Review Report

May 22, 2017

Pharmaceuticals and Medical Devices Agency

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

Brand Name	Stivarga Tablets 40 mg
Non-proprietary Name	Regorafenib Hydrate (JAN*)
Applicant	Bayer Yakuhin, Ltd.
Date of Application	October 31, 2016
Dosage Form/Strength	Each tablet contains 40 mg of regorafenib (41.49 mg as regorafenib hydrate).
Application Classification	Prescription drug (4) Drugs with new indication(s)
Items Warranting Special Mention	Priority Review (PSEHB/PED Notification No. 0117-2 dated January 17, 2017)
Reviewing Office	Office of New Drug V

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has efficacy in the treatment of unresectable hepatocellular carcinoma progressed after cancer chemotherapy and that the product has acceptable safety in view of its benefits.

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

Indications

Unresectable, advanced/recurrent colorectal cancer; gastrointestinal stromal tumor progressed after cancer chemotherapy; and unresectable hepatocellular carcinoma progressed after cancer chemotherapy

(Underline denotes additions.)

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.

Condition of Approval

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

**Japanese Accepted Name (modified INN)*

Attachment

Review Report (1)

April 12, 2017

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

Product Submitted for Approval

Brand Name	Stivarga Tablets 40 mg
Non-proprietary Name	Regorafenib Hydrate
Applicant	Bayer Yakuhin, Ltd.
Date of Application	October 31, 2016
Dosage Form/Strength	Each tablet contains 40 mg of regorafenib (41.49 mg as regorafenib hydrate).
Proposed Indication(s)	Unresectable, advanced/recurrent colorectal cancer; gastrointestinal stromal tumor progressed after cancer chemotherapy; and unresectable hepatocellular carcinoma progressed after cancer chemotherapy (Underline denotes additions.)
Proposed 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.

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List of Abbreviations

AFP	alpha-fetoprotein
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BCRP	breast cancer resistance protein
BMI	body mass index
BRAF	v-raf murine sarcoma viral oncogene homolog B1
C_{avg}	average plasma concentration
CI	confidence interval
CR	complete response
CrCL	creatinine clearance
ECOG	Eastern Cooperative Oncology Group
eGFR	estimated glomerular filtration rate
FGFR	fibroblast growth factor receptor
GGT	γ-glutamyltransferase
GIST	gastrointestinal stromal tumor
IDMC	independent data monitoring committee
ITT	intention-to-treat
Japanese clinical practice guidelines	Clinical Practice Guidelines for Hepatocellular Carcinoma 2013 ed. by the Japan Society of Hepatology
KIT	stem cell growth factor receptor
MedDRA	Medical Dictionary for Regulatory Activities
NCCN guidelines	National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Hepatobiliary Cancers
NCI-ODWG	National Cancer Institute Organ Dysfunction Working Group
NCI-PDQ	National Cancer Institute Physician Data Query
neomycin	neomycin sulfate
OS	overall survival
partial change application	application for partial change approval
PDGFR	platelet-derived growth factor receptor
P-gp	P-glycoprotein
PK	pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency
PPK	population pharmacokinetics
PR	partial response
PS	performance status
PT	preferred term
QD	quaque die
RECIST	Response Evaluation Criteria in Solid Tumors
regorafenib	regorafenib hydrate
regorafenib/digoxin	concomitant use of regorafenib with digoxin
regorafenib/neomycin	concomitant use of regorafenib with neomycin
regorafenib/rosuvastatin	concomitant use of regorafenib with rosuvastatin
RET	rearranged during transfection
rosuvastatin	rosuvastatin calcium
SOC	system organ class
sorafenib	sorafenib tosilate
TIE2	angiopoietin receptor
TTP	time to progression
VEGFR	vascular endothelial growth factor receptor

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

1.1 Overview of the product submitted for approval

Regorafenib hydrate (referred to as regorafenib) is a low molecular weight compound discovered by Bayer HealthCare, Germany. Regorafenib inhibits 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), rearranged during transfection (RET), and v-raf murine sarcoma viral oncogene homolog B1 (BRAF). Regorafenib is expected to suppress tumor growth by inhibiting signaling mediated by the actions of these kinases.

In Japan, regorafenib was approved for the indication of "unresectable, advanced/recurrent colorectal cancer" in March 2013, and for "gastrointestinal stromal tumor progressed after cancer chemotherapy" in August 2013.

1.2 Development history etc.

The clinical development of regorafenib for patients with hepatocellular carcinoma began with a foreign phase II study (Study 14596) in patients with unresectable hepatocellular carcinoma progressed after the treatment with sorafenib tosilate (sorafenib) that was conducted by Bayer HealthCare, Germany, in September 2009. A phase III study (Study 15982) began in May 2013 in patients with unresectable hepatocellular carcinoma progressed after the sorafenib therapy.

In the US and EU, an application for regorafenib was filed in October and November 2016, respectively, using data from Studies 14596 and 15982 as the pivotal study, respectively. Both are currently under review.

As of February 2017, regorafenib has not been approved for indication of hepatocellular carcinoma in any country or region.

In Japan, patient enrollment in Study 15982 was started in [redacted] 201[redacted].

The applicant has recently submitted a partial change application for regorafenib seeking approval of an additional indication, i.e., hepatocellular carcinoma, using data from Study 15982 as the pivotal study.

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

Because the current application relates to the new indication, data relating to quality were not submitted.

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

Because the current application relates to the new indication and non-clinical pharmacology had been evaluated for the approval of new drug application, no new study data on non-clinical pharmacology were submitted.

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

Because the current application relates to the new indication and non-clinical pharmacokinetics had been evaluated for the approval of the new drug application, no new study data on non-clinical pharmacokinetics were submitted.

5. Toxicity and Outline of the Review Conducted by PMDA

Because the current application relates to the new indication, toxicity data were omitted.

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

Because the current application relates to the new indication, and the biopharmaceutic studies and associated analytical methods had been evaluated for the approval of the new drug application, no new study data on biopharmaceutic studies and associated analytical methods were submitted.

6.1 Clinical pharmacology

The pharmacokinetics (PK) of regorafenib and its metabolites (M-2 [pyridine *N*-oxide form] and M-5 [pyridine *N*-oxideamide form]) in healthy adult subjects and patients with cancer were evaluated following the administration of regorafenib alone or in combination with neomycin sulfate (neomycin) (regorafenib/neomycin).[1)] In addition, the effect of regorafenib on the PK of digoxin and rosuvastatin calcium (rosuvastatin) was evaluated.

6.1.1 Drug interactions

6.1.1.1 Drug interaction study with digoxin or rosuvastatin (CTD 5.3.3.4.2, Study 16674 [April 2014 to ongoing (data cut-off, April 27, 2015)])

An open-label, uncontrolled study was conducted in 42 patients with advanced solid tumors (30 patients included in the PK analysis) to evaluate the effect of regorafenib on the PK of digoxin (P-glycoprotein [P-gp] substrate) and rosuvastatin (breast cancer resistance protein [BCRP] substrate). Subjects received oral regorafenib 160 mg quaque die (QD) on Days 1 to 21 and a single dose of oral digoxin 0.5 mg or rosuvastatin 5 mg 7 days before the start of regorafenib and on Day15.[2)]

The geometric mean ratios of C_{max} and AUC_{24h} [90% confidence interval (CI)] of the combination of regorafenib with digoxin [regorafenib/digoxin] to digoxin alone were 1.12 [0.963, 1.31] and 1.05 [0.968, 1.15], respectively. The geometric mean ratios of C_{max} and AUC_{24h} [90% CI] of the combination of regorafenib with rosuvastatin [regorafenib/rosuvastatin] to rosuvastatin alone were 4.55 [3.45, 6.01] and 3.82 [3.18, 4.60], respectively.

As above, the concomitant use of regorafenib had no clear effect on the exposure to P-gp substrate but increased the exposure to BCRP substrate. The applicant explained that a caution should be given about the concomitant use of regorafenib with a BCRP substrate.

6.1.1.2 Drug interaction study with neomycin (CTD 5.3.3.4.1, Study 16675 [December 2013 to April 2014])

An open-label, uncontrolled study was conducted in 27 healthy adult subjects (27 subjects included in the PK analysis) to evaluate the effect of neomycin on the PK of regorafenib and its metabolites (M-2 and M-5). In Period 1, subjects received a single dose of oral regorafenib 160 mg. In Period 2, subjects received a single dose of oral regorafenib 160 mg and oral neomycin 1000 mg thrice daily from 4 days before the day of regorafenib dosing. A ≥14-day washout period was required between Periods 1 and 2.

The geometric mean ratios of C_{max} and AUC_{inf} [90% CI] of regorafenib/neomycin to regorafenib alone were 0.962 [0.836, 1.11] and 0.943 [0.857, 1.04], respectively, those of M-2 were 0.184 [0.153, 0.222] and 0.237 [0.198, 0.283], respectively, and those of M-5 were 0.196 [0.166, 0.230] and 0.141 [0.112, 0.177], respectively.

The applicant's explanation about the above study data:
M-2 undergoes enterohepatic circulation, and M-5 is formed from M-2 (see "Review Report for Stivarga Tablets 40 mg, dated March 4, 2013"). Thus the decrease in plasma exposure to M-2 and M-5 observed is presumably due to a decreased reabsorption of M-2 through an inhibition of M-2 glucuronide deconjugation caused by the effect of neomycin on the gastrointestinal flora. The impact of the decreased plasma exposure to M-2 and M-5 on the efficacy of regorafenib is considered limited because the tumor growth inhibitory effect of regorafenib is primarily mediated by unchanged regorafenib (see "initial application dossier for Stivarga Tablets 40 mg"), and given the plasma unbound fractions of regorafenib (0.39%-0.58%), M-2 (0.185%-0.190%), and M-5 (0.05%) (see "Review Report for Stivarga Tablets 40 mg, dated March 4, 2013").

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1) Fradiomycin sulfate (approved in Japan only for a topical formulation).

2) Patients for whom PK blood sampling could not be appropriately performed on Day 15 or 16 of Cycle 1 (each cycle consisting of 28 days) received digoxin or rosuvastatin on Day 15 of Cycle 2 and underwent an additional PK blood sampling.

6.1.2 Foreign phase I study to evaluate the effect of severe renal impairment on the PK of regorafenib and its metabolites (CTD 5.3.3.3.1, Study 16653 [June 2013 to July 2015])

The data from a foreign phase I study (Study 11650) submitted for the initial application of regorafenib indicated no impact of mild and moderate renal impairment on the PK of regorafenib or its metabolites (M-2 and M-5) (see "Review Report for Stivarga Tablets 40 mg, dated March 4, 2013"). For the current application, the effect of severe renal impairment on the PK of regorafenib and its metabolites (M-2 and M-5) was investigated.

An open-label, uncontrolled study was conducted in (a) 18 patients with advanced solid tumors who have normal renal function or mild renal impairment and (b) 6 patients with advanced solid tumors who have severe renal impairment (all of the 24 patients included in PK analysis) to evaluate the effect of severe renal impairment on the PK of regorafenib and its metabolites (M-2 and M-5). In Period 1, subjects received a single dose of oral regorafenib 160 mg. In Period 2, subjects received oral regorafenib 160 mg QD for 3 weeks followed by a 1-week washout period.[3)] The plasma concentrations of regorafenib and its metabolites (M-2 and M-5) were determined (Table 1). A ≥5-day washout period was required between Periods 1 and 2.

After a single dose or multiple doses (on Day 21 in Period 2), no clear differences were observed in the exposure (C_{max} and AUC_{last}) to regorafenib between patients with normal renal function or mild renal impairment and patients with severe renal impairment, while the exposure (C_{max} and AUC_{last}) to M-2 and M-5 decreased in patients with severe renal impairment. The applicant explained that the decreased exposure to M-2 and M-5 in patients with severe renal impairment is not a significant change given large inter-individual variability.

Based on the above, the applicant explained that severe renal impairment is not likely to have a clinically significant impact on the PK of regorafenib or its metabolites (M-2 and M-5).

