CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

203085Orig1s007

Trade Name:	Stivarga
Generic or Proper Name:	regorafenib
Sponsor:	Bayer HealthCare Pharmaceuticals, Inc.
Approval Date:	April 27, 2017
Indication:	STIVARGA is a kinase inhibitor indicated for the treatment of patients with: • Metastatic colorectal cancer (CRC) who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF therapy, and if RAS wild-type, an anti-EGFR therapy. • Locally advanced, unresectable or metastatic gastrointestinal stromal tumor (GIST) who have been previously treated with imatinib mesylate and sunitinib malate. • Hepatocellular carcinoma (HCC) who have been previously treated with sorafenib.

CENTER FOR DRUG EVALUATION AND RESEARCH

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203085/S-007

SUPPLEMENT APPROVAL

Bayer HealthCare Pharmaceuticals, Inc.
Attention: Lisa Chao, Ph. D.
Deputy Director, Global Regulatory Affairs, Specialty Medicine
100 Bayer Boulevard, P.O. Box 915
Whippany, NJ 07981-0915

Dear Dr. Chao:

Please refer to your Supplemental New Drug Application (sNDA) dated October 30, 2016, received October 31, 2016, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Stivarga (regorafenib) tablets, 40 mg.

This Prior Approval supplemental new drug application provides for a new indication for the use of Stivarga (regorafenib) for the treatment of patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib.

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

WAIVER OF HIGHLIGHTS SECTION

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert, text for the patient package insert), with the addition of any labeling changes in pending "Changes Being

Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf.

Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf.

For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Anuja Patel, Senior Regulatory Health Project Manager, at (301) 796-9022.

Sincerely,

{See appended electronic signature page}

Patricia Keegan, M.D.
Division Director
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE:
Content of Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

PATRICIA KEEGAN
04/27/2017

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203085Orig1s007

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use STIVARGA safely and effectively. See full prescribing information for STIVARGA.

STIVARGA® (regorafenib) tablets, for oral use
Initial U.S. Approval: 2012

WARNING: HEPATOTOXICITY
See full prescribing information for complete boxed warning.
- **Severe and sometimes fatal hepatotoxicity has occurred in clinical trials. (5.1)**
- **Monitor hepatic function prior to and during treatment. (5.1)**
- **Interrupt and then reduce or discontinue STIVARGA for hepatotoxicity as manifested by elevated liver function tests or hepatocellular necrosis, depending upon severity and persistence. (2.2)**

---------- RECENT MAJOR CHANGES ----------

Indications and Usage, Colorectal Cancer (1.1)	6/2016
Indications and Usage, Hepatocellular Carcinoma (1.3)	4/2017
Dosage and Administration, Dose Modifications (2.2)	4/2017
Warnings and Precautions (5.1-5.8)	4/2017

---------- INDICATIONS AND USAGE ----------
STIVARGA is a kinase inhibitor indicated for the treatment of patients with:
- Metastatic colorectal cancer (CRC) who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF therapy, and, if RAS wild-type, an anti-EGFR therapy. (1.1)
- Locally advanced, unresectable or metastatic gastrointestinal stromal tumor (GIST) who have been previously treated with imatinib mesylate and sunitinib malate. (1.2)
- Hepatocellular carcinoma (HCC) who have been previously treated with sorafenib (1.3)

---------- DOSAGE AND ADMINISTRATION ----------
- Recommended dose: 160 mg orally, once daily for the first 21 days of each 28-day cycle. (2.1)
- Take STIVARGA after a low-fat meal. (2.1, 12.3)

---------- DOSAGE FORMS AND STRENGTHS ----------
Tablets: 40 mg (3)

---------- CONTRAINDICATIONS ----------
None.

---------- WARNINGS AND PRECAUTIONS ----------
- Hepatotoxicity: Monitor liver function tests. Withhold and then reduce or discontinue STIVARGA based on severity and duration. (5.1)
- Infections: Withhold STIVARGA in patients with worsening or severe infections. (5.2)
- Hemorrhage: Permanently discontinue STIVARGA for severe or life-threatening hemorrhage. (5.3)
- Gastrointestinal perforation or fistula: Discontinue STIVARGA. (5.4)
- Dermatologic toxicity: Withhold and then reduce or discontinue STIVARGA depending on severity and persistence of dermatologic toxicity. (5.5)
- Hypertension: Temporarily or permanently withhold STIVARGA for severe or uncontrolled hypertension. (5.6)
- Cardiac ischemia and infarction: Withhold STIVARGA for new or acute cardiac ischemia/infarction and resume only after resolution of acute ischemic events. (5.7)
- Reversible posterior leukoencephalopathy syndrome (RPLS): Discontinue STIVARGA. (5.8)
- Wound healing complications: Discontinue STIVARGA before surgery. Discontinue in patients with wound dehiscence. (5.9)
- Embryo-fetal toxicity: Can cause fetal harm. Advise women of potential risk to a fetus and to use effective contraception during treatment and for 2 months after the final dose. Advise males to use effective contraception for 2 months after the final dose. (5.10, 8.1, 8.3)

---------- ADVERSE REACTIONS ----------
The most common adverse reactions (≥20%) are pain (including gastrointestinal and abdominal pain), HFSR, asthenia/fatigue, diarrhea, decreased appetite/food intake, hypertension, infection, dysphonia, hyperbilirubinemia, fever, mucositis, weight loss, rash, and nausea. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Bayer HealthCare Pharmaceuticals Inc. at 1-888-842-2937 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

---------- DRUG INTERACTIONS ----------
- Strong CYP3A4 inducers: Avoid strong CYP3A4 inducers. (7.1)
- Strong CYP3A4 inhibitors: Avoid strong CYP3A4 inhibitors. (7.2)
- BCRP substrates: Monitor patients closely for symptoms of increased exposure to BCRP substrates. (7.3)

---------- USE IN SPECIFIC POPULATIONS ----------
Nursing Mothers: Discontinue drug or nursing, taking into consideration the importance of the drug to the mother. (8.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 4/2017

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FULL PRESCRIBING INFORMATION

WARNING: HEPATOTOXICITY

- **Severe and sometimes fatal hepatotoxicity has occurred in clinical trials *[see Warnings and Precautions (5.1)]*.**
- **Monitor hepatic function prior to and during treatment *[see Warnings and Precautions (5.1)]*.**
- **Interrupt and then reduce or discontinue STIVARGA for hepatotoxicity as manifested by elevated liver function tests or hepatocellular necrosis, depending upon severity and persistence *[see Dosage and Administration (2.2)]*.**

1 INDICATIONS AND USAGE

1.1 Colorectal Cancer

STIVARGA is indicated for the treatment of patients with metastatic colorectal cancer (CRC) who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF therapy, and, if RAS wild-type, an anti-EGFR therapy.

1.2 Gastrointestinal Stromal Tumors

STIVARGA is indicated for the treatment of patients with locally advanced, unresectable or metastatic gastrointestinal stromal tumor (GIST) who have been previously treated with imatinib mesylate and sunitinib malate.

1.3 Hepatocellular Carcinoma

STIVARGA is indicated for the treatment of patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dose

The recommended dose is 160 mg STIVARGA (four 40 mg tablets) taken orally once daily for the first 21 days of each 28-day cycle. Continue treatment until disease progression or unacceptable toxicity.

Take STIVARGA at the same time each day. Swallow tablet whole with water after a low-fat meal that contains less than 600 calories and less than 30% fat *[see Clinical Pharmacology (12.3)]*. Do not take two doses of STIVARGA on the same day to make up for a missed dose from the previous day.

2.2 Dose Modifications

If dose modifications are required, reduce the dose in 40 mg (one tablet) increments; the lowest recommended daily dose of STIVARGA is 80 mg daily.

Interrupt STIVARGA for the following:

- Grade 2 hand-foot skin reaction (HFSR) [palmar-plantar erythrodysesthesia syndrome (PPES)] that is recurrent or does not improve within 7 days despite dose reduction; interrupt therapy for a minimum of 7 days for Grade 3 HFSR
- Symptomatic Grade 2 hypertension
- Any Grade 3 or 4 adverse reaction
- Worsening infection of any grade

Reduce the dose of STIVARGA to 120 mg:

- For the first occurrence of Grade 2 HFSR of any duration
- After recovery of any Grade 3 or 4 adverse reaction except infection
- For Grade 3 aspartate aminotransferase (AST)/alanine aminotransferase (ALT) elevation, only resume if the potential benefit outweighs the risk of hepatotoxicity

Reduce the dose of STIVARGA to 80 mg:

- For re-occurrence of Grade 2 HFSR at the 120 mg dose
- After recovery of any Grade 3 or 4 adverse reaction at the 120 mg dose (except hepatotoxicity or infection)

Discontinue STIVARGA permanently for the following:

- Failure to tolerate 80 mg dose
- Any occurrence of AST or ALT more than 20 times the upper limit of normal (ULN)
- Any occurrence of AST or ALT more than 3 times ULN with concurrent bilirubin more than 2 times ULN
- Re-occurrence of AST or ALT more than 5 times ULN despite dose reduction to 120 mg
- For any Grade 4 adverse reaction; only resume if the potential benefit outweighs the risks

3 DOSAGE FORMS AND STRENGTHS

STIVARGA is a 40 mg, light pink, oval-shaped, film-coated tablet, debossed with 'BAYER' on one side and '40' on the other side.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Hepatotoxicity

Severe drug-induced liver injury with fatal outcome occurred in STIVARGA-treated patients in clinical trials. In most cases, liver dysfunction occurred within the first 2 months of therapy and was characterized by a hepatocellular pattern of injury.

In the CORRECT study, fatal hepatic failure occurred in 1.6% of patients in the regorafenib arm and in 0.4% of patients in the placebo arm. In the GRID study, fatal hepatic failure occurred in 0.8% of patients in the regorafenib arm. In the RESORCE study, there was no increase in the incidence of fatal hepatic failure as compared to placebo *[see Adverse Reactions (6.1)]*.

Obtain liver function tests (ALT, AST, and bilirubin) before initiation of STIVARGA and monitor at least every two weeks during the first 2 months of treatment. Thereafter, monitor monthly or more frequently as clinically indicated. Monitor liver function tests weekly in patients experiencing elevated liver function tests until improvement to less than 3 times the ULN or baseline.

Temporarily hold and then reduce or permanently discontinue STIVARGA depending on the severity and persistence of hepatotoxicity as manifested by elevated liver function tests or hepatocellular necrosis *[see Dosage and Administration (2.2) and Use in Specific Populations (8.6)]*.

5.2 Infections

STIVARGA caused an increased risk of infections. The overall incidence of infection (Grades 1-5) was higher (32% vs. 17%) in 1142 STIVARGA-treated patients as compared to the control arm in randomized placebo-controlled trials.The incidence of grade 3 or greater infections in STIVARGA treated patients was 9%. The most common infections were urinary tract infections (5.7%), nasopharyngitis (4.0%), mucocutaneous and systemic fungal infections (3.3%) and pneumonia (2.6%). Fatal outcomes caused by infection occurred more often in patients treated with STIVARGA (1.0%) as compared to patients receiving placebo (0.3%); the most common fatal infections were respiratory (0.6% in STIVARGA-treated patients vs 0.2% in patients receiving placebo).

Withhold STIVARGA for Grade 3 or 4 infections, or worsening infection of any grade. Resume STIVARGA at the same dose following resolution of infection *[see Dosage and Administration (2.2)]*.

5.3 Hemorrhage

STIVARGA caused an increased incidence of hemorrhage. The overall incidence (Grades 1-5) was 18.2% in 1142 patients treated with STIVARGA and 9.5% in patients receiving placebo in randomized, placebo-controlled trials. The incidence of grade 3 or greater hemorrhage in patients treated with STIVARGA was 3.0%. The incidence of fatal

hemorrhagic events was 0.7%, involving the central nervous system or the respiratory, gastrointestinal, or genitourinary tracts.

Permanently discontinue STIVARGA in patients with severe or life-threatening hemorrhage. Monitor INR levels more frequently in patients receiving warfarin *[see Clinical Pharmacology (12.3)]*.

