mg/L) of regorafenib, M-2, and M-5 (CV %) were 1.77 (95), 1.11 (156), and 0.859 (145), respectively, while in 14 Caucasian patients after a 7-day washout period subsequent to the multiple doses, these values were 0.051 (260), 0.026 (393), and 0.277 (447), respectively, indicating that the plasma concentrations of M-5 were higher than those of regorafenib and M-2 after the washout period.

4.(ii).A.(2).6) Foreign phase II study (5.3.5.2.2, 5.3.5.2.3; Study 11726 [20 - ongoing (Data cut-off; , 20)])

An open-label study was conducted in 49 patients with renal cell carcinoma (14 patients included in the PK analysis) to evaluate the PK of regorafenib and the metabolites (M-2, M-5) after multiple oral dose of regorafenib 160 mg QD on the 3/1 schedule. Regorafenib was administered to fasted or low-fat fed patients.

The plasma concentration-time curves of regorafenib and the metabolites (M-2, M-5) were multimodal. The AUC and C_{max} values of metabolites (M-2, M-5) showed large inter-individual variability; after 15-day repeated administration, the geometric mean $AUC_{0\text{-}24,ss}$ (mg•h/L) (AUC_{last} only for M-5) of regorafenib, M-2, and M-5 (CV %) were 58.3 (34), 41.3 (47), and 24.7 (109), respectively, while the geometric mean $C_{max,ss}$ (mg/L) (CV %) were 4.49 (33), 2.83 (53), and 1.57 (122), respectively. The applicant explained that the half-life of M-5 was not measured in this study, but the elimination profile indicated that the half-life of M-5 is longer than that of M-2, which suggests that the plasma concentrations of the metabolites have not reached the steady state on Day 15.

4.(ii).A.(3) Drug-drug interaction study

4.(ii).A.(3).1) Drug interaction study with mFOLFOX6 or FOLFIRI (5.3.3.2.6, Study 11656 [20 - ongoing (Data cut-off; , 20)])

In an open-label study in 45 foreign patients with colorectal cancer, regorafenib was concomitantly administered with mFOLFOX6 or FOLFIRI. One cycle consists of 28-day, regorafenib was orally administered at the dose of 160 mg QD on Day 4 to 10 and Day 18 to 24, and mFOLFOX6 or FOLFIRI was given on Day 1 and Day 15; and this cycle was repeated 6 times in total.

The PK analysis populations for regorafenib and the metabolites (M-2, M-5) (plasma), oxaliplatin (total plasma platinum concentration and unbound platinum), irinotecan (plasma irinotecan, SN-38 [metabolites]), and 5-FU (plasma) included 35, 12, 11, and 16 patients, respectively. The plasma concentrations of regorafenib and the metabolites and PK parameters of concomitant drugs are as shown in the table below.

The AUC of irinotecan and SN-38 on Day 1 in Cycle 2 (concomitant use with regorafenib)

increased by 28% and 44%, respectively, compared with those on Day 1 in Cycle 1 (FOLFIRI alone). The applicant explained that these increases were caused by inhibition of regorafenib against glucuronidation of SN-38, because regorafenib and the metabolites (M-2, M-5) have inhibitory effects against UGT1A1 [see "3.(ii).A.(5).1) Enzyme inhibition"]; and SN-38 is a substrate of UGT1A1. Furthermore, concomitant use with regorafenib increased the exposures of irinotecan and SN-38. The applicant thus explained that they will provide a caution about concomitant use of regorafenib and irinotecan.

The AUC value of total plasma platinum on Day 1 in Cycle 2 (concomitant use with regorafenib) increased by 39% compared with that on Day 1 in Cycle 1 (mFOLFOX6 alone). However, no marked changes were observed in the C_{max} of total plasma platinum, or AUC or C_{max} of unbound platinum. However, the applicant explained their view that it would not be necessary to provide a caution about the increase of the AUC of total platinum; because (1) the increase of the AUC of total platinum observed in this study was unlikely to be related to concomitant use of regorafenib taking into account that it has been reported that multiple administrations of oxaliplatin result in accumulation of the total platinum concentration (*Clin Cancer Res.* 2000;6:1205-18) and (2) no marked changes were observed in concentration of the active unbound platinum form.

The concomitant use of regorafenib did not remarkably affect the AUC or C_{max} values of 5-FU.

Plasma concentrations of regorafenib and the metabolites (M-2, M-5) following concomitant use with mFOLFOX6 or FOLFIRI

	Day of measurement	Combination regimen	n	Plasma concentration (μg/L)					
				Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6
Regorafenib	Day 1	mFOLFOX6	17	-	55.4 (619)	46.6*1 (1070)	86.2*2 (658)	101*3 (955)	92.3*4 (48)
	Day 15		19	152 (115)	68.4*1 (680)	39.7*2 (976)	56.0*3 (537)	58.2*5 (656)	55.9*6 (800)
	Day 1	FOLFIRI	13	-	141 (355)	167*7 (524)	273*8 (78)	140*9 (302)	51.4*10 (1290)
	Day 15		14	225 (108)	216 (382)	240*7 (110)	161*9 (151)	55.4*12 (76,500)	137*10 (515)
M-2	Day 1	mFOLFOX6	17	-	14.4 (798)	16.9*1 (712)	21.5*2 (561)	39.3*3 (1836)	20.4*4 (452)
	Day 15		19	63.8 (178)	18.9*1 (635)	13.1*2 (586)	16.0*3 (1,526)	16.2*5 (1816)	20.0*6 (748)
	Day 1	FOLFIRI	13	-	40.3 (306)	43.7*7*11 (901)	67.7*8 (157)	25.0*9 (529)	7.59*10*11 (3018)
	Day 15		14	136 (130)	67.1*11 (357)	48.4*7 (206)	34.1*9*11 (883)	18.0*11*12 (6608)	25.5*10 (994)
M-5	Day 1	mFOLFOX6	17	-	62.0*11 (887)	53.4*1*11 (1401)	55.3*2 (274)	88.5*3*11 (3,112)	56.6*4 (480)
	Day 15		19	210 (244)	58.6*1 (704)	34.0*2*11 (1161)	79.0*3 (792)	44.8*5*11 (3579)	39.8*6*11 (3055)
	Day 1	FOLFIRI	13	-	84.9 (156)	60.4*7 (338)	74.6*8 (188)	38.1*6 (166)	10.9*10*11 (2,801)
	Day 15		14	254 (124)	79.1*11 (407)	65.3*7 (162)	40.6*6*11 (1088)	22.6*12 (458)	24.8*10 (536)

Geometric mean value (CV %), *1: n = 13, *2: n = 10, *3: n = 12, *4: n = 5, *5: n = 8, *6: n = 6, *7: n = 11, *8: n = 9, *9: n = 6, *10: n = 3, *11: for specimens at < lower limit of quantitation (2 μg/L), the concentration was provisionally set at 1/2 of the lower limit of quantitation; *12: n = 4

PK parameters of each drug and its metabolite: mFOLFOX6 or FOLFIRI alone or concomitant use with regorafenib

	Dosing regimen	n	AUC (mg·h/L)	C_{max} (mg/L)	t_{max}*1 (h)	$t_{1/2}$ (h)
Irinotecan	FOLFIRI	11	10.7 (24.2)	1.91 (33.2)	1.6 (0.6, 2)	8.47 (27.3)
	FOLFIRI + regorafenib	11	13.8 (35.6)	2.33 (70.0)	1.9 (0.8, 3)	7.84 (26.2)
SN-38	FOLFIRI	11	0.367 (42.7)	33.6 (105)*2	2.1 (0.6, 4)	16.8 (39.1)*2
	FOLFIRI + regorafenib	11	0.450 (57.8)	30.4 (47.8)*2	2.6 (1, 7)	19.3 (66.6)*2
Total platinum	mFOLFOX6	12	81.0 (22.2)	2.16 (22.8)	2.0 (1, 2)	46.4 (17.6)
	mFOLFOX6 + regorafenib	12	113 (11.4)	2.36 (17.5)	2.0 (1, 2)	52.0 (23.6)
Unbound platinum	mFOLFOX6	10	4.18 (39.0)	0.800 (32.7)	1.9 (1, 2)	17.2 (18.2)
	mFOLFOX6 + regorafenib	10	4.90 (15.2)	0.960 (19.5)	1.5 (1, 2)	19.0 (17.7)
5-FU	mFOLFOX6	12	123 (73.1)*3	19.1 (164)	0.1 (0.02, 46)	0.418 (513)*3
	mFOLFOX6 + regorafenib	12	140 (106)*3	19.2 (414)*4	0.1 (0.03, 48)*4	2.38 (1810)*3
	FOLFIRI	4	259 (79.4)	23.6 (92.1)	0.1 (0.08, 24)	0.200 (136)
	FOLFIRI + regorafenib	4	-	21.6 (1280)	12 (0.05, 46)	-

Geometric mean value (CV %), *1: Median (range), *2: n = 10, *3: n = 9, *4: n = 11

4.(ii).A.(3).2) Concomitant administration study of various CYP probe substrates (5.3.3.4.3, Study 12434 [[redacted] 20[redacted] - ongoing (Data cut-off; [redacted], 20[redacted])])

An open-label study was conducted in 40 foreign patients with solid tumor to evaluate effects of regorafenib on the PK of various CYP substrates. In Group A (20 patients, 15 patients included in the PK analysis), warfarin potassium (CYP2C9 substrate), omeprazole (CYP2C19 substrate), and midazolam (CYP3A4 substrate) were administered 7 days before the initiation of Cycle 1 and on Day 14 in Cycle 1, and in Group B (20 patients, 15 patients included in the PK analysis), rosiglitazone (CYP2C8 substrate) was administered 7 days before the initiation of Cycle 1 and on Day 14 in Cycle 1. Also, regorafenib was administered at the dose of 160 mg QD from Day 1 to Day 21 followed by a 7-day washout period. All drugs were administered to the patients after a low-fat meal.

The PK parameters of each substrate following administration of the substrate alone (7 days before the initiation of Cycle 1) and following concomitant use with regorafenib (Day 14 in Cycle 1) are as shown in the table below. Following administration of omeprazole alone and in combination with regorafenib, the geometric mean values (CV %) of the plasma concentration ratios of 5-OH omeprazole to omeprazole at 6 hours were 0.732 (156) and 0.637 (105), respectively, with no marked differences. The applicant explained that the plasma concentration ratios of 5-OH omeprazole to omeprazole at 2 hours were not calculated, because the PK data at 2 hours were available only from the limited number of patients. Regarding the PK parameters of warfarin, the exposure of S-warfarin following concomitant use of warfarin and regorafenib was higher than that following administration of warfarin alone, suggesting that regorafenib may have an inhibitory effect against CYP2C9. In addition, the exposure of 7-OH warfarin also increased. The applicant explained the increase in exposure would be attributable to decreased glucuronidation of 7-OH warfarin, because *in vitro* examination shows that regorafenib and the metabolites (M-2, M-5) have inhibitory effects against UGT1A1 ("3.(ii).A.(5).1) Enzyme inhibition") and it has been reported that UGT1A1 is involved in glucuronidation of 7-OH warfarin (*Drug Metab Rev.* 2010;42:55-61). The effects of regorafenib on the PK parameters of midazolam and rosiglitazone were mild enough to be not clinically relevant or not observed.

PK parameters of each drug or its metabolite following single administration of the drug with/without regorafenib

	Administration of the drug with/without regorafenib	AUC (μg·h/L)	AUC_{last} (μg·h/L)	C_{max} (μg/L)	t_{max} *1 (h)	$t_{1/2}$ (h)
Group A (warfarin potassium, omeprazole, and midazolam groups)						
S-warfarin	Without regorafenib	18,500*2 (41.2)	17,200 (34.9)	442 (29.0)	2.00 (1.98, 4.07)	39.8*2 (27.2)
	With regorafenib	21,700*3 (27.7)	19,800*4 (36.2)	550*4 (29.4)	2.06*4 (2.00, 4.33)	43.9*3 (19.3)
7-OH warfarin	Without regorafenib	-	3670 (72.8)	54.8 (51.8)	24.0 (7.75, 48.0)	-
	With regorafenib	-	4170 (149)	63.4 (54.6)	24.0 (7.97, 48.0)	-
Midazolam	Without regorafenib	32.9 (48.5)	30.1 (48.7)	9.68 (42.5)	0.500 (0.483, 1.98)	3.41 (73.2)
	With regorafenib	35.1 (63.8)	35.6 (75.0)	12.4 (47.0)	0.500 (0.500, 3.97)	3.49 (68.5)
1-OH midazolam	Without regorafenib	9.04 (40.3)	7.71 (44.7)	3.20 (52.7)	0.517 (0.483, 1.98)	2.03 (47.7)
	With regorafenib	10.5 (69.6)	9.29 (76.0)	3.96 (62.9)	0.500 (0.500, 3.97)	2.13 (45.3)
Group B (rosiglitazone group)						
Rosiglitazone	Without regorafenib	1077 (36.0)	973 (38.1)	171 (35.9)	2.00 (0.500, 6.00)	3.76 (25.2)
	With regorafenib	1046*5 (37.3)	939*2 (41.6)	170*2 (49.7)	2.00*2 (0.500, 7.98)	3.84*5 (27.6)
N-desmethyl rosiglitazone	Without regorafenib	2200*5 (30.4)	1486 (41.1)	67.3 (24.8)	8.00 (4.00, 8.08)	16.9*5 (34.0)
	With regorafenib	1867*3 (28.1)	1366*2 (33.7)	66.3*2 (24.7)	7.67*2 (4.00, 24.0)	15.4*3 (19.3)

Geometric mean value (CV %), n = 15, *1: Median (range), *2: n = 13, *3: n = 9, *4: n = 14, *5: n = 12

4.(ii).A.(3).3) Drug interaction study with ketoconazole (5.3.3.4.1, Study 12435 [[redacted] 20[redacted] to [redacted] 20[redacted]])

An open-label study was conducted in 24 foreign healthy adult subjects to evaluate effects of ketoconazole (CYP3A4 inhibitor) on the PK of regorafenib and the metabolites (M-2, M-5) (the table below). In Cohort 1, single oral dose of regorafenib was administered at the dose of 80 mg in the first period, and in the second period, multiple oral dose of ketoconazole was administered at the dose of 400 mg QD for 7 days, and regorafenib was administered at the dose of 80 mg on Day 5 of ketoconazole administration. In Cohort 2, single oral dose of regorafenib was administered at the dose of 160 mg in the first period, and in the second period, multiple dose of ketoconazole was administered at the dose of 400 mg QD for 18 days, and regorafenib was administered at the dose of 160 mg on Day 5 of ketoconazole administration. Regorafenib and ketoconazole were administered to low-fat fed subjects.

Following concomitant use of ketoconazole, the AUC and C_{max} of regorafenib increased, while those of M-2 and M-5 markedly decreased.

PK parameters of regorafenib and the metabolites (M-2, M-5) following administration of regorafenib with or without ketoconazole

	Administration of regorafenib alone/ With ketoconazole	n	AUC (mg·h/L)	AUC_{last} (mg·h/L)	C_{max} (mg/L)	t_{max}* (h)	$t_{1/2}$ (h)
Cohort 1 (regorafenib 80 mg)							
Regorafenib	Administration of regorafenib alone	6	44.2 (19.9)	44.0 (19.5)	1.10 (22.8)	4.00 (4.00, 16.0)	38.9 (26.4)
	With ketoconazole	6	56.1 (24.5)	55.8 (24.3)	1.44 (24.8)	4.00 (4.00, 4.00)	37.0 (18.6)
M-2	Administration of regorafenib alone	6	19.5 (42.6)	19.3 (43.0)	0.48 (38.4)	8.00 (4.00, 16.0)	28.5 (22.1)
	With ketoconazole	6	1.32 (66.7)	1.01 (65.6)	0.0157 (54.2)	24.0 (12.0, 24.0)	44.0 (35.0)
M-5	Administration of regorafenib alone	6	5.57 (67.4)	5.11 (71.4)	0.04 (67.4)	48.0 (16.0, 96.0)	74.5 (9.9)
	With ketoconazole	6	0.814 (187.7)	0.100 (964.6)	0.004 (81.7)	12.0 (4.00, 24.0)	122 (200.8)
Cohort 2 (regorafenib 160 mg)							
Regorafenib	Administration of regorafenib alone	18	64.2 (39.1)	63.8 (39.2)	2.01 (35.1)	4.00 (2.00, 12.0)	30.5 (16.7)
	With ketoconazole	18	85.0 (33.3)	84.8 (33.3)	2.82 (42.3)	4.00 (4.00, 16.00)	34.3 (24.0)
M-2	Administration of regorafenib alone	18	42.0 (53.6)	41.8 (53.7)	1.19 (38.7)	4.0 (4.00, 16.0)	28.0 (24.6)
	With ketoconazole	18	2.36 (52.8)	1.88 (67.4)	0.0326 (60.1)	16.0 (4.00, 48.0)	38.2 (41.9)
M-5	Administration of regorafenib alone	18	16.10 (90.2)	15.6 (92.6)	0.148 (91.6)	48.0 (12.0, 72.0)	61.5 (27.0)
	With ketoconazole	18	1.16 (102.9)	0.48 (169.6)	0.009 (79.4)	12.0 (4.00, 48.0)	75.8 (88.9)

Geometric mean value (CV %), *: Median (range)

4.(ii).A.(3).4) Drug interaction study with rifampicin (5.3.3.4.2, Study 15524 [[redacted] to [redacted]])

An open-label study was conducted in 24 foreign healthy adult subjects (22 subjects included in the PK analysis) to evaluate effects of rifampicin (CYP3A4 inducer) on the PK of regorafenib and the metabolites (M-2, M-5). In the first period, single oral dose of regorafenib was administered at the dose of 160 mg. In the second period, multiple oral dose of rifampicin was administered at the dose of 600 mg QD for 9 days, and regorafenib was concomitantly administered at the dose of 160 mg on Day 7 of rifampicin administration. Regorafenib was administered to subjects in the fasted condition, while rifampicin was administered 1 hour before a meal or 2 hours after a meal except for the day on which rifampicin and regorafenib were concomitantly administered to subjects in the fasted condition (the table below).

Following concomitant use of regorafenib and rifampicin, the AUC and C_{max} of regorafenib decreased, while those values of M-5 increased, compared with those values following administration of regorafenib alone. On the other hand, the C_{max} of M-2 increased with statistical significance, but no significant change was observed in the AUC. The applicant explained that concomitant use of regorafenib and CYP3A4 inducers should be avoided, since such concomitant use may decrease the plasma regorafenib concentrations, causing decreased efficacy.

PK parameters of regorafenib and the metabolites (M-2, M-5) following administration of regorafenib with or without rifampicin

	Administration of regorafenib alone/ With rifampicin	AUC (mg·h/L)	AUC_{last} (mg·h/L)	C_{max} (mg/L)	t_{max}* (h)	$t_{1/2}$ (h)
Regorafenib	Administration of regorafenib alone	50.6 (36.5)	50.3 (36.3)	1.53 (34.4)	4.00 (2.00, 4.20)	37.0 (23.5)
	With rifampicin	25.5 (30.6)	25.3 (30.9)	1.23 (50.8)	4.00 (2.00, 4.03)	27.0 (32.5)
M-2	Administration of regorafenib alone	24.6 (46.3)	24.4 (46.6)	0.924 (40.1)	4.00 (2.00, 4.20)	34.0 (32.2)
	With rifampicin	22.4 (42.0)	22.1 (42.5)	1.46 (49.3)	4.00 (4.00, 4.03)	19.3 (33.2)
M-5	Administration of regorafenib alone	9.34 (53.8)	8.94 (54.4)	0.087 (52.5)	24.0 (4.05, 96.0)	67.7 (20.9)
	With rifampicin	34.0 (61.1)	32.8 (61.7)	0.364 (70.2)	23.9 (4.00, 72.0)	68.9 (26.8)

Geometric mean value (CV %), n = 22, *: Median (range)

4.(ii).A.(4) Foreign phase I study on the relationship of exposure level with changes in QT/QTc interval (5.3.4.2.1, Study 14814 [[redacted] - ongoing (Data cut-off; [redacted])])

An open-label study in which multiple-dose of regorafenib 160 mg was administered to 53 foreign patients with solid tumors QD on the 3/1 schedule was conducted to investigate the effects on ECG and left ventricular ejection fraction (LVEF).

Of 30 patients included in the ECG analysis, 1 patient who did not take regorafenib as specified was excluded due to poor compliance, and data from the remaining 29 patients were used to calculate the Fridericia-corrected QTc interval (QTcF) and Bazett-corrected QTc interval (QTcB) at the time of t_{max} on Day 21. The mean changes from baseline (msec) [90% CI] in QTcF and QTcB in 29 patients were -2 [-6, 3] and -3 [-8, 2], respectively, and those in 25 patients for whom doses were not adjusted were -2 [-8, 3] and -4 [-10, 1], respectively. No clear positive correlation was observed between plasma concentrations of regorafenib and the metabolites (M-2, M-5) and changes from baseline in QTcF.

Of 27 patients included in the LVEF analysis, 14 patients received at least 2 cycles of regorafenib without dose adjustment. In these 14 patients, the mean ± SD of changes (%) from baseline in LVEF on Day 21 of Cycle 2 was -0.1 ± 8.6. In the overall LVEF analysis population (n = 27), the mean ± SD of changes (%) from baseline in LVEF on Day 21 of Cycle 2 (n = 22), Day 1 of Cycle 5 (n = 9), and Day 1 of Cycle 8 (n = 3) were + 1.4 ± 8.4, -0.4 ± 5.2, and + 4.0 ± 4.6, respectively.

Based on the above results, the applicant explained that regorafenib has neither clinically significant QTc interval prolongation effect nor effect on LVEF.

4.(ii).A.(5) Population pharmacokinetics (PPK) analysis

The PK model was initially established from the PK data (67 patients, 5026 measurement points) obtained from the foreign phase I study (Study 11650) in patients with solid tumor. The PPK analysis using Nonlinear Mixed Effect Model (NONMEM) was then performed on the PK data (381 patients, 3696 measurement points) of the global phase III study (Study 14387) in patients with colorectal cancer, which was conducted using the initially established PK model. The PK profile of regorafenib was evaluated by a 2-compartment model with first order absorption, and the PK profile of M-2 and M-5 were evaluated by a 2-compartment model with Michaelis-Menten-style elimination kinetics. In this analysis, the following covariates were examined for the CL of regorafenib, Michaelis-Menten constant (KM-M2) of M-2, and fraction ratio of

metabolism from M-2 to M-5 (FRM5): body weight, BMI, height, age, eGFR, total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, albumin, total protein, hematocrit, hemoglobin, sex, race (Caucasian, Black, Asian, and the other races), and hepatic function classification at the baseline.

The CLs of regorafenib in Study 11650 and Study 14387 were 1.75 and 1.43 L/h, respectively. Total bilirubin was identified as a significant covariate for the CL of regorafenib, and the CL of regorafenib decreased with increasing total bilirubin. Body weight was identified as a significant covariate for KM-M2, and the exposure of M-2 decreased with increasing body weight.

4.(ii).A.(6) PK of regorafenib in Japanese and foreign subjects

The PK data of the Japanese clinical study (Study 13172) and foreign clinical studies (Study 11650 and Study 11726 in Caucasian subjects, Study 14996 in Chinese, Study 14596 in Korean) were investigated for ethnic differences in the PK of regorafenib.

The PK parameters of regorafenib and the metabolites (M-2, M-5) in each ethnic group following the single oral dose of regorafenib 160 mg are as shown in the table below. The geometric mean AUC and C_{max} of regorafenib and M-2 in Japanese subjects tended to be lower than those in Caucasian subjects, but the distributions of the AUC and C_{max} generally fell within the range of the corresponding values in Caucasian subjects. Any ethnic group showed large inter-individual variability of the AUC and C_{max} of regorafenib and the metabolites (M-2, M-5).

PK parameters of regorafenib and the metabolites (M-2 and M-5) following single dose of regorafenib 160 mg in each study

		Study 11650 (Caucasian)	Study 13172 (Japanese)	Study 14996 (Chinese)
n		12	15	9
Regorafenib	AUC (μg·h/L)	70,449 (35.2)*1	34,560 (84.2)	117,410 (64.7)*2
	C_{max} (μg/L)	2534 (42.7)	1374 (108)	2975 (36.9)
M-2	AUC (μg·h/L)	27,994 (48.4)*2	7821 (301)	62,442 (92.3)
	C_{max} (μg/L)	834 (64.3)	273 (389)	1243 (61.4)
M-5	AUC (μg·h/L)	-	3442 (112)*3	12,117 (44.4)*4
	C_{max} (μg/L)	78.3 (88.1)	31.1 (167)*3	181 (65.3)

Geometric mean value (CV %), *1: n = 6, *2: n = 8, *3: n = 13, *4: n = 3

The PK parameters of regorafenib and the metabolites (M-2, M-5) following multiple oral dose of regorafenib at the dose of 160 mg QD are as shown in the table below. The geometric mean $AUC_{0\text{-}24,ss}$ and $C_{max,ss}$ of regorafenib and the metabolites (M-2, M-5) in Japanese subjects tended to be lower than those in Caucasian subjects, but the distributions of individual values for the $AUC_{0\text{-}24,ss}$ and $C_{max,ss}$ generally fell within the range of the corresponding values in Caucasian subjects. In addition, the distributions of individual values for the $AUC_{0\text{-}24,ss}$ and $C_{max,ss}$ in Japanese subjects fell within the range of corresponding values in the other Asian groups (Chinese, Korean). Based on the above, the applicant considered that the exposure in the Asian groups including Japanese subjects is not substantially different from the exposure in Caucasian subjects.

PK parameters of regorafenib and the metabolites (M-2, M-5) following multiple doses of regorafenib 160 mg in each study

		Caucasian		Japanese	Korean	Chinese
		Study 11650	Study 11726	Study 13172	Study 14596	Study 14996
n		25	14	12	7	2
Regorafenib	$AUC_{0\text{-}24,ss}$ (μg·h/L)	53,217 (74.3)	58,286 (34.4)	33,043 (68.5)	25,975 (39.5)	50,102 (54.7)
	$C_{max,ss}$ (μg/L)	3655 (59.2)	4486 (33.2)	2522 (77.0)	2368 (40.2)	4042 (56.6)
M-2	$AUC_{0\text{-}24,ss}$ (μg·h/L)	44,422 (88.3)*	-	15,623 (213)	8680 (119)	78,898 (24.4)
	$C_{max,ss}$ (μg/L)	2968 (72.4)*	-	1040 (214)	891 (83.0)	4909 (27.8)
M-5	$AUC_{0\text{-}24,ss}$ (μg·h/L)	58,873 (194)*	-	7118 (459)	3216 (224)	175,887 (58.5)
	$C_{max,ss}$ (μg/L)	3606 (181)*	-	515 (414)	367 (164)	9931 (46.7)

Geometric mean value (CV %), *: n = 17

4.(ii).A.(7) Pharmacodynamics

In the foreign phase I study (Study 11650) in patients with solid tumor, effects of regorafenib on plasma concentrations of vascular endothelial growth factor (VEGF) and soluble VEGF receptor-2 (sVEGFR-2) were evaluated. Although the plasma concentrations of VEGF at the end of each Cycle (on Day 21 in each of Cycles 1, 2, and 3) were higher than the baseline, no dose-dependency was observed. On the other hand, the plasma concentrations of sVEGFR-2 at the end of each Cycle (on Day 21 in each of Cycles 1, 2, and 3) were lower than the baseline in most patients. The geometric mean value (range) of change rates of the plasma concentrations of sVEGFR-2 on Day 21 in Cycle 1 was 0.593 (0.382, 0.829) (160 mg group) to 0.945 (0.826, 1.08) (10 mg group), showing that regorafenib tended to produce a dose-dependent decrease in the plasma concentrations of sVEGFR-2 in the ≥60 mg/day groups.

In Study 11650, effects of regorafenib on the tumor blood flow rate/tumor vascular permeability were evaluated by dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI). In the gadolinium curve, a decreasing trend of iAUC60 values (AUC of intratumoral gadolinium for 60 minutes after injection of a contrast agent) was observed; the geometric mean value (range) of change rates of the iAUC60 values from the baseline on Day 21 in Cycle 1 at each dose was 0.410 (0.129, 0.950) (at the dose of 160 mg) to 1.04 (0.871, 1.235) (at the dose of 30 mg); and the decreasing trend of the iAUC60 values was significant at the dose of ≥120 mg.