Table 1. PK parameters of regorafenib and its metabolites (M-2 and M-5) by severity of renal impairment

Date	Severity of renal impairment[*1]	Analyte	n	C_{max} (mg/L)	t_{max}[*2] (h)	AUC_{last} (mg·h/L)	$t_{1/2}$ (h)
Day 1 in Period 1	Normal or mild	regorafenib	18	2.45 (47.0)	4.03 (1.00, 24.0)	67.2 (45.5)	28.7 (23.0)[*3]
		M-2	18	1.01 (66.7)	4.03 (1.00, 24.0)	27.8 (80.4)	26.2 (25.7)[*4]
		M-5	18	0.0877 (125)	47.8 (6.00, 96.1)	5.25 (145)	-
	Severe	regorafenib	6	2.00 (69.7)	3.04 (1.00, 23.8)	76.6 (50.3)	27.9 (32.0)[*5]
		M-2	6	0.525 (69.6)	6.04 (1.98, 23.8)	19.0 (58.7)	25.5 (24.0)[*6]
		M-5	6	0.0341 (67.0)	48.9 (24.1, 95.8)	2.34 (79.8)	-
Day 21 in Period 2	Normal or mild	regorafenib	13	3.52 (54.9)	3.97 (0, 23.8)	133 (55.1)	-
		M-2	13	3.52 (58.8)	4.12 (0, 23.9)	136 (64.9)	-
		M-5	13	3.25 (133)	0 (0, 24.0)	183 (128)	-
	Severe	regorafenib	4	2.87 (62.2)	4.25 (0, 10.0)	111 (54.8)	-
		M-2	4	2.29 (257)	4.00 (0, 10.0)	92.3 (280)	-
		M-5	4	2.23 (659)	0 (0, 8.00)	134 (459)	-

Geometric mean (coefficient of variation %); -, Not calculated, [*1] Subjects with creatinine clearance (CrCL) of ≥60 mL/min were considered to have normal renal function or mild renal impairment. Subjects with CrCL of 15 to 29 mL/min were considered to have severe renal impairment, [*2] Median (range), *3 n = 6; [*4] n = 13, [*5] n = 3, [*6] n = 4.

6.1.3 PPK analysis

A population pharmacokinetic (PPK) model was established by using a nonlinear mixed-effect model (NONMEM software version 7.2.0) based on the PK data (902 subjects, 27,194 measurement points) of regorafenib and its metabolites (M-2 and M-5) obtained from a total of 14 studies consisting of a Japanese phase I study (Study 13172), foreign phase I studies (Studies 11650, 11651, 12434, 12435, 12437, 14656, 14814, 14996, and 15524), foreign phase II studies (Studies 11726 and 14596), a foreign phase III study (Study 14387) (see "Review Report for Stivarga Tablets 40 mg, dated March 4, 2013"), and a global phase III study (Study 14874) (see "Review Report for Stivarga Tablets 40 mg, dated July 9, 2013"). Then, a PPK analysis was conducted based on pooled PK data (339 patients, 3210 measurement points) from a foreign phase III study (Study 15808) in patients with colorectal cancer and

3) Patients from whom PK blood sample was not collected appropriately in Cycle 1 (each cycle consisting of 28 days) underwent an additional PK blood sampling etc. in Cycle 2.

a global phase III study (Study 15982) in patients with hepatocellular carcinoma. The PK profile of regorafenib was evaluated by a 2-compartment model with first-order absorption, the PK profile of M-2 was evaluated by a 2-compartment model with regorafenib concentration-dependent formation of M-2, and the PK profile of M-5 was evaluated by a 2-compartment model with regorafenib and M-2 concentration-dependent formation of M-5.

In this analysis, the effect of following covariates were examined on the average plasma concentration (C_{avg}) of regorafenib and that of regorafenib and its metabolites (M-2 and M-5) in subjects receiving oral regorafenib 160 mg QD for 3 weeks: morbidity (patients with cancer versus healthy adult subjects), sex, body weight, body mass index (BMI), age, race, estimated glomerular filtration rate (eGFR), total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), liver function,[4)] albumin, total protein, hematocrit, and hemoglobin. Morbidity (patients with cancer versus healthy adult subjects), sex, BMI, age, albumin, and hemoglobin were identified as significant covariates on the C_{avg} of regorafenib, and morbidity (patients with cancer versus healthy adult subjects), sex, body weight, age, ALT, and hemoglobin were identified as significant covariates on the C_{avg} of regorafenib and its metabolites (M-2 and M-5). The applicant explained that the effects of these covariates on the PK of regorafenib and that of regorafenib and its metabolites (M-2 and M-5) were within the inter-individual variability in the C_{avg} of regorafenib (84.1%) and regorafenib and its metabolites (M-2 and M-5) (180%), respectively, and are thus considered limited.

6.1.4 Relationship between exposure and efficacy or safety

6.1.4.1 Relationship between exposure and efficacy

A relationship between the exposure to regorafenib[5)] (C_{avg} up to Cycle 1) and the overall survival (OS) or time to progression (TTP) was evaluated by multivariate Cox regression analysis using the data from a global phase III study (Study 15982). The results revealed no clear relationship between the C_{avg} up to Cycle 1 and the OS or TTP.

6.1.4.2 Relationship between exposure and safety

Based on the data from a global phase III study (Study 15982), a relationship between the safety (i.e., incidences of all adverse events and serious adverse events reported by subjects who received regorafenib) and the exposure to regorafenib or to plasma unbound regorafenib and its metabolites (M-2 and M-5)[5)] was evaluated by stratifying the exposure into 3 groups based on the C_{avg} up to Cycle 1 and that up to Cycle 2. The results revealed no clear relationship between the incidence of any types of adverse events and the exposure to regorafenib or to plasma unbound regorafenib and its metabolites (M-2 and M-5) as measured by the C_{avg} up to Cycle 1 or that up to Cycle 2.

6.R Outline of the review conducted by PMDA

Based on the submitted data, PMDA has concluded that the applicant's explanation about the PK of regorafenib and its metabolites (M-2 and M-5) is acceptable.

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

The applicant submitted efficacy and safety evaluation data, namely, the results from a total of 2 studies shown in Table 2, including 1 global phase III study and 2 foreign phase II studies. The applicant also submitted the results from a total of 4 studies shown in Table 2, including 3 foreign phase I studies and 1 foreign phase III study as reference data.

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4) Determined according to National Cancer Institute Organ Dysfunction Working Group (NCI-ODWG) liver function classification.

5) Estimated from the PPK analysis [see Section "6.1.3 PPK analysis"].

Table 2. List of clinical studies to evaluate efficacy and safety

Data category	Region	Study title	Phase	Study population	Number of subjects	Dosage regimen	Main endpoint
Evaluation	Global	Study 15982	III	Patients with unresectable hepatocellular carcinoma progressed after sorafenib therapy	573 (a) 379 (b) 194	In each 4-week treatment cycle, oral doses of (a) regorafenib 160 mg or (b) placebo were administered QD for 3 weeks followed by a 1-week washout period.	Efficacy Safety
	Foreign	Study 14596	II	Patients with unresectable hepatocellular carcinoma progressed after sorafenib therapy	56	In each 4-week treatment cycle, oral doses of regorafenib 160 mg were administered QD for 3 weeks followed by a 1-week washout period.	Efficacy Safety
Reference	Foreign	Study 16674	I	Patients with advanced solid tumors	42 (a) 23 (b) 19	Oral doses of regorafenib 160 mg were administered QD from Day 1 to Day 21 and a single oral dose of (a) digoxin 0.5 mg or (b) rosuvastatin 5 mg was administered 7 days before the start of regorafenib and on Day15.	Safety PK
		Study 16675	I	Healthy adults	27	Period 1: A single oral dose of regorafenib 160 mg was administered. Period 2: A single oral dose of regorafenib 160 mg was administered and thrice daily oral doses of neomycin 1000 mg were administered from 4 days before until the day of regorafenib dosing.	Safety PK
		Study 16653	I	Patients with advanced solid tumors who have normal renal function or renal impairment	24	Period 1: A single oral dose of regorafenib 1000 mg was administered. Period 2: Oral doses of regorafenib 160 mg were administered QD for 3 weeks followed by a 1-week washout period.	Safety PK
		Study 15808	III	Patients with metastatic colorectal cancer progressed after cancer chemotherapy	204 (a) 136 (b) 68	In each 4-week treatment cycle, oral doses of (a) regorafenib 160 mg or (b) placebo were administered QD for 3 weeks followed by a 1-week washout period.	Efficacy Safety

Each of the clinical studies is summarized below.

Major adverse events other than death observed in each clinical study are described in Section "7.3 Adverse events etc., observed in clinical studies," and PK-related study results are described in Section "6.1 Clinical pharmacology."

7.1 Evaluation data

7.1.1 Global study

7.1.1.1 Global phase III study (CTD 5.3.5.1.1, Study 15982 [May 2013 to February 2016])

A double-blind, randomized, controlled study was conducted in patients with unresectable hepatocellular carcinoma progressed after sorafenib therapy[6)] (target sample size, 560 subjects) to compare the efficacy and safety between regorafenib and placebo at 152 study sites in 21 countries and regions including Japan.

6) Patients who (a) are not eligible for local therapy, (b) are tolerant of sorafenib therapy, and (c) have liver function of Child-Pugh Class A were included.

In each 4-week treatment cycle, subjects received oral doses of regorafenib 160 mg or placebo QD for 3 weeks followed by a 1-week washout period. Treatment was continued until disease progression or any of the discontinuation criteria met.

All 573 subjects who were enrolled and randomized in the study (379 in the regorafenib group, 194 in the placebo group) were included in the intention-to-treat (ITT) population, which was used for the efficacy analysis. Of the ITT population, 567 subjects (374 in the regorafenib group, 193 in the placebo group) were included in the safety analysis, and 6 subjects (5 in the regorafenib group, 1 in the placebo group) were excluded because they did not receive the study drug.

The primary endpoint for this study was OS. A total of 2 interim analyses were planned. The first interim analysis was scheduled to be conducted when the cumulative total of events reached approximately 111 to assess futility using O'Brien-Fleming type beta spending function approach of Lan-DeMets. The second interim analysis was scheduled when the cumulative total of events reached approximately 259 to assess efficacy. O'Brien-Fleming type alpha spending function approach was used to adjust the type I error rate. However, because of the possibility that the number of events would reach 259 before enrolling the number of Chinese patients required for the marketing approval application in China, the second interim analysis was canceled to secure the number of subjects required for the application in China.

From the efficacy viewpoint, an interim analysis was performed to assess futility with a data cut-off date of November 16, 2014, which was when the cumulative total of events reached 133. Because the upper limit of the CI of the hazard ratio for regorafenib to placebo was <1.108, the independent data monitoring committee (IDMC) recommended to continue the study.

The final OS analysis was conducted with a data cut-off date of February 29, 2016. The data from the analysis and the Kaplan-Meier curve are shown in Table 3 and Figure 1, respectively, demonstrating the superiority of regorafenib over placebo.

Table 3. Final OS analysis data (ITT population; data cut-off date, February 29, 2016)

	Regorafenib	Placebo
Number of subjects	379	194
Number of deaths (%)	233 (61.5)	140 (72.2)
Median [95% CI] (months)	10.6 [9.1, 12.1]	7.8 [6.3, 8.8]
Hazard ratio [95% CI][*1]	0.627 [0.500, 0.785]	
P-value (one-sided)[*2]	<0.0001	

[*1] Stratified Cox regression analysis with region (Asia, non-Asia), Eastern Cooperative Oncology Group (ECOG) performance status (PS) (0, 1), alpha-fetoprotein (AFP) (<400 ng/mL, ≥400 ng/mL), extrahepatic lesions (with, without), and vascular invasion (with, without) as stratification factors; [*2] Stratified log-rank test with region (Asia, non-Asia), ECOG PS (0, 1), AFP (<400 ng/mL, ≥400 ng/mL), extrahepatic lesions (with, without), and vascular invasion (with, without) as stratification factors, significance level (one-sided) of 0.025.