5.4 Gastrointestinal Perforation or Fistula

Gastrointestinal perforation occurred in 0.6% of 4518 patients treated with STIVARGA across all clinical trials of STIVARGA administered as as single agent; this included eight fatal events.

Gastrointestinal fistula occurred in 0.8% of patients treated with STIVARGA and 0.2% of patients in placebo arm across randomized, placebo-controlled trials. Permanently discontinue STIVARGA in patients who develop gastrointestinal perforation or fistula.

5.5 Dermatologic Toxicity

In randomized, placebo-controlled trials, adverse skin reactions occurred in 71.9% of patients in the regorafenib arm and in 25.5% of patients in the placebo arm, including hand-foot skin reaction (HFSR) also known as palmar-plantar erythrodysesthesia syndrome (PPES), and severe rash requiring dose modification.

In the randomized, placebo-controlled trials, the overall incidence of HFSR was higher in 1142 STIVARGA-treated patients (53%) than in the placebo-treated patients (8%). Most cases of HFSR in STIVARGA-treated patients appeared during the first cycle of treatment. The incidences of Grade 3 HFSR (16% versus <1%), Grade 3 rash (3% versus <1%), serious adverse reactions of erythema multiforme (<0.1% vs. 0%) and Stevens-Johnson Syndrome (<0.1% vs. 0%) were also higher in STIVARGA-treated patients *[see Adverse Reactions (6.1)]*. Across all trials, a higher incidence of HFSR was observed in Asian patients treated with STIVARGA (all grades: 72%; Grade 3: 18%) *[see Use in Specific Populations (8.8)]*.

Toxic epidermal necrolysis occurred in 0.02% of 4518 STIVARGA-treated patients across all clinical trials of STIVARGA administered as a single agent.

Withhold STIVARGA, reduce the dose, or permanently discontinue STIVARGA depending on the severity and persistence of dermatologic toxicity *[see Dosage and Administration (2.2)]*. Institute supportive measures for symptomatic relief.

5.6 Hypertension

In randomized, placebo-controlled trials, hypertensive crisis occurred in 0.2% of patients in the regorafenib arms and in none of the patients in the placebo arms. STIVARGA caused an increased incidence of hypertension (30% versus 8% in CORRECT, 59% versus 27% in GRID, and 31% versus 6% in RESORCE) *[see Adverse Reactions (6.1)]*. The onset of hypertension occurred during the first cycle of treatment in most patients who developed hypertension (67% in randomized, placebo-controlled trials).

Do not initiate STIVARGA unless blood pressure is adequately controlled. Monitor blood pressure weekly for the first 6 weeks of treatment and then every cycle, or more frequently, as clinically indicated. Temporarily or permanently withhold STIVARGA for severe or uncontrolled hypertension *[see Dosage and Administration (2.2)]*.

5.7 Cardiac Ischemia and Infarction

STIVARGA increased the incidence of myocardial ischemia and infarction (0.9% vs 0.2%) in randomized placebo-controlled trials *[see Adverse Reactions (6.1)]*. Withhold STIVARGA in patients who develop new or acute onset cardiac ischemia or infarction. Resume STIVARGA only after resolution of acute cardiac ischemic events, if the potential benefits outweigh the risks of further cardiac ischemia.

5.8 Reversible Posterior Leukoencephalopathy Syndrome

Reversible posterior leukoencephalopathy syndrome (RPLS), a syndrome of subcortical vasogenic edema diagnosed by characteristic finding on MRI, occurred in one of 4800 STIVARGA-treated patients across all clinical trials. Perform an evaluation for RPLS in any patient presenting with seizures, severe headache, visual disturbances, confusion or altered mental function. Discontinue STIVARGA in patients who develop RPLS.

5.9 Wound Healing Complications

No formal studies of the effect of regorafenib on wound healing have been conducted. Since vascular endothelial growth factor receptor (VEGFR) inhibitors such as STIVARGA can impair wound healing, discontinue treatment with STIVARGA at least 2 weeks prior to scheduled surgery. The decision to resume STIVARGA after surgery should be based on clinical judgment of adequate wound healing. Discontinue STIVARGA in patients with wound dehiscence.

5.10 Embryo-Fetal Toxicity

Based on animal studies and its mechanism of action, STIVARGA can cause fetal harm when administered to a pregnant woman. There are no available data on STIVARGA use in pregnant women. Regorafenib was embryolethal and teratogenic in rats and rabbits at exposures lower than human exposures at the recommended dose, with increased incidences of cardiovascular, genitourinary, and skeletal malformations. Advise pregnant women of the potential risk to a fetus.

Advise females of reproductive potential to use effective contraception during treatment with STIVARGA and for 2 months after the final dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with STIVARGA and for 2 months after the final dose *[see Use in Specific Populations (8.1), (8.3)]*.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in the labeling:

- Hepatotoxicity *[see Warnings and Precautions (5.1)]*
- Infections *[(see Warnings and Precautions (5.2)]*
- Hemorrhage *[see Warnings and Precautions (5.3)]*
- Gastrointestinal Perforation or Fistula *[see Warnings and Precautions (5.4)]*
- Dermatological Toxicity *[see Warnings and Precautions (5.5)]*
- Hypertension *[see Warnings and Precautions (5.6)]*
- Cardiac Ischemia and Infarction *[see Warnings and Precautions (5.7)]*
- Reversible Posterior Leukoencephalopathy Syndrome (RPLS) *[see Warnings and Precautions (5.8)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rate observed in practice.

The data described in the WARNINGS AND PRECAUTIONS section reflect exposure to STIVARGA in more than 4800 patients who were enrolled in four randomized, placebo-controlled trials (n=1142), an expanded access program (CONSIGN, n=2864), or single arm clinical trials (single agent or in combination with other agents). There were 4518 patients who received STIVARGA as a single agent; the distribution of underlying malignancies was 80% CRC, 4% GIST, 10% HCC, 6% other solid tumors; and 74% were White, 11% Asian, and 15% race not known. Among these 4518 patients, 83% received STIVARGA for at least 21 days and 20% received STIVARGA for 6 months or longer.

In randomized placebo-controlled trials (CORRECT, GRID, RESORCE and CONCUR), the most frequently observed adverse drug reactions (≥20%) in patients receiving STIVARGA are pain (including gastrointestinal and abdominal pain), HFSR, asthenia/fatigue, diarrhea, decreased appetite/food intake, hypertension, infection, dysphonia, hyperbilirubinemia, fever, mucositis, weight loss, rash, and nausea.

Colorectal Cancer

The safety data described below, except where noted, are derived from a randomized (2:1), double-blind, placebo-controlled trial (CORRECT) in which 500 patients (median age 61 years; 61% men) with previously-treated metastatic colorectal cancer (CRC) received STIVARGA as a single agent at the dose of 160 mg daily for the first 3 weeks of each 4 week treatment cycle and 253 patients (median age 61 years; 60% men) received placebo. The median duration of therapy was 1.7 months (range 2 days, 10.8 months) for patients receiving STIVARGA. Due to adverse reactions, 61% of the patients receiving STIVARGA required a dose interruption and 38% of the patients had their dose reduced. Adverse reactions that resulted in treatment discontinuation occurred in 8.2% of STIVARGA-treated patients compared to 1.2% of patients who received placebo. Hand-foot skin reaction (HFSR) and rash were the most common reasons for permanent discontinuation of STIVARGA.

Table 1 provides the incidence of adverse reactions (≥10%) in patients in CORRECT.

Table 1: Adverse drug reactions reported in ≥10% of patients treated with STIVARGA in CORRECT and reported more commonly than in patients receiving placebo[a]

Adverse Reactions	STIVARGA (N=500)		Placebo (N=253)	
	Grade		Grade	
	All %	≥ 3 %	All %	≥ 3 %
General disorders and administration site conditions				
Asthenia/fatigue	64	15	46	9
Pain	59	9	48	7
Fever	28	2	15	0
Metabolism and nutrition disorders				
Decreased appetite and food intake	47	5	28	4
Skin and subcutaneous tissue disorders				
HFSR/PPES	45	17	7	0
Rash [b]	26	6	4	<1
Gastrointestinal disorders				
Diarrhea	43	8	17	2
Mucositis	33	4	5	0
Investigations				
Weight loss	32	<1	10	0
Infections and infestations				
Infection [c]	31	9	17	6
Vascular disorders				
Hypertension	30	8	8	<1
Hemorrhage [c]	21	2	8	<1
Respiratory, thoracic and mediastinal disorders				
Dysphonia	30	0	6	0
Nervous system disorders				
Headache	10	<1	7	0

[a] Adverse reactions graded according to National Cancer Institute Common Toxicity for Adverse Events version 3.0 (NCI CTCAE v3.0).

[b] The term rash represents reports of events of drug eruption, rash, erythematous rash, generalized rash, macular rash, maculo-papular rash, papular rash, and pruritic rash.

[c] Fatal outcomes observed.

Table 2 provides laboratory abnormalities observed in CORRECT.

Table 2: Laboratory test abnormalities reported in CORRECT

Laboratory Parameter	STIVARGA (N=500 [a])			Placebo (N=253 [a])		
	Grade [b]			Grade [b]		
	All %	3 %	4 %	All %	3 %	4 %
Blood and lymphatic system disorders						
Anemia	79	5	1	66	3	0
Thrombocytopenia	41	2	<1	17	<1	0
Neutropenia	3	1	0	0	0	0
Lymphopenia	54	9	0	35	4	<1
Metabolism and nutrition disorders						
Hypocalcemia	59	1	<1	18	1	0
Hypokalemia	26	4	0	8	<1	0
Hyponatremia	30	7	1	22	4	0
Hypophosphatemia	57	31	1	11	4	0
Hepatobiliary disorders						
Hyperbilirubinemia	45	10	3	17	5	3
Increased AST	65	5	1	46	4	1
Increased ALT	45	5	1	30	3	<1
Renal and urinary disorders						
Proteinuria[c]	84	2	0	61	1	0
Investigations						
Increased INR[d]	24	4	N/A	17	2	N/A
Increased Lipase	46	9	2	19	3	2
Increased Amylase	26	2	<1	17	2	<1

[a] % based on number of patients with post-baseline samples which may be less than 500 (regorafenib) or 253 (placebo).
[b] NCI CTCAE v3.0.
[c] Based on urine protein-creatinine ratio data.
[d] International normalized ratio: No Grade 4 denoted in NCI CTCAE, v3.0.

Gastrointestinal Stromal Tumors

The safety data described below are derived from a randomized (2:1), double-blind, placebo-controlled trial (GRID) in which 132 patients (median age 60 years; 64% men) with previously-treated GIST received STIVARGA as a single agent at a dose of 160 mg daily for the first 3 weeks of each 4 week treatment cycle and 66 patients (median age 61 years; 64% men) received placebo. The median duration of therapy was 5.7 months (range 1 day, 11.7 months) for patients receiving STIVARGA. Dose interruptions for adverse events were required in 58% of patients receiving STIVARGA and 50% of patients had their dose reduced. Adverse reactions that resulted in treatment discontinuation were reported in 2.3% of STIVARGA-treated patients compared to 1.5% of patients who received placebo.

Table 3 provides the incidence of adverse reactions (≥10%) in patients in GRID.

Table 3: Adverse reactions reported in ≥10% patients treated with STIVARGA in GRID and reported more commonly than in patients receiving placebo[a]

Adverse Reactions	STIVARGA (N=132)		Placebo (N=66)	
	Grade		Grade	
	All %	≥ 3 %	All %	≥ 3 %
Skin and subcutaneous tissue disorders				
HFSR/PPE	67	22	12	2
Rash [b]	30	7	3	0
Alopecia	24	2	2	0
General disorders and administration site conditions				
Asthenia/Fatigue	52	4	39	2
Fever	21	0	11	2
Vascular disorders				
Hypertension	59	28	27	5
Hemorrhage	11	4	3	0
Gastrointestinal disorders				
Pain	60	8	55	14
Diarrhea	47	8	9	0
Mucositis	40	2	8	2
Nausea	20	2	12	2
Vomiting	17	<1	8	0
Respiratory, thoracic and mediastinal disorders				
Dysphonia	39	0	9	0
Infections and infestations				
Infection [c]	32	5	5	0
Metabolism and nutrition disorders				
Decreased appetite and food intake	31	<1	21	3
Hypothyroidism [d]	18	0	6	0
Nervous system disorders				
Headache	16	0	9	0
Investigations				
Weight loss	14	0	8	0
Musculoskeletal and connective tissue disorders				
Muscle spasms	14	0	3	0

[a] Adverse reactions graded according to NCI CTCAE v4.0.
[b] The term rash represents reports of events of rash, erythematous rash, macular rash, maculo-papular rash, papular rash and pruritic rash.
[c] Fatal outcomes observed.
[d] Hypothyroidism incidence based on subset of patients with normal TSH and no thyroid supplementation at baseline.