The applicant explained the proposed Dosage and Administration of regorafenib as follows:
Data from Study 11650 and Study 11651 showed that the exposure ($AUC_{0\text{-}24,ss}$, $C_{max,ss}$) of regorafenib and the metabolites (M-2, M-5) following administration of regorafenib 160 mg QD on the 3/1 schedule was higher than that following continuous administration of regorafenib 100 mg QD [see "4.(ii).A.(2).1) Foreign phase I study and "4.(ii).A.(2).2) Foreign phase I study"]. Based on the above, the applicant considered that higher efficacy was expected for the administration of regorafenib 160 mg QD on the 3/1 schedule compared with the continuous administration of regorafenib 100 mg QD. Accordingly, the applicant decided to proceed with the subsequent development under the administration of regorafenib 160 mg QD on the 3/1 schedule.
Data from Study 11650 showed that following multiple administration of regorafenib 160 mg QD on the 3/1 schedule, the concentrations of unbound regorafenib, M-2, and M-5 at the $C_{max,ss}$ were calculated to be 40, 12 and 3 nmol/L, respectively, and those at the trough were calculated to be 27, 10 and 3 nmol/L, respectively; these concentrations fell within the range of IC_{50} of regorafenib against various kinases [see "3.(i).A.(1) Primary pharmacodynamics"].

4.(ii).A.(8) Relationship of the exposure with efficacy and safety

4.(ii).A.(8).1) Relationship of the exposure with efficacy

The foreign phase I study (Study 11650) in patients with solid tumor did not show a clear relationship of the $AUC_{0\text{-}24,ss}$ of regorafenib with the best overall response.

In the global phase III study (Study 14387) in colorectal cancer patients with distant metastases (metastatic colorectal cancer), the relationship of the exposure of regorafenib with the efficacy was evaluated. Throughout Cycle 1 to 6, no clear relationship was observed between the mean plasma regorafenib concentration in each Cycle and the overall survival (OS) or progression-free survival.

4.(ii).A.(8).2) Relationship of the exposure with the safety

Data from phase I studies (Study 11650, Study 13172, Study 14996) and phase II studies (Study 14596, Study 11726) did not show clear relationships of the $AUC_{0\text{-}24,ss}$ and C_{max} of regorafenib with severities of the adverse events (all adverse events related to the study drug).

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

4.(ii).B.(1) PK of regorafenib in Japanese and foreign subjects

In regards to the AUC and C_{max} of regorafenib and the metabolites (M-2, M-5) in Japanese subjects tending to be lower than those in Caucasian subjects [see "4.(ii).A.(6) PK of regorafenib in Japanese and foreign subjects"], PMDA asked the applicant to explain causes of the lower values and recommended dosage and administration in Japanese subjects.

The applicant responded as follows:

As of now, the cause of the above finding has not been identified. However, in Study 14387 in patients with colorectal cancer, no significant differences were observed in efficacy between Japanese subjects and the entire study population, and regorafenib 160 mg QD on the 3/1 schedule was tolerable in the Japanese population [see "4.(iii).B.(2).3) Efficacy in Japanese patients"]. Therefore, the applicant considered that the administration of regorafenib 160 mg QD on the 3/1 schedule, which was set in Study 14387, can be defined as the dosage regimen for Japanese patients as done for Caucasian patients.

PMDA considers as follows:

The PK of regorafenib in Japanese subjects was investigated only with regorafenib 160 mg QD adminitered on the 3/1 schedule, which is the proposed dosage and administration. There is, therefore, a limitation to the PK comparison of regorafenib between Japanese and foreign subjects in terms of the linearity of the PK of regorafenib, etc. Distributions of individual values for AUC and C_{max} of regorafenib and the metabolites (M-2, M-5) following administration of regorafenib at a dose of 160 mg almost overlap between Japanese and Caucasian, but, the exposure levels of regorafenib and the metabolites (M-2, M-5) tend to be lower in Japanese subjects than in Caucasian subjects even if data from the 2 patients in whom plasma concentrations of regorafenib and the metabolites (M-2, M-5) were markedly lower than those in the other patients in Study 13172 are excluded [see "4.(ii).A.(2).3) Japanese phase I study"]. However, it is unnecessary to set the dosage for Japanese patients as different from that for foreign patients at present for the following reasons: in Study 14387, it was not suggested that efficacy in the Japanese study sub-population was siginificantly different from that in the entire study population, and the 3/1 schedule of regorafenib 160 mg QD was tolerable in the Japanese population. However, it is necessary to continue collecting information, including published literature, about differences in PK of regorafenib between Japanese and foreign patients and the causes thereof.

4.(ii).B.(2) Pharmacokinetic interaction

Due to concomitant use of ketoconazole, a CYP3A4 inhibitor, the AUC and C_{max} of regorafenib increased, while the AUC and C_{max} of the metabolites (M-2, M-5) markedly decreased [see "4.(ii).A.(3).3) Drug interaction study with ketoconazole"].

PMDA asked the applicant to explain their view on whether or not caution against concomitant use of regorafenib with CYP3A4 inhibitors should be provided.

The applicant responded as follows:

The applicant claims that concomitant use with CYP3A4 inhibitors is unlikely to reduce the efficacy of regorafenib, taking into account that the exposure levels of the metabolites (M-2, M-5) markedly decreased due to concomitant use with ketoconazole, but the exposure level of regorafenib was increased. In addition, the applicant considers at present that concomitant use of regorafenib with CYP3A4 inhibitors is unlikely to cause clinically significant issues, since Study 14387 did not show clear differences in the safety profile of regorafenib between the administrations with and without CYP3A4 inhibitors. However, the applicant will provide a caution about pharmacokinetic interaction between regorafenib and CYP3A4 inhibitors, in consideration that they have not evaluated the effects of concomitant use with the CYP3A4 inhibitors on the PK of regorafenib following multiple administration.

Based on the finding that the variation of the exposure profiles of regorafenib and the metabolites was observed following the concomitant use with ketoconazole, PMDA considered it necessary to provide a caution about concomitant use with the CYP3A4 inhibitors. Therefore, PMDA accepted the response. However, the PK data from Study 12434 [see "4.(ii).A.(3).2) Concomitant administration study of various CYP probe substrates"] indicated that concomitant use with regorafenib may affect the PK profiles of warfarin and midazolam. PMDA thus consider it necessary to appropriately provide the relevant information.

4.(iii) Summary of clinical efficacy and safety

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

As the efficacy and safety evaluation data, the results from a total of 8 studies, including 1 Japanese phase I study, 6 foreign phase I studies, and 1 global phase III study, were submitted. As the reference data, the results from 7 foreign studies were submitted.

List of clinical studies for efficacy and safety

Data type	Study region	Study title	Phase	Study population	Number of enrollment	Outline of the dosage and administration	Main endpoint
Evaluation	Japan	13172	I	Advanced solid tumor	15	Single oral dose of regorafenib 160 mg followed by a 6-day washout period and then oral dose of regorafenib 160 mg on the 3/1 schedule	PK Safety
	Global	14387	III	Metastatic colorectal cancer	760 (a) 505 (b) 255	Oral dose of (a) regorafenib 160 mg or (b) placebo on the 3/1 schedule with BSC	Efficacy Safety
	Foreign	11650	I	Patients with advanced solid tumor*1	76	Cohort 1: Single oral dose of regorafenib 10 mg (liquid preparation) on Day 1 followed by a 6-day washout period and then repeat oral dose for 7 days followed by a 14-day washout period Cohort 2-9, oral administration at the following doses on the 3/1 schedule Cohort 2: Regorafenib 10 mg (liquid preparation) Cohort 3: Regorafenib 30 mg (liquid preparation) Cohort 4: Regorafenib 60 mg (liquid preparation, conventional tablets or [redacted] tablets) Cohort 5: Regorafenib 120 mg (liquid preparation) Cohort 6: Regorafenib 120 mg (20 mg tablets [redacted] tablets] 6 tablets) Cohort 7: Regorafenib 160 mg (20 mg tablets [redacted] tablets] 8 tablets) Cohort 8: Regorafenib 220 mg (100 mg tablets [redacted] tablets] 2 tablets + 20 mg tablets [redacted] tablets] 1 tablet) Cohort 9: Regorafenib 160 mg (100 mg tablets [redacted] tablets] 1 tablet + 20 mg tablets [redacted] tablets] 3 tablets)	PK Safety
		12437	I	Healthy adult male subjects	48	Single oral dose of regorafenib 160 mg (four 40 mg tablets) followed by a 7-day washout period and then single oral dose of regorafenib 100 mg tablet and three 20 mg tablets	PK Safety
		14656	I	Healthy adult male subjects	24	Single oral dose of regorafenib 160 mg to fasted, low-fat breakfast fed, and high-fat breakfast fed subjects	PK Safety
		12436	I	Healthy adult male subjects	4	Single oral dose of [^{14}C] regorafenib 120 mg (liquid preparation)	PK Safety
		12435	I	Healthy adult male subjects	24	Single oral dose of regorafenib 80 mg or 160 mg (first session, regorafenib alone; second session, concomitant use with ketoconazole on Day 5 of multiple dose of ketoconazole 400 mg)	PK Safety
		15524	I	Healthy adult male subjects	24	Single oral dose of regorafenib 160 mg on Day 1 and Day 21 (first session, regorafenib alone; second session, concomitant use with rifampicin on Day 7 of multiple dose of rifampicin 600 mg)	PK Safety
Reference	Foreign	11651	I	Advanced solid tumor	84	Once-daily oral dose of regorafenib 20, 40, 100, 120, and 140 mg	PK Safety
		14996	I	Advanced solid tumor	12	Single oral dose of regorafenib 160 mg followed by a 6-day washout period and then oral dose of regorafenib 160 mg on the 3/1 schedule	PK Safety
		11656	I	Metastatic colorectal cancer	45	28-day for 1 cycle, once-daily oral dose of regorafenib 160 mg on Days 4-10 and Days 18-24 with mFOLFOX6*2 or FOLFIRI*3 given on Day 1 and Day 15	PK Safety
		12434	I	Advanced solid tumor	16	Oral dose of regorafenib 160 mg on the 3/1 schedule with probe substrates (CYP2C9, CYP2C19, CYP3A4, CYP2C8) concomitantly administered on Day 14 in Cycle 1	PK Safety
		14814	I	Advanced solid tumor	25	Oral dose of regorafenib 160 mg on the 3/1 schedule	PK Safety
		14596	II	Hepatocellular carcinoma	36	Oral dose of regorafenib 160 mg on the 3/1 schedule	Safety
		11726	II	Unresectable or metastatic renal cell carcinoma	49	Oral dose of regorafenib 160 mg on the 3/1 schedule	Safety

PK: Pharmacokinetics, BSC: Best supportive care

*1: Cohort 9 included patients with metastatic colorectal cancer

*2: Rapid intravenous administration of oxaliplatin 85 mg/m^2, calcium folinate 400 mg/m^2, and 5-FU 400 mg/m^2 as well as continuous intravenous infusion of 5-FU 2400 mg/m^2 (for 46 hours)

*3: Rapid intravenous administration of irinotecan 180 mg/m^2, calcium folinate 400 mg/m^2, and 5-FU 400 mg/m^2 as

well as continuous intravenous infusion of 5-FU 2400 mg/m^2 (for 46 hours)

Each of the clinical studies is summarized as follows.
Major adverse events other than death observed in each clinical study are described in "4.(iv) Adverse events observed in clinical studies", and PK-related study data are described in "4.(i) Summary of biopharmaceutic studies and associated analytical methods" and "4.(ii) Summary of clinical pharmacology studies."

Evaluation data

(1) Clinical pharmacology studies

The results from the following 5 clinical pharmacology studies in healthy adult male subjects were submitted [see "4.(i) Summary of biopharmaceutic studies and associated analytical methods" and "4.(ii) Summary of clinical pharmacology studies"]. No death occurred throughout the study period in these studies.

1) Foreign phase I study (5.3.1.2.1, Study 12437 [to 20])
2) Foreign phase I study (5.3.1.1.1, Study 14656 [20 to 20])
3) Foreign phase I study (5.3.3.1.1, Study 12436 [to 20])
4) Foreign phase I study (5.3.3.4.1, Study 12435 [to 20])
5) Foreign phase I study (5.3.3.4.2, Study 15524 [to 20])

(2) Japanese clinical studies

Phase I study (5.3.3.2.4, Study 13172 [20 - ongoing (Data cut-off; , 20)])

An open-label uncontrolled study was conducted in patients with progressive solid tumor (target sample size of 12) at 4 study sites to evaluate the PK and safety of regorafenib.

A single oral dose of regorafenib 160 mg was administered on Day 1, and starting from Day 8, oral dose of regorafenib 160 mg on the 3/1 schedule was continued until the progression or study discontinuation criteria were met. Regorafenib was given to patients after light breakfasts (approximately 300 kcal).

Of 16 subjects enrolled in the study, 15 subjects received regorafenib, except for 1 ineligible subject, and were included in the efficacy and safety analyses.

Regarding safety, there were no deaths reported during the dosing period or within 30 days after the last dose.

(3) Global study

Global phase III study (5.3.5.1.1, Study 14387 [20 - ongoing (Data cut-off; , 20)])

A double-blind, randomized, controlled study was conducted at 105 sites in 15 countries including Japan to compare efficacy and safety between regorafenib and placebo in combination with best supportive care (BSC) in patients with metastatic colorectal cancer (target sample size of 690) who have progressed after the standard chemotherapy (chemotherapy including fluorinated pyrimidine antineoplastic drugs, oxaliplatin, irinotecan, and bevacizumab [genetical recombination] [bevacizumab]) as well as, if Kirsten rat sarcoma 2 viral oncogene homolog [*KRAS*] gene in the tumor tissue is wild-type, cetuximab [genetical recombination] [cetuximab] or panitumumab [genetical recombination] [panitumumab]).

Oral administration of regorafenib 160 mg or placebo on the 3/1 schedule was continued until the progression or study discontinuation criteria were met. Regorafenib was to be administered with approximately 240 mL of water after low-fat breakfasts (calories from the fat accounted for <30%

of the total calories).

All of 760 patients enrolled in this study (505 patients in regorafenib group, 255 patients in placebo group) were included in the intent to treat (ITT) population for efficacy analysis. Except for 7 patients (5 patients in regorafenib group, 2 patients in placebo group) who did not receive the study drug (regorafenib or placebo), 753 patients were included in the safety analysis.

The primary endpoint for this study was OS. A total of 2 interim analyses were planned for this study; one interim analysis was planned to evaluate the futility when the number of events reached approximately 30% of that necessary for the final efficacy analysis (582 events); and the other interim analysis was planned to evaluate efficacy and futility when the number of events reached approximately 70% of that necessary for the analysis. To set the early study discontinuation criteria for efficacy, Lan-DeMets alpha spending function of the O'Brien-Fleming type was used.

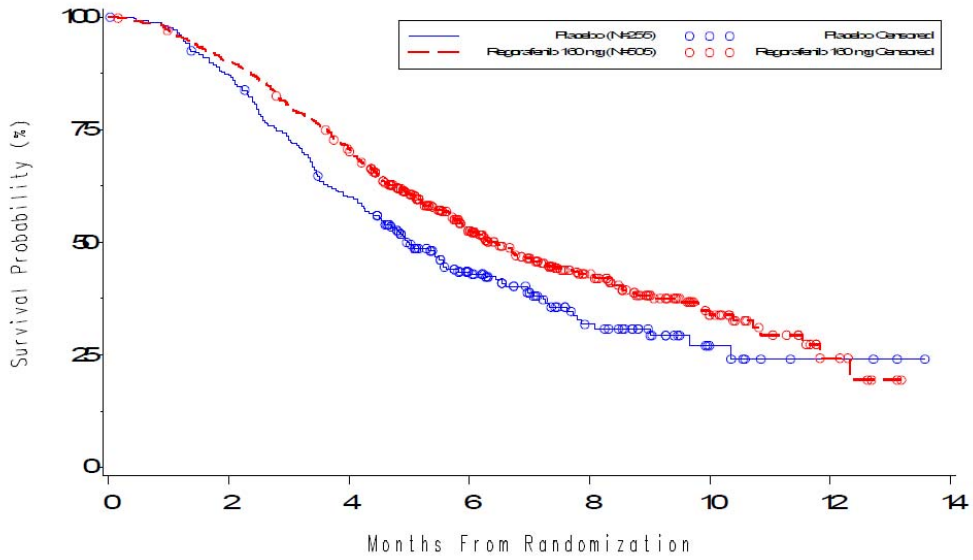
When the number of observed events reached approximately 52% of that necessary for the final efficacy analysis, the first interim analysis was performed to review information related to the safety and the hazard ratio for OS. The independent data monitoring committee recommended the continuation of the study. In the second interim analysis (data cut-off date, [redacted], 20[redacted]), the committee concluded that clear prolongation of OS was confirmed in the regorafenib group and recommended early study discontinuation in accordance with the previously specified early study discontinuation criteria for efficacy. In accordance with this recommendation, the study was discontinued, and the concerned interim analysis results were defined as the final results for the OS.

Regarding efficacy, the analysis results for the OS, which was the primary endpoint in the second interim analysis (data cut-off date, [redacted], 20[redacted]), are as follows.

Analysis results for the OS (ITT population, n = 760)

	Regorafenib group	Placebo group
Number of patients	505	255
Number of deaths (%)	275 (54.5)	157 (61.6)
OS median [95% CI] (days)	196 [178, 222]	151 [131, 177]
Hazard ratio [95% CI]	0.774 [0.636, 0.942]	
P value (one-sided)[*1, *2]	0.005178	

*1: Stratified by log-rank test using treatment history with anti-VEGF antibody (treated or none), period after diagnosis of metastasis (≥18 months, <18 months), and geographic classification (region 1, region 2, region 3) as stratification factors, *2: one-sided significance level, 0.009279



Patients at Risk						
Placebo	221	150	75	32	9	3
Regorafenib 160 mg	452	352	187	93	33	7

Regarding safety, 69 of 500 patients in the regorafenib group (13.8%) and 41 of 253 patients in the placebo group (16.2%) died during the dosing period or within 30 days after the last dose. Of the causes of death except for progression (58 patients in regorafenib group, 35 patients in placebo group), those in the regorafenib group included pneumonia (2 patients), upper gastrointestinal haemorrhage, rectal and vaginal haemorrhage , pulmonary haemorrhage, cardiac arrest, general physical health deterioration, intestinal obstruction, cerebrovascular accident, sudden death, and unknown death (1 patient each). Of these, rectal and vaginal haemorrhage, pulmonary haemorrhage, cerebrovascular accident, and sudden death (1 patient each) were determined to have a causal relationship with the study drug. In the placebo group, the causes of death included sudden death (2 patients), pneumonia (2 patients, of them, 1 patient experienced pneumonia and ileus), cardiac arrest, and general physical health deterioration (1 patient each).

(4) Foreign clinical studies

Phase I study [5.3.3.2.1, Study 11650 [[redacted] 20[redacted] - ongoing (Data cut-off; [redacted] [redacted], 20[redacted])]

An open-label uncontrolled study was conducted in patients with progressive solid tumor (target sample size of 47, 3-20 patients for each cohort) at 3 sites to evaluate the MTD, safety, and PK of regorafenib.

In Cohort 1, a single oral dose of regorafenib 10 mg was administered on Day 1, and starting from Day 8, oral dose of regorafenib QD was continued for 7 days followed by a 14-day washout period. In Cohorts 2 to 8, oral administration of regorafenib 10 to 220 mg on the 3/1 schedule was continued until the disease progressed or the study discontinuation criteria were met. Regorafenib was to be given after light breakfasts (approximately 300 kcal).

In Cohort 9 which included patients with metastatic colorectal cancer, oral dose of regorafenib 160 mg on the 3/1 schedule was continued until the disease progressed or the study discontinuation criteria were met.

Of 85 patients enrolled in this study, 76 patients received regorafenib, except for 9 ineligible

subjects, and were included in the safety analyses.

Regarding safety, 8 deaths occurred during the dosing period or within 30 days after the last dose. Except for progression (7 patients), the cause of the death was pneumonia (1 patient), for which a causal relationship with regorafenib was ruled out.

Reference data
Foreign clinical studies

1) Phase I study (5.3.3.2.2, 5.3.3.2.3; Study 11651 [[redacted], 20[redacted] - ongoing (Data cut-off; [redacted], 20[redacted])])

An open-label uncontrolled study was conducted in patients with progressive solid tumor (target sample size of 60-80) at 1 site to evaluate the safety and PK of regorafenib.

Of 106 patients enrolled in this study, 84 patients received regorafenib. Seven deaths occurred during the dosing period or within 30 days after the last dose. The causes of the deaths included progression (6 patients) and other (1 patient), for which a causal relationship with regorafenib was ruled out.

2) Phase I study (5.3.3.2.5, Study 14996 [[redacted], 20[redacted] - ongoing (Data cut-off; [redacted], 20[redacted])])

An open-label uncontrolled study was conducted in patients with progressive solid tumor (target sample size of 12) at 4 sites to evaluate the safety and PK of regorafenib.

Of 17 patients enrolled in this study, 12 patients received regorafenib. Three deaths occurred during the dosing period or within 30 days after the last dose. The cause of all deaths was progression, and a causal relationship with regorafenib was ruled out.

3) Phase I study (5.3.3.2.6, Study 11656 [[redacted], 20[redacted] - ongoing (Data cut-off; [redacted], 20[redacted])])

An open-label uncontrolled study was conducted in patients with metastatic colorectal cancer (target sample size of 60) at 8 sites to evaluate the safety, PK, and pharmacodynamics of regorafenib.

Of 48 patients enrolled in this study, 45 patients received regorafenib. Three deaths occurred during the dosing period or within 30 days after the last dose. The causes of the deaths included progression (2 patients) and hepatic failure (1 patient). A causal relationship of hepatic failure with regorafenib could not be ruled out.

4) Phase II study (5.3.5.2.1, Study 14596 [[redacted], 20[redacted] - ongoing (Data cut-off; [redacted], 20[redacted])])

An open-label uncontrolled study was conducted in patients with hepatocellular carcinoma (target sample size of 36) at 13 sites to evaluate the safety and efficacy of regorafenib.

Of 56 patients enrolled in this study, 36 patients received regorafenib. Five deaths occurred during the dosing period or within 30 days after the last dose. The causes of the deaths included hepatic impairment/hepatic failure (2 patients), central nerve haemorrhage (2 patients), and haematoma (1 patient). A causal relationship of haematoma with regorafenib could not be ruled out.

5) Phase II study (5.3.5.2.2, 5.3.5.2.3; Study 11726 [[redacted], 20[redacted] - ongoing (Data cut-off; [redacted], 20[redacted])])

An open-label uncontrolled study was conducted in patients with unresectable or metastatic renal cell carcinoma (target sample size of 41) at 18 sites to evaluate the safety and efficacy of regorafenib.

Of 64 patients enrolled in this study, 49 patients received regorafenib. Four deaths occurred during the dosing period or within 30 days after the last dose. The causes of the deaths included pulmonary thrombosis/embolism, cardiac ischaemia/myocardial infarction, cardio-respiratory arrest, and metastases to lung (1 patient each). Causal relationship of any of these causes with regorafenib could not be ruled out.

6) Phase I study (5.3.4.2.1, Study 14814 [[redacted], 20[redacted] - ongoing (Data cut-off; [redacted], 20[redacted])])

An open-label uncontrolled study was conducted in patients with progressive solid tumor (target sample size of 50) at 6 sites to evaluate the safety, PK, and efficacy of regorafenib.

Of 64 patients enrolled in this study, 53 patients received regorafenib.Five deaths occurred during the dosing period or within 30 days after the last dose. The cause of all deaths was progression, and a causal relationship with regorafenib was ruled out.

7) Phase I study (5.3.3.4.3, Study 12434 [[redacted] 20[redacted] - ongoing (Data cut-off; [redacted], 20[redacted])])

An open-label uncontrolled study was conducted in patients with progressive solid tumor (target sample size of 40) at 4 sites to evaluate the safety and efficacy of regorafenib.

Of 47 patients enrolled in this study, 40 patients received regorafenib. Four death occurred during the dosing period or within 30 days after the last dose. The causes of the deaths included progression and gastrointestinal perforation (2 patients each). A causal relationship of gastrointestinal perforation with regorafenib could not be ruled out.

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

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

In the global phase III study (Study 14387), the initial specifications of Interactive Voice Response System (IVRS) used for randomization had a different definition for the "geographic classification*," one of the stratification factors, from that in the protocol (geographic classification of Italy was mistakingly defined as "3" instead of "1"). An error thus occurred in the stratification for "geographic classification."

PMDA asked the applicant to explain the effects of the stratification error on the efficacy evaluation.

The applicant responded as follows:
In Study 14387, permuted block randomization was applied to stratification. The stratification information in the IVRS had errors involving a total of 33 patients (15 patients in placebo group, 18 patients in regorafenib group), of whom 28 patients had the wrong information entered by the study site. The information with errors involving the remaining 5 patients (3 patients in placebo group, 2 patients in regorafenib group) were related to the incorrect definition for "geographic classification," and the study drug was given according to the initially randomized dose group. After recognition of the concerned mistake, the sponsor revised the specifications and corrected the database referred to by IVRS, and confirmed that no same mistake had been made after the correction.

To investigate effects of the error in stratification on the efficacy evaluation in this study, the following two analyses were performed on the primary endpoint of the OS: (1) one analysis was performed using the IVRS-database information at the time of randomization; and (2) the other analysis was performed without adjustment according to the stratification factors. The consequently obtained analysis data were compared with the main analysis data obtained from

the stratification information recorded in the case report forms. The hazard ratio [95% CI] of the regorafenib group to the placebo group in the main analysis was 0.774 [0.636, 0.942], and the hazard ratio in analyses (1) and (2) was 0.773 [0.634, 0.942] and 0.767 [0.630, 0.933], respectively, which were similar to that in the main analysis.

*: Region 1 (North America, Western Europe, Israel, Australia), Region 2 (Asia), and Region 3 (South America, Turkey, Eastern Europe)

PMDA considers as follows:
Before using IVRS in the randomization, the applicant should have checked the system during the establishment thoroughly and should have taken preventive measures for eliminating errors in entry. Although it is difficult to strictly analyze the effects of the stratification error due to the incorrect definition of a randomization factor on the efficacy evaluation in Study 14387, PMDA has concluded that the relevant study data can be used in the primary efficacy evaluation, because (1) the mistake in the definition of a randomization factor was found soon after the initiation of Study 14387 and then corrected; and (2) sensitivity analysis results showed no effects of the stratification factor on the efficacy result in Study 14387.

Based on the above, PMDA has concluded that the most important clinical study in the efficacy and safety evaluation of regorafenib among studies included in the submitted evaluation data is Study 14387, which included patients with metastatic colorectal cancer who have progressed after the standard chemotherapy. Therefore, PMDA has decided to evaluate the data mainly from this study.

4.(iii).B.(2) Efficacy
As a result of the following review, PMDA has concluded that the efficacy of regorafenib is demonstrated in patients with metastatic colorectal cancer who have progressed after standard chemotherapy.

4.(iii).B.(2).1) Control group
PMDA asked the applicant to explain the appropriateness of including the placebo as the control in Study 14387.

The applicant responded as follows:
The standard therapy for incurable, unresectable, advanced/recurrent colorectal cancer at the study baseline was not considerably different among Japan, the US, and Europe (*National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology. Colon Cancer.* [NCCN Guidelines] [v.3.2010], *Ann Oncol.* 2010;21 [Suppl 5];V93-7, *Japanese Society for Cancer of the Colon and Rectum guidelines 2010 for the treatment of colorectal cancer.* Kanehara & Co., Ltd.; 2010 [JSCCR Guidelines for the Treatment of Colorectal Cancer]). The pharmacotherapy for incurable, unresectable, advanced/recurrent colorectal cancer includes fluorinated pyrimidine antineoplastic drugs, oxaliplatin, irinotecan, bevacizumab, cetuximab, or panitumumab.

The first-line therapy is generally given as (1) combination regimen of fluorouracil, calcium folinate (or calcium levofolinate), and oxaliplatin (FOLFOX) or (2) a regimen of bevacizumab added to FOLFIRI, or cetuximab or panitumumab added to FOLFIRI in patients with wild-type *KRAS* gene.