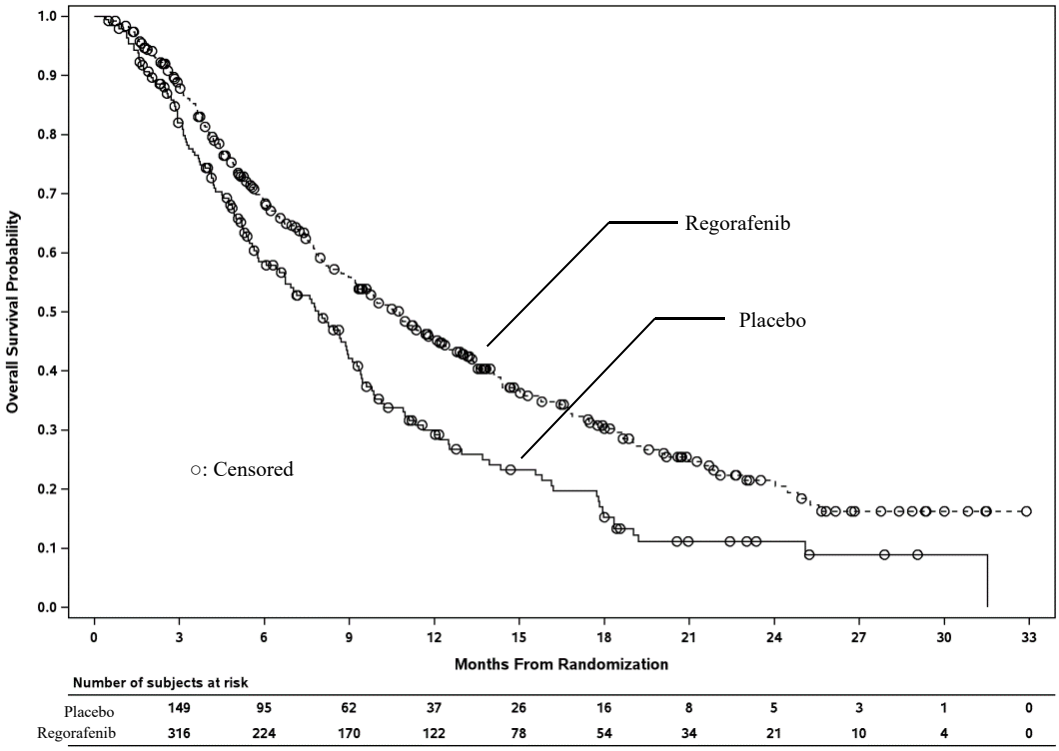

Figure 1. Kaplan-Meier OS curves at final analysis (ITT population; data cut-off date, February 29, 2016)

The safety evaluation revealed deaths of 50 of 374 subjects (13.4%) in the regorafenib group and 38 of 193 subjects (19.7%) in the placebo group during the treatment period or within 30 days after the last dose of the study drug. The causes of deaths other than disease progression (7 subjects in the regorafenib group, 11 subjects in the placebo group) included general physical health deterioration in 17 subjects, hepatic failure, ascites, dyspnoea, and shock haemorrhagic in 2 subjects each, and myocardial infarction, duodenal perforation, death, acute hepatic failure, hepatorenal syndrome, lung infection, peritonitis bacterial, pneumonia, sepsis, septic shock, craniocerebral injury, blood pressure decreased, haemorrhage intracranial, hepatic encephalopathy, meningorrhagia, bronchial obstruction, respiratory failure, and hypovolaemic shock in 1 subject each in the regorafenib group; and general physical health deterioration in 9 subjects, hepatic failure in 5 subjects, respiratory failure, upper gastrointestinal haemorrhage, and hepatic haemorrhage in 2 subjects each, and cardiac arrest, ascites/encephalopathy, oesophageal varices haemorrhage, multiple organ dysfunction syndrome, hepatorenal syndrome, tumour haemorrhage, and hepatic encephalopathy in 1 subject each in the placebo group. A causal relationship to the study drug could not be ruled out for myocardial infarction, duodenal perforation, death, general physical health deterioration, hepatic encephalopathy, meningorrhagia, and shock haemorrhagic in 1 subject each in the regorafenib group and hepatic failure in 2 subjects in the placebo group.

7.1.2 Foreign clinical study

7.1.2.1 Foreign phase II study (CTD 5.3.5.2.1, Study 14596 [September 2009 to March 2013])

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

In each 4-week treatment cycle, subjects received oral regorafenib 160 mg QD for 3 weeks followed by a 1-week washout period. Treatment was continued until disease progression or the discontinuation criteria met.

Of 56 enrolled in the study, 36 subjects who received regorafenib were included in both efficacy and safety analyses.

The safety analysis revealed that 8 of 36 subjects (22.2%) died during the treatment period or within 30 days after the last dose of the study drug. The causes of death other than disease progression (4 subjects) included cachexia, cerebral haemorrhage, haemorrhage intracranial, and haematoma in 1 subject each. A causal relationship to the study drug could not be ruled out for haematoma in 1 subject.

7.2 Reference data

7.2.1 Clinical pharmacology

The applicant submitted data from the following studies as clinical pharmacology data [see Section "6.1 Clinical pharmacology"]. In the following 3 studies in healthy adults and patients with advanced solid tumors, 4 of 42 subjects (9.5%) in Study 16674 died during the treatment period or within 30 days after the last dose of the study drug. The causes of death included general physical health deterioration, cancer pain, cardiac arrest, and lung infection in 1 subject each. A causal relationship to the study drug was ruled out for all events.

7.2.1.1 Foreign phase I study (CTD 5.3.3.4.2, Study 16674 [Ongoing since April 2014 (data cut-off, April 27, 2015)])

7.2.1.2 Foreign phase I study (CTD 5.3.3.4.1, Study 16675 [December 2013 to April 2014])

7.2.1.3 Foreign phase I study (CTD 5.3.3.3.1, Study 16653 [June 2013 to July 2015])

7.2.2 Foreign clinical study

7.2.2.1 Foreign phase III study (CTD 5.3.5.4.1, Study 15808 [April 2012 to November 2013])

A double-blind, randomized, controlled study was conducted in patients with metastatic colorectal cancer progressed after cancer chemotherapy (target sample size, 200 subjects) at 25 study sites to compare the efficacy and safety between regorafenib and placebo.

In each 4-week treatment cycle, subjects received oral regorafenib 160 mg or placebo QD for 3 weeks followed by a 1-week washout period. Treatment was continued until disease progression or the discontinuation criteria met.

All 204 subjects enrolled and randomized in the study (136 in the regorafenib group, 68 in the placebo group) received the study drug and were included in the safety analysis.

The safety analysis revealed deaths of 12 of 136 subjects (8.8%) in the regorafenib group and 7 of 68 subjects (10.3%) in the placebo group during the treatment period or within 30 days after the last dose of the study drug. The causes of deaths other than disease progression (8 subjects in the regorafenib group, 6 subjects in the placebo group) included cardiac arrest, multiple organ dysfunction syndrome, death, and lung infection in 1 subject each in the regorafenib group. A causal relationship to the study drug could not be ruled out for cardiac arrest and death in 1 subject each in the regorafenib group.

7.R Outline of the review conducted by PMDA

7.R.1 Data for review

Recognizing the importance of the global phase III study in patients with unresectable hepatocellular carcinoma progressed after cancer chemotherapy (Study 15982) for the evaluation of the efficacy and safety of regorafenib, PMDA decided to conduct the review with a focus on Study 15982. The efficacy in Japanese patients was to be reviewed in terms of consistency between the entire and Japanese populations in Study 15982 based on "Basic Principles on Global Clinical Trials" (PFSB/ELD Notification No.0928010 dated September 28, 2007) and "Basic Principles on Global Clinical Trials (Reference Cases)" (Administrative Notice dated September 5, 2012), etc. However, taking into account the proportion of Japanese patients, PMDA decided to review the data based not only on the primary but also on the secondary endpoint data.

7.R.2 Efficacy

As a result of the following review, PMDA has concluded that regorafenib is effective in patients with unresectable hepatocellular carcinoma progressed after cancer chemotherapy.

7.R.2.1 Control group, efficacy endpoints, and evaluation results

The applicant's rationale for the selection of the control group and the primary endpoint in Study 15982: Placebo was used as control because of no established standard therapy available for the intended patient population for Study 15982 at the time of planning of the study.

OS was selected as the primary endpoint for Study 15982 because the treatment for patients with unresectable hepatocellular carcinoma progressed after cancer chemotherapy is aimed to prolong survival.

PMDA's view:
PMDA accepted the applicant's explanation about the selection of the control group and primary endpoint of Study 15982.

The efficacy of regorafenib was demonstrated in the intended patient population of Study 15982 based on the superiority of regorafenib over placebo in OS demonstrated in the study [see Section "7.1.1.1 Global phase III study"].

7.R.2.2 Efficacy in Japanese patients

The data and the Kaplan-Meier curve obtained from the final OS analysis conducted on the Japanese population in Study 15982 are shown in Table 4 and Figure 2, respectively.

Table 4. Final OS analysis data on Japanese population (ITT population; data cut-off date, February 29, 2016)

	Regorafenib	Placebo
Number of subjects	30	10
Number of deaths (%)	19 (63.3)	9 (90.0)
Median [95% CI] (months)	13.3 [9.1, 18.8]	12.4 [2.0, 18.1]
Hazard ratio [95% CI]*	0.90 [0.39, 2.08]	

* Unstratified Cox regression model

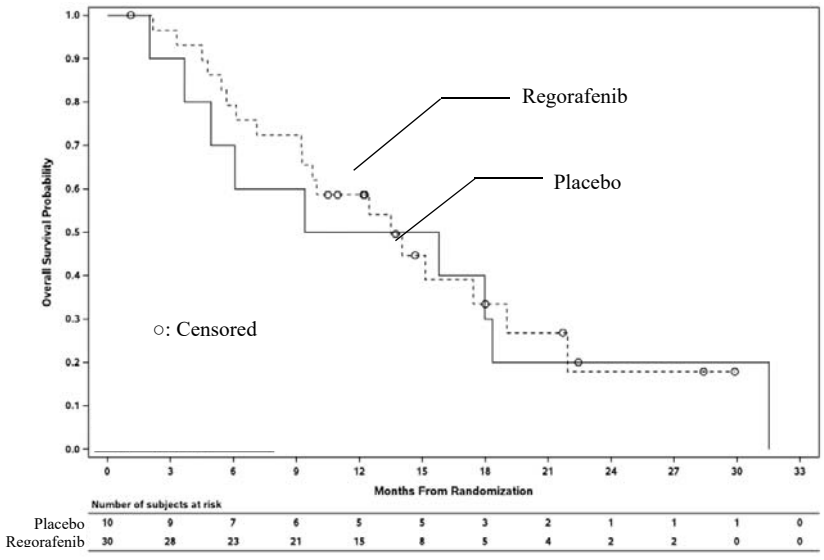

Figure 2. Kaplan-Meier OS curves at final analysis on Japanese population (ITT population; data cut-off date, February 29, 2016)

The secondary endpoint of Study 15982 was response (complete response [CR] + partial response [PR]) rate [95% CI] based on Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. In the entire study population, the response rate was 6.6% [4.3%, 9.6%] (25 of 379 subjects) in the regorafenib group and 2.6% [0.8%, 5.9%] (5 of 194 subjects) in the placebo group. The response rates in the Japanese population were 16.7% [5.6%, 34.7%] (5 of 30 subjects) in the regorafenib group and 0% (0 of 10 subjects) in the placebo group.

PMDA's view:
The small numbers of Japanese subjects and OS events in Study 15982 limited the evaluation of the efficacy of regorafenib in Japanese patients based on the OS data from the Japanese population. Nevertheless, the results in Japanese population did not tend to be clearly inconsistent with those in the entire population, and regorafenib is, therefore, expected to have efficacy in Japanese patients.

7.R.3 Safety [for adverse events, see Section "7.3 Adverse events etc. observed in clinical studies"]

The use of regorafenib for the approved indications requires attention to the adverse events (hand and foot syndrome, hepatic function disorder, hypertension [hypertensive crisis], haemorrhage, thromboembolism, gastrointestinal perforation or fistula, Stevens-Johnson syndrome/toxic epidermal necrolysis, posterior reversible encephalopathy, interstitial lung disease, and platelets decreased) that were identified in the previous review (see "Review Report for Stivarga Tablets 40 mg, dated March 4, 2013," "Review Report for Stivarga Tablets 40 mg, dated July 9, 2013," and for Stivarga Tablets package insert). As a result of the observations in the following subsections, PMDA has concluded that these are attention-required adverse events during the use of regorafenib in patients with unresectable hepatocellular carcinoma progressed after cancer chemotherapy as well.

As mentioned, regorafenib must be administered with attention to the particular adverse events. PMDA, however, concluded that regorafenib is tolerated by patients with hepatocellular carcinoma as long as their attending physicians with adequate knowledge and experience in cancer chemotherapy continue to follow appropriately, such as by monitoring and controlling of adverse events and dose reduction, interruption, or discontinuation.