Table 4 provides laboratory abnormalities observed in GRID.

Table 4: Laboratory test abnormalities reported in GRID

Laboratory Parameter	STIVARGA (N=132 [a])			Placebo (N=66 [a])		
	Grade [b]			Grade [b]		
	All %	3 %	4 %	All %	3 %	4 %
Blood and lymphatic system disorders						
Thrombocytopenia	13	1	0	2	0	2
Neutropenia	16	2	1	12	3	0
Lymphopenia	30	8	0	24	3	0
Metabolism and nutrition disorders						
Hypocalcemia	17	2	0	5	0	0
Hypokalemia	21	3	0	3	0	0
Hypophosphatemia	55	20	2	3	2	0
Hepatobiliary disorders						
Hyperbilirubinemia	33	3	1	12	2	0
Increased AST	58	3	1	47	3	0
Increased ALT	39	4	1	39	2	0
Renal and urinary disorders						
Proteinuria [c]	59	3	- [d]	53	3	- [d]
Investigations						
Increased Lipase	14	0	1	5	0	0

[a] Percent based on number of patients with post-baseline samples which may be less than 132 (regorafenib) or 66 (placebo).
[b] NCI CTCAE v4.0.
[c] Based on urine protein-creatinine ratio data.
[d] No Grade 4 denoted in NCI CTCAE v4.0.

Hepatocellular Carcinoma

The safety data described below are derived from a randomized (2:1), double-blind, placebo-controlled trial (RESORCE) in which patients with previously-treated HCC received either STIVARGA (n=374) 160 mg orally on days 1-21 of each 4 week treatment cycle or placebo (n=193). The median age was 63 years, 88% were men, 98% had Child-Pugh A cirrhosis, 66% had an ECOG performance status (PS) of 0 and 34% had PS of 1. The median duration of therapy was 3.5 months (range 1 day to 29.4 months) for patients receiving STIVARGA. Of the patients receiving STIVARGA, 33% were exposed to STIVARGA for greater than or equal to 6 months and 14% were exposed to STIVARGA for greater than or equal to 12 months. Dose interruptions for adverse events were required in 58.3% of patients receiving STIVARGA and 48% of patients had their dose reduced. The most common adverse reactions requiring dose modification (interruption or dose reduction) were HFSR/PPES (20.6%), blood bilirubin increase (5.9%), fatigue (5.1%) and diarrhea (5.3%). Adverse reactions that resulted in treatment discontinuation were reported in 10.4% of STIVARGA-treated patients compared to 3.6% of patients who received placebo; the most common adverse reactions requiring discontinuation of STIVARGA were HFSR/PPES (1.9%) and AST increased (1.6%).

Table 5 provides the incidence of adverse reactions (≥10%) in patients in RESORCE.

Table 5: Adverse reactions reported in ≥10% of patients treated with STIVARGA in RESORCE and reported more commonly than in patients receiving placebo[a]

Adverse Reactions	STIVARGA (N=374)		Placebo (N=193)	
	Grade		Grade	
	All %	≥ 3 %	All %	≥ 3 %
Skin and subcutaneous tissue disorders				
HFSR/PPE	51	12	7	<1
General disorders and administration site conditions				
Pain	55	9	44	8
Asthenia/Fatigue	42	10	33	5
Fever	20	0	7	0
Vascular disorders				
Hypertension	31	15	6	5
Hemorrhage [b]	18	5	16	8
Gastrointestinal disorders				
Diarrhea	41	3	15	0
Nausea	17	<1	13	0
Vomiting	13	<1	7	<1
Mucositis	13	1	2	≤1
Respiratory, thoracic and mediastinal disorders				
Dysphonia	18	0	2	0
Infections and infestations				
Infection [b]	31	8	18	6
Metabolism and nutrition disorders				
Decreased appetite and food intake	31	3	15	2
Investigations				
Weight loss	13	2	4	0
Musculoskeletal and connective tissue disorders				
Muscle spasms	10	0	2	0

[a] Adverse reactions graded according to NCI CTCAE v4.0.
[b] Fatal outcomes observed.

Other clinically significant adverse reactions observed in less than 10% of STIVARGA-treated patients were: alopecia (7%), hypothyroidism (6.4%), pancreatitis (1.6%), exfoliative rash (1.3%), tremor (1.3%), erythema multiforme (0.8%), myocardial ischemia (0.8%), gastrointestinal fistula (0.3%), and myocardial infarction (0.3%).

Table 6 provides laboratory abnormalities observed in RESORCE.

Table 6: Laboratory test abnormalities reported in RESORCE

Laboratory Parameter	STIVARGA (N=374 [a])			Placebo (N=193 [a])		
	Grade [b]			Grade [b]		
	All %	3 %	4 %	All %	3 %	4 %
Blood and lymphatic system disorders						
Thrombocytopenia	63	5	<1	50	0	0
Neutropenia	14	3	0	15	<1	<1
Lymphopenia	68	16	2	59	11	<1
Metabolism and nutrition disorders						
Hypocalcemia	23	<1	0	10	0	0
Hypokalemia	31	4	<1	9	2	0
Hypophosphatemia	70	32	2	31	7	0
Hepatobiliary disorders						
Hyperbilirubinemia	78	13	3	55	11	5
Increased AST	93	16	2	84	17	3
Increased ALT	70	6	<1	59	5	0
Renal and urinary disorders						
Proteinuria [c]	51	17	- [d]	37	3	- [d]
Investigations						
Increased INR	44	<1	- [d]	35	2	- [d]
Increased Lipase	41	11	3	27	8	1
Increased Amylase	23	3	<1	19	2	<1

[a] Percent based on number of patients with post-baseline samples which may be less than 374 (regorafenib) or 193 (placebo).
[b] NCI CTCAE v4.0.
[c] Based on dipstick data.
[d] No Grade 4 denoted in NCI CTCAE v4.0.

6.2 Postmarketing Experience

The following adverse reaction has been identified during postapproval use of STIVARGA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure:

- hypersensitivity reaction

7 DRUG INTERACTIONS

7.1 Effect of Strong CYP3A4 Inducers on Regorafenib

Co-administration of a strong CYP3A4 inducer with STIVARGA decreased the plasma concentrations of regorafenib, increased the plasma concentrations of the active metabolite M-5, and resulted in no change in the plasma concentrations of the active metabolite M-2 *[see Clinical Pharmacology (12.3)]*, and may lead to decreased efficacy. Avoid concomitant use of STIVARGA with strong CYP3A4 inducers (e.g. rifampin, phenytoin, carbamazepine, phenobarbital, and St. John's Wort).

7.2 Effect of Strong CYP3A4 Inhibitors on Regorafenib

Co-administration of a strong CYP3A4 inhibitor with STIVARGA increased the plasma concentrations of regorafenib and decreased the plasma concentrations of the active metabolites M-2 and M-5 *[see Clinical Pharmacology (12.3)]*, and may lead to increased toxicity. Avoid concomitant use of STIVARGA with strong CYP3A4 inhibitors (e.g. clarithromycin, grapefruit juice, itraconazole, ketoconazole, nefazodone, posaconazole, telithromycin, and voriconazole).

7.3 Effect of Regorafenib on Breast Cancer Resistance Protein (BCRP) Substrates

Co-administration of STIVARGA with a BCRP substrate increased the plasma concentrations of the BCRP substrate *[see Clinical Pharmacology (12.3)]*. Monitor patients closely for signs and symptoms of exposure related toxicity to the BCRP substrate (e.g. methotrexate, fluvastatin, atorvastatin). Consult the concomitant BCRP substrate product information when considering administration of such products together with STIVARGA.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on animal studies and its mechanism of action, STIVARGA can cause fetal harm when administered to a pregnant woman. There are no available data on STIVARGA use in pregnant women. Administration of regorafenib was embryolethal and teratogenic in rats and rabbits at exposures lower than human exposures at the recommended dose, with increased incidences of cardiovascular, genitourinary, and skeletal malformations *[see Data]*. Advise pregnant women of the potential hazard to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4 % and 15 to 20%, respectively.

Data

Animal Data

In embryo-fetal development studies, a total loss of pregnancy (100% resorption of litter) was observed in rats at doses as low as 1 mg/kg (approximately 6% of the recommended human dose, based on body surface area) and in rabbits at doses as low as 1.6 mg/kg (approximately 25% of the human exposure at the clinically recommended dose measured by AUC).

In a single dose distribution study in pregnant rats, there was increased penetration of regorafenib across the blood-brain barrier in fetuses compared to dams. Daily administration of regorafenib to pregnant rats during organogenesis resulted in fetal findings of delayed ossification at doses ≥ 0.8 mg/kg (approximately 5% of the recommended human dose based on body surface area) and dose-dependent increases in skeletal malformations including cleft palate and enlarged fontanelle at doses ≥ 1 mg/kg (approximately 10% of the clinical exposure based on AUC). At doses ≥ 1.6 mg/kg (approximately 11% of the recommended human dose based on body surface area), there were dose-dependent increases in the incidence of cardiovascular malformations, external abnormalities, diaphragmatic hernia, and dilation of the renal pelvis.

In pregnant rabbits administered regorafenib daily during organogenesis, there were findings of ventricular septal defects evident at the lowest tested dose of 0.4 mg/kg (approximately 7% of the AUC in patients at the recommended dose). At doses of ≥ 0.8 mg/kg (approximately 15% of the human exposure at the recommended human dose based on AUC), administration of regorafenib resulted in dose-dependent increases in the incidence of additional cardiovascular malformations and skeletal anomalies, as well as significant adverse effects on the urinary system including missing kidney/ureter; small, deformed and malpositioned kidney; and hydronephrosis. The proportion of viable fetuses that were male decreased with increasing dose in two rabbit embryo-fetal toxicity studies.

8.2 Lactation

Risk Summary

There are no data on the presence of regorafenib or its metabolites in human milk, the effects of regorafenib on the breastfed infant, or on milk production. In rats, regorafenib and its metabolites are excreted in milk. Because of the potential for serious adverse reactions in breastfed infants from STIVARGA, do not breastfeed during treatment with STIVARGA and for 2 weeks after the final dose.

8.3 Females and Males of Reproductive Potential

Contraception

Females

Use effective contraception during treatment and for 2 months after completion of therapy.

Males

Advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 2 months following the final dose of STIVARGA *[see Nonclinical Toxicology (13.1)]*.

Infertility

There are no data on the effect of STIVARGA on human fertility. Results from animal studies indicate that regorafenib can impair male and female fertility *[see Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

The safety and efficacy of STIVARGA in pediatric patients less than 18 years of age have not been established.

Animal Data

In 28-day repeat-dose studies in rats there were dose-dependent findings of dentin alteration and angiectasis. These findings occurred at regorafenib doses as low as 4 mg/kg (approximately 25% of the AUC in humans at the recommended dose). In 13-week repeat-dose studies in dogs there were similar findings of dentin alteration at doses as low as 20 mg/kg (approximately 43% of the AUC in humans at the recommended dose). Administration of regorafenib in these animals also led to persistent growth and thickening of the femoral epiphyseal growth plate.