The second-line therapy is given as either regimen of FOLFOX or FOLFIRI, whichever has not been used for the first-line therapy, concurrently with bevacizumab, cetuximab or panitumumab.

To patients with wild-type *KRAS* gene in the tumor tissue, cetuximab or panitumumab may be given

alone or concurrently with irinotecan as the third treatment if not used until the secondary treatment.

The applicant considers it appropriate to include the placebo as the control in Study 14387 in patients who have progressed after the above chemotherapy, because the standard chemotherapy for such patients has not been established, and BSC has been routinely provided in the clinical settings to improve the performance status.

PMDA accepted the applicant's explanation.

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

PMDA considers it appropriate to set the OS as the primary endpoint in Study 14387 in patients with metastatic colorectal cancer who have progressed after the standard chemotherapy.

In Study 14387, the OS in the regorafenib group was significantly prolonged compared with the placebo group [see "4.(iii).A. Evaluation data (3) Global study"]. PMDA has concluded that the efficacy in patients of the study was demonstrated. In addition, PMDA confirmed that results of the subgroup analysis including presence/absence of *KRAS* gene mutation, age, sex, race, and previous treatment history were not substantially different from analysis results on the OS in the overall study population.

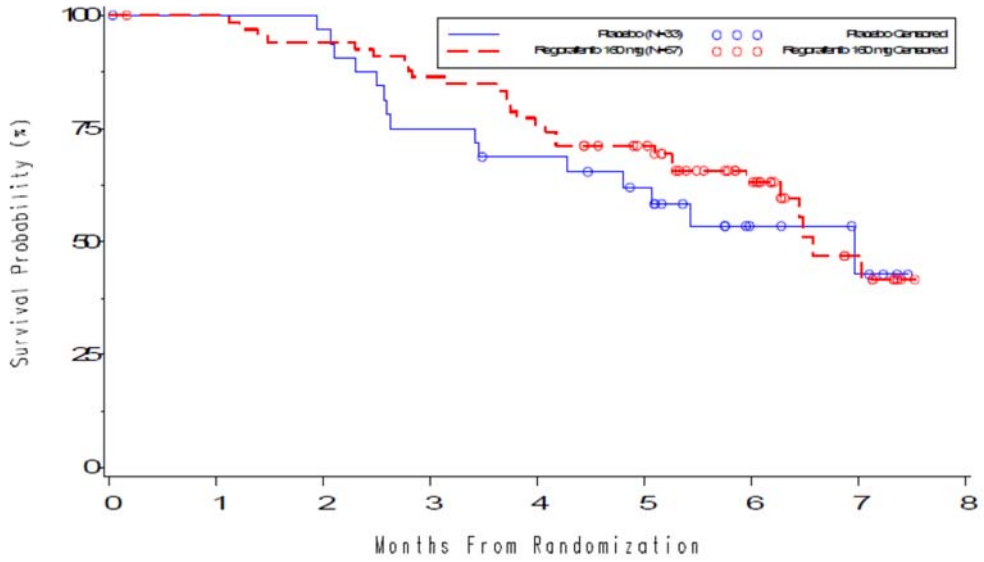
4.(iii).B.(2).3) Efficacy in Japanese patients

Concerning the efficacy of regorafenib in Japanese patients, the applicant explained as follows:
In 100 Japanese patients enrolled in Study 14387 (67 patients in regorafenib group, 33 patients in placebo group), a similar trend was observed as in the overall study population (the table below), and the applicant claims that regorafenib is expected to be effective also in Japanese patients.

Analysis results for the OS in Japanese patients (ITT population, n = 100)

	Regorafenib group	Placebo group
Number of patients	67	33
Number of deaths (%)	28 (41.8)	15 (45.5)
OS median [95% CI] (days)	200 [191, NA]	212 [130, NA]
Hazard ratio [95% CI]	0.806 [0.430, 1.510]	
P value (one-sided)*	0.250	

NA: Not available, *: log-rank test



Patients at Risk							
Placebo	32	31	24	21	17	7	4
Regorafenib 160 mg	66	62	57	50	42	25	9

PMDA confirmed that data on the efficacy of regorafenib in the Japanese patients showed similar trends to those in the overall study population in Study 14387, in terms of not only the primary endpoint, the OS, but also the secondary endpoints, although the number of events analysed was limited. PMDA has thus concluded that the certain efficacy of regorafenib was also demonstrated in Japanese patients.

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

As a result of the following review, PMDA considers that adverse events to which attention should be particularly paid during treatment of regorafenib included hand and foot syndrome, hepatic function disorder, hypertension (hypertensive crisis), haemorrhage, thrombosis or embolism, gastrointestinal perforation or fistula, Stevens-Johnson syndrome/toxic epidermal necrolysis, and posterior reversible encephalopathy.

Concerning the clinical use of regorafenib, PMDA has concluded that regorafenib is tolerable in Japanese patients with colorectal cancer when a physician with sufficient knowledge and experience in cancer chemotherapy implements appropriate treatment including monitoring and management of the above adverse events, dose interruption, dose reduction, and discontinuation. However, the safety information obtained in Japan is limited. PMDA considers it necessary to collect post-marketing information continuously and to provide new safety information to medical practices in an appropriate and prompt manner when such information becomes available.

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

Based on the safety information observed in the regorafenib group and placebo group of Study 14387, the applicant explained the safety profile of regorafenib in patients with colorectal cancer as follows:

The safety information in the regorafenib group and placebo group of Study 14387 is outlined in the table below.

Outline of the safety (Study 14387)

	Number of patients (%)	
	Regorafenib group (n = 500)	Placebo group (n = 253)
All adverse events	498 (99.6)	245 (96.8)
Grade 3 or 4 adverse events	323 (64.6)	87 (34.4)
Grade 5 adverse events	67 (13.4)	37 (14.6)
Serious adverse events	219 (43.8)	100 (39.5)
Adverse events leading to discontinuation	88 (17.6)	32 (12.6)
Adverse events leading to dose reduction	188 (37.6)	8 (3.2)
Adverse events leading to dose interruption	304 (60.8)	55 (21.7)

At all grades, adverse events of which the incidence in the regorafenib group was at least 10% higher than that in the placebo group included decreased appetite, palmar-plantar erythrodysaesthesia syndrome, diarrhoea, fatigue, weight decreased, hypertension, dysphonia, pyrexia, rash, stomatitis, and mucosal inflammation of which only palmar-plantar erythrodysaesthesia syndrome was at Grade ≥3 (the table below). Adverse events leading to dose-reduction of which the incidence in the regorafenib group was at least 3% higher than that in the placebo group included palmar-plantar erythrodysaesthesia syndrome (91 of 500 patients [18.2%] in regorafenib group, 1 of 253 patients [0.4%] in placebo group) and diarrhoea (19 of 500 patients [3.8%], 0 of 253 patients). Adverse events leading to dose interruption of which the incidence in the regorafenib group was at least 3% higher than that in the placebo group included palmar-plantar erythrodysaesthesia syndrome (94 of 500 patients [18.8%] in regorafenib group, 0 of 253 patients in placebo group), diarrhoea (31 of 500 patients [6.2%], 2 of 253 patients [0.8%]), pyrexia (23 of 500 patients [4.6%], 3 of 253 patients [1.2%]), and rash (18 of 500 patients [3.6%], 0 of 253 patients). Adverse events leading to discontinuation of which the incidence in the regorafenib group was at least 1% higher than that in the placebo group included palmar-plantar erythrodysaesthesia syndrome (7 of 500 patients [1.4%] in regorafenib group, 0 of 253 patients in placebo group).

Adverse events of which the incidence in the regorafenib group is ≥10% (Study 14387)

Preferred Term (MedDRA Ver. 14.1)	Number of patients (%)					
	Regorafenib group (n = 500)			Placebo group (n = 253)		
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
Number of patients with adverse events	498 (99.6)	280 (56.0)	43 (8.6)	245 (96.8)	67 (26.5)	20 (7.9)
Decreased appetite	234 (46.8)	23 (4.6)	0	72 (28.5)	11 (4.3)	0
Palmar-plantar erythrodysaesthesia syndrome	225 (45.0)	83 (16.6)	0	18 (7.1)	0	0
Diarrhoea	214 (42.8)	41 (8.2)	1 (0.2)	43 (17.0)	5 (2.0)	0
Fatigue	201 (40.2)	45 (9.0)	2 (0.4)	74 (29.2)	13 (5.1)	3 (1.2)
Weight decreased	161 (32.2)	2 (0.4)	0	26 (10.3)	0	0
Hypertension	152 (30.4)	38 (7.6)	0	20 (7.9)	2 (0.8)	0
Dysphonia	150 (30.0)	0	0	16 (6.3)	0	0
Pyrexia	140 (28.0)	9 (1.8)	1 (0.2)	37 (14.6)	0	0
Asthenia	132 (26.4)	33 (6.6)	0	45 (17.8)	10 (4.0)	2 (0.8)
Constipation	119 (23.8)	1 (0.2)	0	48 (19.0)	0	0
Nausea	112 (22.4)	4 (0.8)	0	55 (21.7)	3 (1.2)	0
Rash	110 (22.0)	24 (4.8)	0	8 (3.2)	1 (0.4)	0
Abdominal pain	98 (19.6)	20 (4.0)	0	41 (16.2)	5 (2.0)	1 (0.4)
Dyspnoea	85 (17.0)	8 (1.6)	3 (0.6)	32 (12.6)	9 (3.6)	0
Stomatitis	85 (17.0)	12 (2.4)	0	8 (3.2)	0	0
Mucosal inflammation	82 (16.4)	11 (2.2)	0	4 (1.6)	0	0
Vomiting	80 (16.0)	6 (1.2)	0	41 (16.2)	2 (0.8)	0
Hyperbilirubinaemia	65 (13.0)	23 (4.6)	2 (0.4)	17 (6.7)	9 (3.6)	4 (1.6)
Back pain	63 (12.6)	5 (1.0)	0	25 (9.9)	3 (1.2)	1 (0.4)
Anaemia	55 (11.0)	21 (4.2)	1 (0.2)	21 (8.3)	6 (2.4)	1 (0.4)
Cough	53 (10.6)	3 (0.6)	0	27 (10.7)	0	0
Headache	51 (10.2)	4 (0.8)	0	17 (6.7)	0	0

PMDA considers as follows:
The incidences of adverse events leading to dose reduction or dose interruption such as palmar-plantar erythrodysaesthesia syndrome and diarrhoea were higher in the regorafenib group than in placebo group, and attention should be paid to the adverse events. However, the incidences of adverse events and serious adverse events leading to discontinuation or deaths were not considerably different between the regorafenib group and placebo group. Regorafenib can be tolerated if appropriate actions such as dose interruption, dose reduction, and discontinuation are taken. Adverse events of which the incidence in the regorafenib group was higher than that in the placebo group including decreased appetite, palmar-plantar erythrodysaesthesia syndrome, diarrhoea, fatigue, weight decreased, hypertension, dysphonia, pyrexia, rash, stomatitis, and mucosal inflammation are considered as regorafenib-treatment-emergent adverse events. Thus, it is necessary to pay attention to these events and to provide appropriate cautions.

4.(iii).B.(3).2) Differences in the safety between Japanese and foreign populations
The applicant explained the differences in the safety of regorafenib between Japanese and foreign populations as follows:
The safety information in Japanese and foreign patients of Study 14387 is outlined in the table below.

Outline of the safety in Japanese and foreign patients (Study 14387)

	Number of patients (%)			
	Japanese patients		Foreign patients	
	Regorafenib group (n = 65)	Placebo group (n = 32)	Regorafenib group (n = 435)	Placebo group (n = 221)
All adverse events	65 (100)	29 (90.6)	433 (99.5)	216 (97.7)
Grade 3 or 4 adverse events	53 (81.5)	10 (31.3)	270 (62.1)	77 (34.8)
Grade 5 adverse events	3 (4.6)	3 (9.4)	64 (14.7)	34 (15.4)
Serious adverse events	18 (27.7)	10 (31.3)	201 (46.2)	90 (40.7)
Adverse events leading to discontinuation	14 (21.5)	2 (6.3)	74 (17.0)	30 (13.6)
Adverse events leading to dose reduction	31 (47.7)	1 (3.1)	157 (36.1)	7 (3.2)
Adverse events leading to dose interruption	54 (83.1)	9 (28.1)	250 (57.5)	46 (20.8)

Adverse events of which the incidence in either Japanese or foreign patients was ≥10% in Study 14387 are as shown in the table below.

Adverse events in the regorafenib group of Study 14387 of which the incidence was at least 20% higher in Japanese patients than in foreign patients included palmar-plantar erythrodysaesthesia syndrome, hypertension, proteinuria, rash, lipase increased, AST increased, and platelet count decreased. Adverse events at Grade ≥3 of which the incidence in Japanese patients was at least 10% higher than that in foreign patients included palmar-plantar erythrodysaesthesia syndrome, lipase increased, AST increased, and hypophosphataemia.

Adverse events of which the incidence in either Japanese or foreign patients was ≥10% (Study 14387)

Preferred term (MedDRA Ver. 14.1)	Number of patients (%)					
	Japanese patients (n = 65)			Foreign patients (n = 435)		
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
Number of patients with adverse events	65 (100)	48 (73.8)	5 (7.7)	433 (99.5)	232 (53.5)	38 (8.7)
Anaemia	1 (1.5)	1 (1.5)	0	54 (12.4)	20 (4.6)	1 (0.2)
Thrombocytopenia	9 (13.8)	0	1 (1.5)	40 (9.2)	12 (2.8)	1 (0.2)
Abdominal pain	3 (4.6)	0	0	95 (21.8)	20 (4.6)	0
Constipation	18 (27.7)	0	0	101 (23.2)	1 (0.2)	0
Diarrhoea	17 (26.2)	2 (3.1)	0	197 (45.3)	39 (9.0)	1 (0.2)
Nausea	18 (27.7)	1 (1.5)	0	94 (21.6)	3 (0.7)	0
Stomatitis	14 (21.5)	1 (1.5)	0	71 (16.3)	11 (2.5)	0
Vomiting	10 (15.4)	2 (3.1)	0	70 (16.1)	4 (0.9)	0
Asthenia	0	0	0	132 (30.3)	33 (7.6)	0
Fatigue	33 (50.8)	5 (7.7)	1 (1.5)	168 (38.6)	40 (9.2)	1 (0.2)
Mucosal inflammation	1 (1.5)	0	0	81 (18.6)	11 (2.5)	0
Pyrexia	23 (35.4)	2 (3.1)	0	117 (26.9)	7 (1.6)	1 (0.2)
Hyperbilirubinaemia	5 (7.7)	2 (3.1)	0	60 (13.8)	21 (4.8)	2 (0.5)
ALT increased	13 (20.0)	5 (7.7)	0	15 (3.4)	4 (0.9)	2 (0.5)
AST increased	17 (26.2)	8 (12.3)	0	17 (3.9)	3 (0.7)	0
Blood ALP increased	13 (20.0)	4 (6.2)	0	19 (4.4)	7 (1.6)	0
Blood amylase increased	9 (13.8)	3 (4.6)	0	5 (1.1)	1 (0.2)	1 (0.2)
Blood bilirubin increased	11 (16.9)	0	0	20 (4.6)	5 (1.1)	2 (0.5)
Blood lactate dehydrogenase increased	10 (15.4)	0	0	5 (1.1)	0	0
Lipase increased	18 (27.7)	9 (13.8)	1 (1.5)	10 (2.3)	4 (0.9)	5 (1.1)
Platelet count decreased	16 (24.6)	3 (4.6)	0	12 (2.8)	2 (0.5)	0
Weight decreased	13 (20.0)	0	0	148 (34.0)	2 (0.5)	0
Decreased appetite	38 (58.5)	6 (9.2)	0	196 (45.1)	17 (3.9)	0
Hypophosphataemia	11 (16.9)	8 (12.3)	0	12 (2.8)	8 (1.8)	0
Back pain	5 (7.7)	0	0	58 (13.3)	5 (1.1)	0
Dysgeusia	7 (10.8)	0	0	31 (7.1)	0	0
Headache	5 (7.7)	0	0	46 (10.6)	4 (0.9)	0
Neuropathy peripheral	7 (10.8)	0	0	12 (2.8)	1 (0.2)	0
Proteinuria	26 (40.0)	4 (6.2)	0	11 (2.5)	4 (0.9)	0
Cough	5 (7.7)	1 (1.5)	0	48 (11.0)	2 (0.5)	0
Dysphonia	22 (33.8)	0	0	128 (29.4)	0	0
Dyspnoea	4 (6.2)	1 (1.5)	0	81 (18.6)	7 (1.6)	3 (0.7)
Epistaxis	10 (15.4)	0	0	35 (8.0)	0	0
Palmar-plantar erythrodysaesthesia syndrome	52 (80.0)	18 (27.7)	0	173 (39.8)	65 (14.9)	0
Rash	26 (40.0)	2 (3.1)	0	84 (19.3)	22 (5.1)	0
Hypertension	39 (60.0)	7 (10.8)	0	113 (26.0)	31 (7.1)	0

ALP: alkaline phosphatase

In Study 14387, fatal events were reported in a total of 6 Japanese patients (3 patients in regorafenib group [4.6%], 3 patients in placebo group [9.4%]) during the dosing period or within 30 days after treatment discontinuation. Except for one event due to pneumonia in the placebo group, all events were related to progression.

The adverse event leading to dose-reduction of which the incidence in the regorafenib group was at least 5% higher than that in the placebo group was palmar-plantar erythrodysaesthesia syndrome both in Japanese and foreign patients (18 of 65 Japanese patients [27.7%] in regorafenib group, 73 of foreign 435 patients [16.8%] in regorafenib group). Adverse events leading to dose

interruption of which the incidence in the regorafenib group was at least 5% higher than that in the placebo group in Japanese patients included palmar-plantar erythrodysaesthesia syndrome (27 of 65 patients [41.5%] in regorafenib group), AST increased (5 of 65 patients [7.7%] in regorafenib group), pyrexia (5 of 65 patients [7.7%] in regorafenib group), platelet count decreased (4 of 65 patients [6.2%] in regorafenib group), and proteinuria (4 of 65 patients [6.2%] in regorafenib group); and those in foreign patients included palmar-plantar erythrodysaesthesia syndrome (67 of 435 patients [15.4%] in regorafenib group) and diarrhoea (30 of 435 patients [6.9%] in regorafenib group). Adverse events leading to discontinuation of which the incidence in the regorafenib group was at least 3% higher than that in the placebo group in Japanese patients included ALT increased (3 of 65 patients [4.6%] in regorafenib group) and erythema multiforme (3 of 65 patients [4.6%] in regorafenib group), but no such events were found in foreign patients.

PMDA considers as follows:
In Study 14387, some adverse events (palmar-plantar erythrodysaesthesia syndrome, hypertension, proteinuria, rash, lipase increased, AST increased, platelet count decreased) occurred at a different incidence between Japanese and foreign patients, and of adverse events at Grade ≥3, (palmar-plantar erythrodysaesthesia syndrome, lipase increased, AST increased, hypophosphataemia) also occurred at a different incidence. Although it is necessary to appropriately provide cautions and information about these events, the patients rate with whom adverse events leading to treatment discontinuation was low and those events were controlled by dose reduction or dose interruption. Therefore, regorafenib was tolerable to Japanese patients.

In the following section, the adverse events that occurred at a high incidence in the overall study population, at a high incidence in the Japanese patients, the serious adverse events etc. in Study 14387 were mainly reviewed.

4.(iii).B.(3).3) Hepatic function disorder
The applicant explained hepatic function disorder as follows:
In Study 14387, the adverse events as shown in the table below were classified into hepatobiliary disorders. Except for hyperbilirubinaemia of which the incidence was higher in the regorafenib group than in the placebo group, all relevant events occurred at similar incidences in the 2 groups. Deaths due to hepatobiliary disorders occurred in 8 patients in the regorafenib group (1.6%) (hepatic failure in 6 patients and hepatic function abnormal in 2 patients) and 3 in the placebo group (1.2%). All of the above patients did not have preexisting hepatic diseases such as viral hepatitis, but had hepatic metastases. None of them showed any marked increase in AST or ALT to ≥500 U/L, and all of the deaths were determined to be caused by the progression; a causal relationship with regorafenib was thus ruled out.

Hepatobiliary disorders reported by ≥2 patients in either group (Study 14387)

Preferred term (MedDRA Ver. 14.1)	Number of patients (%)					
	Regorafenib group (n = 500)			Placebo group (n = 253)		
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
Hyperbilirubinaemia	65 (13.0)	23 (4.6)	2 (0.4)	17 (6.7)	9 (3.6)	4 (1.6)
Hepatic function abnormal	10 (2.0)	5 (1.0)	0	4 (1.6)	1 (0.4)	0
Hepatic pain	8 (1.6)	3 (0.6)	0	2 (0.8)	0	0
Hepatic failure	7 (1.4)	1 (0.2)	0	4 (1.6)	2 (0.8)	0
Jaundice	6 (1.2)	3 (0.6)	0	1 (0.4)	1 (0.4)	0
Cholestasis	4 (0.8)	3 (0.6)	1 (0.2)	2 (0.8)	0	1 (0.4)
Jaundice cholestatic	3 (0.6)	2 (0.4)	0	1 (0.4)	0	0
Cholangitis	2 (0.4)	1 (0.2)	0	1 (0.4)	0	0
Cholecystitis acute	2 (0.4)	2 (0.4)	0	0	0	0
Liver disorder	2 (0.4)	0	0	0	0	0
Cholelithiasis	1 (0.2)	1 (0.2)	0	2 (0.8)	0	0

In Study 14387, AST increased and ALT increased reported as adverse events occurred in 34 (6.8%) and 28 (5.6%) of 500 patients in the regorafenib group and 9 (3.6%) and 5 (2.0%) of 253 patients in the placebo group, respectively. The incidences of Grade 3 AST increased and ALT increased were 11 (2.2%) and 9 (1.8%) of 500 patients in the regorafenib group and 2 (0.8%) and 0 of 253 patients in the placebo group, respectively. At Grade 4, no such AST increased occurred in either group, while such ALT increased occurred only in the regorafenib group (2 of 500 patients, 0.4%). AST increased and ALT increased reported as laboratory abnormality occurred in 319 (65.0%) and 222 (45.2%) of 491 patients in the regorafenib group and 115 (45.6%) and 75 (29.8%) of 252 patients in the placebo group, respectively; the incidences were higher in the regorafenib group than in the placebo group. Grade 3 laboratory abnormalities of AST increased and ALT increased occurred in 26 (5.3%) and 24 (4.9%) of 491 patients in the regorafenib group and 11 (4.4%) and 7 (2.8%) of 252 patients in the placebo group, respectively; and those at Grade 4 occurred in 3 (0.6%) and 3 (0.6%) of 491 patients in the regorafenib group and 2 (0.8%) and 1 (0.4%) of 252 patients in the placebo group, respectively.

Hy's law criteria (>3-fold the upper limit of normal [ULN] of AST or ALT, <2-fold the ULN of alkaline phosphatase [ALP], and ≥2-fold the ULN of total bilirubin) met in 4 patients in the regorafenib group (including 1 Japanese patient) and in 1 patient in the placebo group; and of these, 2 patients in the regorafenib group (including 1 Japanese patient) and 1 patient in the placebo group were found to have hepatic metastases. Of the remaining 2 patients who did not have hepatic metastases in the regorafenib group, 1 patient seemed to be complicated by haemolysis and infectious disease and did not experience the same event after the reinitiation of regorafenib; the concerned event in this patient was considered possibly unrelated to regorafenib. In the other remaining patient, the concerned event resolved after discontinuation of regorafenib, suggesting relationship with regorafenib.

Furthermore, according to definitions of drug-induced liver injury (DILI)* proposed by the International DILI Expert Working Group, search for severe DILI was performed using Global Pharmacovigilance (GPV) database which covered all clinical studies of regorafenib. As of the database cut-off date for this analysis ([redacted], 20[redacted]), approximately 1319 subjects received regorafenib, and of these, 3 patients (including 2 Japanese patients) were found to experience severe DILI. All of the 3 patients experienced lethal hepatocellular injury type of liver disorder with clinical manifestations of hepatic failure such as ascites, neuropathy, and coagulation abnormal within 2 months after the initiation of treatment with regorafenib (29-41 days after the initiation of the treatment). Of these 3 patients, excluding 1 Japanese patient, 2 patients had hepatic metastases, and the events in both patients were determined to have a causal relationship with regorafenib.

* Definitions of severe DILI according to the International DILI Expert Working Group criteria
- Death or transplantation due to DILI
- Elevated ALT to ≥3-fold the ULN (if the baseline value exceeds the ULN, ≥3-fold the baseline value) or elevated ALP to ≥2-fold the ULN (if the baseline value exceeds the ULN, ≥2-fold the baseline value) without bone lesions, and elevated total bilirubin to >2-fold the ULN and applicable to at least one of the following conditions:
  PT-INR ≥1.5, ascites or encephalopathy without preexisting hepatic cirrhosis, the other organ failure possibly due to DILI, or symptomatic hepatitis (fatigue, nausea, vomiting, right upper quadrant pain, pruritus, skin eruption, jaundice, weakness, inappetence, and weight decreased, judged to be due to DILI by a physician in charge)

Marked transaminase elevations but not meeting the definitions of severe DILI (AST or ALT >500 U/L) were found in 5 patients (including 2 Japanese patients); in 3 of these patients, a causal relationship of the event with regorafenib could not be ruled out. In the 3 patients, liver disorder developed within 42 to 138 days after the initiation of treatment with regorafenib. Of the three, excluding 1 patient with progressive hepatic metastases, 2 patients recovered from the disorder following dose interruption or discontinuation of regorafenib.

As described the above, most of the patients with the events recovered following dose interruption or discontinuation of regorafenib. The applicant claims that regorafenib was tolerable in patients even after development of hepatic function disorder if appropriate actions are taken. However, patients who died due to hepatic function disorder were reported, and in most of the patients, hepatic function disorder occurred within 2 months after the initiation of the treatment. The applicant also considers it necessary to carefully perform hepatic function tests for 2 months after the initiation of the treatment. Accordingly, the applicant plans to provide cautions about the timing of the hepatic function tests, actions to be taken to hepatic function disorder, and dose adjustment criteria through the package insert etc.

PMDA considers as follows:
The applicant should periodically perform the hepatic function test before and during treatment with regorafenib and pay attention to onset of hepatic function disorder, taking into account that it has been reported that patients experienced hepatic function disorder following treatment with regorafenib and resulting in death. PMDA considered the applicant's explanation acceptable that most serious hepatic function disorder events occurred within these 2 months and the hepatic function test should be performed with special cautions for at least 2 months after the initiation of thetreatment. However, hepatic function disorder also occurred in some patients at >2 months after the initiation of the treatment. Thus, it is necessary to provide information about the occurrence of hepatic function disorder (time of onset, severity, actions at the onset) and frequency of hepatic function tests specified in the protocol (every week until Cycle 2, every other week from Cycle 3 to 6 months after the initiation of the treatment) and to monitor the patients in a timely manner. In addition, PMDA also considers it necessary to appropriately provide information about the criteria for dose interruption, dose reduction, or discontinuation of regorafenib specified in the protocol so that sufficient actions can be taken at the time of onset of hepatic function disorder in accordance with these criteria.

4.(iii).B.(3).4) Skin and subcutaneous tissue disorders

The applicant explained skin and subcutaneous tissue disorders as follows:
In Study 14387, skin and subcutaneous tissue disorders occurred in 360 of 500 patients (72.0%) in the regorafenib group and 60 of 253 patients (23.7%) in the placebo group (the table below). The Grade 4 event was only Stevens-Johnson syndrome that occurred in 1 patient (0.2%) in the regorafenib group.

Skin and subcutaneous tissue disorders that occurred at the incidence of at least 2% in either group (Study 14387)

Preferred term (MedDRA Ver. 14.1)	Number of patients (%)			
	Regorafenib group (n = 500)		Placebo group (n = 253)	
	All grades	Grade 3	All grades	Grade 3
Palmar-plantar erythrodysaesthesia syndrome	225 (45.0)	83 (16.6)	18 (7.1)	0
Rash	110 (22.0)	24 (4.8)	8 (3.2)	1 (0.4)
Dry skin	44 (8.8)	0	8 (3.2)	0
Alopecia	38 (7.6)	0	4 (1.6)	0
Pruritus	24 (4.8)	0	11 (4.3)	0
Erythema	17 (3.4)	0	7 (2.8)	0
Hyperhidrosis	13 (2.6)	0	2 (0.8)	0
Night sweats	9 (1.8)	0	5 (2.0)	0

Of events classified into skin and subcutaneous tissue disorders, "hand and foot syndrome," "rash," and "severe skin adverse reactions" (Standardised MedDRA Queries, SMQs)* were defined as notably specified events, and further investigated as follows.