7.R.3.1 Safety profile

The applicant's explanation about the safety profile of regorafenib:
Table 5 summarizes the safety of regorafenib in Study 15982 based on the data of the regorafenib group.

Table 5. Summary of safety profile (Study 15982)

	Number of subjects (%)	
	Regorafenib N = 374	Placebo N = 193
All adverse events	374 (100)	179 (92.7)
Grade ≥3 adverse events	298 (79.7)	113 (58.5)
Adverse events resulting in death	50 (13.4)	38 (19.7)
Serious adverse events	166 (44.4)	90 (46.6)
Adverse events leading to treatment discontinuation	93 (24.9)	37 (19.2)
Adverse events leading to dose interruption	218 (58.3)	56 (29.0)
Adverse events leading to dose reduction	179 (47.9)	15 (7.8)

Adverse events with a ≥10% higher incidence in the regorafenib group than in the placebo group were palmar-plantar erythrodysaesthesia syndrome (193 subjects [51.6%] in the regorafenib group, 13 subjects [6.7%] in the placebo group), diarrhoea (156 subjects [41.7%], 29 subjects [15.0%]), decreased appetite (116 subjects [31.0%], 27 subjects [14.0%]), hypertension (115 subjects [30.7%], 12 subjects [6.2%]), pyrexia (73 subjects [19.5%], 13 subjects [6.7%]), and dysphonia (67 subjects [17.9%], 3 subjects [1.6%]). Grade ≥3 adverse events with ≥2% higher incidence in the regorafenib group were hypertension (55 subjects [14.7%], 9 subjects [4.7%]), palmar-plantar erythrodysaesthesia syndrome (46 subjects [12.3%], 1 subject [0.5%]), hypophosphataemia (31 subjects [8.3%], 3 subjects [1.6%]), lipase increased (25 subjects [6.7%], 3 subjects [1.6%]), fatigue (23 subjects [6.1%], 7 subjects [3.6%]), asthenia (14 subjects [3.7%], 2 subjects [1.0%]), diarrhoea (12 subjects [3.2%], 0 subject), and platelet count decreased (10 subjects [2.7%], 0 subject). There were neither serious adverse events nor adverse events leading to treatment discontinuation with ≥2% higher incidence with regorafenib.

The applicant's explanation about the difference in the safety profile between patients with hepatocellular carcinoma and patients with unresectable, advanced/recurrent colorectal cancer or gastrointestinal stromal tumor (GIST) progressed after cancer chemotherapy (the approved indications):
Table 6 is a comparison of the incidences of adverse events occurring in subjects receiving regorafenib between Study 15982 and global phase III study in patients with unresectable, advanced/recurrent

colorectal cancer (Study 14387) and global phase III study in patients with GIST progressed after cancer chemotherapy (Study 14874). In Study 14874, subjects received oral regorafenib 160 mg QD for 3 weeks followed by a 1-week washout period in each 4-week treatment cycle.

Table 6. Summary of safety in patients with hepatocellular carcinoma, colorectal cancer, and GIST

	Number of subjects (%)		
	Study 15982	Study 14387	Study 14874
	Hepatocellular carcinoma N = 374	Colorectal cancer N = 500	GIST N = 132
All adverse events	374 (100)	498 (99.6)	132 (100)
Grade ≥3 adverse events	298 (79.7)	396 (79.2)	105 (79.5)
Adverse events resulting in death	50 (13.4)	67 (13.4)	8 (6.1)
Serious adverse events	166 (44.4)	226 (45.2)	42 (31.8)
Adverse events leading to treatment discontinuation	93 (24.9)	92 (18.4)	10 (7.6)
Adverse events leading to dose interruption	218 (58.3)	314 (62.8)	83 (62.9)
Adverse events leading to dose reduction	179 (47.9)	201 (40.2)	67 (50.8)

Adverse events of any grade with ≥5% higher incidence in the regorafenib group of Study 15982 than in the regorafenib group of Studies 14387 and 14874 were AST increased (96 subjects [25.7%] in Study 15982, 35 subjects [7.0%] in Study 14387, and 12 subjects [9.1%] in Study 14874), blood bilirubin increased (93 subjects [24.9%], 31 subjects [6.2%], and 11 subjects [8.3%]), ascites (58 subjects [15.5%], 23 subjects [4.6%], and 4 subjects [3.0%]), oedema peripheral (56 subjects [15.0%], 46 subjects [9.2%], and 7 subjects [5.3%]), ALT increased (54 subjects [14.4%], 27 subjects[5.4%], and 9 subjects [6.8%]), hypoalbuminaemia (52 subjects [13.9%], 16 subjects [3.2%], and 5 subjects [3.8%]), abdominal pain upper (48 subjects [12.8%], 39 subjects [7.8%], and 8 subjects [6.1%]), and γ-glutamyltransferase (GGT) increased (23 subjects [6.1%], 5 subjects[1.0%], and 1 subject [0.8%]). Grade ≥3 adverse events with ≥5% higher incidence in the regorafenib group of Study 15982 than in the regorafenib group of Studies 14387 and 14874 were AST increased (43 subjects [11.5%], 11 subjects [2.2%], and 3 subjects [2.3%]) and blood bilirubin increased (28 subjects [7.5%], 7 subjects [1.4%], and 2 subjects [1.5%]). There were neither adverse events resulting in death, serious adverse events, nor adverse events leading to treatment discontinuation with ≥5% higher incidence in the regorafenib group of Study 15982 than in the regorafenib group of Studies 14387 and 14874.

PMDA's view:
The majority of the adverse events reported more frequently in the regorafenib group than in the placebo group in Study 15982 are the known adverse events of regorafenib. While patients with hepatocellular carcinoma experienced adverse events more frequently than patients with cancer types for which the use of regorafenib has been approved, these events were considered attributable to their primary disease, and the incidences of serious adverse events did not tend to be high. Regorafenib is therefore tolerated by patients with hepatocellular carcinoma as long as their attending physicians with adequate knowledge and experience in cancer chemotherapy continue to follow appropriately, such as by monitoring and controlling of adverse events and dose reduction, interruption, or discontinuation.

7.R.3.2 Difference in safety between Japanese and non-Japanese subjects

The applicant's explanation about the difference in safety of regorafenib between Japanese and non-Japanese subjects:
Summary of safety in Japanese and non-Japanese subjects receiving regorafenib in Study 15982 is shown in Table 7.

Table 7. Summary of safety profile (Study 15982)

	Number of subjects (%)	
	Japanese N = 30	Non-Japanese N = 344
All adverse events	30 (100)	344 (100)
Grade ≥3 adverse events	27 (90.0)	271 (78.8)
Adverse events resulting in death	2 (6.7)	48 (14.0)
Serious adverse events	12 (40.0)	154 (44.8)
Adverse events leading to treatment discontinuation	6 (20.0)	87 (25.3)
Adverse events leading to dose interruption	26 (86.7)	192 (55.8)
Adverse events leading to dose reduction	21 (70.0)	158 (45.9)

Adverse events of any grade with ≥20% higher incidence in Japanese subjects than in non-Japanese subjects include palmar-plantar erythrodysaesthesia syndrome (23 Japanese [76.7%], 170 non-Japanese [49.4%]), decreased appetite (19 Japanese [63.3%], 96 non-Japanese [27.9%]), AST increased (16 Japanese [53.3%], 80 non-Japanese [23.3%]), malaise (15 Japanese [50.0%], 7 non-Japanese [2.0%]), dysphonia (14 Japanese [46.7%], 52 non-Japanese [15.1%]), pyrexia (13 Japanese [43.3%], 60 non-Japanese [17.4%]), hypoalbuminaemia (12 Japanese [40.0%], 40 non-Japanese [11.6%]), ALT increased (10 Japanese [33.3%], 44 non-Japanese [12.8%]), and hypophosphataemia (10 Japanese [33.3%], 26 non-Japanese [7.6%]). Grade ≥3 adverse events with ≥10% higher incidence in Japanese subjects than in non-Japanese subjects include hypophosphataemia (8 Japanese [26.7%], 23 non-Japanese [6.7%]), palmar-plantar erythrodysaesthesia syndrome (7 Japanese [23.3%], 39 non-Japanese [11.3%]), lipase increased (7 Japanese [23.3%], 18 non-Japanese [5.2%]), decreased appetite (5 Japanese [16.7%], 5 non-Japanese [1.5%]), and hypoalbuminaemia (4 Japanese [13.3%], 2 non-Japanese [0.6%]). There were neither adverse events resulting in death, serious adverse events, nor adverse events leading to treatment discontinuation with ≥10% higher incidence in Japanese subjects than in non-Japanese subjects.

PMDA's view:
Only a limited number of Japanese patients with hepatocellular carcinoma received regorafenib, and this precludes accurate comparison of the safety between Japanese and non-Japanese patients. However, regorafenib is tolerated by Japanese patients with hepatocellular carcinoma in light of the following observations:

- The adverse events occurring more frequently in Japanese subjects than in non-Japanese subjects were all known to be associated with regorafenib or may be attributed to the subjects' primary diseases.
- No clear differences were observed in the occurrence of adverse events resulting in death, serious adverse events, or adverse events leading to treatment discontinuation. These events were controllable by dose reduction or interruption.

The following subsection is a summary of PMDA's observations with a focus on hepatic function disorder that is a primary disease-related event.

7.R.3.3 Hepatic function disorder

The applicant's explanation about the incidence of hepatic function disorder associated with regorafenib:
Adverse events related to hepatic function disorder were tabulated by Medical Dictionary for Regulatory Activities (MedDRA) preferred term (PT) classified into the MedDRA SMQ (MedDRA ver. 19.0) of "Hepatic disorders (broad)."

The incidence of hepatic function disorder in Study 15982 is shown in Table 8.

Table 8. Incidence of hepatic function disorder with an incidence of ≥5% in either group (Study 15982)

PT (MedDRA ver.19.1)	Number of subjects (%)			
	Regorafenib N = 374		Placebo N = 193	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Hepatic function disorder	208 (55.6)	115 (30.7)	84 (43.5)	49 (25.4)
AST increased	96 (25.7)	43 (11.5)	38 (19.7)	22 (11.4)
Blood bilirubin increased	93 (24.9)	28 (7.5)	31 (16.1)	18 (9.3)
Ascites	58 (15.5)	18 (4.8)	31 (16.1)	12 (6.2)
ALT increased	54 (14.4)	11 (2.9)	21 (10.9)	5 (2.6)
Hypoalbuminaemia	52 (13.9)	6 (1.6)	14 (7.3)	1 (0.5)
GGT increased	23 (6.1)	13 (3.5)	13 (6.7)	6 (3.1)
Blood ALP increased	22 (5.9)	7 (1.9)	8 (4.1)	4 (2.1)

In Study 15982, hepatic function disorder resulted in death of 8 subjects (2.1%) in the regorafenib group (hepatic failure in 3 subjects, ascites in 2 subjects, and acute hepatic failure, hepatic encephalopathy, and hepatorenal syndrome in 1 subject each) and 9 subjects (4.7%) in the placebo group (hepatic failure in 5 subjects, and ascites, hepatic encephalopathy, hepatorenal syndrome, and oesophageal varices haemorrhage in 1 subject each). A causal relationship to the study drug could not be ruled out for hepatic encephalopathy in 1 subject in the regorafenib group and hepatic failure in 2 subjects in the placebo group. Serious hepatic function disorder occurred in 41 subjects (11.0%) in the regorafenib group (ascites and hepatic failure in 9 subjects each, hepatic encephalopathy in 7 subjects, oesophageal varices haemorrhage in 4 subjects, hepatic cirrhosis, hepatic function abnormal, jaundice cholestatic, and liver abscess in 2 subjects each, and acute hepatic failure, AST increased, blood bilirubin increased, hepatitis acute, hepatobiliary disease, hepatorenal syndrome, hypoalbuminaemia, and jaundice in 1 subject each [subjects may have had ≥2 events]) and 29 subjects (15.0%) in the placebo group (hepatic failure in 9 subjects, ascites in 6 subjects, hepatic encephalopathy and hepatic function abnormal in 3 subjects each, blood bilirubin increased, jaundice, and liver abscess in 2 subjects each, and hepatorenal syndrome, hyperbilirubinaemia, jaundice cholestatic, and oesophageal varices haemorrhage in 1 subject each [subjects may have had ≥2 events]). A causal relationship to the study drug could not be ruled out for hepatic encephalopathy in 3 subjects and AST increased, ascites, hepatic failure, and hepatic function abnormal in 1 subject each in the regorafenib group; and hepatic failure in 3 subjects and hepatic function abnormal in 1 subject in the placebo group.