8.5 Geriatric Use

Of the 1142 STIVARGA-treated patients enrolled in randomized, placebo-controlled trials, 40% were 65 years of age and over, while 10% were 75 and over. No overall differences in efficacy were observed between these patients and younger patients. There was an increased incidence of Grade 3 hypertension (18% versus 9%) in the placebo-controlled trials among STIVARGA-treated patients 65 years of age and older as compared to younger patients. In addition, one Grade 4 hypertension event has been reported in the 65 years and older age group and none in the younger age group.

8.6 Hepatic Impairment

No dose adjustment is recommended in patients with mild (total bilirubin ≤ULN and AST >ULN, or total bilirubin >ULN to ≤1.5 times ULN) or moderate (total bilirubin >1.5 to ≤3 times ULN and any AST) hepatic impairment, *[see Clinical Pharmacology (12.3)]*. Closely monitor patients with hepatic impairment for adverse reactions *[see Warnings and Precautions (5.1)]*.

STIVARGA is not recommended for use in patients with severe hepatic impairment (total bilirubin >3x ULN) as STIVARGA has not been studied in this population.

8.7 Renal Impairment

No dose adjustment is recommended for patients with renal impairment. The pharmacokinetics of regorafenib have not been studied in patients who are on dialysis and there is no recommended dose for this patient population *[see Clinical Pharmacology (12.3)]*.

8.8 Race

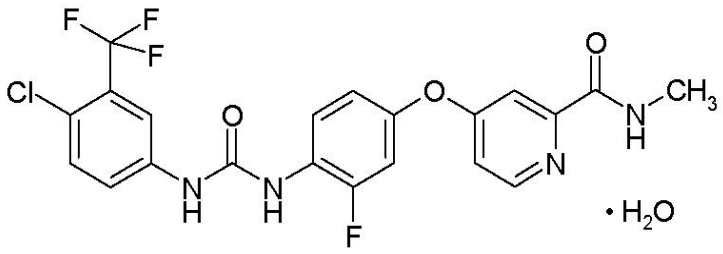
Based on pooled data from three placebo-controlled trials (CORRECT, GRID and CONCUR), a higher incidence of HFSR and liver function test abnormalities occurred in Asian patients treated with STIVARGA as compared with Whites *[see Warnings and Precautions (5.1, 5.5)]*. No starting dose adjustment is necessary based on race.

10 OVERDOSAGE

The highest dose of STIVARGA studied clinically is 220 mg per day. The most frequently observed adverse drug reactions at this dose were dermatological events, dysphonia, diarrhea, mucosal inflammation, dry mouth, decreased appetite, hypertension, and fatigue. There is no known antidote for STIVARGA overdose. In the event of suspected overdose, interrupt STIVARGA, institute supportive care, and observe until clinical stabilization.

11 DESCRIPTION

STIVARGA (regorafenib) is a multikinase inhibitor with the chemical name 4-[4-({[4-chloro-3-(trifluoromethyl) phenyl] carbamoyl} amino)-3-fluorophenoxy]-N-methylpyridine-2-carboxamide monohydrate. Regorafenib has the following structural formula:



Regorafenib is a monohydrate and it has a molecular formula $C_{21}H_{15}ClF_4N_4O_3 \cdot H_2O$ and a molecular weight of 500.83. Regorafenib is practically insoluble in water, slightly soluble in acetonitrile, methanol, ethanol, and ethyl acetate and sparingly soluble in acetone.

STIVARGA tablets for oral administration are formulated as light pink, oval-shaped tablets debossed with "BAYER" on one side and "40" on the other. Each tablet contains 40 mg of regorafenib in the anhydrous state, which corresponds to 41.49 mg of regorafenib monohydrate, and the following inactive ingredients: cellulose microcrystalline, croscarmellose sodium, magnesium stearate, povidone, and colloidal silicon dioxide. The film-coating contains the following inactive ingredients: ferric oxide red, ferric oxide yellow, lecithin (soy), polyethylene glycol 3350, polyvinyl alcohol, talc, and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Regorafenib is a small molecule inhibitor of multiple membrane-bound and intracellular kinases involved in normal cellular functions and in pathologic processes such as oncogenesis, tumor angiogenesis, metastasis and tumor immunity. In in vitro biochemical or cellular assays, regorafenib or its major human active metabolites M-2 and M-5 inhibited the activity of RET, VEGFR1, VEGFR2, VEGFR3, KIT, PDGFR-alpha, PDGFR-beta, FGFR1, FGFR2, TIE2, DDR2, TrkA, Eph2A, RAF-1, BRAF, BRAF V600E, SAPK2, PTK5, Abl and CSF1R at concentrations of regorafenib that have been achieved clinically. In in vivo models, regorafenib demonstrated anti-angiogenic activity in a rat tumor model and inhibition of tumor growth in several mouse xenograft models including some for human colorectal carcinoma, gastrointestinal stromal and hepatocellular carcinoma. Regorafenib also demonstrated anti-metastatic activity in a mouse xenograft model and two mouse orthotopic models of human colorectal carcinoma.

12.2 Pharmacodynamics

Cardiac Electrophysiology

The effect of multiple doses of STIVARGA (160 mg once daily for 21 days) on the QTc interval was evaluated in an open-label, single-arm study in 25 patients with advanced solid tumors. No large changes in the mean QTc interval (i.e., > 20 msec) were detected in the study.

12.3 Pharmacokinetics

Absorption

Following a single 160 mg dose of STIVARGA in patients with advanced solid tumors, regorafenib reaches a geometric mean peak plasma level (C_{max}) of 2.5 µg/mL at a median time of 4 hours and a geometric mean area under the plasma concentration vs. time curve (AUC) of 70.4 µg*h/mL. The AUC of regorafenib at steady-state increases less than dose proportionally at doses greater than 60 mg. At steady-state, regorafenib reaches a geometric mean C_{max} of 3.9 µg/mL and a geometric mean AUC of 58.3 µg*h/mL. The coefficient of variation of AUC and C_{max} is between 35% and 44%.

The mean relative bioavailability of tablets compared to an oral solution is 69% to 83%.

In a food-effect study, 24 healthy men received a single 160 mg dose of STIVARGA on three separate occasions: under a fasted state, with a high-fat meal and with a low-fat meal. A high-fat meal (945 calories and 54.6 g fat) increased the mean AUC of regorafenib by 48% and decreased the mean AUC of the M-2 and M-5 metabolites by 20% and 51%, respectively, as compared to the fasted state. A low-fat meal (319 calories and 8.2 g fat) increased the mean AUC of regorafenib, M-2 and M-5 by 36%, 40% and 23%, respectively as compared to fasted conditions. STIVARGA was administered with a low-fat meal in the CORRECT and GRID studies *[see Dosage and Administration (2.1), Clinical Studies (14)]*.

Distribution

Regorafenib undergoes enterohepatic circulation with multiple plasma concentration peaks observed across the 24-hour dosing interval. Regorafenib is highly bound (99.5%) to human plasma proteins.

Elimination

Following a single 160 mg oral dose of STIVARGA, the geometric mean (minimum to maximum) elimination half-lives for regorafenib and the M-2 metabolite in plasma are 28 hours (14 to 58 hours) and 25 hours (14 to 32 hours), respectively. M-5 has a longer mean (minimum to maximum) elimination half-life of 51 hours (32 to 70 hours).

Metabolism

Regorafenib is metabolized by CYP3A4 and UGT1A9. The main circulating metabolites of regorafenib measured at steady-state in human plasma are M-2 (N-oxide) and M-5 (N-oxide and N-desmethyl). Both metabolites have similar in vitro pharmacological activity and steady-state concentrations as regorafenib. M-2 and M-5 are highly protein bound (99.8% and 99.95%, respectively).

Excretion

Approximately 71% of a radiolabeled dose was excreted in feces (47% as parent compound, 24% as metabolites) and 19% of the dose was excreted in urine (17% as glucuronides) within 12 days after administration of a radiolabeled oral solution at a dose of 120 mg.

Specific Populations

Age, sex, race and weight had no clinically meaningful effect on the pharmacokinetics of regorafenib.

Hepatic Impairment

Based on a population pharmacokinetic analysis, no clinically important differences in the mean total exposure of regorafenib, including M-2 and M-5, were noted amongst patients with normal liver function (total bilirubin and AST ≤ ULN, n=744), mild hepatic impairment (total bilirubin ≤ ULN and AST >ULN or total bilirubin >ULN to ≤1.5x ULN, n=437), and moderate hepatic impairment (total bilirubin >1.5x to ≤3x ULN and any AST, n=36). The pooled analysis included 391 patients with HCC of whom 116, 249, and 26 were categorized as having normal liver function, mild, and

moderate hepatic impairment, respectively. The pharmacokinetics of regorafenib were not evaluated in patients with severe hepatic impairment (total bilirubin >3x ULN).

Renal Impairment

The pharmacokinetics of regorafenib, M-2, and M-5 was evaluated in 6 patients with severe renal impairment (CLcr 15-29 mL/min) and 18 patients with normal/mild renal function (CLcr ≥60 mL/min) following the administration of STIVARGA at a dose of 160 mg daily for 21 days. No differences in the mean steady-state exposure of regorafenib, M-2, or M-5 were observed in patients with severe renal impairment compared to patients with normal renal function. The pharmacokinetics of regorafenib has not been studied in patients with end-stage renal disease on dialysis.

Drug Interaction Studies

Effect of Regorafenib on Cytochrome P450 Substrates: In vitro studies suggested that regorafenib is an inhibitor of CYP2C8, CYP2C9, CYP2B6, CYP3A4 and CYP2C19; M-2 is an inhibitor of CYP2C9, CYP2C8, CYP3A4 and CYP2D6, and M-5 is an inhibitor of CYP2C8. In vitro studies suggested that regorafenib is not an inducer of CYP1A2, CYP2B6, CYP2C19, and CYP3A4 enzyme activity.

Patients with advanced solid tumors received single oral doses of CYP substrates, 2 mg of midazolam (CYP3A4), 40 mg of omeprazole (CYP2C19) and 10 mg of warfarin (CYP2C9) or 4 mg of rosiglitazone (CYP2C8) one week before and two weeks after STIVARGA at a dose of 160 mg once daily. No clinically meaningful effect was observed in the mean AUC of rosiglitazone (N=12) or the mean omeprazole (N=11) plasma concentrations measured 6 hours after dosing or the mean AUC of midazolam (N=15). The mean AUC of warfarin (N=8) increased by 25% *[see Warnings and Precautions (5.2)]*.

Effect of CYP3A4 Strong Inducers on Regorafenib: Twenty-two healthy men received a single 160 mg dose of STIVARGA alone and then 7 days after starting rifampin. Rifampin, a strong CYP3A4 inducer, was administered at a dose of 600 mg daily for 9 days. The mean AUC of regorafenib decreased by 50% and mean AUC of M-5 increased by 264%. No change in the mean AUC of M-2 was observed *[see Drug Interactions (7.1)]*.

Effect of CYP3A4 Strong Inhibitors on Regorafenib: Eighteen healthy men received a single 160 mg dose of STIVARGA alone and then 5 days after starting ketoconazole. Ketoconazole, a strong CYP3A4 inhibitor, was administered at a dose of 400 mg daily for 18 days. The mean AUC of regorafenib increased by 33% and the mean AUC of M-2 and M-5 both decreased by 93% *[see Drug Interactions (7.2)]*.

Effect of Neomycin on Regorafenib: Twenty-seven healthy men received a single 160 mg dose of STIVARGA and then 5 days after starting neomycin. Neomycin, a non-absorbable antibiotic, was administered at a dose of 1 gram three times daily for 5 days. No clinically meaningful effect on the mean AUC of regorafenib was observed; however, the mean AUC of M-2 decreased by 76% and the mean AUC of M-5 decreased by 86%. The decreased exposure of M-2 and M-5 may result in a decreased efficacy of STIVARGA. The effects of other antibiotics on the exposure of regorafenib and its active metabolites have not been studied.

Effect of Regorafenib on UGT1A1 Substrates: In vitro studies showed that regorafenib, M-2, and M-5 competitively inhibit UGT1A9 and UGT1A1 at therapeutically relevant concentrations. Eleven patients received irinotecan-containing combination chemotherapy with STIVARGA at a dose of 160 mg. The mean AUC of irinotecan increased by 28% and the mean AUC of SN-38 increased by 44% when irinotecan was administered 5 days after the last of 7 daily doses of STIVARGA.