*: MedDRA preferred terms (actual events) that can be included in hand and foot syndrome, rash, and severe skin adverse reactions SMQ
- Hand and foot syndrome; Palmar-plantar erythrodysaesthesia syndrome, palmar erythema, and plantar erythema
- Rash; Drug eruption, rash, rash erythematous, rash generalised, rash macular, rash maculo-papular, rash papular, and rash pruritic
- Severe skin adverse reactions SMQ; Blister, conjunctivitis, drug eruption, erythema multiforme, exfoliative rash, genital ulceration, mouth ulceration, pemphigoid, skin exfoliation, Stevens-Johnson syndrome, stomatitis, and toxic skin eruption

In Study 14387, hand and foot syndrome occurred in 226 of 500 patients (45.2%) in the regorafenib group and 18 of 253 patients (7.1%) in the placebo group; rash occurred in 129 of 500 patients (25.8%) and 9 of 253 patients (3.6%); and severe skin adverse reactions SMQ occurred in 105 of 500 patients (21.0%) and 10 of 253 patients (4.0%). The incidence of any relevant event was higher in the regorafenib group than in the placebo group. No events of hand and foot syndrome or rash were classified at Grade 4, and of severe skin adverse reactions SMQ, only 1 event of Stevens-Johnson syndrome (0.2%) in the regorafenib group was classified at Grade 4 as aforementioned. In studies other than Study 14387, toxic epidermal necrolysis and rash maculo-papular occurred each in 1 patient (both serious), according to the report on [redacted].

As described above, skin and subcutaneous tissue disorders such as hand and foot syndrome (including palmar-plantar erythrodysaesthesia syndrome) and rash occurred more frequently in the regorafenib group than in the placebo group, and especially the incidence was high in the Japanese patients [see "4.(iii).B.(3).2 Differences in the safety between Japanese and foreign populations"]. However, palmar-plantar erythrodysaesthesia syndrome and rash led to the study discontinuation only in 7 (1.4%) and 4 (0.8%) of 500 patients, respectively. The applicant thus claims that these events can be managed by actions such as dose interruption and dose reduction of regorafenib. As measures against hand and foot syndrome, preventive actions before treatment with regorafenib and the manifestations (action to cuticular thickening, application of moisturizing cream etc.) are important. If skin manifestations occur, symptomatic treatment, dose interruption or dose reduction of regorafenib, and, if severe, discontinuation should be considered. Cautions about Stevens-Johnson syndrome/toxic epidermal necrolysis will be appropriately provided in the package insert.

PMDA considers as follows:
It is necessary to pay attention to skin and subcutaneous tissue disorders, especially hand and foot syndrome (including palmar-plantar erythrodysaesthesia syndrome) and rash, because the relevant events frequently occur; the incidences were higher in Japanese patients than in the overall study population; and furthermore the proportion of events leading to dose reduction or dose interruption was high. On the other hand, the events infrequently led to discontinuation of regorafenib. Thus, regorafenib is tolerable if preventive actions and symptomatic treatment in response to the manifestation of symptoms are given as done in Study 14387, and appropriate actions such as dose interruption and dose reduction of regorafenib are taken in accordance with the criteria specified in the clinical studies. However, Stevens-Johnson syndrome and toxic epidermal necrolysis were reported in clinical studies as events of which causal relationships with regorafenib could not be ruled out. It is necessary to provide cautions and information about incidence of skin disorder including the above events to medical practices.

4.(iii).B.(3).5) Hypertension (hypertensive crisis)
The applicant explained hypertension following treatment with regorafenib as follows:
In Study 14387, hypertension occurred in 152 of 500 patients (30.4%) in the regorafenib group and 20 in 253 patients (7.9%) in the placebo group. The Grade 3 event occurred in 38 of 500 patients (7.6%) in the regorafenib group and 2 of 253 patients (0.8%) in the placebo group, and no Grade 4/5 event was reported. No patients discontinued the study drug due to hypertension, and in the regorafenib group, dose reduction and dose interruption due to hypertension was reported in 16 patients (3.2%) and 13 patients (2.6%), respectively. Hypertension occurred in 140 of 152 patients within the first 2 cycles (Weeks 1 to Week 8). Subgroup analysis according to presence or absence of concomitant hypertension at the baseline showed that Grade 3 hypertension occurred in 28 of 211 patients with hypertension (13.3%) and 10 of 289 patients without hypertension (3.5%); the incidence in the patients with hypertension was higher than that in the patients without hypertension.

Hypertensive crisis reported by 1 subject each in Study 14387 and Study 11651 as an event at Grade 3, and posterior reversible encephalopathy related to hypertension reported by 1 subject in ongoing Study 14874 which includes patients with gastrointestinal stromal tumor [see "4.(iii).B.(3).10) Posterior reversible encephalopathy"].

As described the above, hypertension frequently occurred following treatment with regorafenib, but the applicant claims that hypertension can be managed if the blood pressure is confirmed to have been controlled in hypertensive patients at the baseline, the blood pressure is periodically monitored during the treatment with regorafenib, and actions are taken at the discretion of the attending physician, such as conventional antihypertensive therapy and dose interruption or dose reduction of regorafenib in response to the onset of hypertension.

PMDA considers as follows:
Hypertension frequently occurred especially in Japanese patients [see "4.(iii).B.(3).2) Differences in the safety between Japanese and foreign populations"], but infrequently led to discontinuation, dose interruption or dose reduction. Thus, hypertension can be controlled by (a) monitoring blood pressure periodically during the treatment and (b) taking appropriate actions such as antihypertensive medications at the onset of hypertension. However, serious adverse events such as hypertensive crisis also occurred following treatment with regorafenib, and the incidence of Grade 3 hypertension was high in patients complicated with hypertension. Therefore, it is necessary to pay thorough attention to changes in blood pressure and determine dose interruption or discontinuation at the time of onset of unmanageable serious hypertension. Accordingly, cautions should be provided to medical practices to ensure that the blood pressure is measured periodically before and during treatment with regorafenib, and appropriate actions such as antihypertensive medications are taken at the onset of hypertension.

4.(iii).B.(3).6) Haemorrhage

The applicant explained haemorrhage following treatment with regorafenib as follows:

In Study 14387, an analysis was performed by haemorrhage (excluding laboratory test terms) SMQ*. Haemorrhage occurred in 107 of 500 patients (21.4%) in the regorafenib group and 19/253 patients (7.5%) in the placebo group. The Grade 3 event occurred in 7 of 500 patients (1.4%) in the regorafenib group and 2 of 253 patients (0.8%) in the placebo group; and no Grade 4 events were reported. Deaths due to haemorrhage occurred in 4 of 500 patients (0.8%) only in the regorafenib group. Rectal and vaginal haemorrhage and pulmonary haemorrhage that occurred each in 1 patient were reported as the events determined to be causally related to regorafenib.

Haemorrhage leading to discontinuation and dose interruption of regorafenib was reported by 3 (0.6%) and 7 (1.4%) of 500 patients in the regorafenib group, respectively, but haemorrhage leading to dose-reduction was not reported.

* MedDRA preferred terms (actual events) that can be included in haemorrhage (excluding laboratory test terms) SMQ
Anal haemorrhage, blood urine present, conjunctival haemorrhage, gastric haemorrhage, gingival bleeding, haemarthrosis, haematemesis, haematochezia, haematoma, haematuria, haemoptysis, haemorrhoidal haemorrhage, intra-abdominal haemorrhage, lip haemorrhage, lower gastrointestinal haemorrhage, melaena, metrorrhagia, mouth haemorrhage, oesophageal haemorrhage, penile haemorrhage, post procedural haemorrhage, pulmonary haemorrhage, rectal haemorrhage, red blood cells urine positive, scrotal haematocoele, splenic haematoma, subcutaneous haematoma, tumour haemorrhage, upper gastrointestinal haemorrhage, urinary bladder haemorrhage, vaginal haemorrhage, and oesophageal varices haemorrhage

Analysis was performed on the incidences of haemorrhage according to presence or absence of concomitant anticoagulant medication. The incidence of haemorrhage in the regorafenib group was 18.7% (25 of 134 patients with anticoagulant medication) and 11.2% (41 of 366 patients without such medication); the incidence of haemorrhage was higher in patients with anticoagulant medication than in those without. However, the incidence of Grade ≥3 haemorrhage was 1.5% (2 of 134 patients with anticoagulant medication) and 2.2% (8 of 366 patients without such medication), which were similar. In the regorafenib group, the minimum platelet count before haemorrhage, maximum prothrombin international normalized ratio (PT-INR), and maximum activated partial thromboplastin time (aPTT) were compared between 10 patients with Grade ≥3 haemorrhage and those without haemorrhage. The minimum platelet count in patients with haemorrhage was lower than that in those without, but fell within the normal range, and the mean maximum PT-INR and mean maximum aPTT were similar.

Based on the above, the applicant considers that anticoagulant medication may put patients at a high risk of haemorrhage but is unlikely to contribute to development of serious haemorrhage events.

Concerning haemorrhage events, PMDA asked the applicant to explain the safety in patients with metastases to brain, which was specified as the exclusion criterion in Study 14387, and patients with Grade ≥3 haemorrhage within 4 weeks before the initiation of the treatment.

The applicant responded as follows:

In Study 14387, 2 patients with metastases to brain were included in the regorafenib group, but no suspected cerebral haemorrhage events were reported. In Study 11651 and Study 12434, from which data were used as reference, patients with metastases to brain were considered eligible if the following criteria were met: (1) “at least 6 months have passed since the last treatment, the imaging shows that the tumor has not grown within 2 weeks before enrollment, and the clinical conditions are stable at the time of inclusion”; and (2) “no treatment has been given to brain tumor or metastases to brain, and both sponsor and investigator judge that the patient can participate in

the study." In these 2 studies, a total of 3 patients with metastases to brain were included, but no suspected cerebral haemorrhage events occurred. In Study 14387, patients with Grade ≥3 haemorrhage within 4 weeks before the initiation of the treatment were not included; the information about the safety of regorafenib in such patients is unavailable. Based on the above, the applicant considers, at present, it unnecessary to provide special cautions on this matter after market launch, but plans to provide medical professionals with information materials so that they will be informed of the exclusion criteria in Study 14387.

PMDA considers as follows:
Serious haemorrhage events occurred after treatment with regorafenib, leading to death in some patients, attention should be paid to haemorrhage. Furthermore, since a high haemorrhage risk has been suggested, special attention should be paid to patients with anticoagulant medication. As patients with haemorrhage and patients with clinically suspected metastases to the brain were excluded from Study 14387, the safety information in these excluded patients was limited. In consideration of the limitation of the safety information, information such as the exclusion criteria specified in clinical studies should be provided to medical practices.

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

The applicant explained thromboembolism following treatment with regorafenib as follows:
The incidence of thromboembolism in Study 14387 is as shown in the table below. Arterial thromboembolism occurred in 9 patients (1.8%) in the regorafenib group and 2 patients (0.8%) in the placebo group. Of these events, ischaemic heart disease occurred in 6 patients in the regorafenib group (1.2%, myocardial ischaemia [3 patients], acute myocardial infarction [1 patient], myocardial infarction [1 patient], troponin increased [1 patient]) and 1 patient in the placebo group (0.4%, angina pectoris [1 patient]); the incidence was higher in the regorafenib group than in the placebo group. The incidences of the other venous thromboembolism and arterial thromboembolism were not increased following treatment with regorafenib.

Thromboembolism events (vascular occlusion, thrombosis, embolism) (Study 14387)

	Number of patients (%)					
	Regorafenib group (n = 500)			Placebo group (n = 253)		
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
Pulmonary embolism (MedDRA Preferred term)	4 (0.8)	0	4 (0.8)	3 (1.2)	0	1 (0.4)
Other venous thromboembolism*1	6 (1.2)	3 (0.6)	0	2 (0.8)	2 (0.8)	0
Arterial thromboembolism	9 (1.8)	1 (0.2)	3 (0.6)	2 (0.8)	1 (0.4)	1 (0.4)
Ischaemic heart disease*2	6 (1.2)	0	2 (0.4)	1 (0.4)	1 (0.4)	0
Ischemic cerebrovascular condition*3	2 (0.4)	0	1 (0.2)	1 (0.4)	0	1 (0.4)
Non-cardiac and non-cerebral events*4	1 (0.2)	1 (0.2)	0	0	0	0

*1: Including MedDRA Preferred terms of deep vein thrombosis, pelvic venous thrombosis, venous thrombosis, and vena cava thrombosis, *2: Including MedDRA Preferred terms of acute myocardial infarction, angina pectoris, myocardial infarction, myocardial ischaemia, and troponin increased, *3: Including MedDRA Preferred terms of cerebral ischaemia and cerebrovascular accident, *4: Non-cardiac or cerebrovascular embolism

The incidence of ischaemic heart disease was analyzed according to presence or absence of a cardiovascular risk factor under the definitions by which presence of at least one of diabetes (excluding pregnancy in diabetic), hypertension, and hyperlipidaemia was defined as presence of a cardiovascular risk factor, and absence of any of these disorders was defined as absence of a cardiovascular risk factor. Ischaemic heart disease occurred in 3 of 237 patients with a cardiovascular risk (1.3%) and 3 of 263 patients without such risk (1.1%); presence of the risk factors did not increase the incidence of ischaemic heart disease. However, the number of patients who developed ischaemic heart disease was limited, and the results have to be interpreted

carefully.

PMDA considers as follows:
Thromboembolism events including death occurred following treatment with regorafenib, and other multiple kinase inhibitors are known to cause thromboembolism as adverse drug reactions, thus, it is necessary to pay attention to these events.

4.(iii).B.(3).8) Gastrointestinal perforation or fistula

The applicant explained gastrointestinal perforation or fistula following treatment with regorafenib as follows:
In Study 14387, the applicant identified gastrointestinal perforation as gastrointestinal perforation MLG* using the MedDRA Labeling Grouping (MLG), which was developed by Bayer Pharma AG. Only Grade 4 large intestine perforation that occurred in 1 patient (0.4%) in the placebo group was classified as gastrointestinal perforation MLG, and no such events were found in the regorafenib group.

* MedDRA preferred terms included in gastrointestinal perforation MLG
Duodenal perforation, gastric perforation, gastrointestinal perforation, ileal perforation, intestinal perforation, jejunal perforation, large intestine perforation, oesophageal perforation, rectal perforation, and small intestinal perforation

For digestive tract fistula, relevant MLG was not defined, and thus of adverse events according to MedDRA Preferred terms, events including the word "fistula" in the term were defined as "digestive tract fistula" events. Digestive tract fistula events that occurred in Study 14387 included Grade 2 enterocutaneous fistula in 1 patient (0.2%) and Grade 3 enterovesical fistula, fistula, and ileal fistula each in 1 patient (0.2%) in the regorafenib group as well as Grade 3 gastrointestinal fistula in 1 patient (0.4%) in the placebo group.
As described the above, in Study 14387, gastrointestinal perforation did not occur in the regorafenib group, and the incidences of digestive tract fistula were low, which were similar between the regorafenib group and placebo group.

Using gastrointestinal perforation SMQ*, the events that occurred in 21 patients were identified in GPV database (as of [redacted], 20[redacted]). PMDA asked the applicant to explain details of the identified events.

* MedDRA preferred terms (actual events) that can be included in gastrointestinal perforation SMQ
Intestinal perforation, duodenal perforation, small intestinal perforation, large intestine perforation, ileal perforation, gastrointestinal fistula, colonic fistula, enterovesical fistula, jejunal fistula, ileal fistula, colonic fistula, abdominal abscess, peritoneal abscess, abscess intestinal, and anal abscess

The applicant responded as follows:
Of 21 patients who experienced adverse events classified into gastrointestinal perforation SMQ, 3 patients with colorectal cancer (2 patients with large intestine perforation, 1 patient with gastrointestinal fistula) did not receive regorafenib, suggesting that the risk of gastrointestinal perforation and fistula was potentially related to the underlying disease. In addition, the events in 2 patients were iatrogenic (distal ileal perforation by lower gastrointestinal endoscopy, large intestine perforation by ablation radiofrequency), and neither perforation nor fistula was actually observed in 4 patients, but abscess associated with the primary disease was observed.

Of the remaining 12 patients with the events, all of 5 patients with digestive tract fistula had underlying disease or showed progression; causal relationships were ruled out. The last 7 patients experienced gastrointestinal perforation. Although they had extensive intraperitoneal malignancy, or medical history (diverticulitis, constipation, gastrooesophageal reflux disease, autoimmune inflammatory diseases) or concomitant drugs (nonsteroidal antiinflammatory drugs, narcotic

analgesics) that may put the patient at risk, a causal relationship of the event with regorafenib was not ruled out. Of these 7 patients, 4 patients died and 3 patients were recovering.

In the 12 patients who experienced digestive tract fistula or perforation, neither coexisting intestinal obstruction nor specified perforation sites were observed. Patients who experienced gastrointestinal perforation or fistula were not re-administered with regorafenib.

Based on the above, the applicant explained that treatment with regorafenib may increase the risk of gastrointestinal perforation or fistula, but most of these events were related to the underlying diseases.

PMDA considers as follows:
In clinical studies, gastrointestinal perforation or fistula occurred and deaths were observed in some patients, and of 7 patients in whom gastrointestinal perforation was identified in the GPV database, 2 patients had lung cancer without intra-abdominal malignant lesions; that is, patients without intra-abdominal tumor also experienced gastrointestinal perforation. PMDA thus considers it necessary to pay attention to these events during treatment with regorafenib as with other multiple kinase inhibitors.

4.(iii).B.(3).9) Proteinuria

The applicant explained on the occurrence of proteinuria after the administration of regorafenib as follows:
In Study 14387, laboratory test abnormality in proteinuria occurred in 292 of 489 patients (59.7%) in the regorafenib group and 84 of 246 patients (34.1%) in the placebo group. The Grade 3 event occurred in 2 of 489 patients (0.4%) in the regorafenib group and 1 of 246 patients (0.4%) in the placebo group; the incidences were similar between the 2 groups. No Grade 4 events were observed. Proteinuria reported as an adverse event occurred in 37 of 500 patients (7.4%) in the regorafenib group and 6 of 253 patients (2.4%) in the placebo group. Of them, a Grade 3 event occurred in 8 of 500 patients (1.6%) in the regorafenib group and 1 of 253 patients (0.4%) in the placebo group, but no Grade 4 events were observed. In the regorafenib group (500 patients), proteinuria led to discontinuation of regorafenib in 2 patients (0.4%), and to dose reduction in 3 patients (0.6%) and dose interruption in 6 patients (1.2%).

In Study 14387, changes in eGFR from the baseline to completion of regorafenib administration were examined. The eGFR values were calculated according to MDRD equation. The mean baseline values were similar between the 2 groups, and the changes until the completion of the administration were 8.3 mL/min/1.73 m^2 in the regorafenib group and -3.7 mL/min/1.73 m^2 in the placebo group; this value in the regorafenib group was higher than its mean baseline value.

Furthermore, MedDRA Preferred terms of the adverse events related to renal failure that occurred either in the regorafenib group or placebo group were renal failure, renal failure acute, and renal impairment, which were all defined as the events included in renal failure acute SMQ for evaluation. The incidence of renal failure acute SMQ was 2.4% (12 of 500 patients) in the regorafenib group and 2.4% (6 of 253 patients) in the placebo group. The incidence of creatinine laboratory abnormality was 15.9% (78 of 490 patients) in the regorafenib group and 15.9% (40 of 252 patients) in the placebo group; no differences were observed between the 2 groups.

As described above, the incidence of proteinuria was increased following treatment with regorafenib, but most of the events were classified as Grade ≤2. The applicant claims that there was no sign that proteinuria led to renal failure.

PMDA considers as follows:
Regarding proteinuria, the incidence of renal impairment such as nephrotic syndrome and renal

failure did not increase, and the number of patients who required discontinuation, dose reduction, or dose interruption of regorafenib was small. PMDA considers that regorafenib was tolerable in the patients even if proteinuria develops. However, proteinuria frequently develops following treatment with regorafenib. PMDA thus considers it necessary to periodically monitor the urine before and during treatment with regorafenib and to provide cautions so that appropriate actions can be taken in response to the onset of proteinuria.

4.(iii).B.(3).10) Posterior reversible encephalopathy

The applicant explained posterior reversible encephalopathy as follows:

Of all serious adverse events reported by [redacted], 20[redacted], posterior reversible Grade 4 encephalopathy was reported by 1 patient in Study 14874 which included patients with gastrointestinal stromal tumor. In this patient, neurological symptoms (amaurosis, disorientation, convulsion, unrest) and hypertension (170/80 mmHg) occurred 12 hours after the first dose of regorafenib, and the head MRI showed non-specific signal disturbance consistent with the diagnosis of posterior reversible encephalopathy. Following discontinuation of regorafenib and intensive care control, the patient recovered on the following day of the onset.

PMDA considers that the serious condition of this event was observed following treatment with regorafenib. Although this occurred only in 1 patient as of now, it is necessary to pay attention to posterior reversible encephalopathy.

4.(iii).B.(3).11) Wound healing

The applicant explained wound healing following treatment with regorafenib as follows:

In Study 14387, wound-healing disturbance did not occur in the regorafenib group, but did occur in 2 of 253 patients (0.8%) in the placebo group. From the submitted evaluation data and reference data, data of the clinical studies (Study 11650, Study 11651, Study 11726, Study 13172, Study 14387, Study 14596, Study 14996), in which regorafenib alone was given to cancer patients and of which clinical study reports were prepared, were pooled to create the database (pooled analysis database). Of clinical studies included in the pooled database, in the phase I study and phase II study in which regorafenib was given at the doses of 60 to 160 mg on the 3/1 schedule, wound-healing disturbance occurred in 3 of 168 patients (1.8%) (2 patients for Grade 1, 1 patient for Grade 4). In Study 14387, the incidence of wound-healing disturbance was higher in the placebo group than in the regorafenib group. The applicant considers that regorafenib does not increase the risk of wound-healing disturbance. However, no data are available from patients who resumed regorafenib administration after major surgery.

However, it is known that other drugs with anti-angiogenic effect cause wound healing delayed. Regorafenib, which has the same effect, may cause wound-healing disturbance. Therefore, if surgery is indicated for patients who have been receiving regorafenib, temporary dose interruption may be needed, and the washout period of 2 weeks is considered appropriate; the period consists of approximately 10 days equivalent to 5 times the mean elimination half-life (51 hours) of M-5, which has the longest half-life among regorafenib and its active metabolites, and 4 days of the safety margin. The resumption timing after the surgery can be individually determined based on the wound healing conditions of the surgery of the patient by the attending physician.

PMDA considers as follows:

It is known that other multiple kinase inhibitors including VEGFR delay wound healing. In Study 14387, “patients who had invasive major surgery, incisional open biopsy, or severe trauma within 28 days before treatment initiation” were excluded; the safety of these patients remains unknown. In consideration of the above, PMDA considers it necessary to interrupt regorafenib administration before major surgery and then carefully determine whether or not the treatment can be resumed according to patient’s conditions such as wound healing. In addition, information about the exclusion criteria specified in clinical studies of regorafenib should be appropriately

provided.

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

The applicant explained hypophosphataemia following treatment with regorafenib as follows:
In Study 14387, laboratory abnormalities of hypophosphataemia occurred in 282 of 491 patients (57.4%) in the regorafenib group and 28 of 252 patients (11.1%) in the placebo group. A Grade 3 event occurred in 150 of 491 patients (30.5%) in the regorafenib group and 9 of 252 patients (3.6%) in the placebo group, and a Grade 4 event occurred in 3 of 491 patients (0.6%) only in the regorafenib group. The incidence in Japanese patients was 55.4% (36 of 65 patients) in the regorafenib group and 15.6% (5 of 32 patients) in the placebo group; a Grade 3 event occurred in 27 of 65 patients (41.5%) in the regorafenib group and 4 of 32 patients (12.5%) in the placebo group, and no Grade 4 events were observed. Hypophosphataemia reported as an adverse event occurred in 23 of 500 patients (4.6%) in the regorafenib group and 2 of 253 patients (0.8%) in the placebo group; a Grade 3 event occurred in 16 of 500 patients (3.2%) in the regorafenib group and 1 of 253 patients (0.4%) in the placebo group, and no Grade 4 events were observed. The incidences were higher in the Japanese patients than in foreign patients [see "4.(iii).B.(3).2) Differences in the safety between Japanese and foreign populations"].

In the regorafenib group, adverse events[*1] potentially related to hypophosphataemia (Grade ≥3 laboratory abnormalities, irrespective of the onset time) occurred in 23 of 156 patients (14.7%) who experienced hypophosphataemia and 75 of 344 patients (21.8%) who did not experience hypophosphataemia, while in the placebo group, these events occurred in 3 of 9 patients (33.3%) and 37 of 244 patients (15.2%), respectively.

*1 Cardiac failure (cardiac failure SMQ[*2] excluding oedema and oedema neonatal), muscle-related events (muscle disorder, muscle enzyme increased, muscle fatigue, muscular weakness, blood creatine phosphokinase increased, and rhabdomyolysis), central nervous system events (seizure, confusion/disorientation, consciousness decreased, and encephalopathy noninfective/delirium), and bone pain (bone pain, coccydynia, musculoskeletal chest pain, musculoskeletal pain, and pain in jaw)
*2 MedDRA preferred terms (actual events) that can be included in cardiac failure SMQ
Cardiac failure acute, cardiomegaly, oedema peripheral, and orthopnoea

Next, PMDA asked the applicant to explain any approach to onset of hypophosphataemia specified for the clinical studies and the treatment practices actually given in Study 14387.

The applicant explained as follows:
In Study 14387, no specific approach to onset of hypophosphataemia was established, but 10 patients received treatment for hypophosphataemia. Of 10 patients, 7 patients with a Grade 3 event and 3 patients with a Grade 2 event received sodium phosphate or potassium phosphate.

Based on the above, hypophosphataemia reported as a laboratory abnormality frequently occurred, and the incidence in Japanese patients was especially high. However, no relationship between the onset of hypophosphataemia and complications potentially induced by hypophosphataemia, such as cardiac failure, and musculoskeletal and central nervous system events, was observed.

Hypophosphataemia following treatment with regorafenib frequently occurred and some needed to be treated although the incidence of serious complications was low. Also, the incidence of the event was higher in Japanese patients than in foreign patients [see "4.(iii).B.(3).2) Differences in the safety between Japanese and foreign populations"]. PMDA thus considers it necessary to provide information about the incidence of the event in Japan and foreign countries.

4.(iii).B.(3).13) Infections

The applicant explained infections following treatment with regorafenib (events under MedDRA System Organ Class "Infections and infestations") as follows:

In Study 14387, infections occurred in 154 of 500 patients (30.8%) in the regorafenib group and 43 of 253 patients (17.0%) in the placebo group; the incidence was higher in the regorafenib group than in the placebo group. Grade 3 or 4 infections occurred in 41 of 500 patients (8.2%) in the regorafenib group and 14 of 253 patients (5.5%) in the placebo group; no differences were found in incidence between the 2 groups. A Grade 5 event occurred in 3 of 500 patients (0.6%) in the regorafenib group and 2 of 253 patients (0.8%) in the placebo group, and the incidences were also similar in the 2 groups. These infections were not related to regorafenib. Of the events under MedDRA Preferred Terms, events of which the incidence was higher in the regorafenib group than in the placebo group included urinary tract infection (36 of 500 patients [7.2%] in the regorafenib group, 7 of 253 patients [2.8%] in the placebo group), nasopharyngitis (17 of 500 patients [3.4%], 3 of 253 patients [1.2%], respectively), cystitis (12 of 500 patients [2.4%], 1 of 253 patients [0.4%], respectively), and gastroenteritis (6 of 500 patients [1.2%], 1 of 253 patients [0.4%], respectively).

As described above, the incidence of these infections was high, but the severity was generally found to be low. Mucosal infection may be related to mucositis attributable to regorafenib.

Infections following treatment with regorafenib were mostly at Grade <3, and incidences of Grade ≥3 infections were similar between the regorafenib group and placebo group; the relationship between regorafenib and onset of serious infections remains unclear at present. PMDA, however, considers it necessary to pay attention to the infections, because serious infections actually occurred in some patients.