PMDA's view:
In patients with hepatocellular carcinoma, the incidences of any grades and Grade ≥3 hepatic function disorder in the regorafenib group were higher than in patients with colorectal cancer or GIST [see Section "7.R.3.1 Safety profile"], and the incidences of these adverse events were high in the placebo group as well. This indicates that patients' primary disease may have affected the incidences of relevant events in patients with hepatocellular carcinoma. Nevertheless, given the fact that the incidences of hepatic function disorder of any grades were higher in the regorafenib group than in the placebo group in Study 15982, hepatic function disorder is an attention-requiring event in patients with hepatocellular carcinoma receiving regorafenib as well as in those with the other diseases.

Fatal hepatic encephalopathy, etc. occurred in Study 15982 and a causal relationship to regorafenib could not be ruled out for the events. However, these fatal events may be attributable to patients' primary disease, and the incidences of Grade ≥3 hepatic function disorders were similar between regorafenib and placebo. Given these observations, there is no need to call additional attention to these events at present. New information on hepatic function disorder in patients with hepatocellular carcinoma receiving regorafenib should be appropriately provided to healthcare professionals if such information becomes available in the future.

7.R.4 Clinical positioning and indication

The proposed indication of regorafenib was "unresectable hepatocellular carcinoma." The following statements were added 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.

- The efficacy and safety of regorafenib as the first-line therapy have not been established.

As a result of the review in Sections "7.R.2 Efficacy" and "7.R.3 Safety" and the subsections below, PMDA has concluded that the "Indications" section should state "unresectable hepatocellular carcinoma progressed after cancer chemotherapy" along with the following cautionary advice 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.

- The efficacy and safety of regorafenib have not been established in patients with hepatocellular carcinoma eligible for local therapies (e.g., percutaneous ethanol injection, radiofrequency ablation, microwave coagulation, hepatic arterial embolization/hepatic arterial chemoembolization, and radiotherapy).

- The efficacy and safety of regorafenib as the first-line therapy have not been established.

7.R.4.1 Intended patient populations

The National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Hepatobiliary Cancers (NCCN guidelines) (v.1.2017), an overseas clinical practice guidelines have the following description on the treatment of hepatocellular carcinoma with regorafenib. There was no description on treatment of hepatocellular carcinoma with regorafenib in Clinical Practice Guidelines for Hepatocellular Carcinoma 2013 edited by the Japan Society of Hepatology (Japanese clinical practice guidelines), the National Cancer Institute Physician Data Query (NCI-PDQ) (dated January 31, 2017), or major Japanese and foreign textbooks on clinical oncology.

- Regorafenib is recommended for patients with unresectable hepatocellular carcinoma with Child-Pugh Class A progressed after sorafenib therapy.

The applicant's explanation about clinical positioning of regorafenib and the proposed indication:
Regorafenib can be a new treatment option for the patient population eligible for Study 15982, which demonstrated the clinical benefit of regorafenib. Therefore, the "Clinical Studies" section of the package insert has a note that the subjects of Study 15982 have a history of well-tolerated sorafenib therapy. Also, the "Precautions for Indications" section gives the following cautions with proposed indication of "unresectable hepatocellular carcinoma."

- 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.
- The efficacy and safety of regorafenib as the first-line therapy have not been established.

According to the inclusion criteria for Study 15982, subjects must have liver function of Child-Pugh Class A [see Section "7.1.1.1 Global phase III study"]. PMDA asked the applicant to explain whether regorafenib is recommended for patients who are not classified as Child-Pugh Class A.

The applicant's response:
Study 15982 was designed to be conducted in patients classified as Child-Pugh Class A. However, 4 subjects enrolled in the study were found to be classified as Child-Pugh Class B during treatment with regorafenib. Although no particular safety concerns were found in the 4 patients, regorafenib is not recommended for patients with Child-Pugh Class B because of the paucity of the patients who underwent Study 15982.

PMDA's view:
The applicant's explanation is partly acceptable. However, Study 15982, which demonstrated the clinical benefit of regorafenib, was conducted in patients with unresectable hepatocellular carcinoma progressed after sorafenib therapy, who were ineligible for local therapy. Given this, the "Indication" section of the package insert should clearly state that regorafenib is meant for the treatment of unresectable hepatocellular carcinoma progressed after chemotherapy, with a note that the efficacy and safety of regorafenib have not been established in patients eligible for local therapy.

Accordingly, the "Indication" section of the package insert should define the indication as "unresectable hepatocellular carcinoma progressed after cancer chemotherapy," noting in the "Precautions for Indications" section that Study 15982 was conducted in (a) patients who were tolerant of first-line sorafenib and (b) patients with liver function of Child-Pugh Class A in the "Clinical Studies" section. Further, the following cautions should be given.

- 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.
- The efficacy and safety of regorafenib have not been established in patients with hepatocellular carcinoma eligible for local therapies (e.g., percutaneous ethanol injection, radio-frequency ablation, microwave coagulation, hepatic arterial embolization/hepatic arterial chemoembolization, and radiotherapy).
- The efficacy and safety of regorafenib as the first-line therapy have not been established.

7.R.5 Dosage and administration

The proposed dosage regimen of regorafenib is "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." The following cautions were proposed to be written 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.
- Regorafenib should not be given to fasted patients. It is advisable not to give regorafenib after high-fat meals.
- Criteria for dose reduction, dose interruption, and discontinuation at the onset of adverse drug reactions

As a result of the reviews in Sections "7.R.2 Efficacy" and "7.R.3 Safety" and the following subsections, PMDA has concluded that the proposed descriptions in the "Dosage and Administration" and "Precautions for Dosage and Administration" sections are acceptable.

7.R.5.1 Dosage and administration of regorafenib

The applicant's explanation about the rationale for the proposed dosage regimen of regorafenib in patients with unresectable hepatocellular carcinoma progressed after cancer chemotherapy:
Based on the data from foreign phase I studies (see "Review Report for Stivarga Tablets 40 mg, dated March 4, 2013"), etc., subjects in Study 15982 received oral regorafenib 160 mg QD for 3 weeks followed by a 1-week washout in each 4-week treatment cycle. The proposed dosage regimen of regorafenib was selected based on the dosage regimen used in Study 15982, which demonstrated the clinical benefit of regorafenib in patients with unresectable hepatocellular carcinoma progressed after cancer chemotherapy.

The criteria for dose reduction, interruption, and discontinuation of regorafenib in Study 15982 were more relaxed in terms of dose adjustment for patients with hepatic function disorder than those shown in the current package insert due to the characteristics of the primary disease taken into consideration. The criteria also allowed re-escalation of regorafenib after dose reduction. However, in Study 15982,

only a limited subjects underwent dose adjustment according to the relaxed criteria or dose re-escalation. Therefore, dose adjustment for patients with hepatocellular carcinoma should also be based on the criteria shown in the "Precautions for Dosage and Administration" section of the current package insert.

PMDA accepted the applicant's explanation.

7.R.6 Post-marketing investigations

The applicant's explanation about the post-marketing surveillance plan:
In order to evaluate the safety of regorafenib in its post-marketing clinical use, the applicant plans to conduct post-marketing surveillance for regorafenib in Japan as a part of a global observational study in patients with unresectable hepatocellular carcinoma receiving regorafenib.

The key survey item of the surveillance is hepatic function disorder. Hepatic function disorder was selected because Grade ≥3 hepatic function disorder occurred more frequently with regorafenib in Japanese population than in the entire population of Study 15982 and because the study was conducted in patients with hepatocellular carcinoma.

The planned sample size is 150 considering the incidence of hepatic function disorder in Japanese patients who received regorafenib in Study 15982.

The follow-up period is planned to be 2 years taking account of the limited data on the long-term safety of regorafenib. Available data do not indicate safety concerns such as a possible increase in adverse events in prolonged use of regorafenib. In Study 15982, however, the median treatment duration was 15.6 weeks and maximum treatment duration was 128 weeks.

PMDA's view:
Based on the discussions in Sections "7.R.3.1 Safety profile" and "7.R.3.3 Hepatic function disorder" as well as the following observation, there are no safety issues newly identified in the current application, and, at present, there is not much need for post-marketing surveillance in patients with unresectable hepatocellular carcinoma progressed after cancer chemotherapy to be conducted immediately after approval. Safety data collected through daily pharmacovigilance activities will suffice.

- To date, safety data from 1268 patients are available from the post-marketing surveillance in patients with unresectable, advanced/recurrent colorectal cancer and patients with GIST progressed after cancer chemotherapy, which are the approved indications of regorafenib. Therefore, a certain amount of safety data from Japanese patients who received regorafenib are available.

7.3 Adverse events etc., observed in clinical studies

Deaths in the clinical studies revealed by the safety evaluation data were described in Sections "7.1 Evaluation data" and "7.2 Reference data." Major adverse events other than deaths are shown below.

7.3.1 Global phase III study (Study 15982)

Adverse events occurred in 374 of 374 subjects (100%) in the regorafenib group and 179 of 193 subjects (92.7%) in the placebo group. A causal relationship to the study drug could not be ruled out for events in 347 of 374 subjects (92.8%) in the regorafenib group and 101 of 193 subjects (52.3%) in the placebo group. Adverse events with an incidence of ≥10% in either group are shown in Table 9.

Table 9. Adverse events with an incidence of ≥10% in either group

SOC PT (MedDRA ver.19.1)	Number of subjects (%)			
	Regorafenib N = 374		Placebo N = 193	
	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	374 (100)	298 (79.7)	179 (92.7)	113 (58.5)
Blood and lymphatic system disorders				
Anaemia	51 (13.6)	15 (4.0)	21 (10.9)	11 (5.7)
Gastrointestinal disorders				
Abdominal pain	80 (21.4)	10 (2.7)	30 (15.5)	5 (2.6)
Abdominal pain upper	48 (12.8)	3 (0.8)	17 (8.8)	2 (1.0)
Ascites	58 (15.5)	18 (4.8)	31 (16.1)	12 (6.2)
Constipation	65 (17.4)	1 (0.3)	21 (10.9)	1 (0.5)
Diarrhoea	156 (41.7)	12 (3.2)	29 (15.0)	0
Nausea	67 (17.9)	2 (0.5)	26 (13.5)	0
Vomiting	47 (12.6)	3 (0.8)	13 (6.7)	1 (0.5)
General disorders and administration site conditions				
Asthenia	57 (15.2)	14 (3.7)	18 (9.3)	2 (1.0)
Fatigue	108 (28.9)	23 (6.1)	48 (24.9)	7 (3.6)
General physical health deterioration	44 (11.8)	38 (10.2)	27 (14.0)	25 (13.0)
Oedema peripheral	56 (15.0)	0	26 (13.5)	0
Pyrexia	73 (19.5)	0	13 (6.7)	0
Investigations				
ALT increased	54 (14.4)	11 (2.9)	21 (10.9)	5 (2.6)
AST increased	96 (25.7)	43 (11.5)	38 (19.7)	22 (11.4)
Blood bilirubin increased	93 (24.9)	28 (7.5)	31 (16.1)	18 (9.3)
Weight decreased	52 (13.9)	7 (1.9)	8 (4.1)	0
Metabolism and nutrition disorders				
Decreased appetite	116 (31.0)	10 (2.7)	27 (14.0)	3 (1.6)
Hypoalbuminaemia	52 (13.9)	6 (1.6)	14 (7.3)	1 (0.5)
Musculoskeletal and connective tissue disorders				
Back pain	45 (12.0)	8 (2.1)	17 (8.8)	2 (1.0)
Muscle spasms	38 (10.2)	0	4 (2.1)	0
Respiratory, thoracic and mediastinal disorders				
Cough	41 (11.0)	1 (0.3)	13 (6.7)	0
Dysphonia	67 (17.9)	0	3 (1.6)	0
Skin and subcutaneous tissue disorders				
Palmar-plantar erythrodysaesthesia syndrome	193 (51.6)	46 (12.3)	13 (6.7)	1 (0.5)
Vascular disorders				
Hypertension	115 (30.7)	55 (14.7)	12 (6.2)	9 (4.7)