Effect of Regorafenib on BCRP Substrates: Administration of regorafenib (160 mg for 14 days) prior to administration of a single dose of rosuvastatin (5 mg), a BCRP substrate, resulted in a 3.8-fold increase in mean exposure (AUC) of rosuvastatin and a 4.6-fold increase in C_{max} *[see Drug Interactions (7.3)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Studies examining the carcinogenic potential of regorafenib have not been conducted. Regorafenib itself did not demonstrate genotoxicity in in vitro or in vivo assays; however, a major human active metabolite of regorafenib, (M-2), was positive for clastogenicity, causing chromosome aberration in Chinese hamster V79 cells.

Dedicated studies to examine the effects of regorafenib on fertility have not been conducted; however, there were histological findings of tubular atrophy and degeneration in the testes, atrophy in the seminal vesicle, and cellular debris and oligospermia in the epididymides in male rats at doses similar to those in human at the clinical recommended dose based on AUC. In female rats, there were increased findings of necrotic corpora lutea in the ovaries at the same exposures. There were similar findings in dogs of both sexes in repeat dose studies at exposures approximately 83% of the human exposure at the recommended human dose based on AUC. These findings suggest that regorafenib may adversely affect fertility in humans.

13.2 Animal Toxicology and/or Pharmacology

In a chronic 26-week repeat dose study in rats there was a dose-dependent increase in the finding of thickening of the atrioventricular valve. At a dose that resulted in an exposure of approximately 12% of the human exposure at the recommended dose, this finding was present in half of the examined animals.

14 CLINICAL STUDIES

14.1 Colorectal Cancer

The clinical efficacy and safety of STIVARGA were evaluated in an international, multicenter, randomized (2:1), double-blind, placebo-controlled trial [Study "Patients with metastatic COloRectal cancer treated with REgorafenib or plaCebo after failure of standard Therapy" (CORRECT); NCT 01103323)] in 760 patients with previously-treated metastatic colorectal cancer. The major efficacy outcome measure was overall survival (OS); additional efficacy outcome measures included progression-free survival (PFS) and overall tumor response rate.

Patients were randomized to receive 160 mg regorafenib orally once daily (N=505) plus best supportive care (BSC) or placebo (N=255) plus BSC for the first 21 days of each 28-day cycle. STIVARGA was administered with a low-fat breakfast that contains less than 30% fat *[see Dosage and Administration (2.1), Clinical Pharmacology (12.3)]*. Treatment continued until disease progression or unacceptable toxicity.

Baseline demographics were: median age 61 years, 61% men, 78% White, and all patients had an ECOG performance status of 0 or 1. The primary sites of disease were colon (65%), rectum (29%), or both (6%). History of KRAS evaluation was reported for 729 (96%) patients; 430 (59%) of these patients were reported to have KRAS mutation. The median number of prior lines of therapy for metastatic disease was 3. All patients received prior treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, and with bevacizumab. All but one patient with KRAS mutation-negative tumors received panitumumab or cetuximab.

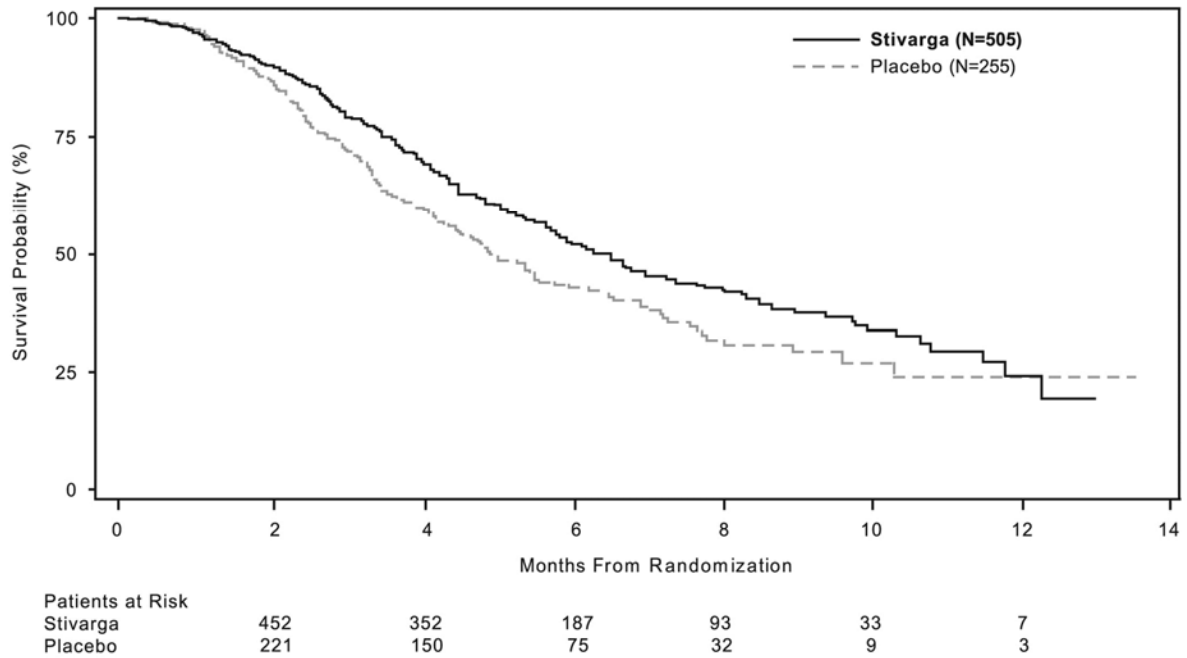
The addition of STIVARGA to BSC resulted in a statistically significant improvement in survival compared to placebo plus BSC (see Table 7 and Figure 1).

Table 7: Efficacy Results from CORRECT

	STIVARGA (N=505)	Placebo (N=255)
Overall Survival		
Number of Deaths (%)	275 (55%)	157 (62%)
Median Overall Survival (months)	6.4	5.0
95% CI [a]	(5.8, 7.3)	(4.4, 5.8)
HR (95% CI)	0.77 (0.64, 0.94)	
Stratified log-rank test p-value [b, c]	0.0102	
Progression-Free Survival		
Number of Deaths or Progressions (%)	417 (83%)	231 (91%)
Median Progression-Free Survival (months)	2.0	1.7
95% CI	(1.9, 2.3)	(1.7, 1.8)
HR (95% CI)	0.49 (0.42, 0.58)	
Stratified log-rank test p-value [c]	<0.0001	
Overall Response Rate		
Overall Response, N (%)	5 (1%)	1 (0.4%)
95% CI	0.3%, 2.3%	0%, 2.2%

[a] CI=confidence interval.
[b] Stratified by geographic region and time from diagnosis of metastatic disease.
[c] Crossed the O'Brien-Fleming boundary (two-sided p-value < 0.018) at second interim analysis.

Figure 1: Kaplan-Meier Curves of Overall Survival



14.2 Gastrointestinal Stromal Tumors

The efficacy and safety of STIVARGA were evaluated in an international, multicenter, randomized (2:1), double-blind, placebo-controlled trial [Study "GIST Regorafenib In progressive Disease" (GRID); NCT 01271712] in 199 patients with unresectable, locally advanced or metastatic gastrointestinal stromal tumor (GIST), who had been previously treated with imatinib mesylate and sunitinib malate. Randomization was stratified by line of therapy (third vs. four or more) and geographic region (Asia vs. rest of the world).

The major efficacy outcome measure of GRID was progression-free survival (PFS) based on disease assessment by independent radiological review using modified RECIST 1.1 criteria, in which lymph nodes and bone lesions were not target lesions and progressively growing new tumor nodule within a pre-existing tumor mass was progression. The key secondary outcome measure was overall survival.

Patients were randomized to receive 160 mg regorafenib orally once daily (N=133) plus best supportive care (BSC) or placebo (N=66) plus BSC for the first 21 days of each 28-day cycle. Treatment continued until disease progression or unacceptable toxicity. In GRID, the median age of patients was 60 years, 64% were men, 68% were White, and all patients had baseline ECOG performance status of 0 (55%) or 1 (45%). At the time of disease progression as assessed by central review, the study blind was broken and all patients were offered the opportunity to take STIVARGA at the investigator's discretion. Fifty-six (85%) patients randomized to placebo and 41 (31%) patients randomized to STIVARGA received open-label STIVARGA.

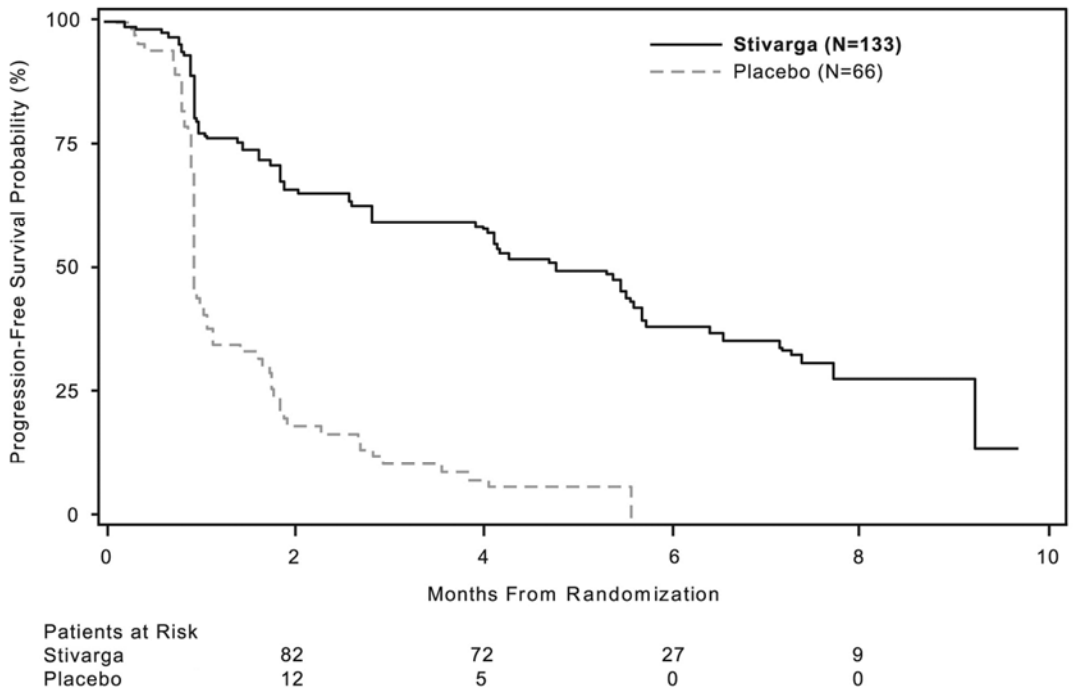
A statistically significant improvement in PFS was demonstrated among patients treated with STIVARGA compared to placebo (see Table 8 and Figure 2). There was no statistically significant difference in overall survival at the time of the planned interim analysis based on 29% of the total events for the final analysis.

Table 8: Efficacy Results for GRID

	STIVARGA (N=133)	**Placebo (N=66)**
Progression-Free Survival		
Number of Deaths or Progressions (%)	82 (62%)	63 (96%)
Median Progression-Free Survival (months)	4.8	0.9
95% CI	(3.9, 5.7)	(0.9, 1.1)
HR (95% CI)	0.27 (0.19, 0.39)	
Stratified log-rank test p-value [a]	<0.0001	
Overall Survival		
Number of Deaths (%)	29 (22%)	17 (26%)
Median Overall Survival (months)	NR[b]	NR[b]
HR (95% CI)	0.77 (0.42, 1.41)	
Stratified log-rank test p-value [a, b]	0.2	

[a] Stratified by line of treatment and geographical region.
[b] NR: Not reached.