4.(iii).B.(3).14) Lipase increased, amylase increased, and pancreatitis

The applicant explained lipase increased, amylase increased, and pancreatitis following treatment with regorafenib as follows:

In Study 14387, laboratory abnormalities of lipase increased occurred in 226 of 491 patients (46.0%) in the regorafenib group and 47 of 251 patients (18.7%) in the placebo group. A Grade 3 event occurred in 46 of 491 patients (9.4%) in the regorafenib group and 7 of 251 patients (2.8%) in the placebo group, and a Grade 4 event occurred in 10 of 491 patients (2.0%) in the regorafenib group and 4 of 251 patients (1.6%) in the placebo group. Lipase increased reported as an adverse event occurred in 28 of 500 patients (5.6%) in the regorafenib group and 3 of 253 patients (1.2%) in the placebo group. A Grade 3 event occurred in 13 of 500 patients (2.6%) in the regorafenib group and 1 of 253 patients (0.4%) in the placebo group, and a Grade 4 event occurred in 6 of 500 patients (1.2%) in the regorafenib group and 1 of 253 patients (0.4%) in the placebo group.

In Study 14387, laboratory abnormalities of amylase increased occurred in 125 of 491 patients (25.5%) in the regorafenib group and 42 of 251 patients (16.7%) in the placebo group. A Grade 3 event occurred in 11 of 491 patients (2.2%) in the regorafenib group and 5 of 251 patients (2.0%) in the placebo group, and a Grade 4 event occurred in 2 of 491 patients (0.4%) in the regorafenib group and 1 of 251 patients (0.4%) in the placebo group. Blood amylase increased reported as an adverse event occurred in 14 of 500 patients (2.8%) in the regorafenib group and 1 of 253 patients (0.4%) in the placebo group. A Grade 3 event occurred in 4 of 500 patients (0.8%) in the regorafenib group and 1 of 253 patients (0.4%) in the placebo group, and a Grade 4 event occurred in 1 of 500 patients (0.2%) only in the regorafenib group.

In Study 14387, pancreatitis acute and pancreatitis occurred only in 1 patient in the regorafenib group and 1 patient in the placebo group, respectively, and both events were at Grade ≤2.

Although the relationship of lipase and amylase increased following treatment with regorafenib with pancreatitis and pancreatitis acute remains unclear, lipase and amylase increased constantly occurred and the incidences were higher in Japanese patients than in foreign patients [see

"4.(iii).B.(3).2) Differences in the safety between Japanese and foreign populations"]. PMDA thus considers it necessary to provide information about the incidence of the event in Japan and foreign countries.

4.(iii).B.(3).15) Platelet count decreased

The applicant explained platelet count decreased following treatment with regorafenib as follows:
In Study 14387, laboratory abnormalities of platelet count decreased occurred in 199 of 491 patients (40.5%) in the regorafenib group and 42 of 250 patients (16.8%) in the placebo group. A Grade 3 event occurred in 12 of 491 patients (2.4%) in the regorafenib group and 1 of 251 patients (0.4%) in the placebo group, and a Grade 4 event occurred in 2 of 491 patients (0.4%) only in the regorafenib group. Platelet count decreased reported as an adverse event occurred in 28 of 500 patients (5.6%) in the regorafenib group and 3 of 253 patients (1.2%) in the placebo group. A Grade 3 event occurred in 5 of 500 patients (1.0%) only in the regorafenib group. Platelet count decreased did not lead to discontinuation of regorafenib in any patient, but led to dose reduction and dose interruption in 3 patients (0.6%) and 6 patients (1.2%), respectively in the regorafenib group.

The mean minimum platelet count in 10 patients with Grade ≥3 haemorrhage events was lower than in patients without haemorrhage events, but the mean minimum count fell within the normal range. The platelet count decreased is thus unlikely to substantially contribute to serious haemorrhage events [see "4.(iii).B.(3).6) Haemorrhage"].

The incidences of adverse events of white blood cell count decreased, neutrophil count decreased, and haemoglobin decreased were all low. Compared with these low incidences, the incidence of platelet count decreased was high, but the cause for the difference remained unclear.

PMDA considers as follows:
Although platelet count decreased occurred more frequently in the regorafenib group than in the placebo group, but the event did not lead to discontinuation of regorafenib. PMDA thus considers that regorafenib was tolerable by actions such as dose reduction and dose interruption. At present, no clear relationship of serious haemorrhage events with regorafenib is observed in any patient. However, since the incidence in Japanese patients was higher than that in foreign patients in clinical studies [see "4.(iii).B.(3).2) Differences in the safety between Japanese and foreign populations"], PMDA thus considers it necessary to provide information about the finding.

4.(iii).B.(3).16) Dysphonia

The applicant explained dysphonia following treatment with regorafenib as follows:
In Study 14387, dysphonia occurred in 150 of 500 patients (30.0%) in the regorafenib group and 16 of 253 patients (6.3%) in the placebo group; the severity was all Grade ≤2. The event did not lead to discontinuation or dose-reduction of the study drug in any patient.

Although the severity was Grade ≤2 in any event, dysphonia frequently occurred in clinical studies. PMDA thus consider it necessary to provide cautions about the event as well as information about its frequent occurrence.

4.(iii).B.(3).17) Keratoacanthoma and squamous cell carcinoma of the skin

In Study 14387, keratoacanthoma and squamous cell carcinoma of the skin occurred each in 1 patient. PMDA asked the applicant to explain details of patients with the concerned event and incidence in the other than Study 14387.

The applicant responded as follows:
In a 73 year-old male patient with colorectal cancer, both keratoacanthoma and squamous cell carcinoma of the skin was observed. Grade 3 squamous cell carcinoma of the skin occurred approximately at 9 months of regorafenib treatment, followed by Grade 1 keratoacanthoma at approximately 11 months of treatment. Both events resolved by surgical resection. At present, the relationships of regorafenib with keratoacanthoma and squamous cell carcinoma of the skin remain unclear. In Study 11651, a 65 year-old female patient with neuroendocrine adenocarcinoma experienced Grade 3 squamous cell carcinoma of the skin at approximately 4 months of regorafenib treatment and recovered following surgical resection.

PMDA considers as follows:
Keratoacanthoma and squamous cell carcinoma of the skin occurred only in 2 patients, and the mechanism of the onset remains unknown. Therefore, although a relationship of regorafenib with these events remains unclear, it is necessary to provide information about these events. In addition, the applicant should collect information about post-marketing occurrence of these events including publications and provide information appropriately, when new information becomes available.

4.(iii).B.(3).18) Hypothyroidism
The applicant explained hypothyroidism following treatment with regorafenib as follows:
In Study 14387, adverse events reported as hypothyroidism occurred in 21 of 500 patients (4.2%) in the regorafenib group and 1 of 253 patients (0.4%) in the placebo group. All the events were at Grade ≤2, and 3 of 21 patients (14.3%) recovered or were recovering. The event occurred between 15 days (Cycle 1) and 188 days (Cycle 7) after the initiation of administration and most frequently occurred during Cycle 3 (i.e. 8 of 21 patients). Laboratory abnormalities were investigated in the patients in whom values of free triiodothyronine (FT3), free thyroxin (FT4), and thyroid stimulating hormone (TSH) changed to levels of laboratory abnormalities (low or high values) from their normal values at baseline. The investigation was carried out for each cycle until Cycle 6, because the number of patients significantly decreased in the placebo group in Cycle 7 thereafter. In each cycle, FT3 low value was observed in 4.7% to 8.5% in the regorafenib group and 0% to 6.7% in the placebo group, and FT4 low value was observed in 1.1% to 4.2% in the regorafenib group and 1.8% to 8.3% in the placebo group; both groups showed similar percentages. In each cycle, patients with a TSH high value were observed in 6.1% to 18.5% in the regorafenib group and 0% to 9.1% in the placebo group; the incidence tended to be higher in the regorafenib group than in the placebo group.

In the pooled analysis database, hypothyroidism was reported by 45 of 772 patients (5.8%) in the regorafenib group. Of these patients, only 1 patient experienced a Grade 3 event, and the remaining 44 patients experienced Grade ≤2 events. Including patients in whom laboratory abnormalities observed were not reported as adverse events, 52 of 772 patients (6.7%) received hormone replacement therapy.

With respect to clinical symptoms* that may develop in association with thyroid hormone (FT3, FT4) decreased and hypothyroidism, the incidence of each symptom was compared between patients in whom either the FT3 or FT4 level was found to be below the lower limit of normal during regorafenib administration and patients in whom both hormone levels remained normal throughout the administration using the odds ratios. Patients with decreased thyroid hormones tended to experience dysphonia more frequently than patients with the normal values (odds ratio, 1.75 [95% CI, 1.203, 2.557]). No relationship was observed between decreased thyroid hormones and the other clinical symptoms listed below.

* Alopecia, bradycardia, constipation, fatigue/asthenia, dry skin, dysphonia, dyspnoea, oedema peripheral, paraesthesia, and pericardial effusion/pleural effusion

As described above, hypothyroidism observed during the treatment with regorafenib was mild, scarcely leading to serious clinical symptoms. However, some patients actually received hormone replacement therapy. The applicant will thus provide cautions about the event in the package insert.

Hypothyroidism including a laboratory abnormality was observed following treatment with regorafenib, and some patients needed hormone replacement therapy. Therefore, PMDA considers it necessary to provide information about the incidence and a caution that thyroid function tests should be performed periodically during treatment with regorafenib.

4.(iii).B.(3).19) Interstitial lung disease

Because other multiple kinase inhibitors are associated with onset of interstitial lung disease, PMDA asked the applicant to explain interstitial lung disease following treatment with regorafenib.

The applicant responded as follows:

The search in the GPV database using interstitial lung disease SMQ* identified the following 4 patients (3 patients in Study 14387, 1 patient in currently ongoing Study 14874).

* MedDRA preferred terms that can be included in Interstitial lung disease SMQ
Acute interstitial pneumonitis, allergic granulomatous angiitis, alveolar proteinosis, alveolitis, alveolitis allergic, alveolitis fibrosing, alveolitis necrotising, bronchiolitis, diffuse alveolar damage, eosinophilia myalgia syndrome, eosinophilic pneumonia, eosinophilic pneumonia acute, eosinophilic pneumonia chronic, idiopathic pneumonia syndrome, idiopathic pulmonary fibrosis, interstitial lung disease, lung infiltration, necrotising bronchiolitis, obliterative bronchiolitis, pneumonitis, progressive massive fibrosis, pulmonary fibrosis, pulmonary necrosis, pulmonary radiation injury, pulmonary toxicity, pulmonary vasculitis, radiation alveolitis, radiation fibrosis - lung, radiation pneumonitis, transfusion-related acute lung injury, acute lung injury, acute respiratory distress syndrome, antisynthetase syndrome, complications of transplanted lung, Goodpasture's syndrome, Langerhans' cell histiocytosis, lung transplant rejection, lupus pneumonitis, lymphangioleiomyomatosis, organising pneumonia, pneumonitis chemical, polyarteritis nodosa, pulmonary alveolar haemorrhage, pulmonary eosinophilia, pulmonary granuloma, pulmonary haemosiderosis, pulmonary renal syndrome, pulmonary sarcoidosis, rheumatoid lung, sarcoidosis, systemic sclerosis pulmonary, toxic oil syndrome, and Wegener's granulomatosis

Severity, actions, and outcome of the events identified by interstitial lung disease SMQ

Study	MedDRA Preferred terms	Grade	Number of days to onset	Treatment	Causal relationship with regorafenib	Outcome	Remarks
14387 (regorafenib group)	Acute respiratory distress syndrome	5	34	Admission to ICU, pharmacotherapy (steroid, antibiotics, bronchodilator, morphine, vasopressor agent)	None	Death	In addition to acute respiratory distress syndrome due to sepsis, a cardiogenic factor was suspected.
14387 (regorafenib group)	Lung infiltration	3	107	Pharmacotherapy (voriconazole)	Related	Not recovered	Regorafenib continued because of asymptomatic condition, but *Candida sake, Aspergillus niger* were positive in sputum culture.
14387 (placebo group)	Pneumonitis	3	181	Pharmacotherapy (antibiotics)	-	Recovered	Infection and disease progression as factors other than regorafenib
14874 (regorafenib group)	Acute respiratory distress syndrome	5	202	Pharmacotherapy (diuretic, cardiotonic agent)	Related	Death	Comorbidity (Type I neurofibromatosis) and reduced general condition due to disease progression as factors other than regorafenib

Disease progression and pneumonia-related sepsis were involved as background factors in acute respiratory distress syndrome observed in Study 14387, and a causal relationship with regorafenib was thus ruled out. Lung infiltration was asymptomatic, while sputum culture test was positive for *Candida* and *Aspergillus*. Although it was determined to be related to regorafenib, the treatment was continued. Acute respiratory distress syndrome in Study 14874 was determined to have a causal relationship with regorafenib, but concomitant type I neurofibromatosis and gastrointestinal stromal tumor, the primary disease, were also identified as the other factors. The event did not occur in Japanese patients who received regorafenib.

On the other hand, according to the interim report of all-case surveillance (November 2011) of sorafenib tosylate, an inhibitor against various kinases similar to regorafenib, in patients with renal cell carcinoma, the post-marketing incidence of interstitial lung disease in Japan was 0.29% (7 of 2407 patients); according to the interim report of all-case surveillance (May 2012) of the above inhibitor in patients with hepatocellular carcinoma, it was 0.77% (8 of 1045 patients); and according to the final report of all-case surveillance (March 2012) of sunitinib malate, an inhibitor similar to regorafenib like the above, in patients with gastrointestinal stromal tumor and renal cell carcinoma, the post-marketing incidence of lung disorder such as interstitial pneumonia was 0.21% (1 of 470 patients) and 0.84% (14 of 1671 patients), respectively.

In consideration of accumulated post-marketing safety information of the other inhibitors, the applicant thus considers it also necessary to carefully monitor the incidence of the event during regorafenib administration after market launch.

PMDA considers as follows:
In clinical studies, interstitial lung disease did not occur following treatment with regorafenib. However, in consideration of the occurrence in use of other multiple kinase inhibitors as with regorafenib and the exclusion criterion statement of "patients having active signs or symptoms of interstitial lung disease" in Study 14387, PMDA considers it necessary to appropriately provide

information about the criteria specified in clinical studies of regorafenib. Interstitial lung disease following treatment with regorafenib have not been reported at present, PMDA considers it unnecessary to provide cautions in the package insert, but information about post-marketing occurrence of the event should be collected and appropriately provided, when new information becomes available.

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

PMDA reviewed the clinical guideline and textbooks for treatment strategy against incurable, unresectable, advanced/recurrent colorectal cancer in Japan and foreign countries and confirmed the followings. At present, *De Vita, Hellman, and Rosenverg's Cancer: Principles & Practices of Oncology* 9th edition (Lippincott Williams & Wilkins. PA, USA: 2011), one of the internationally recognized textbooks on oncology has no descriptions about regorafenib.

Clinical guideline

- NCCN guideline (v.3.2013)
  Referring to data from Study 14387 in patients with metastatic colorectal cancer who have progressed after the standard chemotherapy, the guideline has a description that regorafenib is used as the third treatment for patients with *KRAS* gene mutation and as the third or fourth treatment for patients with wild-type *KRAS* gene.

The applicant explained clinical positioning of regorafenib as follows:
In Study 14387, regorafenib extended OS in patients with metastatic colorectal cancer who have progressed after conventional standard chemotherapy, and the tolerable safety profile was obtained. Regorafenib can be positioned as a new treatment option for these patients.

PMDA accepted the explanation of the applicant about the clinical positioning of regorafenib based on discussions in "4.(iii).B.(2) Efficacy" and "4.(iii).B.(3) Safety".

4.(iii).B.(5) Indication

The proposed indication was "Incurable, unresectable, advanced/recurrent colorectal cancer." Precautions for Indications section in the draft package insert stated that (1) efficacy and safety of regorafenib have not been established for use in postoperative adjuvant chemotherapy; and (2) eligible patients should be selected with full knowledge of information in the "Clinical Studies" section and sufficient understanding of efficacy and safety of regorafenib.

PMDA asked the applicant to explain for what patients regorafenib is recommended among patients with "incurable, unresectable, advanced/recurrent colorectal cancer," which was the proposed indication.

The applicant responded as follows:
Patients with "incurable, unresectable, advanced/recurrent colorectal cancer" that is the proposed indication are almost equivalent to patients with "metastatic colorectal cancer" included in Study 14387. According to the section for chemotherapy in the JSCCR Guidelines 2010 for the Treatment of Colorectal Cancer, systemic chemotherapy can be indicated for patients with unresectable advanced/recurrent colon cancer. The studies, in which regorafenib was concomitantly given to patients with colorectal cancer as the first- or second-line therapy, were completed, but no confirmatory controlled-study data are currently available. The applicant thus considers that the patients with treatment history of standard chemotherapy, the same patient population as patients included in Study 14387, can be recommended to receive regorafenib.

PMDA considers as follows:
Based on discussion in the sections "4.(iii).B.(2) Efficacy," "4.(iii).B.(3) Safety," and "4.(iii).B.(4) Clinical positioning," regorafenib can be recommended for patients with incurable, unresectable,

advanced/recurrent colorectal cancer who have progressed after conventional standard chemotherapy.

Taking account of the following points, the caution should be provided in the Precautions for Indications section stating that the efficacy and safety of regorafenib as the first- or second-line therapy have not been established. However, regorafenib will be used by physicians with sufficient knowledge and experience in cancer chemotherapy, the indication of regorafenib can be set as "incurable, unresectable, advanced/recurrent colorectal cancer" as proposed.

- For incurable, unresectable, advanced/recurrent colorectal cancer, the standard treatment using existing antineoplastic drugs (fluoropyrimidines, oxaliplatin, irinotecan, and bevacizumab, or cetuximab or panitumumab for patients with wild-type *KRAS* gene) has been established (JSCCR Guidelines 2010 for the Treatment of Colorectal Cancer, NCCN guideline, etc.).

Furthermore, because regorafenib has not been clinically used in postoperative adjuvant chemotherapy, caution should be provided in Precautions for Indications section stating that efficacy and safety of regorafenib have not been established for use in postoperative adjuvant chemotherapy.

4.(iii).B.(6) Dosage and administration

Based on the discussion below, PMDA has concluded that it is appropriate to set the dosage and administration of regorafenib as proposed in the response of the applicant [see "4.(i) Summary of biopharmaceutic studies and associated analytical methods"]; "The usual adult dosage is 160 mg of regorafenib orally administered once daily after a meal for 3 weeks followed by 1-week off therapy. The above regimen should be repeated in a 4-week cycle. The dose may be reduced according to the patient's condition." In addition, the following contents should be included in the Precautions for Dosage and Administration section to provide caution and information.

- The efficacy and safety of concomitant use of regorafenib with the other antineoplastic drugs have not been established.
- Criteria for dose reduction, dose interruption, and discontinuation at the onset of adverse events (hand and foot syndrome, liver function test abnormal)

4.(iii).B.(6).1) Dosage and administration of regorafenib

The applicant explained the justification of the dosage and administration of regorafenib as follows:

In Study 11650, a foreign phase I study, regorafenib was administered at the doses of 10 to 220 mg on the the 3/1 schedule. The MTD in the 3/1 schedule was determined to be 160 mg once daily (QD). In Study 11651, a foreign phase I study, regorafenib was continuously administered at the doses of 20 to 140 mg QD without a washout period. The MTD in continuous administration was determined to be 100 mg QD.

Based on data from the above 2 clinical studies and based on the following points, the 3/1 schedule at 160 mg QD was selected as the recommended dosage and administration of regorafenib for phase II and III studies.

- The safety and tolerability at the MTD were similar between the 3/1 schedule and continuous administration schedule, but the total dose of regorafenib at the MTD for 4 weeks was 20% higher in the 3/1 schedule (3360 mg) than in the continuous administration schedule (2800 mg). The applicant thus considered that the 3/1 schedule could bring more effects than the continuous administration schedule.
- The washout period in the 3/1 schedule may serve as an opportunity of recovery from the

toxicity. The progression control rates in Study 11651 (continuous administration schedule) and Study 11650 (3/1 schedule) were 37% (29 of 79 patients) and 58% (44 of 76 patients), respectively; the effect in the 3/1 schedule was not inferior to that in the continuous administration.

- The AUC_{0-24} and C_{max} of regorafenib and 2 active metabolites, M-2 and M-5, at the steady state were expected to be higher in the 3/1 schedule than in the continuous administration; the higher effects can be expected with the 3/1 schedule.

In Study 13172, a Japanese phase I study, regorafenib was administered once daily at the dose of 160 mg on the the 3/1 schedule. The tolerability in Japanese patients was confirmed, and no large difference was found in PK of regorafenib between ethical groups. In Study 14387, in which the concerned dosage and administration were set, the efficacy was confirmed even in the Japanese sub-group with the tolerable safety profile. As the dosage and administration of regorafenib, the 3/1 schedule at 160 mg QD was proposed.

Based on the administration method set in Study 14387, the pivotal study demonstrating efficacy and safety, PMDA has concluded that the dosage and administration of regorafenib can be set as proposed.

4.(iii).B.(6).2 Concomitant use with the other antineoplastic drugs

PMDA asked the applicant to explain the concomitant use potential of regorafenib with the other antineoplastic drugs and the safety of such concomitant use.

The applicant responded as follows:

Study 11656, Study 11728, and Study 15579 are ongoing or completed as clinical studies in which regorafenib is concomitantly administered with the other antineoplastic drugs. In Study 11656, patients with metastatic colorectal cancer were included for first- or second-line therapy, and concomitant use with mFOLFOX6 and FOLFIRI were evaluated in 25 patients (17 patients for first-line therapy, 5 patients for second-line therapy, 3 patients for other treatment) and 20 patients (14 patients for first-line therapy, 6 patients for second-line therapy), respectively, with favorable tolerability. Study 11728 was a phase II study intended to evaluate efficacy and safety of concomitant use of regorafenib with mFOLFOX6, which was given as the first-line therapy, in patients with metastatic colorectal cancer. As of [redacted], 20[redacted], 54 patients have been included in this study, but study data have not been obtained. Study 15579 was a randomized phase II study intended to compare combination regimens of FOLFIRI between regorafenib and the placebo in patients with metastatic colorectal cancer who had *KRAS* or *BRAF* gene mutation and had previously received FOLFOX as the first-line therapy. As of [redacted], 20[redacted], 9 patients have been included in this study, but study data have not been obtained.

Based on the above, no data from controlled studies including the sufficient number of patients are available, and the safety of concomitant use of regorafenib with the other antineoplastic drugs has not been established. The applicant will provide a caution in the Precautions for Dosage and Administration section, stating that efficacy and safety of concomitant use of regorafenib with theother antineoplastic drugs have not been established.

PMDA considers that the efficacy and safety of such combination remain unknown at present, and it is necessary to provide the caution stating that the efficacy and safety of concomitant use of regorafenib with the other antineoplastic drugs have not been established.

4.(iii).B.(6).3 Dose adjustment

The applicant explained the dose adjustment of regorafenib as follows:

In Study 14387, any clinically significant toxicity event was graded in accordance with Common

Terminology Criteria for Adverse Events (CTCAE) Ver. 3.0, and based on the grade of the event, discontinuation or dose-reduction of regorafenib was implemented. In response to the occurrence of hand and foot syndrome, liver function test abnormal, hypertension, or any other toxicity event related to regorafenib, the dose had to be reduced by 40 mg in each step, or the treatment should be discontinued when dose reduction of >80 mg was needed. When recovery was not confirmed even after 4-week discontinuation, the administration of regorafenib should be discontinued. The patients who recovered from the toxicity event to the baseline condition following dose-reduction were allowed to increase the dose to the previous level by the judgment of a principal investigator (subinvestigator).

The package insert (draft) has specified the dose adjustment only for the adverse events of hand and foot syndrome and liver function test abnormal, which needs attention following treatment with regorafenib and weighs in the dose adjustment criteria.

The specific dose adjustment procedure for hand and foot syndrome in the package insert (draft) remains unchanged from that in Study 14387, while the procedure for the liver function test abnormal (AST and ALT increased, bilirubin elevated) for which a causal relationship with regorafenib cannot be ruled out is changed from that in Study 14387 as shown in the table below.

Dose adjustment procedure for liver function test abnormal (Study 14387 and package insert [draft])

Criteria in Study 14387				
Grade (CTCAE ver. 3.0)	Initial occurrence	Resumption of regorafenib administration	Reoccurrence	Description in the package insert (draft)
Increased to Grade 1 from Grade 0 at the baseline or increased to Grade 2 from Grade 1 at the baseline	Continue the treatment at the same dose level		Continue the treatment at the same dose level	Continue the treatment irrespective of the frequency
Increased to Grade 2 from Grade 0 at the baseline	Interrupt treatment until the toxicity resolves to Grade ≤1.	Resume the treatment at the 1-step reduced dose (by 40 mg)*[1].	Discontinue regorafenib	
Increased to Grade 3 irrespective of baseline grade	Interrupt treatment until the toxicity resolves to Grade ≤1 if Grade ≤1 at the baseline. Interrupt treatment until the toxicity resolves to Grade 2 if Grade 2 at the baseline.	Resume the treatment at the 1-step reduced dose (by 40 mg)*[1].	Discontinue regorafenib	Initial occurrence Interrupt treatment until transaminases return to <3-fold ULN or baseline. In the case where treatment benefit outweighs the risk, resume the treatment at the reduced dose (by 40 mg [1 tablet]). 2nd occurrence Discontinue regorafenib

Criteria in Study 14387				Description in the package insert (draft)
Grade (CTCAE ver. 3.0)	Initial occurrence	Resumption of regorafenib administration	Reoccurrence	
Increased to Grade 4 irrespective of baseline grade	Discontinue regorafenib			Discontinue regorafenib
AST or ALT increased associated with bilirubin increased	In the case where AST or ALT exceeds 8-fold the ULN, and bilirubin value increases from the previous value irrespective of the extent, consider discontinuation of regorafenib even if it is the initial occurrence.			In the case where AST or ALT exceeds 3-fold the ULN, and bilirubin value exceeds 2-fold the ULN, discontinue regorafenib.*2

*1 If all measured values continuously remain stable for the duration of at least 2 cycles, the dose may be increased by judgment of the investigator. [Note by PMDA: This is not included in the draft package insert]

*2 Because regorafenib inhibits UGT1A1 glucuronidation, in patients with Gilbert's syndrome, indirect bilirubin may be increased. For patients with Gilbert's syndrome, the dose should be adjusted in accordance with the criteria for AST or ALT but not those for bilirubin values.

The protocol for Study 14387 specified that patients without liver disorder at the baseline should withdraw from regorafenib in the case of the occurrence of Grade 2 hepatic function disorder. However, of 16 patients in the regorafenib group in which the grade of AST or ALT increased from Grade ≤1 at the baseline to Grade 2, only 1 patient actually withdrew. Of 15 patients who continued the treatment, 2 patients showed further aggravation to Grade 3, 1 patient showed progression, for which a causal relationship to regorafenib was ruled out, and 1 patient was recovering following temporary dose interruption. The package insert (draft) has specified that regorafenib may be continued until Grade 3 hepatic function disorder occurs irrespective of presence or absence of hepatic function disorder at the baseline, because in the draft, temporary dose interruption is indicated at the occurrence of Grade 3 hepatic function disorder, and more strict discontinuation criteria are separately set for increases of AST and ALT accompanied by increase of bilirubin value because those events may progress to serious hepatic function disorder.

PMDA considers as follows:
It is appropriate to include the same dose adjustment procedure for regorafenib at the occurrence of hand and foot syndrome as specified in Study 14387 in the package insert to provide a caution. Concerning actions at the occurrence of liver function test abnormal, it is acceptable to indicate temporary dose interruption at the initial occurrence of the event at Grade ≥3, because continuous administration of regorafenib was mostly tolerable in patients with Grade 2 liver function test abnormal when the treatment was continued; and more strict discontinuation criteria are separately set for increases of AST and ALT accompanied by increase of bilirubin value. However, it is necessary to appropriately provide information about detailed procedures for temporary dose interruption and dose adjustment at the occurrence of liver function test abnormal in Study 14387 and laboratory test interval.