Serious adverse events occurred in 166 of 374 subjects (44.4%) in the regorafenib group and 90 of 193 subjects (46.6%) in the placebo group. These were general physical health deterioration in 39 subjects (10.4%), ascites and hepatic failure in 9 subjects (2.4%) each, hepatic encephalopathy in 7 subjects (1.9%), pneumonia and back pain in 6 subjects (1.6%) each, pyrexia and dyspnoea in 5 subjects (1.3%) each, oesophageal varices haemorrhage, tumour pain, and pleural effusion in 4 subjects (1.1%) each, anaemia, acute coronary syndrome, diarrhoea, pancreatitis, upper gastrointestinal haemorrhage, asthenia, dehydration, encephalopathy, haemoptysis, and shock haemorrhagic in 3 subjects (0.8%) each, atrial fibrillation, abdominal pain, abdominal pain lower, fatigue, hepatic cirrhosis, hepatic function abnormal, hepatic haemorrhage, jaundice cholestatic, abdominal infection, liver abscess, lung infection, sepsis, hypoglycaemia, hyponatraemia, seizure, renal failure, and pneumonitis in 2 subjects (0.5%) each, and thrombocytopenia, atrial flutter, myocardial infarction, retinal artery occlusion, abdominal pain upper, constipation, diverticulum intestinal, duodenal perforation, dysphagia, gastritis, gastrointestinal haemorrhage, haematemesis, pancreatitis acute, rectal haemorrhage, stomatitis, death, malaise, acute hepatic failure, cholangitis, cholecystitis, gallbladder obstruction, hepatitis acute, hepatobiliary disease, hepatorenal syndrome, jaundice, bronchitis, Candida infection, cellulitis, Escherichia sepsis, gastroenteritis, lower respiratory tract infection, lung abscess, peritonitis, peritonitis bacterial, septic shock, streptococcal bacteraemia, subcutaneous abscess, tracheitis, urinary tract infection, urosepsis, craniocerebral injury, femur fracture, pelvic fracture, spinal compression fracture, AST increased, blood bilirubin increased, blood pressure decreased, general physical condition abnormal, decreased appetite, hypoalbuminaemia, malnutrition, muscular weakness, musculoskeletal chest pain, musculoskeletal pain, myalgia, neck pain, pain in extremity, pathological fracture, adenocarcinoma gastric, cancer pain, infected neoplasm, large intestine benign neoplasm, thyroid neoplasm, tumour associated fever, brain

oedema, cerebrovascular accident, epilepsy, haemorrhage intracranial, meningorrhagia, myasthenia gravis, paraesthesia, quadriparesis, status epilepticus, syncope, anxiety, calculus urinary, cystitis noninfective, ureterolithiasis, bronchial obstruction, interstitial lung disease, pneumonia aspiration, pulmonary oedema, respiratory distress, respiratory failure, tracheal disorder, blister, palmar-plantar erythrodysaesthesia syndrome, skin ulcer, embolism, hypertensive crisis, and hypovolaemic shock in 1 subject (0.3%) each in the regorafenib group; and general physical health deterioration in 24 subjects (12.4%), hepatic failure in 9 subjects (4.7%), ascites in 6 subjects (3.1%), abdominal pain in 4 subjects (2.1%), upper gastrointestinal haemorrhage, hepatic function abnormal, decreased appetite, encephalopathy, hepatic encephalopathy, and respiratory failure in 3 subjects (1.6%) each, gastrointestinal haemorrhage, intra-abdominal haemorrhage, bile duct stenosis, hepatic haemorrhage, jaundice, liver abscess, blood bilirubin increased, hypercalcaemia, back pain, acute kidney injury, dyspnoea, and haemoptysis in 2 subjects (1.0%) each, and anaemia, haemorrhagic anaemia, cardiac arrest, abdominal discomfort, abdominal distension, gastritis, haematemesis, lower gastrointestinal haemorrhage, obstruction gastric, oesophageal haemorrhage, oesophageal varices haemorrhage, multiple organ dysfunction syndrome, pain, pyrexia, cholangitis, hepatorenal syndrome, hyperbilirubinaemia, jaundice cholestatic, portal vein thrombosis, peritonitis, pleural infection bacterial, pneumonia, wound infection bacterial, femur fracture, pubis fracture, spinal compression fracture, hyperglycaemia, arthralgia, bone pain, pain in extremity, pathological fracture, metastases to lung, tumour haemorrhage, cerebral haematoma, headache, hemiparesis, sciatica, renal failure, pelvic pain, atelectasis, pleural effusion, deep vein thrombosis, and orthostatic hypotension in 1 subject (0.5%) each in the placebo group. A causal relationship to the study drug could not be ruled out for general physical health deterioration in 5 subjects, hepatic encephalopathy in 3 subjects, anaemia, acute coronary syndrome, diarrhoea, and upper gastrointestinal haemorrhage in 2 subjects each, and thrombocytopenia, atrial fibrillation, myocardial infarction, retinal artery occlusion, abdominal pain, ascites, duodenal perforation, dysphagia, gastrointestinal haemorrhage, pancreatitis, stomatitis, asthenia, death, fatigue, hepatic failure, hepatic function abnormal, streptococcal bacteraemia, urosepsis, AST increased, decreased appetite, dehydration, malnutrition, infected neoplasm, meningorrhagia, renal failure, dyspnoea, palmar-plantar erythrodysaesthesia syndrome, embolism, hypertensive crisis, and shock haemorrhagic in 1 subject each in the regorafenib group; and hepatic failure in 3 subjects, and general physical health deterioration, hepatic function abnormal, and renal failure in 1 subject each in the placebo group.

Adverse events led to discontinuation of the study drug in 93 of 374 subjects (24.9%) in the regorafenib group and 37 of 193 subjects (19.2%) in the placebo group. These were, namely, general physical health deterioration in 14 subjects (3.7%), AST increased in 9 subjects (2.4%), blood bilirubin increased in 8 subjects (2.1%), palmar-plantar erythrodysaesthesia syndrome in 7 subjects (1.9%), hepatic failure in 6 subjects (1.6%), fatigue in 5 subjects (1.3%), asthenia in 4 subjects (1.1%), abdominal pain, ALT increased, and hepatic encephalopathy in 3 subjects (0.8%) each, acute coronary syndrome, ascites, and jaundice cholestatic in 2 subjects (0.5%) each, and anaemia, thrombocytopenia, myocardial infarction, retinal artery occlusion, diarrhoea, oesophageal varices haemorrhage, upper gastrointestinal haemorrhage, malaise, oedema peripheral, acute hepatic failure, hepatic function abnormal, hepatic haemorrhage, hepatitis acute, hyperbilirubinaemia, Escherichia sepsis, liver abscess, lung infection, peritonitis, peritonitis bacterial, pneumonia, bilirubin conjugated increased, blood creatinine increased, general physical condition abnormal, prothrombin time shortened, decreased appetite, hypoalbuminaemia, neck pain, pathological fracture, adenocarcinoma gastric, brain neoplasm, tumour pain, epilepsy, quadriparesis, disorientation, cystitis noninfective, proteinuria, respiratory distress, tracheal disorder, embolism, hypertension, and hypovolaemic shock in 1 subject (0.3%) each in the regorafenib group; and blood bilirubin increased in 7 subjects (3.6%), ascites and general physical health deterioration in 4 subjects (2.1%) each, fatigue, hepatic failure, hepatic function abnormal, and AST increased in 3 subjects (1.6%) each, asthenia and hepatic haemorrhage in 2 subjects (1.0%) each, and cardiac arrest, diarrhoea, obstruction gastric, upper gastrointestinal haemorrhage, multiple organ dysfunction syndrome, pyrexia, bile duct stenosis, hepatorenal syndrome, jaundice cholestatic, liver abscess, femur fracture, blood creatinine increased, GGT increased, protein urine present, decreased appetite, oesophageal carcinoma, tumour haemorrhage, cerebral haematoma, and respiratory failure in 1 subject (0.5%) each in the placebo group. A causal relationship to the study drug could not be ruled out for palmar-plantar erythrodysaesthesia syndrome in 7 subjects, AST increased in 6 subjects, fatigue

and blood bilirubin increased in 3 subjects each, acute coronary syndrome, abdominal pain, general physical health deterioration, and hepatic encephalopathy in 2 subjects each, and thrombocytopenia, myocardial infarction, retinal artery occlusion, diarrhoea, upper gastrointestinal haemorrhage, asthenia, malaise, oedema peripheral, hepatic failure, hyperbilirubinaemia, ALT increased, bilirubin conjugated increased, blood creatinine increased, proteinuria, embolism, and hypertension in 1 subject each in the regorafenib group; and asthenia, fatigue, general physical health deterioration, hepatic failure, hepatic function abnormal, AST increased, and protein urine present in 1 subject each in the placebo group.

7.3.2 Foreign phase II study (Study 14596)

Adverse events occurred in 36 of 36 subjects (100%). A causal relationship to the study drug could not be ruled out for events in 35 of 36 subjects (97.2%). Adverse events with an incidence of ≥20% are shown in Table 10.

Table 10. Adverse events with an incidence of ≥20%

SOC	Number of subjects (%)	
PT	N = 36	
(MedDRA ver.19.0)	All Grades	Grade ≥3
All adverse events	36 (100)	32 (88.9)
Endocrine disorders		
Hypothyroidism	12 (33.3)	0
Gastrointestinal disorders		
Abdominal pain	14 (38.9)	5 (13.9)
Ascites	10 (27.8)	3 (8.3)
Constipation	13 (36.1)	0
Diarrhoea	20 (55.6)	2 (5.6)
Nausea	15 (41.7)	0
Vomiting	8 (22.2)	0
General disorders and administration site conditions		
Asthenia	11 (30.6)	3 (8.3)
Fatigue	18 (50.0)	6 (16.7)
Pyrexia	12 (33.3)	0
Hepatobiliary disorders		
Hyperbilirubinaemia	9 (25.0)	7 (19.4)
Investigations		
Weight decreased	10 (27.8)	0
Metabolism and nutrition disorders		
Decreased appetite	18 (50.0)	0
Nervous system disorders		
Headache	9 (25.0)	0
Renal and urinary disorders		
Proteinuria	9 (25.0)	2 (5.6)
Respiratory, thoracic and mediastinal disorders		
Dysphonia	12 (33.3)	0
Skin and subcutaneous tissue disorders		
Palmar-plantar erythrodysaesthesia syndrome	20 (55.6)	5 (13.9)
Vascular disorders		
Hypertension	13 (36.1)	1 (2.8)

Serious adverse events occurred in 22 of 36 subjects (61.1%). These were, namely, anaemia, hepatic function abnormal, hyperbilirubinaemia, and cachexia in 2 subjects (5.6%) each and acute myocardial infarction, atrial fibrillation, atrioventricular block complete, hypoacusis, abdominal pain, diarrhoea, faeces discoloured, gastrointestinal haemorrhage, rectal haemorrhage, asthenia, death, fatigue, pyrexia, hepatic failure, anaphylactic reaction, fall, arthralgia, bone cancer, ataxia, cerebral haemorrhage, haemorrhage intracranial, hepatic encephalopathy, pleural effusion, and haematoma in 1 subject (2.8%) each. A causal relationship to the study drug could not be ruled out for anaemia, atrial fibrillation, diarrhoea, fatigue, pyrexia, fall, and haematoma in 1 subject (2.8%) each.

Adverse events led to discontinuation of the study drug in 19 of 36 subjects (52.8%). The events were, namely, fatigue and hyperbilirubinaemia in 3 subjects (8.3%) each, asthenia in 2 subjects (5.6%), leukopenia, thrombocytopenia, acute myocardial infarction, atrial fibrillation, atrioventricular block complete, diarrhoea, dysphagia, pyrexia, decreased appetite, hypoalbuminaemia, arthralgia, ataxia, cerebral haemorrhage, hepatic encephalopathy, phobia, proteinuria, erythema, palmar-plantar

erythrodysaesthesia syndrome, and haematoma in 1 subject (2.8%) each. A causal relationship to the study drug could not be ruled out for fatigue in 3 subjects and atrial fibrillation, diarrhoea, dysphagia, asthenia, decreased appetite, proteinuria, erythema, palmar-plantar erythrodysaesthesia syndrome, and haematoma in 1 subject each.