Figure 2: Kaplan-Meier Curves of Progression-Free Survival for GRID



14.3 Hepatocellular Carcinoma (HCC)

The clinical efficacy and safety of STIVARGA were evaluated in an international, multicenter, randomized (2:1), double-blind, placebo-controlled trial [Study "REgorafenib after SORafenib in patients with hepatoCEllular carcinoma" (RESORCE); NCT 01774344]. The study enrolled adults with Child-Pugh A and Barcelona Clinic Liver Cancer Stage Category B or C hepatocellular carcinoma, with documented disease progression following sorafenib. The median duration of previous sorafenib treatment was 7.8 months; patients who permanently discontinued sorafenib due to toxicity or were unable to tolerate sorafenib doses of 400 mg once daily were ineligible.

Patients were randomized to receive 160 mg regorafenib orally once daily plus best supportive care (BSC) or matching placebo plus BSC for the first 21 days of each 28-day cycle until disease progression or unacceptable toxicity. Randomization was stratified by geographical region (Asia vs rest of world), ECOG performance status (0 vs 1), alpha-fetoprotein levels (<400 ng/mL vs ≥400 ng/mL), extrahepatic disease (presence vs absence), and macrovascular invasion (presence vs absence). The major efficacy outcome measure was overall survival (OS). Additional outcome measures were progression-free survival (PFS), overall tumor response rate (ORR) and duration of response as assessed by investigators using RECIST 1.1 and using modified RECIST (mRECIST) for HCC. Patients continued therapy with STIVARGA until clinical or radiological disease progression or unacceptable toxicity.

The characteristics of the study population were a median age of 63 years (range 19 to 85 years); 88% male; 41% Asian, 36% White, and 21% not reported; 66% had ECOG performance status (PS) of 0 and 34% had ECOG PS of 1; 98% had Child-Pugh A and 2% had Child-Pugh B. Risk factors for underlying cirrhosis included hepatitis B (38%), alcohol use (25%), hepatitis C (21%), and non-alcoholic steato hepatitis (7%). Macroscopic vascular invasion or extra-hepatic tumor spread was present in 81% of patients. Barcelona Clinic Liver Cancer (BCLC) was stage C in 87% and stage B in 13% of patients. All patients received prior sorafenib and 61% received prior loco-regional transarterial embolization or chemoinfusion procedures.

Efficacy results are summarized in Table 9 and Figure 3 below.

Table 9: Efficacy Results from Study RESORCE

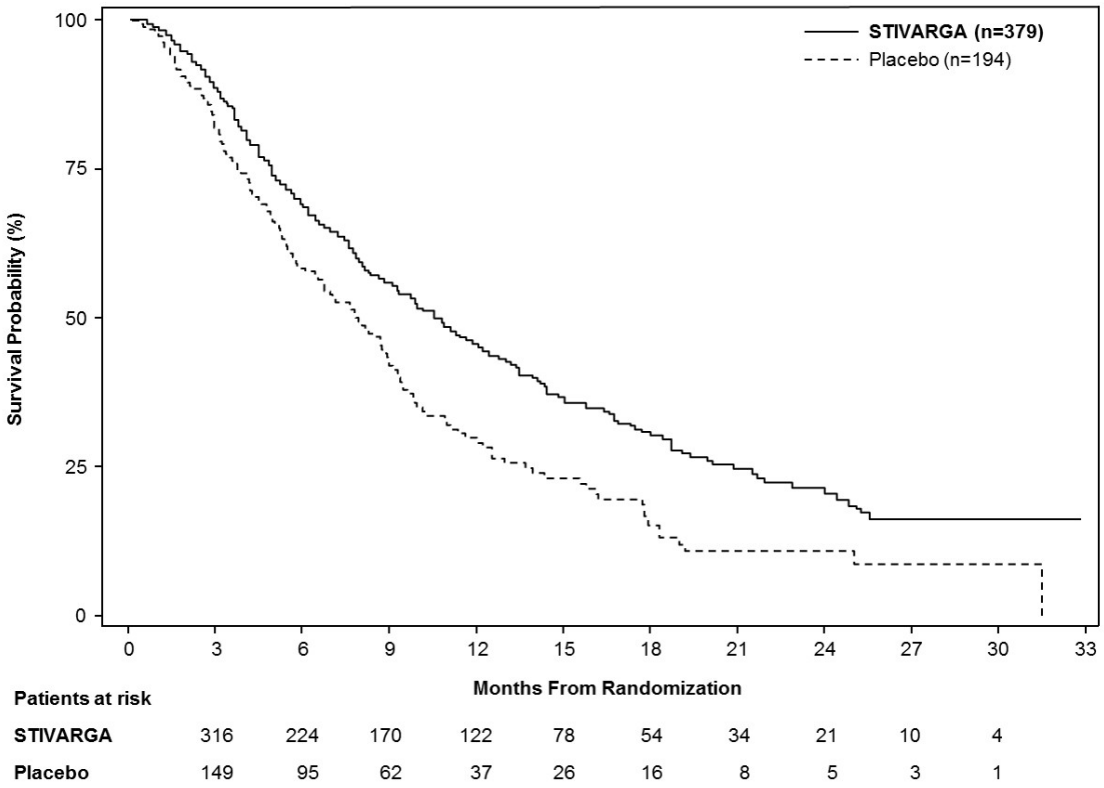
	STIVARGA n=379	**Placebo n=194**
Overall Survival		
Number of Deaths (%)	233 (62)	140 (72)
Median OS in months (95% CI[a])	10.6 (9.1, 12.1)	7.8 (6.3, 8.8)
Hazard Ratio[b] (95% CI[a])	0.63 (0.50, 0.79)	
P-value[c]	<0.0001	
Progression-free Survival (mRECIST)		
Number of Events (%)	293 (77)	181(93)
Progressive Disease	274 (72)	173 (89)
Death	19 (5)	8 (4)
Median PFS in months (95% CI[a])	3.1 (2.8, 4.2)	1.5 (1.4, 1.6)
Hazard Ratio[b] (95% CI[a])	0.46 (0.37, 0.56)	
P-value[c]	<0.0001	
Progression-free Survival (RECIST 1.1)		
Number of Events (%)	288 (76)	184 (95)
Progressive Disease	270 (71)	175 (90)
Death	18 (5)	9 (5)
Median PFS in months (95% CI[a])	3.4 (2.9, 4.2)	1.5 (1.4, 1.5)
Hazard Ratio[b] (95% CI[a])	0.43 (0.35, 0.52)	
Overall Response (mRECIST)		
Overall Response Rate	11%	4%
95% CI[a]	(8%, 14%)	(2%, 8%)
Complete Response	0.5%	0
Partial Response	10%	4%
Overall Response (RECIST 1.1)		
Overall Response Rate	7%	3%
95% CI[a]	(4%, 10%)	(1%, 6%)
Complete Response	0	0
Partial Response	7%	3%

[a] CI=confidence interval.

[b] Estimated with Cox proportional hazard model stratified by geographic region, ECOG performance status, Alpha-fetoprotein level, presence versus absence of extrahepatic disease, and presence versus absence of macrovascular invasion.

[c] Log rank test stratified by geographic region, ECOG performance status, Alpha-fetoprotein level, presence versus absence of extrahepatic disease, and presence versus absence of macrovascular invasion.

Figure 3: Kaplan-Meier Curve of Overall Survival from Study RESORCE



16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

Tablets are supplied in packages containing three bottles, with each bottle containing 28 tablets, for a total of 84 tablets per package (NDC 50419-171-03).

Storage and Handling

Store STIVARGA at 25°C (77°F); excursions are permitted from 15 to 30°C (59 to 86°F) [see USP Controlled Room Temperature].

Store tablets in the original bottle and do not remove the desiccant. Keep the bottle tightly closed after first opening.

Discard any unused tablets 7 weeks after opening the bottle. Dispose of unused tablets in accordance with local requirements.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Hepatotoxicity

Advise patients that they will need to undergo monitoring for liver damage and to report immediately any signs or symptoms of severe liver damage to their healthcare provider *[see Warnings and Precautions (5.1), Use in Specific Populations (8.6)]*.

Infections

Advise patients to contact their healthcare provider if they experience signs and symptoms of infection *[see Warnings and Precautions (5.2)]*.

Hemorrhage

Advise patients to contact their healthcare provider for unusual bleeding, bruising, or symptoms of bleeding, such as lightheadedness *[see Warnings and Precautions (5.3)]*.

Gastrointestinal Perforation or Fistula

Advise patients to contact a healthcare provider immediately if they experience severe pains in their abdomen, persistent swelling of the abdomen, high fever, chills, nausea, vomiting, or dehydration *[see Warnings and Precautions (5.4)]*.

Dermatologic Toxicity

Advise patients to contact their healthcare provider if they experience skin changes including HFSR, rash, pain, blisters, bleeding, or swelling *[see Warnings and Precautions (5.5)]*.

Hypertension

Advise patients they will need to undergo blood pressure monitoring and to contact their healthcare provider if blood pressure is elevated or if symptoms from hypertension occur including severe headache, lightheadedness, or neurologic symptoms *[see Warnings and Precautions (5.6)]*.

Cardiac Ischemia and Infarction

Advise patients to seek immediate emergency help if they experience chest pain, shortness of breath, feel dizzy, or feel like passing out *[see Warnings and Precautions (5.7)]*.

Reversible Posterior leukoencephalopathy syndrome

Advise patients to contact their healthcare provider if they experience signs and symptoms of RPLS *[see Warnings and Precautions (5.8)]*.

Wound Healing Complications

Advise patients to contact their healthcare provider if they plan to undergo a surgical procedure or had recent surgery *[see Warnings and Precautions (5.9)]*.

Embryo-Fetal Toxicity

Advise patients that regorafenib can cause fetal harm. Advise a pregnant woman of the potential risk to a fetus *[see Warnings and Precautions (5.10), Use in Specific Populations (8.1, 8.3)]*.

Females and Males of Reproductive Potential

- Advise women of reproductive potential of the need for effective contraception during STIVARGA treatment and for 2 months after completion of treatment. Instruct women of reproductive potential to immediately contact her healthcare provider if pregnancy is suspected or confirmed during or within 2 months of completing treatment with STIVARGA *[see Warnings and Precautions (5.10) and Use in Specific Populations (8.1, 8.3)]*.
- Advise men of reproductive potential of the need for effective contraception during STIVARGA treatment and for 2 months after completion of treatment *[see Use in Specific Populations (8.3)]*.

Lactation

Advise nursing mothers that it is not known whether regorafenib is present in breast milk and discuss whether to discontinue nursing or to discontinue regorafenib *[see Use in Specific Populations (8.2)]*.

Administration

- Advise patients to swallow the STIVARGA tablet whole with water at the same time each day following a low-fat meal. Inform patients that the low-fat meal should contain less than 600 calories and less than 30% fat *[see Dosage and Administration (2.1)]*.
- Advise patients to store medicine in the original container. Do not place medication in daily or weekly pill boxes. Discard any remaining tablets 7 weeks after opening the bottle. Tightly close bottle after each opening and keep the desiccant in the bottle *[see How Supplied (16)]*.

Dosing Instructions

Advise patients to take STIVARGA after a low fat meal. Advise patients to take any missed dose on the same day, as soon as they remember, and that they must not take two doses on the same day to make up for a dose missed on the previous day *[see Dose and Administration (2.1)]*.

Patient Information
STIVARGA (sti-VAR-gah)
(regorafenib)
tablets

What is the most important information I should know about STIVARGA?

STIVARGA can cause serious side effects, including:

Liver problems. STIVARGA can cause liver problems which can be serious and sometimes lead to death. Your healthcare provider will do blood tests to check your liver function before you start taking STIVARGA and during your treatment with STIVARGA to check for liver problems. Tell your healthcare provider right away if you get any of these symptoms of liver problems during treatment:

- yellowing of your skin or the white part of your eyes (jaundice)
- nausea or vomiting
- dark "tea-colored" urine
- change in sleep pattern

What is STIVARGA?

STIVARGA is a prescription medicine used to treat people with:

- colon or rectal cancer that has spread to other parts of the body and for which they have received previous treatment with certain chemotherapy medicines
- a rare stomach, bowel, or esophagus cancer called GIST (gastrointestinal stromal tumors) that cannot be treated with surgery or that has spread to other parts of the body and for which they have received previous treatment with certain medicines
- a type of liver cancer called hepatocellular carcinoma (HCC) in people who have been previously treated with sorafenib

It is not known if STIVARGA is safe and effective in children less than 18 years of age.