4.(iii).B.(7) Post-marketing investigations

The applicant explained post-marketing investigations as follows:
The applicant plans post-marketing surveillance by a central registration system (this surveillance) in patients with colorectal cancer who have received regorafenib in order to evaluate the safety of regorafenib in the post-marketing use settings.

As the primary investigation parameters of this surveillance, hepatic function disorder, hypertension/hypertensive crisis, haemorrhage, hand and foot syndrome, all of which frequently occurred in clinical studies, will be set to search for factors related to their development.

The number of patients to be included in the analysis population is set as 1065 patients (target number is 1200 in consideration of dropout). This sample size was calculated as the size necessary to detect the event at the incidence of 0.5% in at least 3 patients with the probability of 90% based on the fact that potentially lethal interstitial lung disease occurred at the incidence of approximately 0.5% in the treatment of other multiple kinase inhibitors. The events set as primary investigation parameters occurred at the incidence of ≥1% in clinical studies, the applicant considers it possible to make an adequate search for factors related to the occurrence by accumulating data from the planned number of patients.

The enrollment period for patients will be approximately 1 year. The observation period is set at 6 months, because the median progression-free survival in the regorafenib group in the Japanese population in Study 14387 was 59 days with the maximum of 172 days; most adverse events occurred during the early phase of regorafenib treatment; and no special safety concern was raised in patients who were treated with the drug for >6 months of treatment.

PMDA considers as follows:
Adverse events following treatment with regorafenib were almost similar to the events of the other multiple kinase inhibitors, but incidences of individual events differ among the inhibitors. The safety information submitted for this application is not sufficient to ensure the safety of regorafenib in Japanese patients. Thus, it is necessary to promptly conduct the post-marketing surveillance to obtain the safety information of regorafenib in clinical settings in Japan, thereby providing the surveillance results to medical practices for information sharing.

The planned number of patients may allow the applicant to perform an exploratory investigation of factors related to the occurrence of adverse events, but the investigation will remain exploratory. At present, compared with the concerned exploratory investigation, it is more important to set appropriate primary parameters to investigate situations and onset timings of the events leading to dose interruption, dose reduction, or discontinuation of regorafenib in clinical settings. The number of patients to be enrolled in the surveillance should be eventually determined based on the primary investigation parameters. With respect to the observation period, the proposed plan is acceptable.

4.(iv) Adverse events observed in clinical studies

Of clinical data, deaths, which were reported in the clinical studies and submitted as the safety evaluation data, are presented in "4.(iii) Summary of clinical efficacy and safety," and other major adverse events are as shown below. The number of each adverse event is a calculation result including multiple events observed in one subject.

4.(iv).(1) Japanese phase I study (Study 13172)

Adverse events were observed in 15 of 15 patients (100%), for which no causal relationship with regorafenib could be ruled out. Adverse events with an incidence of ≥20% are as shown in the table below.

Adverse events

Organ class/event term (NCI CTCAE Ver. 3.0)	Number of patients (%)	
	Regorafenib group (n = 15)	
	All grades	Grade ≥3
All adverse events	15 (100)	12 (80)
Blood/bone marrow		
Haemoglobin decreased	7 (47)	1 (7)
White blood cell decreased	4 (27)	1 (7)
Lymphopenia	5 (33)	4 (27)
Platelets decreased	4 (27)	0
Cardiac general		
Hypertension	5 (33)	0
Coagulation		
PTT prolonged	6 (40)	1 (7)
Constitutional symptoms		
Fatigue (asthenia, lethargy, malaise)	5 (33)	0
Fever (in the absence of neutropenia, where neutropenia is defined as ANC $<1.0 \times 10^9$/L)	4 (27)	0
Weight loss	7 (47)	0
Dermatology/skin		
Hair loss/alopecia (scalp or body)	6 (40)	0
Rash: hand-foot skin reaction	10 (67)	2 (13)
Rash/desquamation	5 (33)	0
Gastrointestinal		
Anorexia	6 (40)	0
Constipation	7 (47)	0
Diarrhea	10 (67)	1 (7)
Nausea	3 (20)	0
Vomiting	3 (20)	0
Lymphatics		
Edema: limb	4 (27)	0
Metabolic/laboratory		
ALP increased	8 (53)	2 (13)
ALT increased	9 (60)	2 (13)
AST increased	10 (67)	2 (13)
Bilirubin increased (hyperbilirubinaemia)	4 (27)	1 (7)
Albumin, serum-low (hypoalbuminaemia)	8 (53)	0
Potassium, serum-low (hypokalaemia)	3 (20)	0
Phosphate, serum-low (hypophosphataemia)	8 (53)	4 (27)
Lipase increased	3 (20)	1 (7)
Metabolic/laboratory - other	9 (60)	0
Proteinuria	7 (47)	1 (7)
Musculoskeletal/soft tissue		
Musculoskeletal/soft tissue - other	3 (20)	0
Neurology		
Neuropathy: Sensory	3 (20)	0
Pain		
Pain - back	3 (20)	1 (7)
Pain - head/headache	3 (20)	0
Pain - muscle	3 (20)	0
Pulmonary/upper respiratory		
Pulmonary/upper respiratory - other	3 (20)	0
Voice changes/dysarthria	5 (33)	0

PTT: Partial thromboplastin time, ANC: Absolute neutrophil count

Serious adverse events were observed in 6 of 15 patients (40%). The observed serious adverse events included stricture/stenosis (including anastomotic), GI-biliary tree in 2 patients (13%); hepatobiliary/pancreas-other in 2 patients (13%); pain-back, obstruction, GI-jejunum, infection with normal ANC or Grade 1 or 2 neutrophils-urinary tract NOS, and disseminated intravascular coagulation (DIC) (1 patient [7%] each). Of the serious adverse events, the ones for which a causal relationship with regorafenib was not ruled out included hepatobiliary/pancreas-other in 2 patients,

and pain-back and DIC (1 patient each).

Adverse events leading to discontinuation of regorafenib were observed in 2 of 15 patients (13%). The relevant observed adverse events included ALT increased, AST increased, and haemoglobin decreased (1 patient [6.7%] each), all for which a causal relationship with regorafenib was not ruled out.

4.(iv).(2) Global phase III study (Study 14387)

Adverse events were observed in 498 of 500 patients (100%) in the regorafenib group and 245 of 253 patients (97%) in the placebo group. The adverse events for which a causal relationship with the study drug could not be ruled out occurred in 465 of 500 patients (93%) in the regorafenib group and 154 of 253 patients (61%) in the placebo group. Adverse events with an incidence of ≥10% in either group are as shown in the table below.

Adverse events

Organ class/event term (NCI-CTCAE Ver.3.0)	Number of patients (%)			
	Regorafenib group (n = 500)		Placebo group (n = 253)	
	All grades	Grade ≥3	All grades	Grade ≥3
All adverse events	498 (100)	390 (78)	245 (97)	124 (49)
Blood/bone marrow				
Haemoglobin decreased	72 (14)	29 (6)	30 (12)	9 (4)
Platelets decreased	78 (16)	19 (4)	6 (2)	1 (<1)
Cardiac general				
Hypertension	152 (30)	38 (8)	20 (8)	2 (1)
Constitutional symptoms				
Fever (in the absence of neutropenia, where neutropenia is defined as ANC <1.0 × 10^9/L)	142 (28)	11 (2)	39 (15)	0
Fatigue (asthenia, lethargy, malaise)	317 (63)	77 (15)	117 (46)	26 (10)
Weight loss	160 (32)	2 (<1)	28 (11)	1 (<1)
Constitutional symptoms - other	53 (11)	35 (7)	33 (13)*	25 (10)
Gastrointestinal				
Anorexia	234 (47)	23 (5)	72 (28)	11 (4)
Constipation	119 (24)	1 (<1)	48 (19)	0
Diarrhea	214 (43)	42 (8)	43 (17)	5 (2)
Mucositis/stomatitis (functional/symptomatic) - oral cavity	144 (29)	16 (3)	12 (5)	0
Nausea	112 (22)	4 (1)	55 (22)	3 (1)
Vomiting	80 (16)	6 (1)	41 (16)	2 (1)
Metabolic/laboratory				
Bilirubin increased (hyperbilirubinaemia)	100 (20)	38 (8)	24 (9)	16 (6)
Neurology				
Neuropathy: Sensory	50 (10)	2 (<1)	25 (10)	0
Pain				
Pain - back	75 (15)	7 (1)	26 (10)	5 (2)
Pain - abdomen NOS	122 (24)	24 (5)	47 (19)	6 (2)
Pain - head/headache	52 (10)	5 (1)	18 (7)	0
Pulmonary/upper respiratory				
Cough	55 (11)	3 (1)	28 (11)	0
Dyspnea (shortness of breath)	91 (18)	16 (3)	33 (13)	10 (4)
Voice changes/dysarthria	160 (32)	1 (<1)	16 (6)	0
Dermatology/skin				
Dry skin	50 (10)	0	10 (4)	0
Rash: hand-foot skin reaction	235 (47)	83 (17)	19 (8)	1 (<1)
Rash/desquamation	145 (29)	29 (6)	13 (5)	1 (<1)

ANC: Absolute neutrophil count, *: including 1 patient with the event at an unknown grade.

Serious adverse events were observed in 219 of 500 patients (44%) in the regorafenib group and 100 of 253 patients (40%) in the placebo group. Serious adverse events reported by ≥5 patients in

the regorafenib group included constitutional symptoms - other in 30 patients (6%), liver dysfunction/failure (clinical) in 16 patients (3%), fever (in the absence of neutropenia, where neutropenia is defined as absolute neutrophil count [ANC] $<1.0 \times 10^9$/L) in 15 patients (3%), death not associated with CTCAE term-disease progression NOS in 14 patients (3%); pain-abdomen NOS in 13 patients (3%); dyspnea (shortness of breath) in 12 patients (2%); obstruction, GI-colon, infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC $<1.0 \times 10^9$/L)-lung (pneumonia) (9 patients [2%] each); diarrhea, bilirubin increased (hyperbilirubinaemia) in 8 patients (2%); cardiac ischemia/infarction in 6 patients (1%); and infection-other and renal failure (5 patients [1%] each), while these in the placebo group included constitutional symptoms-other in 20 patients (8%); obstruction, GI-small bowel NOS in 7 patients (3%); death not associated with CTCAE term-disease progression NOS, and obstruction, GI-colon (6 patients [2%] each); and fatigue in 5 patients (2%). Of the above serious adverse events, the ones for which a causal relationship with the study drug was not ruled out included diarrhea in 7 patients, fever (in the absence of neutropenia, where neutropenia is defined as ANC $<1.0 \times 10^9$/L) in 5 patients, liver dysfunction/failure (clinical) in 4 patients, infection-other in 3 patients, cardiac ischemia/infarction, fatigue, and renal failure (2 patients each), death not associated with CTCAE term-sudden death, constitutional symptoms-other, and dyspnea (shortness of breath) (1 patient each) in the regorafenib group, and fatigue in 1 patient in the placebo group.

Adverse events leading to discontinuation of the study drug were observed in 88 of 500 patients (18%) in the regorafenib group and 32 of 253 patients (13%) in the placebo group. Adverse events leading to the discontinuation reported by ≥3 patients included constitutional symptoms-other in 15 patients (3%), liver dysfunction/failure (clinical) and rash-hand-foot skin reaction (7 patients [1%] each), fatigue, bilirubin increased (hyperbilirubinaemia), and rash/desquamation (5 patients [1%] each), death not associated with CTCAE term-disease progression NOS, anorexia, infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC $<1.0 \times 10^9$/L)-lung (pneumonia), and rash-erythema multiforme (4 patients [1%] each), fever (in the absence of neutropenia, where neutropenia is defined as ANC $<1.0 \times 10^9$/L), ALP increased, ALT increased, and pain-abdomen NOS (3 patients [1%] each) in the regorafenib group, and constitutional symptoms-other in 10 patients (4%); bilirubin increased (hyperbilirubinaemia) in 5 patients (2%), obstruction, GI-small bowel NOS, and liver dysfunction/failure (clinical) (3patients [1%] each) in the placebo group. Of the above adverse events, the ones for which a causal relationship with the study drug was not ruled out included rash-hand-foot skin reaction in 7 patients, rash/desquamation in 5 patients, fatigue in 4 patients, liver dysfunction/failure (clinical), rash-erythema multiforme (3 patients each), ALT increased in 2 patients, fever (in the absence of neutropenia, where neutropenia is defined as ANC $<1.0 \times 10^9$/L), anorexia, pain-abdomen NOS, bilirubin increased (hyperbilirubinaemia), and ALP increased (1 patient each), in the regorafenib group.

4.(iv).(3) Foreign phase I study (Study 11650)

Adverse events were observed in 3 of 3 patients (100%) in Cohorts 1-2, 4 of 5 patients (80%) in Cohort 3, 6 of 6 patients (100%) in Cohort 4, 8 of 8 patients (100%) in Cohort 5, 7 of 7 patients (100%) in Cohort 6, 12 of 12 patients (100%) in Cohort 7, 12 of 12 patients (100%) in Cohort 8, and 23 of 23 patients (100%) in Cohort 9. The adverse events for which a causal relationship with regorafenib could not be ruled out included 1 of 3 patients (33%) in Cohorts 1-2, 2 of 5 patients (40%) in Cohort 3, 3 of 6 patients (50%) in Cohort 4, 7 of 8 patients (88%) in Cohort 5, 7 of 7 patients (100%) in Cohort 6, 12 of 12 patients (100%) in Cohort 7, 12 of 12 patients (100%) in Cohort 8, and 19 of 23 patients (83%) in Cohort 9. Adverse events reported by ≥2 patients in Cohorts 1-2 or with an incidence of ≥30% in Cohorts 3 to 9 are as shown in the table below.

Adverse events

Organ class/event term (NCI CTCAE Ver. 3.0)	Number of patients (%)							
	Cohorts 1-2 (3 patients)		Cohort 3 (5 patients)		Cohort 4 (6 patients)		Cohort 5 (8 patients)	
	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
All adverse events	3 (100)	3 (100)	4 (80)	2 (40)	6 (100)	6 (100)	8 (100)	5 (63)
Constitutional symptoms								
Fever (in the absence of neutropenia, where neutropenia is defined as ANC $<1.0 \times 10^9$/L)	0	0	0	0	3 (50)	0	4 (50)	0
Insomnia	0	0	2 (40)	0	1 (17)	0	2 (25)	
Fatigue (asthenia, lethargy, malaise)	0	0	1 (20)	0	3 (50)	0	4 (50)	1 (13)
Weight loss	0	0	1 (20)	0	2 (33)	0	4 (50)	0
Sweating	0	0	0	0	4 (67)	0	3 (38)	0
Gastrointestinal								
Diarrhea	1 (33)	0	0	0	2 (33)	0	4 (50)	1 (13)
Nausea	2 (67)	0	1 (20)	0	2 (33)	0	0	0
Infection								
Infection with normal ANC or Grade 1 or 2 neutrophils lung (pneumonia)	0	0	0	0	2 (33)	1 (17)	0	0
Infection - other	1 (33)	1 (33)	1 (20)	1 (20)	4 (67)	3 (50)	3 (38)	2 (25)
Pain								
Pain - tumor pain	1 (33)	1 (33)	1 (20)	0	2 (33)	0	4 (50)	0
Pain - head/headache	1 (33)	0	1 (20)	0	2 (33)	0	0	0
Pain - muscle	0	0	1 (20)	0	1 (17)	0	3 (38)	0
Pain - bone	2 (67)	0	0	0	1 (17)	0	0	0
Pain - throat/pharynx/larynx	0	0	0	0	2 (33)	0	0	0
Pulmonary/upper respiratory								
Cough	1 (33)	0	0	0	3 (50)	0	2 (25)	0
Dyspnea (shortness of breath)	2 (67)	0	0	0	3 (50)	1 (17)	2 (25)	0
Voice changes/dysarthria	0	0	2 (40)	0	2 (33)	0	4 (50)	0
Dermatology/skin								
Dry skin	0	0	0	0	1 (17)	0	3 (38)	0
Pruritus/itching	1 (33)	0	0	0	2 (33)	0	1 (13)	0

Adverse events (continued)

Organ class/event term (NCI CTCAE Ver. 3.0)	Number of patients (%)							
	Cohort 6 (7 patients)		Cohort 7 (12 patients)		Cohort 8 (12 patients)		Cohort 9 (23 patients)	
	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
All adverse events	7 (100)	4 (57)	12 (100)	11 (92)	12 (100)	10 (83)	23 (100)	20 (87)
Blood/bone marrow								
Hemoglobin decreased	1 (14)	1 (14)	4 (33)	1 (8)	4 (33)	1 (8)	3 (13)	1 (4)
Cardiac general								
Hypertension	2 (29)	2 (29)	7 (58)	3 (25)	6 (50)	3 (25)	2 (9)	2 (9)
Constitutional symptoms								
Fever (in the absence of neutropenia, where neutropenia is defined as ANC $<1.0 \times 10^9$/L)	1 (14)	0	3 (25)	0	5 (42)	0	4 (17)	0
Insomnia			3 (25)	0	4 (33)	0	2 (9)	0
Fatigue (asthenia, lethargy, malaise)	3 (43)	0	5 (42)	1 (8)	10 (83)	2 (17)	13 (57)	3 (13)
Weight loss	3 (43)	0	8 (67)	0	5 (42)	1 (8)	7 (30)	0
Sweating	4 (57)	0	3 (25)	0	4 (33)	0	1 (4)	0
Gastrointestinal								
Anorexia	3 (43)	0	8 (67)	1 (8)	7 (58)	0	8 (35)	0
Constipation	3 (43)	0	3 (25)	0	3 (25)	0	4 (17)	0
Diarrhea	3 (43)	1 (14)	6 (50)	2 (17)	7 (58)	1 (8)	9 (39)	1 (4)
Dry mouth/salivary gland	2 (29)	0	3 (25)	0	5 (42)	1 (8)	4 (17)	0
Flatulence	3 (43)	0	1 (8)	0	2 (17)	0	1 (4)	0
Mucositis/stomatitis (clinical exam) - oral cavity	5 (71)	0	3 (25)	1 (8)	8 (67)	0	1 (4)	0
Nausea	1 (14)	0	5 (42)	0	6 (50)	0	2 (9)	0
Vomiting	2 (29)	0	4 (33)	0	5 (42)	0	3 (13)	0
Gastrointestinal - other	3 (43)	0	3 (25)	0	2 (17)	1 (8)	2 (9)	1 (4)
Infection								
Infection - other	3 (43)	0	6 (50)	1 (8)	4 (33)	1 (8)	0	0
Lymphatics								
Lymphedema-related fibrosis	3 (43)	0	0	0	2 (17)	0	1 (4)	0
Neurology								
Mood alteration - depression	2 (29)	0	1 (8)	0	4 (33)	0	2 (9)	1 (4)
Pain								
Pain - tumor pain	1 (14)	0	1 (8)	0	4 (33)	4 (33)	2 (9)	1 (4)
Pain - abdomen NOS	3 (43)	0	4 (33)	0	3 (25)	1 (8)	5 (22)	1 (4)
Pain - muscle	4 (57)	0	2 (17)	0	3 (25)	0	2 (9)	0
Pulmonary/upper respiratory								
Cough	4 (57)	0	1 (8)	0	2 (17)	0	4 (17)	0
Dyspnea (shortness of breath)	1 (14)	0	3 (25)	0	7 (58)	1 (8)	4 (17)	0
Voice changes/dysarthria	7 (100)	0	5 (42)	0	9 (75)	1 (8)	7 (30)	0
Dermatology/skin								
Hair loss/alopecia (scalp or body)	4 (57)	0	5 (42)	0	3 (25)	0	2 (9)	0
Dry skin	3 (43)	0	4 (33)	0	6 (50)	0	4 (17)	0
Rash: hand-foot skin reaction	3 (43)	1 (14)	8 (67)	3 (25)	7 (58)	5 (42)	14 (61)	6 (26)
Pruritus/itching	2 (29)	1 (14)	4 (33)	0	2 (17)	1 (8)	0	0
Rash/desquamation	2 (29)	1 (14)	6 (50)	1 (8)	4 (33)	1 (8)	6 (26)	1 (4)

Serious adverse events were observed in 3 of 3 patients (100%) in Cohorts 1-2, 2 of 5 patients (40%) in Cohort 3, 6 of 6 patients (100%) in Cohort 4, 5 of 8 patients (63%) in Cohort 5, 2 of 7 patients (29%) in Cohort 6, 9 of 12 patients (75%) in Cohort 7, 9 of 12 patients (75%) in Cohort 8, and 11 of 23 patients (48%) in Cohort 9. The observed serious adverse events included ileus, GI (functional obstruction of bowel, i.e., neuroconstipation), CNS hemorrhage, and tumor flare (1 patient [33%] each) in Cohorts 1-2; infection-other, CNS cerebrovascular ischemia , and

encephalopathy (1 patient [20%] each) in Cohort 3; infection-other in 2 patients (33%), and cardiac ischemia/infarction, cardiac general-other, infection with normal ANC or Grade 1 or 2 neutrophils-lung (pneumonia), pain-back, pain-chest/thorax NOS, pneumothorax, dyspnea (shortness of breath), and tumor flare (1 patient [17%] each) in Cohort 4; infection-other in 2 patients (25%), and fatigue, dehydration, diarrhea, somnolence/depressed level of consciousness, pain-back, and pain-abdomen NOS (1 patient [13%] each) in Cohort 5; diarrhea, liver dysfunction/failure (clinical), pain-abdomen NOS, and pain-other (1 patient [14%] each) in Cohort 6; hemoglobin decreased in 2 patients (17%), allergic reaction/hypersensitivity (including drug fever), hypertension, cardiac ischemia/infarction, ascites (non-malignant), diarrhea, infection-other, lipase increased, convulsion, neurology-other, pain-joint, obstruction, GU-ureter, and rash/desquamation (1 patient [8%] each) in Cohort 7; hypertension, fatigue, infection-other, and pain-tumor pain (2 patients [17%] each), and death not associated with CTCAE term-disease progression NOS, weight loss, ascites (non-malignant), dehydration, nausea, gastrointestinal-other, hemorrhage, GI-upper GI NOS, liver dysfunction/failure (clinical), dizziness, memory impairment, pain-abdomen NOS, pleural effusion (non-malignant), dyspnea (shortness of breath), bronchospasm, wheezing, rash-hand-foot skin reaction, urticaria (hives, welts, wheals), and tumor flare (1 patient [8%] each) in Cohort 8; constitutional symptoms-other in 3 patients (13%), fatigue and ileus GI (functional obstruction of bowel, i.e., neuroconstipation) (2 patients [9%] each), and platelets decreased, cardiac general-other, death not associated with CTCAE term-disease progression NOS, fever (in the absence of neutropenia, where neutropenia is defined as ANC $<1.0 \times 10^9$/L), ascites (non-malignant), diarrhea, ulcer, GI-duodenum, gastrointestinal-other, infection with normal ANC or Grade 1 or 2 neutrophils-paranasal, mood alteration-depression, pain-abdomen NOS, pain-liver, dyspnea (shortness of breath), and thrombosis/thrombus/embolism (1 patient [4%] each) in Cohort 9. Of the observed serious adverse events, the ones for which a causal relationship with regorafenib was not ruled out included CNS hemorrhage in 1 patient in Cohorts 1-2, infection-other in 2 patients, somnolence/depressed level of consciousness, and pain-abdomen NOS (1 patient each) in Cohort 5, diarrhoea, and pain-other (1 patient each) in Cohort 6, allergic reaction/hypersensitivity (including drug fever), hypertension, cardiac ischemia/infarction, diarrhea, lipase increased, and rash/desquamation (1 patient each) in Cohort 7, hypertension in 2 patients, and fatigue, weight loss, dehydration, pain-abdomen NOS, bronchospasm, wheezing, rash-hand-foot skin reaction, and urticaria (hives, welts, wheals) (1 patient each) in Cohort 8, fatigue in 2 patients, and platelets decreased, constitutional symptoms-other, ulcer, GI, duodenum, and thrombosis/thrombus/embolism (1 patient each) in Cohort 9.

Adverse events leading to discontinuation of regorafenib were observed in 2 of 5 patients (40%) in Cohort 3, 1 of 6 patients (17%) in Cohort 4, 3 of 8 patients (38%) in Cohort 5, 2 of 7 patients (29%) in Cohort 6, 7 of 12 patients (58%) in Cohort 7, 7 of 12 patients (58%) in Cohort 8, and 9 of 23 patients (39%) in Cohort 9. The observed relevant adverse events included encephalopathy, and tumor flare in 1 patient (20%) in Cohort 3; dyspnea (shortness of breath) in 1 patient (17%) in Cohort 4; infection-other, somnolence/depressed level of consciousness, white blood cell decreased, and platelets decreased (1 patient [13%] each) in Cohort 5; pruritus/itching, rash/desquamation, and liver dysfunction/failure (clinical) (1 patient [14%] each) in Cohort 6; pain-joint, ascites (non-malignant), hemoglobin decreased, cardiac ischemia/infarction, diarrhea, neurology-other, allergic reaction/hypersensitivity (including drug fever), and rash/desquamation (1 patient [8%] each) in Cohort 7; weight loss, hypertension, pleural effusion (non-malignant), rash-hand-foot skin reaction, dehydration in 1 , infection-other, fatigue, and tumor flare (1 patient [8%] each) in Cohort 8; and fatigue in 2 patients (9%), ileus GI (functional obstruction of bowel, i.e., neuroconstipation), gastrointestinal-other, platelets decreased, fever (in the absence of neutropenia, where neutropenia is defined as ANC $<1.0 \times 10^9$/L), hypertension, rash-hand-foot skin reaction, constitutional symptoms-other, pain-other, and ulcer, GI-duodenum, bilirubin increased (hyperbilirubinaemia) (1 patient [4%] each) in Cohort 9. Of these adverse events leading to discontinuation, the ones for which a causal relationship with regorafenib was not ruled

out included infection-other, somnolence/depressed level of consciousness, white blood cell decreased, and platelets decreased (1 patient each) in Cohort 5; pruritus/itching and rash/desquamation (1 patient each) in Cohort 6; cardiac ischemia/infarction, diarrhea, allergic reaction/hypersensitivity (including drug fever), and rash/desquamation (1 patient each) in Cohort 7; weight loss, hypertension, rash-hand-foot skin reaction, dehydration, and fatigue (1 patient each) in Cohort 8; and fatigue in 2 patients, platelets decreased, hypertension, rash-hand-foot skin reaction, constitutional symptoms-other, and ulcer, GI-duodenum (1 patient each) in Cohort 9.

4.(iv).(4) Foreign phase I study (Study 12437)

Adverse events were observed in 2 of 24 patients (8%) in the 40 mg × 4 tablets group and 1 of 24 patients (4%) in the 100 mg + 20 mg × 3 tablets group. Of these adverse events, the ones for which a causal relationship with regorafenib could not be ruled out occurred in 1 of 24 patients (4%) in the 100 mg + 20 mg × 3 tablets group. Neither adverse events nor serious adverse events at the incidence of ≥20% were observed.

Adverse events leading to discontinuation of regorafenib were observed in 1 of 24 patients (4%) in the 100 mg + 20 mg × 3 tablets group. The adverse event leading to discontinuation of the study drug was transient blood ALP increased without clinical symptoms that occurred in 1 patient (2%), and a causal relationship with regorafenib was not ruled out.

4.(iv).(5) Foreign phase I study (Study 14656)

Adverse events were observed in 1 of 24 patients (4%) in the high-fat fed group, and no event for which a causal relationship with regorafenib could not be ruled out occurred. None of the adverse events or serious adverse events at the incidence of ≥20% or adverse events leading to discontinuation of regorafenib were observed.

4.(iv).(6) Foreign phase I study (Study 12436)

Adverse events were observed in 1 of 4 patients (25%), and no event for which a causal relationship with regorafenib could not be ruled out occurred. None of the adverse events or serious adverse events reported by ≥2 patients or adverse events leading to discontinuation of regorafenib were observed.

4.(iv).(7) Foreign phase I study (Study 12435)

Adverse events were observed in 2 of 6 patients (33%) who received regorafenib alone at the dose of 80 mg and 2 of 18 patients (11%) who received regorafenib at the dose of 160 mg concomitantly with ketoconazole. None of the events for which a causal relationship with the study drug could not be ruled out occurred.

The adverse event with an incidence of ≥20% was headache in 2 patients (33%) who received regorafenib alone at the dose of 80 mg, and both events were determined to be mild.

Neither serious adverse events nor adverse events leading to discontinuation of the study drug were observed.