7.3.3 Foreign phase I study (Study 16674)

Adverse events occurred in 20 of 22 subjects (90.9%) in the regorafenib/digoxin group and 17 of 17 subjects (100%) in the regorafenib/rosuvastatin group. A causal relationship to the study drug could not be ruled out for events in 20 of 22 subjects (90.9%) in the regorafenib/digoxin group and 17 of 17 subjects (100%) in the regorafenib/rosuvastatin group. Adverse events with an incidence of ≥20% in either group are shown in Table 11.

Table 11. Adverse events with an incidence of ≥20% in either group

SOC PT (MedDRA ver.19.0)	Number of subjects (%)			
	Regorafenib/digoxin N = 22		Regorafenib/rosuvastatin N = 17	
	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	20 (90.9)	17 (77.3)	17 (100)	15 (88.2)
Gastrointestinal disorders				
Diarrhoea	5 (22.7)	1 (4.5)	8 (47.1)	0
Nausea	1 (4.5)	0	4 (23.5)	1 (5.9)
General disorders and administration site conditions				
Fatigue	13 (59.1)	1 (4.5)	10 (58.8)	4 (23.5)
Mucosal inflammation	3 (13.6)	0	6 (35.3)	0
Pyrexia	7 (31.8)	0	3 (17.6)	0
Infections and infestations				
Infection	5 (22.7)	3 (13.6)	4 (23.5)	1 (5.9)
Investigations				
Blood bilirubin increased	6 (27.3)	3 (13.6)	6 (35.3)	0
Lipase increased	2 (9.1)	2 (9.1)	5 (29.4)	4 (23.5)
Platelet count decreased	3 (13.6)	0	4 (23.5)	0
Metabolism and nutrition disorders				
Decreased appetite	8 (36.4)	1 (4.5)	9 (52.9)	0
Hypoalbuminaemia	3 (13.6)	2 (9.1)	4 (23.5)	1 (5.9)
Hypophosphataemia	3 (13.6)	2 (9.1)	5 (29.4)	5 (29.4)
Musculoskeletal and connective tissue disorders				
Bone pain	5 (22.7)	1 (4.5)	1 (5.9)	0
Respiratory, thoracic and mediastinal disorders				
Dyspnoea	1 (4.5)	0	7 (41.2)	0
Skin and subcutaneous tissue disorders				
Dry skin	4 (18.2)	0	5 (29.4)	0
Palmar-plantar erythrodysaesthesia syndrome	9 (40.9)	3 (13.6)	8 (47.1)	2 (11.8)
Vascular disorders				
Hypertension	9 (40.9)	5 (22.7)	8 (47.1)	6 (35.3)

Serious adverse events were reported by 10 of 22 subjects (45.5%) in the regorafenib/digoxin group and 8 of 17 subjects (47.1%) in the regorafenib/rosuvastatin group. Serious adverse events observed included cholangitis and cancer pain in 2 subjects (9.1%) each and abdominal distension, abdominal pain, gastrointestinal haemorrhage, inguinal hernia, general physical health deterioration, pyrexia, urosepsis, dehydration, bone pain, tumour compression, tumour pain, erythema multiforme, palmar-plantar erythrodysaesthesia syndrome, and lymphoedema in 1 subject (4.5%) each in the regorafenib/digoxin group; and atrial flutter, cardiac arrest, tachyarrhythmia, haematemesis, general physical health deterioration, lung infection, pneumonia, dehydration, hypokalaemia, hyponatraemia, intervertebral disc protrusion, pleural effusion, and hypertension in 1 subject (5.9%) each in the regorafenib/rosuvastatin group. A causal relationship to the study drug could not be ruled out for dehydration, erythema multiforme, and palmar-plantar erythrodysaesthesia syndrome in 1 subject each in the regorafenib/digoxin group and hypokalaemia, hyponatraemia, and hypertension in 1 subject each in the regorafenib/rosuvastatin group.

Adverse events led to discontinuation of the study drug in 3 of 22 subjects (13.6%) in the regorafenib/digoxin group and 5 of 17 subjects (29.4%) in the regorafenib/rosuvastatin group. These were, namely, general physical health deterioration, palmar-plantar erythrodysaesthesia syndrome, and

hypertension in 1 subject (4.5%) each in the regorafenib/digoxin group and haematemesis, fatigue, drug-induced liver injury, palmar-plantar erythrodysaesthesia syndrome, and hypertension in 1 subject (5.9%) each in the regorafenib/rosuvastatin group. A causal relationship to the study drug could not be ruled out for palmar-plantar erythrodysaesthesia syndrome and hypertension in 1 subject each in the regorafenib/digoxin group and fatigue, drug-induced liver injury, and hypertension in 1 subject each in the regorafenib/rosuvastatin group.

7.3.4 Foreign phase I study (Study 16675)

Adverse events occurred in 12 of 27 subjects (44.4%) in the regorafenib group and 23 of 26 subjects (88.5%) in the regorafenib/neomycin group. A causal relationship to the study drug could not be ruled out for those occurring in 4 of 27 subjects (14.8%) in the regorafenib group and 2 of 26 subjects (7.7%) in the regorafenib/neomycin group. Adverse events with an incidence of ≥10% in each group included application site erythema in 3 of 27 subjects (11.1%) in the regorafenib group; and diarrhoea in 16 of 26 subjects (61.5%), headache in 6 of 26 subjects (23.1%), and abdominal discomfort and nausea in 4 of 26 subjects (15.4%) each in the regorafenib/neomycin group.

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

7.3.5 Foreign phase I study (Study 16653)

Adverse events were reported by 6 of 6 subjects (100%) with severe renal impairment (severe group) and 18 of 18 subjects (100%) with normal renal function or mild renal impairment (normal/mild group). A causal relationship to the study drug could not be ruled out for the events occurred in 6 of 6 subjects (100%) in the severe group and 18 of 18 subjects (100%) in the normal/mild group. Adverse events with an incidence of ≥40% in either group are shown in Table 12.

Table 12. Adverse events with an incidence of ≥40% in either group

SOC PT (MedDRA ver.19.0)	Number of subjects (%)			
	Severe N = 6		Normal/mild N = 18	
	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	6 (100)	6 (100)	18 (100)	16 (88.9)
Gastrointestinal disorders				
Abdominal pain	3 (50.0)	0	5 (27.8)	0
Constipation	3 (50.0)	0	5 (27.8)	0
Diarrhoea	4 (66.7)	1 (16.7)	8 (44.4)	1 (5.6)
Nausea	6 (100)	0	10 (55.6)	0
Vomiting	4 (66.7)	0	6 (33.3)	0
General disorders and administration site conditions				
Fatigue	3 (50.0)	1 (16.7)	13 (72.2)	2 (11.1)
Metabolism and nutrition disorders				
Decreased appetite	3 (50.0)	0	11 (61.1)	3 (16.7)
Musculoskeletal and connective tissue disorders				
Arthralgia	3 (50.0)	0	5 (27.8)	1 (5.6)
Nervous system disorders				
Headache	2 (33.3)	0	10 (55.6)	0
Renal and urinary disorders				
Proteinuria	3 (50.0)	2 (33.3)	1 (5.6)	0
Respiratory, thoracic and mediastinal disorders				
Dysphonia	2 (33.3)	0	8 (44.4)	0
Skin and subcutaneous tissue disorders				
Palmar-plantar erythrodysaesthesia syndrome	3 (50.0)	2 (33.3)	10 (55.6)	2 (11.1)
Vascular disorders				
Hypertension	4 (66.7)	2 (33.3)	8 (44.4)	4 (22.2)

Serious adverse events occurred in 2 of 6 subjects (33.3%) in the severe group and 9 of 18 subjects (50.0%) in the normal/mild group. These were chest pain and muscular weakness in 1 subject (16.7%) each in the severe group; and small intestinal obstruction in 2 subjects (11.1%) and stress cardiomyopathy, intestinal obstruction, pancreatitis, dehydration, muscular weakness, haematuria,

pleural effusion, rash, deep vein thrombosis, and embolism in 1 subject (5.6%) each in the normal/mild group. A causal relationship to the study drug could not be ruled out for stress cardiomyopathy, dehydration, haematuria, and rash in 1 subject each in the normal/mild group.

Adverse events led to discontinuation of the study drug in 2 of 6 subjects (33.3%) in the severe group and 4 of 18 subjects (22.2%) in the normal/mild group. These were stomatitis and palmar-plantar erythrodysaesthesia syndrome in 1 subject (16.7%) each in the severe group and stress cardiomyopathy, AST increased, muscle spasms, myalgia, headache, and haematuria in 1 subject (5.6%) each in the normal/mild group. A causal relationship to the study drug could not be ruled out for all events.

7.3.6 Foreign phase III study (Study 15808)

Adverse events occurred in 136 of 136 subjects (100%) in the regorafenib group and 60 of 68 subjects (88.2%) in the placebo group. A causal relationship to the study drug could not be ruled out for those in 132 of 136 subjects (97.1%) in the regorafenib group and 31 of 68 subjects (45.6%) in the placebo group. Adverse events with an incidence of ≥20% in either group are shown in Table 13.

Table 13. Adverse events with incidence of ≥20% in either group

SOC PT (MedDRA ver.19.0)	Number of subjects (%)			
	Regorafenib N = 136		Placebo N = 68	
	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	136 (100)	97 (71.3)	60 (88.2)	30 (44.1)
Gastrointestinal disorders				
Diarrhoea	39 (28.7)	3 (2.2)	5 (7.4)	1 (1.5)
General disorders and administration site conditions				
Fatigue	30 (22.1)	4 (2.9)	7 (10.3)	1 (1.5)
Investigations				
ALT increased	44 (32.4)	11 (8.1)	12 (17.6)	1 (1.5)
AST increased	43 (31.6)	13 (9.6)	15 (22.1)	0
Blood bilirubin increased	61 (44.9)	14 (10.3)	14 (20.6)	3 (4.4)
Respiratory, thoracic and mediastinal disorders				
Dysphonia	39 (28.7)	1 (0.7)	0	0
Skin and subcutaneous tissue disorders				
Palmar-plantar erythrodysaesthesia syndrome	98 (72.1)	22 (16.2)	3 (4.4)	0
Vascular disorders				
Hypertension	32 (23.5)	15 (11.0)	4 (5.9)	3 (4.4)

Serious adverse events occurred in 43 of 136 subjects (31.6%) in the regorafenib group and 18 of 68 subjects (26.5%) in the placebo group. These were pyrexia, blood bilirubin increased, and rash in 3 subjects (2.2%) each, anaemia, abdominal pain, death, multiple organ dysfunction syndrome, lung infection, pneumonia, hypoglycaemia, dyspnoea, and respiratory failure in 2 subjects (1.5%) each, and splenic infarction, atrial flutter, cardiac arrest, abdominal distension, abdominal hernia, ascites, diarrhoea, ileus, intestinal obstruction, large intestine perforation, lower gastrointestinal haemorrhage, mechanical ileus, oesophageal varices haemorrhage, vomiting, disease progression, bile duct obstruction, hyperbilirubinaemia, jaundice cholestatic, hypersensitivity, abscess soft tissue, bronchopulmonary aspergillosis, device related infection, peritonitis, sepsis, upper respiratory tract infection, wound infection, radiation proctitis, tibia fracture, ALT increased, blood creatinine increased, back pain, colorectal cancer, intracranial pressure increased, vaginal haemorrhage, pleural effusion, pneumonitis, and pneumothorax in 1 subject (0.7%) each in the regorafenib group; and multiple organ dysfunction syndrome and biliary tract infection in 2 subjects (2.9%) each, and cardiac failure, cardiac fibrillation, tinnitus, abdominal distension, abdominal pain, ascites, ileus, intestinal obstruction, vomiting, death, disease progression, oedema peripheral, pyrexia, jaundice, urinary tract infection, cachexia, neoplasm progression, cerebral artery embolism, dyskinesia, acute kidney injury, dyspnoea, and hypovolaemic shock in 1 subject (1.5%) each in the placebo group. A causal relationship to the study drug could not be ruled out for rash in 3 subjects, blood bilirubin increased in 2 subjects, and anaemia, splenic infarction, cardiac arrest, oesophageal varices haemorrhage, death, wound infection, ALT increased, and hypoglycaemia in 1 subject each in the regorafenib group and cardiac failure, cardiac fibrillation, vomiting, cerebral artery embolism, and acute kidney injury in 1 subject each in the placebo group.