Before taking STIVARGA, tell your healthcare provider about all of your medical conditions, including if you:

- have liver problems in addition to liver cancer
- have bleeding problems
- have high blood pressure
- have heart problems or chest pain
- plan to have any surgical procedures or have had recent surgery
- are pregnant or plan to become pregnant. STIVARGA can harm your unborn baby.
  - Females should use effective birth control during treatment with STIVARGA and for 2 months after your final dose of STIVARGA. Tell your healthcare provider right away if you become pregnant during treatment with STIVARGA or within 2 months after your final dose of STIVARGA.
  - Males with female partners who can become pregnant should use effective birth control during treatment with STIVARGA and for 2 months after your final dose of STIVARGA.
- are breastfeeding or plan to breastfeed. It is not known if STIVARGA passes into your breast milk. Do not breastfeed during treatment with STIVARGA and for 2 weeks after your final dose of STIVARGA.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins and herbal supplements. STIVARGA may affect the way other medicines work, and other medicines may affect how STIVARGA works.

How should I take STIVARGA?

- Take STIVARGA exactly as your healthcare provider tells you.
- You will usually take STIVARGA 1 time a day for 21 days (3 weeks) and then stop for 7 days (1 week). This is 1 cycle of treatment. Repeat this cycle for as long as your healthcare provider tells you to.
- Swallow STIVARGA tablets whole with water following a low-fat meal.
- Take STIVARGA at the same time each day following a low-fat meal that contains less than 600 calories and less than 30% fat.
- If you miss a dose, take it as soon as you remember on that day. Do not take two doses on the same day to make up for a missed dose.
- If you take too much STIVARGA call your healthcare provider or go to the nearest emergency room right away.

What should I avoid while taking STIVARGA?

- Avoid drinking grapefruit juice and taking St. John's Wort during treatment with STIVARGA. These can affect the way STIVARGA works.

What are the possible side effects of STIVARGA?

STIVARGA can cause serious side effects including:

- See "**What is the most important information I should know about STIVARGA?**"
- **Infection.** STIVARGA may lead to a higher risk of infections especially of the urinary tract, nose, throat and lung. STIVARGA may also lead to a higher risk of fungal infections of the mucous membrane, skin or the body. Tell your healthcare provider right away if you get:
  - fever
  - severe cough with or without an increase in mucus (sputum) production
  - severe sore throat
  - shortness of breath
  - burning or pain when urinating
  - unusual vaginal discharge or irritation
  - redness, swelling or pain in any part of the body
- **severe bleeding.** STIVARGA can cause bleeding which can be serious and sometimes lead to death. Tell your healthcare provider if you have any signs of bleeding during treatment with STIVARGA including:
  - vomiting blood or if your vomit looks like coffee-grounds
  - pink or brown urine
  - red or black (looks like tar) stools
  - coughing up blood or blood clots
  - menstrual bleeding that is heavier than normal
  - unusual vaginal bleeding
  - nose bleeds that happen often
  - bruising
  - lightheadedness
- **a tear in your stomach or intestinal wall (bowel perforation).** STIVARGA may cause a tear in your stomach or intestinal wall (bowel perforation) that can be serious and sometimes lead to death. Tell your healthcare provider right away if you get:
  - severe pain in your stomach-area (abdomen)
  - swelling of the abdomen
  - fever
  - chills
  - nausea
  - vomiting
  - dehydration
- **a skin problem called hand-foot skin reaction and severe skin rash**. Hand-foot skin reactions are common and sometimes can be severe. Tell your healthcare provider right away if you get redness, pain, blisters, bleeding, or swelling on the palms of your hands or soles of your feet, or a severe rash.
- **high blood pressure.** Your blood pressure should be checked every week for the first 6 weeks of starting STIVARGA. Your blood pressure should be checked regularly and any high blood pressure should be treated during treatment with STIVARGA. Tell your healthcare provider if you have severe headaches, lightheadedness, or changes in your vision.
- **decreased blood flow to the heart and heart attack.** Get emergency help right away if you get symptoms such as chest pain, shortness of breath, feel dizzy or feel like passing out.
- **a condition called Reversible Posterior Leukoencephalopathy Syndrome (RPLS).** Call your healthcare provider right away if you get severe headaches, seizure, confusion, change in vision, or problems thinking.
- **wound healing problems.** If you need to have a surgical procedure, tell your healthcare provider that you are taking STIVARGA. You should stop taking STIVARGA at least 2 weeks before any planned surgery.

The most common side effects of STIVARGA include:

- pain, including stomach-area (abdomen)
- tiredness, weakness, fatigue
- frequent or loose bowel movements (diarrhea)
- decreased appetite
- infection
- voice changes or hoarseness
- increase in certain liver function test
- fever
- swelling, pain and redness of the lining in your mouth, throat, stomach and bowel (mucositis)
- weight loss

Your healthcare provider may change your dose, temporarily stop, or permanently stop treatment with STIVARGA if you have certain side effects.

These are not all of the possible side effects of STIVARGA.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How do I store STIVARGA?

- Store STIVARGA tablets at room temperature between 68° F to 77° F (20° C to 25°C).
- Keep STIVARGA in the bottle that it comes in. Do not put STIVARGA tablets in a daily or weekly pill box.
- The STIVARGA bottle contains a desiccant to help keep your medicine dry. Keep the desiccant in the bottle.
- Keep the bottle of STIVARGA tightly closed.
- Safely throw away (discard) any unused STIVARGA tablets after 7 weeks of opening the bottle.

Keep STIVARGA and all medicines out of the reach of children.

General information about the safe and effective use of STIVARGA.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use STIVARGA for a condition for which it was not prescribed. Do not give STIVARGA to other people even if they have the same symptoms you have. It may harm them. You can ask your healthcare provider or pharmacist for information about STIVARGA that is written for health professionals.

What are the ingredients in STIVARGA?

Active ingredient: regorafenib

Inactive ingredients: cellulose microcrystalline, croscarmellose sodium, magnesium stearate, povidone and colloidal silicon dioxide.

Film coat: ferric oxide red, ferric oxide yellow, lecithin (soy), polyethylene glycol 3350, polyvinyl alcohol, talc and titanium dioxide.

Manufactured for Bayer HealthCare Pharmaceuticals Inc., Whippany, NJ 07981 USA.
For more information, go to www.STIVARGA-US.com or call 1-888-842-2937.

This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: 4/2017

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203085Orig1s007

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	April 28, 2017
From	Patricia Keegan
Subject	Division Director Summary Review
NDA Supplement #	NDA 203085/S-007
Applicant Name	Bayer Healthcare Pharmaceuticals, Inc.
Date of Submission	October 31, 2016
PDUFA Goal Date	April 30, 2017
Proprietary Name / Established (USAN) Name	Stivarga tablets/ regorafenib
Dosage Forms / Strength	Tablets for oral use/40 mg tablet
Proposed Indication(s)	STIVARGA is indicated for the treatment of patients with hepatocellular carcinoma (HCC) who have been previously treated with (b) (4).
Approved Indication	STIVARGA is indicated for the treatment of patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib
Action:	*Approval*

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Regulatory Project Manager Review	Anuja Patel
Medical Officer Review	Lorraine C. Pelosof
Statistical Review	Xiaoping (Janet) Jiang
Clinical Pharmacology Review	Vadryn Pierre & Youwei Bi
Nonclinical Pharmacology/Toxicology Review	Whitney Helms
OPDP	Carole C. Broadnax
OSE/DMEPA	Otto Townsend
Patient Labeling Team Review	Morgan A. Walker

OND=Office of New Drugs
OPDP=Office of Prescription Drug Promotion
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
OSI=Office \of Scientific Investigations

Division Director Summary Review

1. Introduction

STIVARGA (regorafenib; Bayer Healthcare Pharmaceuticals, Inc.) is a highly promiscuous small molecule inhibitor of multiple membrane-bound and intracellular kinases, including RET, VEGFR1, VEGFR2, VEGFR3, KIT, PDGFR-alpha, PDGFR-beta, FGFR1, FGFR2, TIE2, DDR2, TrkA, Eph2A, RAF-1, BRAF, BRAF V600E, SAPK2, PTK5, Abl and CSF1R. It is approved for: 1) the treatment of patients with metastatic colorectal cancer who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF therapy, and, if RAS wild- type, an anti-EGFR therapy and 2) for the treatment of patients with locally advanced, unresectable or metastatic gastrointestinal stromal tumor (GIST) who have been previously treated with imatinib mesylate and sunitinib malate.

This supplement supports an expansion of the STIVARGA labeling to include a new indication for the treatment of hepatocellular carcinoma in patients with disease progression following sorafenib. The application relies on the results of a single randomized, multicenter, placebo-controlled trial, Study 15982 (RESORCE), to establish the safety and efficacy of regorafenib in this patient population.

Study 15982, entitled: "A randomized, double blind, multicenter phase III study of regorafenib in patients with hepatocellular carcinoma (HCC) after sorafenib (RESORCE)" was a randomized (1:1), placebo-controlled, international, multicenter trial. Key eligibility criteria were histological or cytological confirmation of HCC or non-invasive diagnosis of HCC per American Association for the Study of Liver Diseases (AASLD) criteria with confirmed cirrhosis; able to tolerate sorafenib; disease progression following sorafenib and randomization within 2 to 10 weeks of the last dose of sorafenib; Barcelona Clinic Liver Cancer (BCLC) stage Category B or C and Child-Pugh class A; not a candidate for resection, local ablation, chemoembolization, or liver transplantation; and no prior systemic therapy other than sorafenib. Patients were randomized (2:1) to receive regorafenib 160 mg po daily or matching placebo administered until disease progression or unacceptable toxicity. Randomization was stratified by geographical region (Asia vs. rest of world (ROW)), ECOG performance status (0 vs. 1), alpha feto-protein level (<400 ng/mL vs. ≥400 ng/mL), extrahepatic disease (presence vs. absence), and macrovascular invasion (presence vs. absence).The primary endpoint was overall survival and secondary endpoints were investigator-assessed progression-free survival and overall response rate using both RECIST v1.1 and modified RECIST for HCC.

A total of 573 patients were randomized to receive regorafenib (n=379) or matching placebo (n=194) across 152 clinical sites in the United States, Australia, Europe and Asia. The demographic characteristics of the study population were a median age of 63 years (range 19 to 85 years); 88% male; 41% Asian, and 36% White, and 21 % not reported. Baseline prognostic factors and tumor characteristics of the study population were 66% had ECOG performance status (PS) of 0 and 34% had ECOG PS of 1; 98% had Child-Pugh A and 2%

had Child-Pugh B. Risk factors for underlying cirrhosis included hepatitis B (38%), alcohol use (25%), hepatitis C (21%), and non-alcoholic steatohepatitis (7%). Macroscopic vascular invasion or extra-hepatic tumor spread was present in 81% of patients. Barcelona Clinic Liver Cancer (BCLC) was stage C in 87% and stage B in 13% of patients. All patients received prior sorafenib and 61% received prior loco-regional trans-arterial embolization or trans-arterial chemotherapy infusion procedures.

The trial demonstrated a statistically significant and clinically important improvement in overall survival [hazard ratio (HR) of 0.63 (95% CI: 0.50, 0.79); p<0.0001, stratified log-rank test] with an estimated median survival of 10.8 months in the regorafenib arm and 7.8 months in the placebo arm. Progression-free survival (PFS) was also significantly improved when assessed using mRECIST [HR 0.46 (95% CI: 0.37, 0.56), p<0.0001, stratified log-rank test], with an estimated median PFS of 3.1 months in the regorafenib arm and 1.5 months in the placebo arm. The overall response rate (ORR) was numerically higher for patients randomized to regorafenib (10% vs 4%) compared with the placebo arm. Similar results for PFS and ORR were observed when these endpoints were assessed using RECIST v1.1.