4.(iv).(8) Foreign phase I study (Study 15524)

Adverse events were observed in 6 of 24 patients (25%) following the administration of regorafenib alone, 4 of 23 patients (17%) following the administration of rifampicin alone, and 3 of 22 patients (14%) following the concomitant use of regorafenib and rifampicin. The adverse event for which a causal relationship with the study drug could not be ruled out occurred in 1 of 24 patients (4%) following the administration of regorafenib alone. None of the adverse events or serious adverse events with an incidence of ≥20% or adverse events leading to discontinuation of regorafenib in any groups were observed.

4.(iv).(9) Foreign phase I study (Study 11651)

Adverse events were observed in 2 of 3 patients (67%) in the regorafenib 20 mg group, 8 of 8 patients (100%) in the regorafenib 40 mg group, 56 of 57 patients (98%) in the regorafenib 100 mg group, 5 of 6 patients (83%) in the regorafenib 120 mg group, and 10 of 10 patients (100%) in the regorafenib 140 mg group. The adverse events for which a causal relationship with regorafenib could not be ruled out occurred in 2 of 3 patients (67%) in the regorafenib 20 mg group, 6 of 8 patients (75%) in the regorafenib 40 mg group, 51 of 57 patients (89%) in the regorafenib 100 mg group, 5 of 6 patients (83%) in the regorafenib 120 mg group, and 9 of 10 patients (90%) in the regorafenib 140 mg group. Adverse events with an incidence of ≥40% are as shown in the table below.

Adverse events

Organ class/event term (NCI CTCAE Ver. 3.0)	Number of patients (%)									
	Regorafenib 20 mg (3 patients)		Regorafenib 40 mg (8 patients)		Regorafenib 100 mg (57 patients)		Regorafenib 120 mg (6 patients)		Regorafenib 140 mg (10 patients)	
	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
All adverse events	2 (67)	1 (33)	8 (100)	3 (38)	56 (98)	43 (75)	5 (83)	5 (83)	10 (100)	9 (90)
Constitutional symptoms										
Fatigue (asthenia, lethargy, malaise)	2 (67)	0	5 (63)	0	30 (53)	10 (18)	4 (67)	1 (17)	5 (50)	0
Dermatology/skin										
Rash: hand-foot skin reaction	0	0	1 (13)	0	23 (40)	8 (14)	2 (33)	2 (33)	4 (40)	3 (30)
Rash/desquamation	1 (33)	0	6 (75)	0	19 (33)	0	5 (83)	0	9 (90)	1 (10)
Gastrointestinal										
Constipation	0	0	2 (25)	0	13 (23)	0	3 (50)	0	3 (30)	0
Diarrhea	2 (67)	0	2 (25)	0	15 (26)	1 (2)	2 (33)	0	4 (40)	1 (10)
Mucositis/stomatitis (functional/symptomatic) - oral cavity	0	0	0	0	11 (19)	0	3 (50)	0	4 (40)	0
Metabolic/laboratory										
Bilirubin increased (hyperbilirubinaemia)	0	0	0	0	8 (14)	4 (7)	0	0	5 (50)	2 (20)
Pain										
Pain - back	0	0	1 (13)	0	12 (21)	2 (4)	4 (67)	1 (17)	2 (20)	0
Pain - extremity-limb	0	0	0	0	14 (25)	2 (4)	5 (83)	2 (33)	5 (50)	0
Pain - muscle	0	0	0	0	10 (18)	0	4 (67)	0	3 (30)	0

Serious adverse events were observed in 3 of 8 patients (38%) in the regorafenib 40 mg group, 29 of 57 patients (51%) in the regorafenib 100 mg group, 3 of 6 patients (50%) in the regorafenib 120 mg group, and 5 of 10 patients (50%) in the regorafenib 140 mg group. The observed serious adverse events included obstruction, GI-duodenum, fracture, pain-chest/thorax NOS, dyspnea (shortness of breath), and secondary malignancy (possibly related to cancer treatment) (1 patient [13%] each) in the regorafenib 40 mg group; death not associated with CTCAE term-disease progression NOS in 5 patients (9%), fatigue in 4 patients (7%), cardiac general-other, and infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC $<1.0 \times 10^9$/L)-lung (pneumonia) (3 patients [5%] each), dehydration, gastrointestinal-other, nausea, hemorrhage pulmonary/upper respiratory-respiratory tract NOS, liver dysfunction/failure (clinical), bilirubin (hyperbilirubinaemia), neurology-other, and pain-back (2 patients [4%] each), conduction abnormality/atrioventricular heart block-AV Block-Third degree (complete AV block), hypertension, pericardial effusion (non-malignant), pericarditis, constitutional symptoms-other, fever (in the absence of neutropenia, where neutropenia is defined as ANC $<1.0 \times 10^9$/L), constipation, obstruction, GI-small bowel NOS, infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC $<1.0 \times 10^9$/L)-appendix, infection

(documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 × 10^9/L)-bladder (urinary), infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 × 10^9/L)-blood, infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 × 10^9/L)-bronchus, pancreatitis, infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 × 10^9/L)-urinary tract NOS, edema-limb, sodium, serum-low (hyponatremia), neuropathy-motor, pain-abdomen NOS, pain-chest wall, pain-joint, pain-other, dyspnea (shortness of breath), pneumothorax, renal/genitourinary-other, and thrombosis/thrombus/embolism (1 patient [2%] each) in the regorafenib 100 mg group; supraventricular and nodal arrhythmia-sinus tachycardia, fatigue, infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 × 10^9/L)-lung (pneumonia), vision, blurred vision, ocular/visual-other, pain-chest/thorax NOS, and dyspnea (shortness of breath) (1 patient [17%] each) in the regorafenib 120 mg group; cardiac general-other, hypertension, hypotension, fever (in the absence of neutropenia, where neutropenia is defined as ANC <1.0 × 10^9/L), obstruction, GI-small bowel NOS, infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 × 10^9/L)-bladder (urinary), infection-other, uric acid, serum-high (hyperuricemia), pulmonary/upper respiratory-other, renal failure, and thrombosis/thrombus/embolism (1 patient [10%] each) in the regorafenib 140 mg group. Of these serious adverse events, the ones for which a causal relationship with regorafenib was not ruled out included conduction abnormality/atrioventricular heart block-AV Block-Third degree (complete AV block), cardiac general-other, hypertension, dehydration, nausea, and infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 × 10^9/L)-urinary tract NOS (1 patient each) in the regorafenib 100 mg group and cardiac general-other in 1 patient in the regorafenib 140 mg group.

Adverse events leading to discontinuation of regorafenib were observed in 2 of 8 patients (25%) in the regorafenib 40 mg group, 18 of 57 patients (32%) in the regorafenib 100 mg group, 1 of 6 patients (17%) in the regorafenib 120 mg group, 4 of 10 patients (40%) in the regorafenib 140 mg group. The observed relevant adverse events included secondary malignancy (possibly related to cancer treatment), and obstruction, GI-duodenum (1 patient [13%] each) in the regorafenib 40 mg group; fatigue in 3 patients (5%), death not associated with CTCAE term-disease progression NOS, and neurology-other (2 patients [4%] each), and bilirubin (hyperbilirubinaemia), pancreatitis, cystitis, pain-chest wall, supraventricular and nodal arrhythmia-atrial fibrillation, dysphagia (difficulty swallowing), mood alteration-anxiety, conduction abnormality/atrioventricular heart block-AV Block-Third degree (complete AV block), cardiac general-other, hypertension, ventricular arrhythmia-ventricular tachycardia, obstruction, GI-small bowel NOS, dyspnea (shortness of breath), edema-limb, pain-chest/thorax NOS, constitutional symptoms-other, metabolic/laboratory-other, pain-back, dehydration, and diarrhea (1 patient [2%] each) in the regorafenib 100 mg group; left ventricular systolic dysfunction in 1 patient (17%) in the regorafenib 120 mg group; and thrombosis/thrombus/embolism, fracture, nausea, vomiting, pain-abdomen NOS, obstruction, GI-small bowel NOS, and renal failure (1 patient [10%] each) in the regorafenib 140 mg group. Of these adverse events, the ones for which a causal relationship with regorafenib was not ruled out included bilirubin (hyperbilirubinaemia), mood alteration-anxiety, conduction abnormality/atrioventricular heart block-AV Block-Third degree (complete AV block), cardiac general-other, metabolic/laboratory-other, and diarrhea (1 patient each) in the regorafenib 100 mg group, and left ventricular systolic dysfunction in 1 patient in the regorafenib 120 mg group.

4.(iv).(10) Foreign phase I study (Study 14996)

Adverse events were observed in 12 of 12 patients (100%), and adverse events for which a causal relationship with regorafenib could not be ruled out occurred in 9 of 12 patients (75%). Adverse events with an incidence of ≥20% are as shown in the table below.

Adverse events

Organ class/event term (NCI CTCAE Ver. 3.0)	Number of patients (%)	
	Regorafenib group (n = 12)	
	All grades	Grade ≥3
All adverse events	12 (100)	10 (83)
Constitutional symptoms		
Fatigue (asthenia, lethargy, malaise)	5 (42)	0
Fever (in the absence of neutropenia, where neutropenia is defined as ANC $<1.0 \times 10^9$/L)	7 (58)	0
Dermatology/skin		
Rash: hand-foot skin reaction	6 (50)	1 (8)
Rash/desquamation	3 (25)	1 (8)
Gastrointestinal		
Anorexia	5 (42)	0
Constipation	3 (25)	0
Diarrhea	5 (42)	0
Distension/bloating, abdominal	3 (25)	0
Nausea	5 (42)	1 (8)
Vomiting	4 (33)	1 (8)
Metabolic/laboratory		
Bilirubin increased (hyperbilirubinaemia)	4 (33)	4 (33)
Pain		
Pain - abdomen NOS	4 (33)	0
Pain - back	3 (25)	0
Pain - head/headache	3 (25)	0

Serious adverse events were observed in 7 of 12 patients (58%). The observed serious adverse events included hyperbilirubinaemia in 3 patients (25%), fever in 2 patients (17%), and hypertension, obstruction, GI-colon, ascites, myocardial injury, rectal hemorrhage, non-ST elevated, bacteraemia, infection-chest, transverse colonic fistula, progression (ovarian cancer), edema legs, ascites increased, maculopapular eruption, and intestinal obstruction (1 patient [8%] each). Of these serious adverse events, the ones for which a causal relationship with regorafenib was not ruled out included hypertension, myocardial injury, non-ST elevated, bacteraemia, infection-chest, transverse colonic fistula, and maculopapular eruption (1 patient each).

Adverse events leading to discontinuation of regorafenib occurred in 1 of 12 patients (8%). The observed relevant adverse event was non-ST elevated myocardial infarction in 1 patient, and its causal relationship with the study drug was not ruled out.

4.(iv).(11) Foreign phase I study (Study 11656)

Adverse events were observed in 25 of 25 patients (100%) in the regorafenib + mFOLFOX6 group and 20 of 20 patients (100%) in the regorafenib + FOLFIRI group, and ones for which a causal relationship with the study drug could not be ruled out occurred in 25 of 25 patients (100%) in the regorafenib + mFOLFOX6 group and 19 of 20 patients (95%) in the regorafenib + FOLFIRI group. Adverse events with an incidence of ≥30% in either group are as shown in the table below.

Adverse events

Organ class/event term (NCI CTCAE Ver. 3.0)	Number of patients (%)			
	Regorafenib + mFOLFOX6 (n = 25)		Regorafenib + FOLFIRI (n = 20)	
	All grades	Grade ≥3	All grades	Grade ≥3
All adverse events	25 (100)	23 (72)	20 (100)	16 (80)
Blood/bone marrow				
White blood cell decreased	10 (40)	2 (8)	7 (35)	2 (10)
Neutrophils/granulocytes (ANC/AGC) decreased	11 (44)	8 (32)	11 (55)	9 (45)
Constitutional symptoms				
Fatigue (asthenia, lethargy, malaise)	11 (44)	0	11 (55)	0
Dermatology/skin				
Hair loss/alopecia (scalp or body)	2 (8)	0	8 (40)	0
Rash: hand-foot skin reaction	9 (36)	1 (4)	7 (35)	3 (15)
Rash/desquamation	8 (32)	0	5 (25)	0
Gastrointestinal				
Diarrhea	15 (60)	1 (4)	13 (65)	3 (15)
Mucositis/stomatitis (functional/symptomatic) - oral cavity	10 (40)	2 (8)	7 (35)	0
Nausea	12 (48)	2 (8)	5 (25)	0
Neurology				
Neuropathy: Sensory	11 (44)	1 (4)	4 (20)	0
Pain				
Pain - abdomen NOS	7 (28)	0	8 (40)	1 (5)
Pain - head/headache	10 (40)	0	1 (5)	0
Pulmonary/upper respiratory				
Cough	3 (12)	0	6 (30)	0
Voice changes/dysarthria	8 (32)	0	7 (35)	0

Serious adverse events were observed in 13 of 25 patients (52%) in the regorafenib + mFOLFOX6 group and 6 of 20 patients (30%) in the regorafenib + FOLFIRI group. The observed serious adverse events included thrombosis/thrombus/embolism in 4 patients (16%), cardiac general-other, ileus GI (functional obstruction of bowel, i.e., neuroconstipation), and syncope in 2 patients (8%), and allergic reaction/hypersensitivity (including drug fever), hemoglobin decreased, white blood cell decreased, neutrophils/granulocytes (ANC/AGC) decreased, hypertension, death not associated with CTCAE term-disease progression NOS, constitutional symptoms-other, constipation, diarrhea, mucositis/stomatitis (functional/symptomatic)-oral cavity, perforation, GI-ileum, liver dysfunction/failure (clinical), infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC $<1.0 \times 10^9$/L)-catheter-related, ALT increased, metabolic/laboratory-other, CNS ischemia, and renal failure (1 patient [4%] each) in the regorafenib + mFOLFOX6 group; and thrombosis/thrombus/embolism in 2 patients (10%), and diarrhea, infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC $<1.0 \times 10^9$/L)-lung (pneumonia), infection with normal ANC or Grade 1 or 2 neutrophils-pleura (empyema), and neuropathy-motor (1 patient [5%] each) in the regorafenib + FOLFIRI group. Of these serious adverse events, the ones for which a causal relationship with the study drug was not ruled out included thrombosis/thrombus/embolism in 2 patients, and allergic reaction/hypersensitivity (including drug fever), white blood cell decreased, neutrophils/granulocytes (ANC/AGC) decreased, hypertension, diarrhea, mucositis/stomatitis (functional/symptomatic)-oral cavity, liver dysfunction/failure (clinical), ALT increased, and CNS cerebrovascular ischemia (1 patient each) in the regorafenib + mFOLFOX6 group; and diarrhea, infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC $<1.0 \times 10^9$/L)-lung (pneumonia), infection with normal ANC or Grade 1 or 2 neutrophils-pleura (empyema), and thrombosis/thrombus/embolism (1 patient each) in the regorafenib + FOLFIRI group.

Adverse events leading to discontinuation of the study drug occurred in 12 of 25 patients (48%) in the regorafenib + mFOLFOX6 group and 7 of 20 patients (35%) in the regorafenib + FOLFIRI group. The observed adverse events leading to discontinuation of the study drug included ileus GI (functional obstruction of bowel, i.e., neuroconstipation), neuropathy-sensory, allergic reaction/hypersensitivity (including drug fever), and neutrophils/granulocytes (ANC/AGC) decreased (2 patients [8%] each), and anorexia, dehydration, mucositis/stomatitis (functional/symptomatic)-oral cavity, pulmonaryupper respiratory-other, perforation, GI-ileum, platelets decreased, wound complication-non-infectious, infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC $<1.0 \times 10^9$/L)-catheter-related, CNS ischemia, infection with normal ANC or Grade 1 or 2 neutrophils-urinary tract NOS, rash/desquamation, and voice changes/dysarthria (1 patient [4%] each) in the regorafenib + mFOLFOX6 group; and thrombosis/thrombus/embolism in 2 patients (10%), diarrhea, neuropathy-motor, infection with normal ANC or Grade 1 or 2 neutrophils-pleura (empyema), rash-hand-foot skin reaction, and white blood cell decreased (1 patient [5%] each) in the regorafenib + FOLFIRI group. Of these adverse events, the ones for which a causal relationship with the study drug was not ruled out included neuropathy-sensory in 2 patients, and anorexia, dehydration, mucositis/stomatitis (functional/symptomatic)-oral cavity, allergic reaction/hypersensitivity (including drug fever), wound complication-non-infectious, CNS cerebrovascular ischemia, rash/desquamation, and voice changes/dysarthria (1 patient each) in the regorafenib + mFOLFOX6 group; and thrombosis/thrombus/embolism, diarrhea, infection with normal ANC or Grade 1 or 2 neutrophils-pleura (empyema), rash-hand-foot skin reaction, and white blood cell decreased (1 patient each) in the regorafenib + FOLFIRI group.

4.(iv).(12) Foreign phase I study (Study 12434)

Adverse events were observed in 20 of 20 patients (100%) in Group A and 20 of 20 patients (100%) in Group B. Of the adverse events, the ones for which a causal relationship with regorafenib was not ruled out occurred in 20 of 20 patients (100%) in Group A and 19 of 20 patients (95.0%) in Group B. Adverse events with an incidence of ≥40% in either group are as shown in the table below.

Adverse events

Organ class/event term (NCI CTCAE Ver. 4.0)	Number of patients (%) Group A (n = 20)		Number of patients (%) Group B (n = 20)	
	All grades	Grade ≥3	All grades	Grade ≥3
All adverse events	20 (100)	17 (85)	20 (100)	18 (90)
Gastrointestinal disorders				
Abdominal pain	9 (45)	3 (15)	8 (40)	2 (10)
Constipation	13 (65)	1 (5)	12 (60)	0
Diarrhea	13 (65)	0	13 (65)	2 (10)
Mucositis oral	10 (50)	0	11 (55)	2 (10)
Nausea	10 (50)	0	5 (25)	1 (5)
Vomiting	7 (35)	0	10 (50)	1 (5)
General disorders and administration site conditions				
Fatigue	15 (75)	5 (25)	16 (80)	7 (35)
Pain	4 (20)	0	8 (40)	0
Investigations				
ALT increased	0	0	4 (20)	1 (5)
Metabolism and nutrition disorders				
Anorexia	15 (75)	1 (5)	8 (40)	2 (10)
Musculoskeletal and connective tissue disorders				
Pain in extremity	8 (40)	1 (5)	3 (15)	0
Nervous system disorders				
Dysgeusia	0	0	4 (20)	0
Respiratory, thoracic and mediastinal disorders				
Hoarseness	8 (40)	0	7 (35)	0
Skin and subcutaneous tissue disorders				
Alopecia	7 (35)	0	8 (40)	0
Palmar-plantar erythrodysesthesia syndrome	8 (40)	1 (5)	9 (45)	3 (15)
Rash maculo-papular	3 (15)	1 (5)	8 (40)	3 (15)
Vascular disorders				
Hypertension	11 (55)	3 (15)	8 (40)	4 (20)

Serious adverse events were observed in 12 of 20 patients (60%) in Group A and 10 of 20 patients (50%) in Group B. The observed serious adverse events included gastrointestinal disorders-other, and fever in 2 patients (10%), and abdominal pain, colonic obstruction, constipation, lower gastrointestinal hemorrhage, small intestinal perforation, abdominal infection, infections and infestations-other, investigations-other, anorexia, dehydration, hypophosphataemia, pain in extremity, pelvic infection, neoplasms benign, malignant and unspecified (incl cysts and polyps)-other, and thromboembolism (1 patient [5%] each) in Group A; and small intestinal perforation and neoplasms benign, malignant and unspecified (incl cysts and polyps)-other (2 patients [10%] each), and febrile neutropenia, duodenal perforation, esophageal hemorrhage, gastrointestinal disorders-other, fatigue, non-cardiac chest pain, sepsis, and dehydration (1 patient [5%] each) in Group B. Of these serious adverse events, the ones for which a causal relationship with regorafenib was not ruled out included abdominal pain, colonic obstruction, gastrointestinal disorders-other, lower gastrointestinal hemorrhage, small intestinal perforation, fever, pelvic infection, investigations-other, dehydration, and hypophosphataemia (1 patient each) in Group A; and febrile neutropenia, duodenal perforation, esophageal hemorrhage, small intestinal perforation, fatigue, non-cardiac chest pain, and dehydration (1 patient each) in Group B.

Adverse events leading to discontinuation of regorafenib were observed in 3 of 20 patients (15%) in Group A and 9 of 20 patients (45%) in Group B. The observed relevant adverse events included constipation, diarrhea, vomiting, fatigue, pain in extremity, and hoarseness (1 patient [5%] each) in Group A; and small intestinal perforation and neoplasms benign, malignant and unspecified (incl cysts and polyps)-other in 2 patients (10%), and diarrhea, duodenal perforation, pain, AST increased, dehydration, musculoskeletal and connective tissue disorder-other, pruritus, rash acneiform, and rash maculo-papular (1 patient [5%] each) in Group B. Of these adverse events, the ones for which a causal relationship with regorafenib was not ruled out included small

intestinal perforation in 2 patients, and duodenal perforation and dehydration (1 patient each) in Group B.

4.(iv).(13) Foreign phase I study (Study 14814)

Adverse events were observed in 53 of 53 patients (100%), and those for which a causal relationship with regorafenib could not be ruled out occurred in 51 of 53 patients (96%). Adverse events with an incidence of ≥20% are as shown in the table below.

Adverse events

Organ class/event term (NCI CTCAE Ver. 4.0)	Number of patients (%)	
	Regorafenib group 160 mg (n = 53)	
	All grades	Grade ≥3
All adverse events	53 (100)	38 (72)
Gastrointestinal disorders		
Mucositis oral	20 (38)	1 (2)
Diarrhea	18 (34)	3 (6)
Nausea	17 (32)	3 (6)
Vomiting	11 (21)	3 (6)
General disorders and administration site conditions		
Fatigue	18 (34)	1 (2)
Metabolism and nutrition disorders		
Anorexia	20 (38)	0
Musculoskeletal and connective tissue disorders		
Pain in extremity	13 (25)	2 (4)
Respiratory, thoracic and mediastinal disorders		
Hoarseness	12 (23)	0
Skin and subcutaneous tissue disorders		
Palmar-plantar erythrodysesthesia syndrome	17 (32)	4 (8)
Vascular disorders		
Hypertension	13 (25)	5 (9)

Serious adverse events were observed in 22 of 53 patients (42%). The observed serious adverse events included neoplasms benign, malignant and unspecified (incl cysts and polyps)-other, and blood bilirubin increased (4 patients [8%] each), abdominal pain, diarrhea, and pleural effusion (2 patients [4%] each), and anemia, cardiac arrest, pericardial effusion, sinus tachycardia, anal fistula, ascites, nausea, small intestinal perforation, vomiting, pain, cholecystitis, enterocolitis infectious, sepsis, INR increased, platelet count decreased, dehydration, hyperglycemia, hyperkalemia, hyponatremia, cognitive disturbance, mental disorder-other, renal failure acute, pharyngeal hemorrhage, pneumonitis, respiratory, thoracic and mediastinal disorders-other, hypertension, and thromboembolic event (1 patient [2%] each). Of these serious adverse events, the ones for which a causal relationship with regorafenib was not ruled out included blood bilirubin increased in 2 patients, and diarrhea and small intestinal perforation (1 patient each).

Adverse events leading to discontinuation of regorafenib were observed in 8 of 53 patients (15%). The observed adverse events included blood bilirubin increased in 2 patients (4%), and anorectal infection, ascites, palmar-plantar erythrodysesthesia syndrome, pleural effusion, pain, and lower gastrointestinal hemorrhage (1 patient [2%] each). Of these adverse events, the ones for which a causal relationship with regorafenib was not ruled out included blood bilirubin increased in 2 patients, and palmar-plantar erythrodysesthesia syndrome and lower gastrointestinal hemorrhage (1 patient each).

4.(iv).(14) Foreign phase II study (Study 14596)

Adverse events were observed in 36 of 36 patients (100%), and the ones for which a causal relationship with regorafenib was not ruled out occurred in 35 of 36 patients (97%). Adverse events with an incidence of ≥20% are as shown in the table below.

Adverse events

Organ class/event term (NCI-CTCAE Ver. 3.0)	Number of patients (%)	
	Regorafenib group (n = 36)	
	All grades	Grade ≥3
All adverse events	36 (100)	28 (78)
Cardiac general		
Hypertension	11 (31)	1 (3)
Constitutional symptoms		
Fatigue (asthenia, lethargy, malaise)	25 (69)	8 (22)
Fever (in the absence of neutropenia, where neutropenia is defined as ANC $<1.0 \times 10^9$/L)	11 (31)	0
Weight loss	8 (22)	0
Dermatology/skin		
Rash: hand-foot skin reaction	18 (50)	5 (14)
Endocrine		
Thyroid function, low (hypothyroidism)	16 (44)	1 (3)
Gastrointestinal		
Anorexia	14 (39)	0
Constipation	10 (28)	0
Diarrhea	19 (53)	2 (6)
Nausea	13 (36)	0
Pain		
Pain - abdomen NOS	9 (25)	3 (8)
Pain - back	8 (22)	1 (3)
Pain - head/headache	8 (22)	0
Pulmonary/upper respiratory		
Voice changes/dysarthria	13 (36)	0

Serious adverse events were observed in 12 of 36 patients (33%). The observed serious adverse events included fatigue, CNS hemorrhage, and liver dysfunction/failure (clinical) (2 patients [6%] each), and allergic reaction/hypersensitivity (including drug fever), ataxia (incoordination), cardiac ischemia/infarction, diarrhea, encephalopathy, hematoma, infection-other, pain-abdomen NOS, hearing (patients without baseline audiogram and not enrolled in a monitoring program), and constitutional symptoms-other (1 patient [3%] each). Of these serious adverse events, the ones for which a causal relationship with regorafenib was not ruled out included fatigue, diarrhea, hematoma, and constitutional symptoms-other (1 patient each).

Adverse events leading to discontinuation of regorafenib were observed in 12 of 36 patients (33%). The observed relevant adverse events included fatigue in 4 patients (11%), and hematoma, diarrhea, dysphagia, rash-hand-foot skin reaction, anorexia, dermatology/skin-other, proteinuria, fever (in the absence of neutropenia, where neutropenia is defined as ANC $<1.0 \times 10^9$/L), white blood cell decreased, platelets decreased, cardiac ischemia/infarction, CNS hemorrhage, ataxia (incoordination), neurology-other, and encephalopathy (1 patient [3%] each). Of these adverse events, the ones for which a causal relationship with regorafenib was not ruled out included fatigue in 3 patients, and hematoma, diarrhea, dysphagia, rash-hand-foot skin reaction, anorexia, dermatology/skin-other, and proteinuria (1 patient each).

4.(iv).(15) Foreign phase II study (Study 11726)

Adverse events were observed in 49 of 49 patients (100%), and the ones for which a causal relationship with regorafenib could not be ruled out occurred in 48 of 49 patients (98%). Adverse events with an incidence of ≥20% are as shown in the table below.

Adverse events

Organ class/event term (NCI-CTCAE Ver. 3.0)	Number of patients (%)	
	Regorafenib group (n = 49)	
	All grades	Grade ≥3
All adverse events	49 (100)	43 (88)
Cardiac general		
Hypertension	26 (53)	3 (6)
Constitutional symptoms		
Fatigue (asthenia, lethargy, malaise)	26 (53)	5 (10)
Fever (in the absence of neutropenia, where neutropenia is defined as ANC $<1.0 \times 10^9$/L)	11 (22)	0
Dermatology/skin		
Hair loss/alopecia (scalp or body)	22 (45)	0
Dermatology/skin - other	11 (22)	1 (2)
Rash: hand-foot skin reaction	35 (71)	16 (33)
Rash/desquamation	23 (47)	3 (6)
Gastrointestinal		
Anorexia	15 (31)	3 (6)
Constipation	16 (33)	0
Diarrhea	24 (49)	5 (10)
Mucositis/stomatitis (functional/symptomatic) - oral cavity	23 (47)	1 (2)
Nausea	15 (31)	0
Vomiting	14 (29)	1 (2)
Pain		
Pain - abdomen NOS	12 (24)	3 (6)
Pain - back	12 (24)	4 (8)
Pain - head/headache	14 (29)	0
Pain - other	10 (20)	4 (8)
Pulmonary/upper respiratory		
Dyspnea (shortness of breath)	16 (33)	3 (6)
Voice changes/dysarthria	17 (35)	0

Serious adverse events were observed in 30 of 49 patients (61%), and ones reported by ≥2 patients included renal failure in 5 patients (10%), and cardiac ischemia/infarction in 4 patients (8%), fatigue, and pain-back each in 3 patients (6%), and rash/desquamation, fracture, syncope, pain-abdomen NOS, pain-other, and pleural effusion (non-malignant) (2 patients [4%] each). Of these serious adverse events, the ones for which a causal relationship with regorafenib was not ruled out included renal failure in 5 patients, cardiac ischemia/infarction in 3 patients, fatigue, rash/desquamation, and syncope (2 patients each), and pain-abdomen NOS in 1 patient.