Adverse events led to discontinuation of the study drug in 19 of 136 subjects (14.0%) in the regorafenib group and 4 of 68 subjects (5.9%) in the placebo group. These events were blood bilirubin increased in 6 subjects (4.4%), ALT increased in 2 subjects (1.5%), and anaemia, cardiac arrest, abdominal hernia, anal fistula, large intestine perforation, general physical health deterioration, bile duct obstruction, bronchopulmonary aspergillosis, AST increased, protein urine present, vaginal fistula, and palmar-plantar erythrodysaesthesia syndrome in 1 subject (0.7%) each in the regorafenib group; and abdominal distension, abdominal pain, dysphagia, small intestinal obstruction, and acute kidney injury in 1 subject (1.5%) each in the placebo group. A causal relationship to the study drug could not be ruled out for blood bilirubin increased in 4 subjects, ALT increased in 2 subjects, and anaemia, cardiac arrest, anal fistula, general physical health deterioration, AST increased, protein urine present, vaginal fistula, and palmar-plantar erythrodysaesthesia syndrome in 1 subject each in the regorafenib group and acute kidney injury in 1 subject in the placebo group.

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

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

The assessment is ongoing. Its results and the conclusion by PMDA will be reported in the Review Report (2).

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

The assessment is ongoing. Its results and the conclusion by PMDA will be reported in the Review Report (2).

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

On the basis of the data submitted, PMDA has concluded that Stivarga has efficacy in the treatment of unresectable hepatocellular carcinoma progressed after cancer chemotherapy and the product has acceptable safety in view of its benefits. Stivarga is clinically significance because it offers a treatment option for unresectable hepatocellular carcinoma progressed after cancer chemotherapy. The indications and post-marketing investigations, etc. are subject to further discussion.

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

Review Report (2)

May 19, 2017

Product Submitted for Approval

Brand Name	Stivarga Tablets 40 mg
Non-proprietary Name	Regorafenib Hydrate
Applicant	Bayer Yakuhin, Ltd.
Date of Application	October 31, 2016

1. Content of the Review

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

1.1 Efficacy

As a result of the review in Section "7.R.2 Efficacy" of the Review Report (1), PMDA has concluded that the efficacy of regorafenib hydrate (referred to as regorafenib) was demonstrated in patients with unresectable hepatocellular carcinoma progressed after the treatment with sorafenib tosilate (sorafenib),[7)] the patient population included in global phase III study (Study 15982), which evaluated the efficacy and safety of regorafenib and demonstrated a significant increase in overall survival (primary endpoint) in the regorafenib group compared with the control (placebo) group.

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

1.2 Safety

As a result of the review in Section "7.R.3 Safety" of the Review Report (1), PMDA has concluded that the use of regorafenib in patients with unresectable hepatocellular carcinoma progressed after cancer chemotherapy require special attention to those adverse identified during the review for the approved indications[8)] (hand and foot syndrome, hepatic function disorder, hypertension [hypertensive crisis], haemorrhage, thromboembolism, gastrointestinal perforation or fistula, Stevens-Johnson syndrome/toxic epidermal necrolysis, posterior reversible encephalopathy, interstitial lung disease, and platelets decreased).

In addition, PMDA has concluded that regorafenib is tolerated as long as their attending physicians with adequate knowledge and experience in cancer chemotherapy continue to follow appropriately, such as by monitoring and controlling of adverse events and dose reduction, interruption, or discontinuation

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

1.3 Clinical positioning and indication

PMDA's conclusion:

As a result of the review in Section "7.R.4 Clinical positioning and indication" of the Review Report (1), the indication of "unresectable hepatocellular carcinoma progressed after cancer chemotherapy" is appropriate. However, the "Clinical Studies" section of the package insert must mention that Study 15982 was conducted in patients who (a) were tolerant of sorafenib and (b) had liver function of Child-Pugh Class A. Further, the "Precautions for Indications" section must give the following cautions.

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7) Patients who (a) are not eligible for local therapy, (b) are tolerant of sorafenib treatment, and (c) have liver function of Child-Pugh Class A were included.

8) Unresectable, advanced/recurrent colorectal cancer, and gastrointestinal stromal tumor progressed after cancer chemotherapy

Precautions for Indications
- 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.

- The efficacy and safety of regorafenib have not been established in patients with hepatocellular carcinoma eligible for local therapies (e.g., percutaneous ethanol injection, radio-frequency ablation, microwave coagulation, hepatic arterial embolization/hepatic arterial chemoembolization, and radiotherapy).

- The efficacy and safety of regorafenib as the first-line therapy have not been established.

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

Thus, PMDA instructed the applicant to include the above statements in the "Indication" and the "Precautions for Indications" sections, and the applicant agreed.

1.4 Dosage and administration

PMDA's conclusion:
As a result of the review in Section "7.R.5 Dosage and administration" of the Review Report (1), the "Dosage and Administration" section of the package insert of regorafenib should state "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." However, the following cautions must be written in the "Precautions for Dosage and Administration" section.

Precautions for Dosage and Administration
- The efficacy and safety of concomitant use of regorafenib with the other antineoplastic drugs have not been established.

- Regorafenib should not be given to fasted patients. It is advisable not to give regorafenib after high-fat meals.

- Criteria for dose reduction, dose interruption, and discontinuation at the onset of adverse drug reactions

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

PMDA thus instructed the applicant to give the above cautions in the "Dosage and Administration" and the "Precautions for Dosage and Administration" sections, and the applicant accepted the instruction.

1.5 Risk management plan (draft)

In order to evaluate the safety of regorafenib in its post-marketing clinical use, the applicant plans to conduct post-marketing surveillance in patients with unresectable hepatocellular carcinoma receiving regorafenib as a part of a global observational study. The target sample size is 150 and the follow-up period is 2 years.

PMDA's conclusion:
As a result of the review in Section "7.R.6 Post-marketing investigations" in the Review Report (1), there is not much need of post-marketing surveillance in patients with unresectable hepatocellular carcinoma progressed after cancer chemotherapy to be conducted immediately after approval. Sufficient safety data on regorafenib will be gathered through routine pharmacovigilance activities.

The conclusion of PMDA was supported by the expert advisors at the Expert Discussion. The following comments were raised from the expert advisors.

- The post-marketing surveillance conducted for the approved indications including unresectable, advanced/recurrent colorectal cancer yielded safety data of regorafenib from 1268 Japanese patients [see Section "7.R.6 Post-marketing investigations" in the Review Report (1)]. The surveillance result may be checked for the occurrence of hepatic function disorder in these patients before making a decision whether to conduct post-marketing surveillance in patients with hepatocellular carcinoma.

PMDA asked the applicant to explain the occurrence of hepatic function disorder found in the post-marketing surveillance conducted for the approved indications.

The applicant's explanation:
The incidence of adverse events of all hepatic function disorders and serious hepatic function disorders were 46.2% (30 subjects) and 6.2% (4 subjects), respectively, in 65 Japanese subjects in the regorafenib group of the global phase III study (Study 14387) conducted in patients with colorectal cancer. The post-marketing surveillance conducted in 1226 patients with colorectal cancer revealed the incidences of all hepatic function disorders and serious hepatic function disorders of 36.5% (448 patients) and 13.9% (170 patients), respectively.

In terms of adverse drug reactions, the incidence of hepatic function disorders of all grades and those of Grade ≥3 was 29.2% (19 subjects) and 10.8% (7 subjects), respectively, in Study 14387. In the post-marketing surveillance, the incidence of the former was 31.3% (384 patients) and the latter 11.5% (141 patients).

PMDA's view:
The incidence of serious adverse events of hepatic function disorder associated with regorafenib observed in Study 14387 was inconsistent with that in the post-marketing surveillance, and the cause of the inconsistency is unclear. However, there were no particular differences in the incidence of adverse drug reactions of all grades or Grade ≥3 hepatic function disorder between Study 14387 and the post-marketing surveillance, and the surveillance revealed neither adverse events requiring additional safety measures nor new safety issues. Therefore, at present, there is not much need for post-marketing surveillance to be conducted immediately after approval in patients with hepatocellular carcinoma.

PMDA instructed the applicant to reconsider the necessity of post-marketing surveillance in patients with hepatocellular carcinoma. The applicant responded that safety data would be collected from patients with unresectable hepatocellular carcinoma progressed after cancer chemotherapy through routine pharmacovigilance activities.

PMDA accepted the applicant's explanation.

In view of the discussion above, PMDA has concluded that the current risk management plan (draft) should include the safety and efficacy specifications presented in Table 14, and that the applicant should conduct additional risk-minimization activities presented in Table 15.

Table 14. Safety and efficacy specifications in the risk management plan (draft)

Safety specification*		
Important identified risks	Important potential risks	Important missing information
• Hepatic function disorder • Thromboembolism • Hypertension/hypertensive crisis • Haemorrhage • Hand and foot syndrome • Posterior reversible encephalopathy syndrome • Gastrointestinal perforation and fistula • Toxic epidermal necrolysis/Stevens-Johnson syndrome (oculomucocutaneous syndrome)/erythema multiforme • Platelets decreased • Interstitial lung disease	• Wound-healing disturbance	Unspecified
Efficacy specification (related to the current partial change approval application)		
None		

* There is no change related to the current partial change approval application.

Table 15. Summary of additional pharmacovigilance activities and risk minimization activities included in the risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimization activities
• Use-results survey in patients with unresectable, advanced/recurrent colorectal cancer and patients with gastrointestinal stromal tumor progressed after cancer chemotherapy • Post-marketing clinical study (extension study following Study 15982)	• Preparation and distribution of materials for healthcare professionals

Underline, activities to be conducted for the additional indication.

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

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

The new drug application data were subjected to a document-based compliance inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. The inspection revealed that some case report data modified or corrected by a sponsor staff member were not able to be viewed by investigators. Despite this area for improvement, the final case report data were checked and confirmed by the investigators after all. PMDA thus concluded that there were no obstacles to conducting its review based on the application documents submitted.

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

The new drug application data (CTD 5.3.5.1.1) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

3. Overall Evaluation

As a result of the above review, PMDA has concluded that regorafenib may be approved for the proposed indication and dosage and administration modified as shown below with the following condition. However, the applicant must ensure that necessary cautions be given in the package insert, information about the proper use of regorafenib be provided to healthcare professionals appropriately in the post-marketing setting, and regorafenib be used properly under the supervision of a physician with adequate knowledge and experience in cancer chemotherapy at an emergency-equipped medical facility. The re-examination period is the remainder of the ongoing re-examination period for initial approval of Stivarga (until March 24, 2021).

Indications (Underline denotes addition.)
Unresectable, advanced/recurrent colorectal cancer; gastrointestinal stromal tumor progressed after cancer chemotherapy; and unresectable hepatocellular carcinoma progressed after cancer chemotherapy

Dosage and Administration (No change)
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.

Condition of Approval
The applicant is required to develop and appropriately implement a risk management plan.

Warnings (No change)
(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 fulminant hepatitis or 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 (No change)
(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 (Underline denotes addition.)
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.

1. Unresectable, advanced/recurrent colorectal cancer
(1) The efficacy and safety of regorafenib as the first- or second-line therapy have not been established.

(2) The efficacy and safety of regorafenib have not been established for use in adjuvant chemotherapy.

2. Gastrointestinal stromal tumor progressed after cancer chemotherapy
(1) Regorafenib should be used for patients who have been treated with imatinib or sunitinib.

(2) The efficacy and safety of regorafenib have not been established for use in adjuvant chemotherapy.

3. Unresectable hepatocellular carcinoma progressed after cancer chemotherapy
(1) The efficacy and safety of regorafenib have not been established in patients with hepatocellular carcinoma eligible for local therapies (e.g., percutaneous ethanol injection, radio-frequency ablation, microwave coagulation, hepatic arterial embolization/hepatic arterial chemoembolization, and radiotherapy).

(2) The efficacy and safety of regorafenib as the first-line therapy have not been established.

Precautions for Dosage and Administration (No change)
(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 are immediately instituted.
Grade 2	1st occurrence: The dose of regorafenib is reduced by 40 mg (1 tablet) and supportive measures for symptomatic relief are 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 are immediately instituted and treatment 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. 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).
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 drug 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).