Adverse events leading to discontinuation of regorafenib were observed in 13 of 49 patients (27%). The observed relevant adverse events included renal failure in 4 patients (8%), and airway obstruction, pain-back, syncope, fatigue, rash/desquamation, rash-hand-foot skin reaction, hemoglobin decreased, liver dysfunction/failure (clinical), muscle weakness, generalized or specific area (not due to neuropathy)-extremity-upper, hemorrhage pulmonary/upper respiratory-nose, cardiac ischemia, pain-chest/thorax NOS, perforation, GI-colon, anorexia, and dizziness (1 patient [2%] each). Of these adverse events, the ones for which a causal relationship with regorafenib was not ruled out included renal failure in 4 patients, and airway obstruction, syncope, fatigue, rash/desquamation, rash-hand-foot skin reaction, hemoglobin decreased, liver dysfunction/failure (clinical), cardiac ischemia, pain-chest/thorax NOS, anorexia, and dizziness (1 patient each).

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

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

A document-based inspection and data integrity assessment were conducted in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the new drug application. As a result, there were no particular problems. Thus, PMDA concluded that there should be no problem with conducting a regulatory review based on the submitted application documents.

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

GCP on-site inspection took place in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the new drug application (5.3.5.1.1). As a result, PMDA concluded that there should be no problem with conducting a regulatory review based on the submitted application documents.

IV. Overall Evaluation

Based on the submitted data, it is concluded that the efficacy of regorafenib in patients with incurable, unresectable, advanced/recurrent colorectal cancer has been demonstrated, and the safety of regorafenib is acceptable in view of its observed benefits. Regorafenib is a drug with a new active ingredient that inhibits phosphorylation by kinases such as vascular endothelial growth factor receptor (VEGFR), angiopoietin receptor (TIE2), platelet-derived growth factor receptor (PDGFR), fibroblast growth factor receptor (FGFR), stem cell growth factor receptor (KIT), RET, and BRAF, and has a clinical significance as a treatment option for incurable, unresectable, advanced/recurrent colorectal cancer. The indications, dosage and administration, post-marketing investigations, etc. will be further discussed at the Expert Discussion.

PMDA considers that regorafenib may be approved if it can be concluded based on comments from the Expert Discussion that there are no particular problems.

Review Report (2)

March 1, 2013

I. Product Submitted for Registration

[Brand name]	Stivarga Tablets 40 mg
[Non-proprietary name]	Regorafenib Hydrate
[Applicant]	Bayer Yakuhin, Ltd.
[Date of application]	July 31, 2012

II. Content of the Review

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

(1) Efficacy

As a result of its review in the "4.(iii).B.(1) Data for review" and "4.(iii).B.(2) Efficacy" sections of the Review Report (1), the global phase III study in colorectal cancer patients with distant metastases (metastatic) who have progressed after standard chemotherapy (Study 14387) showed that regorafenib significantly extended the overall survival as the primary endpoint, and PMDA has concluded that the efficacy of regorafenib can be expected in such patients.

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

(2) Safety

As a result of its review in the "4.(iii).B (3) Safety" section of the Review Report (1), PMDA has concluded that adverse events to which special attention is needed during treatment with regorafenib include hand and foot syndrome, hepatic function disorder, hypertension (hypertensive crisis), haemorrhage, thromboembolism, gastrointestinal perforation or fistula, Stevens-Johnson syndrome/toxic epidermal necrolysis, and posterior reversible encephalopathy; and during use of regorafenib, special attention should be paid to development of these adverse events.

In addition, concerning the clinical use of regorafenib, PMDA has concluded that regorafenib is tolerable in Japanese patients with colorectal cancer when a physician with sufficient knowledge and experience in cancer chemotherapy implements appropriate practices including monitoring and management of the adverse events, dose interruption, dose reduction, and discontinuation.

The above conclusion of PMDA was supported by the expert advisors at the Expert Discussion. The following comments were raised from the expert advisors:

- Some adverse events (hand and foot syndrome, hepatic function disorder) more frequently occurred in Japanese patients than in foreign patients. The applicant should consider including in the package insert detailed information about these events in Japanese patients such as incidences of Grade ≥3 events.
- Hematotoxicity events such as platelets decreased were observed. Regorafenib should be carefully given to patients with bone marrow depression.
- Regorafenib will be mainly indicated for patients with incurable, unresectable,

advanced/recurrent colorectal cancer who have undergone standard treatment; and will be the first oral kinase inhibitor marketed in this disease area. The applicant should provide sufficient information about the patients for whom regorafenib is recommended such as inclusion criteria for clinical studies to ensure that regorafenib will not be given to those in poor performance status without careful consideration.

- In addition to the above events requiring special attention during treatment with regorafenib, the following events that are included in those as indicated in Review Report (1) should be appropriately cautioned and information including their incidence should be provided: proteinuria, hypothyroidism, lipase increased, amylase increased, wound-healing disturbance, and dysphonia.

In view of the comments from the Expert Discussion, PMDA considers as follows:
Although PMDA considers it necessary to provide cautions about hand and foot syndrome and hepatic function disorder of which incidences were higher, especially, in Japanese patients than in foreign patients, the inclusion of incidences of the events by grade in Japanese patients in the package insert is not necessarily needed, because these events were not specific to Japanese patients and were satisfactorily managed by dose interruption or dose reduction of regorafenib as shown by the fact that the events leading to discontinuation of regorafenib in Japanese patients occurred at a low incidence, including hand and foot syndrome in 1 of 65 patients (1.5%), alanine aminotransferase (ALT) increased in 3 of 65 patients (4.6%), and hepatic function abnormal in 1 of 65 patients (1.5%). Accordingly, PMDA has concluded that detailed information about these adverse events such as differences in incidence by grade between foreign patients and Japanese patients should be provided to medical practices through information materials.

In addition, the information about the inclusion criteria for clinical studies and baseline characteristics of the patients actually included in the studies as well as specified actions for haematotoxicity events should be appropriately provided through information materials.

PMDA thus instructed the applicant to appropriately provide cautions and information about the above contents in the package insert or information materials, and the applicant responded that they would follow the instructions.

(3) Clinical positioning and indication
As a result of its review in the "4.(iii).B.(2) Efficacy," "4.(iii).B.(3) Safety," "4.(iii).B.(4) Clinical positioning," and "4.(iii).B.(5) Indication" sections of the Review Report (1), PMDA has concluded that regorafenib can be positioned as a new treatment option for patients with metastatic colorectal cancer who have progressed after conventional standard chemotherapy.

In addition, PMDA considers that the indication of regorafenib can be described as "incurable, unresectable, advanced/recurrent colorectal cancer" as proposed, provided that cautions are given to facilitate appropriate patient selection, by stating that "the efficacy and safety as the first- or second-line therapy have not been established" in addition to "the efficacy and safety of regorafenib have not been established for use in adjuvant chemotherapy."

The above conclusion of PMDA was supported by the expert advisors at Expert Discussion. The following comments were raised from the expert advisors:

- As a third-line therapy, cetuximab (genetical recombination) (cetuximab) or panitumumab (genetical recombination) (panitumumab) may be given to patients with wild-type *KRAS* gene who have not received either drug until second-line therapy. Only with the caution "the efficacy and safety of regorafenib as the first- or second-line therapy have not been established" in the Precautions for Indications section, there is a concern that cetuximab- or panitumumab-naive patients with wild-type *KRAS* gene could receive regorafenib. Clear

cautions should be provided to healthcare professionals that regorafenib is recommended for patients who have received standard chemotherapy (which include fluoropyrimidine antincacncer agents, oxaliplatin, irinotecan hydrochloride, and bevacizumab [genetical recombination], and cetuximab or panitumumab for patients with wild-type *KRAS* gene in the tumor tissue), the same patient population as that included in Study 14387.

- Patients with liver metastases may undergo neoadjuvant chemotherapy, the applicant should consider whether it is necessary to provide a caution, stating that the efficacy and safety of regorafenib have not been established for use in neoadjuvant chemotherapy.

In view of the comments from the Expert Discussion, PMDA considers as follows:
In consideration of the opinion that patients included in clinical studies should be clarified to inform healthcare professionals of the recommended patient population of regorafenib, PMDA has determined that it is appropriate to include not only a detailed description of the history of previous treatments in patients included in clinical studies in the Clinical Studies section but also the following cautions in the Precautions for Indications section:

- Eligible patients should be selected with full knowledge of information in the "Clinical Studies" section such as the history of previous treatments of patients included in clinical studies and sufficient understanding of the efficacy and safety of regorafenib.

Neoadjuvant chemotherapy may be considered for colorectal cancer patients with resectable liver metastases (*National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology. Colon Cancer* [NCCN guideline] [v.3.2013]). However, PMDA has concluded that a caution may not have to be provided, stating that the efficacy and safety of regorafenib have not been established for use in neoadjuvant chemotherapy at present, because (1) clinical positioning of such neoadjuvant treatments has not been established (*Japanese Society for Cancer of the Colon and Rectum [JSCCR] guidelines 2010 for the treatment of colorectal cancer* [Kanehara & Co., Ltd., 2010] [JSCCR Guidelines 2010 for the Treatment of Colorectal Cancer]); and (2) neoadjuvant chemotherapy before radical surgery is not recommended for the patients with resectable colorectal cancer with no metastasis.

PMDA thus instructed the applicant to include the following information in the Indications and Precautions for Indications sections and the applicant responded that they would follow the instructions.

Indications
Incurable, unresectable, advanced/recurrent colorectal cancer

Precautions for Indications

- Efficacy and safety of regorafenib as the first- or second-line therapy have not been established.
- Eligible patients should be selected with full knowledge of information in the section "Clinical Studies," such as the history of previous treatments of patients included in clinical studies and sufficient understanding of the efficacy and safety of regorafenib.
- The efficacy and safety of regorafenib have not been established for use in adjuvant chemotherapy.

(4) Dosage and Administration
As a result of its review in the "4.(iii).B.(6) Dosage and administration" section of the Review Report (1), PMDA has concluded that it is appropriate to set the dosage and administration as follows: "The usual adult dosage is 160 mg of regorafenib orally administered once daily after a meal for 3 weeks followed by 1-week off therapy. The above regimen should be repeated in a 4-week cycle. The dose may be reduced according to the patient's condition." In addition, PMDA

has concluded that the following information should be provided as cautions in the Precautions for Dosage and Administration section:

- The efficacy and safety of concomitant use of regorafenib with the other antineoplastic drugs have not been established.
- Criteria for dose reduction, dose interruption, and discontinuation at the onset of adverse events (hand and foot syndrome, liver function test abnormal)
- Effects of food on PK of regorafenib

The above conclusion of PMDA was supported by the expert advisors at Expert Discussion. The following comments were raised from the expert advisors:

- Information about effects of food on PK of regorafenib should be appropriately provided in the package insert. According to the draft package insert submitted in the application, a caution was provided in the Precautions for Dosage and Administration section, stating that it is advisable to give regorafenib after low-fat meals. However, with this description, the definition of the low-fat meal and specific meal contents may be found unclear in medical practices. To address this concern, the applicant should consider how and what caution or information is provided.
- In addition, taking account of the high incidence of hypertension, the applicant should consider describing the dose adjustment procedure for hypertension in the package insert.

In view of the comments from the Expert Discussion, PMDA considers as follows:
A clinical study evaluating effects of food on PK of regorafenib (Study 14656) has showed that the PK of regorafenib is affected by food. Based on the study data, the protocol for Study 14387 specified that regorafenib should be given after breakfast (fat content <30%), and in this study, efficacy and safety were verified. PMDA thus has concluded that it is appropriate to specify the administration after meals in the Dosage and Administration section, and to provide cautions about the effects of food on PK of regorafenib using clinical pharmacology data and clarify what food should be avoided during regorafenib administration in the Precautions for Dosage and Administration section. In addition, the information about specific meal contents recommended during regorafenib administration in Study 14387 should be provided through the package insert and information materials. Furthermore, PMDA has concluded that the information about dose adjustment procedures for general toxicity events such as hypertension should be provided in the Precautions for Dosage and Administration section.

PMDA thus instructed the applicant to set the Dosage and Administration and Precautions for Dosage and Administration sections as follows and to provide information about specific meal contents recommended during regorafenib administration through information materials etc., and the applicant responded that they would follow the instructions.

Dosage and Administration
The usual adult dosage is 160 mg of regorafenib orally administered once daily after a meal for 3 weeks followed by 1-week off therapy. The above regimen should be repeated in a 4-week cycle. The dose may be reduced according to the patient's condition.

Precautions for Dosage and Administration

- The efficacy and safety of concomitant use of regorafenib with the other antineoplastic drugs have not been established.
- When regorafenib was administered to fasted subjects, the C_{max} and AUC values of the unchanged regorafenib decreased compared with those in fed subjects. Regorafenib should not be given to fasted patients. When regorafenib was administered to high-fat fed subjects,

the C_{max}, and AUC values of the active metabolites decreased compared with those in low-fat fed subjects. It is advisable not to give regorafenib after high-fat meals.

- If an adverse drug reaction is observed, the dose of regorafenib should be reduced, or administration should be interrupted, or discontinued according to the symptom and severity in consideration of the following criteria. If treatment is continued at a reduced dose, the dose of regorafenib should be reduced by 40 mg (1 tablet) in each step (to 80 mg, the lowest once-daily dose).

Hand and foot syndrome

Skin toxicity grade	Occurrence/dose adjustment and treatment
Grade 1	Administration of regorafenib is continued and supportive measures for symptomatic relief is immediately instituted.
Grade 2	1st occurrence: The dose of regorafenib is reduced by 40 mg (1 tablet) and supportive measures for symptomatic relief is immediately instituted. If no improvement occurs, treatment is interrupted for 7 days. If toxicity resolves to Grade 0-1, treatment is resumed. If no improvement occurs within 7 days, refer to the section below.
	No improvement within 7 days or 2nd or 3rd occurrence: Treatment is interrupted until toxicity resolves to Grade 0-1. When resuming treatment with regorafenib, the dose is reduced by 40 mg (1 tablet).
	4th occurrence: Administration of regorafenib is discontinued.
Grade 3	1st or 2nd occurrence: Supportive measures for symptomatic relief is immediately instituted and treatment with regorafenib is interrupted for at least 7 days until toxicity resolves to Grade 0-1. When resuming treatment with regorafenib, the dose is reduced by 40 mg (1 tablet).
	3rd occurrence: Administration of regorafenib is discontinued.

Liver function test abnormal

Severity of liver function test abnormal	Occurrence/dose adjustment and treatment
ALT (GPT) and/or AST (GOT) ≤5-fold the upper limit of normal (ULN)	Administration of regorafenib is continued and liver function test is performed frequently until transaminases return to < 3-fold ULN or baseline.
ALT (GPT) and/or AST (GOT) >5-fold ULN and ≤20-fold ULN	1st occurrence: Treatment with regorafenib is interrupted until transaminases return to <3-fold ULN or baseline. When resuming treatment, the dose of regorafenib is reduced by 40 mg (1 tablet) and liver function tests are frequently performed for at least 4 weeks.
	2nd occurrence: Administration of regorafenib is discontinued.
ALT (GPT) and/or AST (GOT) >20-fold ULN	Administration of regorafenib is discontinued.
ALT (GPT) and/or AST (GOT) >3-fold ULN with concurrent bilirubin >2-fold ULN	Administration of regorafenib is discontinued. Patients with Gilbert's syndrome who show elevated ALT (GPT) and/or AST (GOT) should be managed as per the above outlined criteria for ALT (GPT) and/or AST (GOT) regardless of the bilirubin level specified in this column.

Hypertension

Grade of hypertension	Dose adjustment and treatment
Grade 2 (asymptomatic)	Administration of regorafenib is continued, while antihypertensive therapy is started. If hypertension is not controlled with antihypertensive therapy, the dose of regorafenib is reduced by 40 mg (1 tablet).
Grade 2 (symptomatic)	Treatment with regorafenib is interrupted until symptoms resolve and blood pressure is under control, and then antihypertensive therapy is started. If hypertension is not controlled with antihypertensive therapy after resuming treatment, the dose of regorafenib is reduced by 40 mg (1 tablet).
Grade 3	Treatment with regorafenib is interrupted until symptoms resolve and blood pressure is under control, and then antihypertensive therapy is started. When resuming treatment with regorafenib, the dose is reduced by 40 mg (1 tablet). If hypertension is not controlled with antihypertensive therapy after resuming treatment, the dose of regorafenib is reduced further by 40 mg (1 tablet).
Grade 4	Administration of regorafenib is discontinued.

Other adverse reactions

When a Grade ≥3 adverse drug reaction is observed, administration of regorafenib should be interrupted until the toxicity resolves to Grade ≤2, or discontinuation of administration should be considered. When resuming treatment with regorafenib, the dose is reduced by 40 mg (1 tablet).

(5) Post-marketing investigations

The applicant plans 6-month post-marketing surveillance enrolling 1065 (target number of patients is 1200 in consideration of dropout) patients with incurable, unresectable, advanced/recurrent colorectal cancer for analysis in order to confirm the safety of regorafenib in the clinical settings. As the primary investigation parameters of this surveillance, hepatic function disorder, hypertension/hypertensive crisis, haemorrhage, and hand and foot syndrome, which frequently occurred in the clinical studies, will be set to search for factors related to their development.

As a result of its review in the "4.(iii).B.(7) Post-marketing investigations" section of the Review Report (1), PMDA concluded that the applicant should conduct post-marketing surveillance in order to obtain information on the safety of regorafenib in the clinical settings in Japan and provide the obtained surveillance results to medical practices. However, the applicant should re-consider the primary investigation parameters, because information about dose interruption, dose reduction and discontinuation as actions taken in clinical settings and onset timing of each event during the 6-month observation period are more useful than safety information in using regorafenib in routine clinical practices. Furthermore, the final number of patients to be enrolled in the surveillance should be determined based on the primary investigation parameters.

The above conclusion of PMDA was supported by the expert advisors at Expert Discussion. The following comments were raised from the expert advisors:

- A wide variety of adverse events may occur following treatment with regorafenib, and the applicant should consider increasing the target number of patients.
- The applicant should evaluate the safety of concomitant use of drugs that may pharmacokinetically interact with regorafenib.

In view of the comments from the Expert Discussion, PMDA has concluded that it is necessary to (1) set the primary investigation parameters for the purpose of investigating situations leading to dose interruption, dose reduction, or discontinuation of regorafenib and onset timings of the events in clinical settings and reconsider the target number of patients; and (2) set the additional investigation parameters so that the safety of concomitant use of drugs that may pharmacokinetically interact with regorafenib can be evaluated.

PMDA thus instructed the applicant to reconsider the surveillance plan based on the above discussion.

The applicant responded with the revised details as follows:
As the primary investigation parameters in the post-marketing surveillance, the applicant will set hepatic function disorder, hand and foot syndrome, and hypertension/hypertensive crisis which have been defined as the important identified risk for regorafenib and which are thought to frequently lead to dose interruption or dose reduction of regorafenib. The applicant sets the number of patients to be included in the analysis as 1186 patients (target number of patients is 1250 in consideration of dropout). This sample size is designed to detect an event at the incidence of 0.4% in at least 2 patients with the probability of 95% based on the fact that events of ALT increased and AST increased leading to dose reduction occurred at the lowest incidence of 0.4% (2 of 500 patients) among the primary investigation parameters leading to dose interruption or dose reduction. Furthermore, the applicant will investigate adverse events in concomitant use with drugs potentially affecting the PK of regorafenib.

The applicant plans to perform interim analysis based on the information of the questionnaires collected at 6 months after the market launch and to immediately provide the concerned analysis results to medical practices. However, if the questionnaires from <200 patients are only available at 6 months after the market launch, the applicant will not perform the interim analysis at this time point but will perform it as soon as those from at least 200 patients become available.

PMDA accepted the applicant's response.

(6) Risk Management Plan (RMP)
Taking account of its review in the "4.(iii).B.(3) Safety" and "4.(iii).B.(7) Post-marketing investigations" section of the Review Report (1), as well as the comments from the Expert Discussion, PMDA has concluded that the Risk Management Plan of regorafenib at present should be outlined as follows:

- Of safety investigation parameters, the "Important identified risks" include "hepatic function disorder," "thromboembolism," "hypertension/hypertensive crisis," "haemorrhage," "hand and foot syndrome," "Stevens-Johnson syndrome/toxic epidermal necrolysis/erythema multiforme," "gastrointestinal perforation or fistula," and "posterior reversible encephalopathy," and the "Important potential risks" include "wound-healing disturbance" and "interstitial lung disease."
- As additional pharmacovigilance activities, it is advisable to conduct early post-marketing phase vigilance and post-marketing surveillance.
- As additional risk-minimizing activities, it is advisable to provide information obtained from the early post-marketing phase vigilance and information for proper use of regorafenib to the physicians, pharmacists, and nurses through information materials for healthcare professionals.

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

PMDA thus instructed the applicant to consider the Risk Management Plan based on the above discussion, and the applicant responded that they would develop the plan with the above contents.

III. Overall Evaluation

As a result of the above review, PMDA has concluded that regorafenib may be approved for the following indications and dosage and administration, provided that appropriate cautions will be included in the package insert and information concerning the proper use of regorafenib will be provided appropriately after the market launch, and the proper use of regorafenib will be ensured under the supervision of physicians with sufficient knowledge and experience in cancer chemotherapy at medical institutions with adequate facilities for the treatment of emergencies. The re-examination period is 8 years, the drug substance and the drug product are both classified as powerful drugs, and the product is not classified as a biological product.

[Indication]
Incurable, unresectable, advanced/recurrent colorectal cancer

[Dosage and Administration]
The usual adult dosage is 160 mg of regorafenib orally administered once daily after a meal for 3 weeks followed by 1-week off therapy. The above regimen should be repeated in a 4-week cycle. The dose may be reduced according to the patient's condition.

[Warnings]
1. Regorafenib should be administered only to patients for whom regorafenib is indicated by physicians with sufficient knowledge and experience in cancer chemotherapy at medical institutions with adequate facilities for the treatment of emergencies. Prior to the treatment with regorafenib, the efficacy and risk should be sufficiently explained to patients or their family members, and administration should be started after obtaining consent.
2. Serious hepatic function disorder may occur and fatal outcomes due to hepatic failure have been reported. Before and during the administration of regorafenib, liver function tests should be periodically performed and patients should be closely monitored.

[Contraindications]
1. Patients with a history of hypersensitivity to any ingredients of regorafenib
2. Pregnant women and women who may possibly be pregnant

[Precautions for Indications]
1. The efficacy and safety of regorafenib as the first- or second-line therapy have not been established.
2. Eligible patients should be selected with full knowledge of information in the “Clinical Studies” section, such as the history of previous treatments of patients included in clinical studies and sufficient understanding of the efficacy and safety of regorafenib.
3. The efficacy and safety of regorafenib have not been established for use in adjuvant chemotherapy.

[Precautions for Dosage and Administration]
1. The efficacy and safety of concomitant use of regorafenib with the other antineoplastic drugs have not been established.
2. When regorafenib was administered to fasted subjects, the C_{max} and AUC values of the unchanged regorafenib decreased compared with those in fed subjects. Regorafenib should not be given to fasted patients. When regorafenib was administered to high-fat fed subjects, the C_{max}, and AUC values of the active metabolite decreased compared with those in low-fat fed subjects. It is advisable not to give regorafenib after high-fat meals.
3. If an adverse drug reaction is observed, the dose of regorafenib should be reduced or administration should be interrupted, or discontinued according to the symptom and severity in consideration of the following criteria. If treatment is continued at a reduced dose, the dose of regorafenib should be reduced by 40 mg (1 tablet) in each step (to 80 mg,

the lowest once-daily dose).

Hand and foot syndrome

Skin toxicity grade	Occurrence/dose adjustment and treatment
Grade 1	Administration of regorafenib is continued and supportive measures for symptomatic relief is immediately instituted.
Grade 2	1st occurrence: The dose of regorafenib is reduced by 40 mg (1 tablet) and supportive measures for symptomatic relief is immediately instituted. If no improvement occurs, treatment is interrupted for 7 days. If toxicity resolves to Grade 0-1, treatment is resumed. If no improvement occurs within 7 days, refer to the section below.
	No improvement within 7 days or 2nd or 3rd occurrence: Treatment is interrupted until toxicity resolves to Grade 0-1. When resuming treatment with regorafenib, the dose is reduced by 40 mg (1 tablet).
	4th occurrence: Administration of regorafenib is discontinued.
Grade 3	1st or 2nd occurrence: Supportive measures for symptomatic relief is immediately instituted and treatment is interrupted for at least 7 days until toxicity resolves to Grade 0-1. When resuming treatment, the dose is reduced by 40 mg (1 tablet).
	3rd occurrence: Administration of regorafenib is discontinued.

Liver function test abnormal

Severity of liver function test abnormal	Occurrence/dose adjustment and treatment
ALT (GPT) and/or AST (GOT) ≤5-fold the upper limit of normal (ULN)	Administration of regorafenib is continued and liver function test is performed frequently until transaminases return to < 3-fold ULN or baseline.
ALT (GPT) and/or AST (GOT) >5-fold ULN and ≤20-fold ULN	1st occurrence: Treatment with regorafenib is interrupted until transaminases return to <-3-fold ULN or baseline. When resuming treatment with regorafenib, the dose is reduced by 40 mg (1 tablet) and liver function tests are frequently performed for at least 4 weeks.
	2nd occurrence: Administration of regorafenib is discontinued. Note 1)
ALT (GPT) and/or AST (GOT) >20-fold ULN	Administration of regorafenib is discontinued. Note 1)
ALT (GPT) and/or AST (GOT) >3-fold ULN with concurrent bilirubin > 2-fold ULN	Administration of regorafenib is discontinued. Note 1) Patients with Gilbert's syndrome Note 2) who show elevated ALT (GPT) and/or AST (GOT) should be managed as per the above outlined criteria for ALT (GPT) and/or AST (GOT) regardless of the bilirubin level specified in this column.

Note 1) Perform liver function tests frequently until the values return to a normal range or baseline.

Note 2) Because this drug inhibits UGT1A1 glucuronidation, in patients with Gilbert's syndrome, indirect bilirubin may be increased.

Hypertension

Grade of hypertension	Dose adjustment and treatment
Grade 2 (asymptomatic)	Administration of regorafenib is continued, while antihypertensive therapy is started. If hypertension is not controlled with antihypertensive therapy, the dose of regorafenib is reduced by 40 mg (1 tablet). Note 3)
Grade 2 (symptomatic)	Treatment with regorafenib is interrupted until symptoms resolve and blood pressure is under control, and then antihypertensive therapy is started. If hypertension is not controlled with antihypertensive therapy after resuming treatment, the dose of regorafenib is reduced by 40 mg (1 tablet). Note 3)
Grade 3	Treatment with regorafenib is interrupted until symptoms resolve and blood pressure is under control, and then antihypertensive therapy is started. When resuming treatment with regorafenib, the dose is reduced by 40 mg (1 tablet). Note 3) If hypertension is not controlled with antihypertensive therapy after resuming treatment, the dose of regorafenib is reduced further by 40 mg (1 tablet).
Grade 4	Administration of regorafenib is discontinued.

Note 3) Blood pressure control criterion, blood pressure diastolic at 100 mmHg

Other adverse reactions

When a Grade ≥3 adverse drug reaction is observed, administration of regorafenib should be interrupted until the toxicity resolves to Grade ≤2, or discontinuation of administration should be considered. When resuming treatment with regorafenib, the dose is reduced by 40 mg (1 tablet).

Grades are in accordance with the Common Terminology Criteria for Adverse Events (CTCAE) v3.0.