The toxicity of regorafenib in this patient population was similar to that observed in prior approvals and there was no increase in hepatotoxicity among patients with HCC as compared to those with metastatic colorectal cancer or GIST. Among the 374 patients who received at least one dose of regorafenib in the RESORCE trial, 33% were exposed for ≥6 months and 14% were exposed for ≥ 12 months. Dose interruptions for adverse events were required in 58% of regorafenib-treated patients and 48% of patients had their dose reduced. The most common adverse reactions requiring dose modification (interruption or dose reduction) were hand-foot skin reactions (HFSR; also referred to as palmar-plantar erythrodysesthesia syndrome (PPES)) in 20.6%, hyperbilirubinemia in 5.9%, fatigue in 5.1%; and diarrhea in 5.3%. Adverse reactions that resulted in treatment discontinuation were reported in 10.4% of regorafenib-treated patients compared to 3.6% of placebo-treated patients; the most common adverse reactions requiring discontinuation of regorafenib were HFSR/PPES (1.9%) and increased AST (1.6%).

Pooled analyses to better assess the incidence of serious adverse reactions were conducted among the following populations: 1142 regorafenib-treated patients enrolled in one of four placebo-controlled trials; 4518 regorafenib-treated patients across all clinical trials; and 4800 regorafenib-treated patients enrolled in clinical trials or expanded access programs. The most common serious adverse reactions were ≥ Grade 3 hand-foot skin reaction (HFSR) (16%); ≥ Grade 3 infection (9%); and ≥ Grade 3 hemorrhage (3%). The most common adverse drug reactions (≥20%) among 1142 regorafenib-treated patients were pain (including gastrointestinal and abdominal pain), HFSR, asthenia/fatigue, diarrhea, decreased appetite/food intake, hypertension, infection, dysphonia, hyperbilirubinemia, fever, mucositis, weight loss, rash, and nausea.

A substantive issue identified during review of this application was the submission of modified databases based on audits of clinical study sites in China, which raised concerns regarding the reliability of these “cleaned and locked” datasets. These audits resulted in changes to the efficacy results in a small percentage of patients, which did not alter the overall conclusions

regardless of the dataset used (original or modified) and sensitivity analyses excluding data from Chinese sites also did not alter the conclusions. Thus, FDA agreed with inclusion of the results of the analyses obtained with the revised datasets in the intent-to-treated (all randomized) population in product labeling. In addition, poor characterization of data variables and description of analysis programs in the application resulted in significant delays in review of the safety information and confirmation of Bayer's analyses.

2. Background

Indicated Population and Available Therapy
The American Cancer Society estimates that there will be 40,710 new cases of hepatocellular and intrahepatic bile duct cancer and 28, 920 deaths due to such cancers in the United States in 2017.[1] The 5-year survival rate for patients with regional involvement is 11% and for those with metastatic disease is 3%.[2]

Sorafenib is the only systemic drug that is FDA-approved the treatment of hepatocellular cancer. Sorafenib was approved for "the treatment of patients with unresectable hepatocellular carcinoma (HCC)" on November 16, 2007. This approval was based on demonstration of improved survival [HR 0.69 (95% CI: 0.55, 0.87); p=0.00058] in an international, multicenter, randomized (1:1), double blind, placebo-controlled trial in 602 patients with unresectable hepatocellular carcinoma. The median survival was 10.7 months in the sorafenib arm and 7.9 months in the placebo arm. The trial also demonstrated an improvement in PFS [HR 0.58 (95% CI: 0.45, 0.74); p<0.0001] with median PFS of 5.5 months and 2.8 months in the sorafenib and placebo arms, respectively.

Regulatory History
The clinical development program for the proposed indication was conducted under IND 75642, submitted to FDA in June 2006.

On October 3, 2012, Bayer submitted a new clinical protocol for Study 15982, entitled: "A randomized, double blind, multicenter phase III study of regorafenib in patients with hepatocellular carcinoma (HCC) after sorafenib (RESORCE)" to IND 75642. The design of this protocol was not discussed in an end-of-Phase 2 meeting.

On December 14, 2012, FDA issued an Advice/Information Request letter, containing comments and requests for additional information regarding the RESORCE study. FDA advised that in a future marketing application, Bayer should provide justification that the results of this trial can be extrapolated to the U.S. population and to revise the analysis plan to provide an adjustment for multiplicity if claims would be sought for secondary efficacy endpoints.

[1] https://www.cancer.org/cancer/liver-cancer/about/what-is-key-statistics html
[2] https://cancerstatisticscenter.cancer.org/#/cancer-site/Liver%20and%20intrahepatic%20bile%20duct

On July 26, 2013, Bayer submitted an amended protocol for the RESORCE trial address FDA's comments in the December 14, 2012, letter. The protocol was further amended and submitted to IND 75642 on February 16, 2016, and on December 18, 2015.

On December 18, 2015, Bayer submitted a statistical analysis plan (SAP) for the RESORCE protocol and a revised clinical protocol.

On March 3, 2016, FDA issued Written Responses to a Type C meeting request, providing preliminary advice on the content and format of the planned efficacy supplement to be based on the results of Study 15982. The results of the trial were not included in the meeting briefing package (final analysis projected to occur in Q2 2016)

On April 21, 2016, Bayer submitted a US-specific SAP, dated April 20, 2016, to address FDA comments in the December 14, 2012, Advice letter. Bayer stated that the database lock was planned for April 22, 2016.

On July 21, 2016, a pre-sNDA meeting was held to discuss the results of Study 15982 and the proposed contents of the planned supplement. FDA agreed that the results of Study 15982, supported by activity in a single arm trial (Study 14596) provided sufficient information to allow FDA to evaluate the efficacy and safety of regorafenib in HCC. However, FDA did not agree with the proposed indication and stated (b) (4) but agreed to consider alternate wording supported by "real world evidence" during review of the supplement. FDA agreed with the proposed approach to provide assessment of exposure-response analyses and assessment in subgroups (Asian vs. non-Asian). Finally, FDA agreed on the strategy for a planned rolling review based on possible Fast Track designation.

(b) (4)

On July 28, 2016, FDA granted Fast Track Designation for the clinical development program investigating regorafenib for the "treatment of patients with (b) (4) hepatocellular carcinoma (HCC) who have been previously treated with sorafenib."

On September 1, 2016 submission, Bayer requested permission to submit portions of the application (rolling review). In this request, Bayer provided a schedule for submission. FDA granted this request on October 4, 2016.

On October 6, 2016, Bayer submitted information to Modules 1 and 5 and completed the supplement with a submission on October 30, 2016, and was given priority review designation on December 29, 2016.

3. CMC/ Biopharmaceutics/Device

Not applicable.

4. Nonclinical Pharmacology/Toxicology

I concur with the conclusions reached by the non-clinical pharmacology/toxicology reviewer that there are no outstanding issues that preclude approval. Bayer provided the results of additional non-clinical studies to support modifications to section 12.1 of the US package insert. These included data to support inclusion of CSF1R as a target of regorafenib that is clinically relevant, data to support effects on tumor immunity as a potential mechanism of action, and the results of pharmacology studies characterizing anti-tumor activity.

5. Clinical Pharmacology/Pharmacogenomics

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer that there are no outstanding clinical pharmacology issues that preclude approval. Bayer conducted and provided the results of a post-hoc population pharmacokinetic analysis. The reviewers concluded that this analysis did not identify clinically important differences in the mean total exposure of regorafenib (i.e., regorafenib plus its active metabolites, M2 and M5) in patients with normal hepatic function or with mild or moderate hepatic impairment. There were no patients with severe hepatic impairment (total bilirubin >3x ULN or Child-Pugh C) enrolled in the RESORCE trial, thus there remains no information regarding the pharmacokinetics of regorafenib in patients with severe hepatic impairment. In exposure-response analyses, no relevant relationships were identified between exposure and either efficacy or toxicity.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

This supplement was supported by a single, large, multicenter, placebo-controlled efficacy trial for a supplemental indication. Bioresearch monitoring of clinical study sites was not requested since the trial used a primary efficacy endpoint that is objective and not subject to bias (overall survival) and was statistically robust and supported by treatment effects on secondary efficacy endpoints. Additionally, this is the third trial with regorafenib to demonstrate improvement in survival in patients with cancer (the other settings were treatment of gastrointestinal stromal tumors and metastatic colorectal cancer).

Study Design
This application was supported by the results of a single clinical trial, Study 15982 (RESORCE), titled "A randomized, double blind, placebo-controlled, multicenter phase III study of regorafenib in patients with hepatocellular carcinoma (HCC) after sorafenib."

The key inclusion criterion were either histological or cytological confirmation of HCC or non-invasive diagnosis of HCC per American Association for the Study of Liver Diseases (AASLD) criteria with confirmed cirrhosis; able to tolerate sorafenib at 400 mg daily for at least 20 days with disease progression following sorafenib and randomization within 2 to 10 weeks of the last dose of sorafenib; Barcelona Clinic Liver Cancer (BCLC) stage Category B or C and Child-Pugh class A; not a candidate for resection, local ablation, chemoembolization, or liver transplantation; no prior systemic therapy other than sorafenib. Patients with any of the following were ineligible: bleeding from esophageal varices, uncontrolled ascites or pleural effusions, uncontrolled hypertension; ≥ Grade 3 bleeding within 30 days prior to randomization; arterial or venous thromboembolic events within 6 months prior to randomization; ≥ Grade 3 proteinuria; non-healing wound or bone fracture; hepatitis B infection or hepatitis A infection requiring anti-viral therapy; symptomatic interstitial lung disease; or HIV infection.

Patients were randomized (2:1) to receive

- regorafenib 160 mg orally, once daily for days 1-21 of each 28-day cycle until disease progression, unacceptable toxicity
  OR
- Matching placebo orally, once daily for days 1-21 of each 28-day cycle until disease progression, unacceptable toxicity

Randomization was stratified by geographical region (Asia vs. rest of world (ROW)), ECOG performance status (0 vs. 1), alpha feto-protein level (<400 ng/mL vs. ≥400 ng/mL), extrahepatic disease (presence vs. absence), and macrovascular invasion (presence vs. absence).

Patients were assessed for disease state by CT or MRI every 6 weeks for the first 8 cycles then every 12 weeks thereafter. Assessment of tumor-based endpoints was conducted by

investigators and by an independent radiologic review using RECIST v1.1 and modified RECIST for HCC.[3]

The primary endpoint was overall survival. The assumptions for the study sample size of 560 patients were a true hazard ratio of 0.70 for overall survival, median survival of 8 months in the placebo arm and 11.4 months in the regorafenib arm, and a requirement for 370 deaths to provide 90% power to detect statistically significant difference in survival at a 2-sided significance level of 0.05. Secondary efficacy endpoints were time-to-progression (TTP), progression-free survival (PFS), and overall response rate (ORR).

Results

A total of 573 patients were randomized to receive regorafenib (n=379) or matching placebo (n=194) across 152 clinical sites in the United States, Australia, Europe and Asia. The first visit of the first patient was on May 14, 2013 and the last visit of the last patient was on February 29, 2016. The "study completion date" was February 29, 2016.

The demographic characteristics of the study population were a median age of 63 years (range 19 to 85 years); 88% male; 41% Asian, and 36% White, and 21 % not reported. Baseline prognostic factors and tumor characteristics of the study population were 66% had ECOG performance status (PS) of 0 and 34% had ECOG PS of 1; 98% had Child-Pugh A and 2% had Child-Pugh B. Risk factors for underlying cirrhosis included hepatitis B (38%), alcohol use (25%), hepatitis C (21%), and non-alcoholic steatohepatitis (7%). Macroscopic vascular invasion or extra-hepatic tumor spread was present in 81% of patients. Barcelona Clinic Liver Cancer (BCLC) was stage C in 87% and stage B in 13% of patients. All patients received prior sorafenib and 61% received prior loco-regional trans-arterial embolization or trans-arterial chemotherapy infusion procedures.

The following table, abstracted from product labeling, summarizes the key efficacy results The results for tumor-based endpoints as assessed by investigators according to mRECIST and RECIST v1.1 were similar.

[3] Lencioni R, Llovet JM. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. Semin Liver Dis 2010;30:52-60.

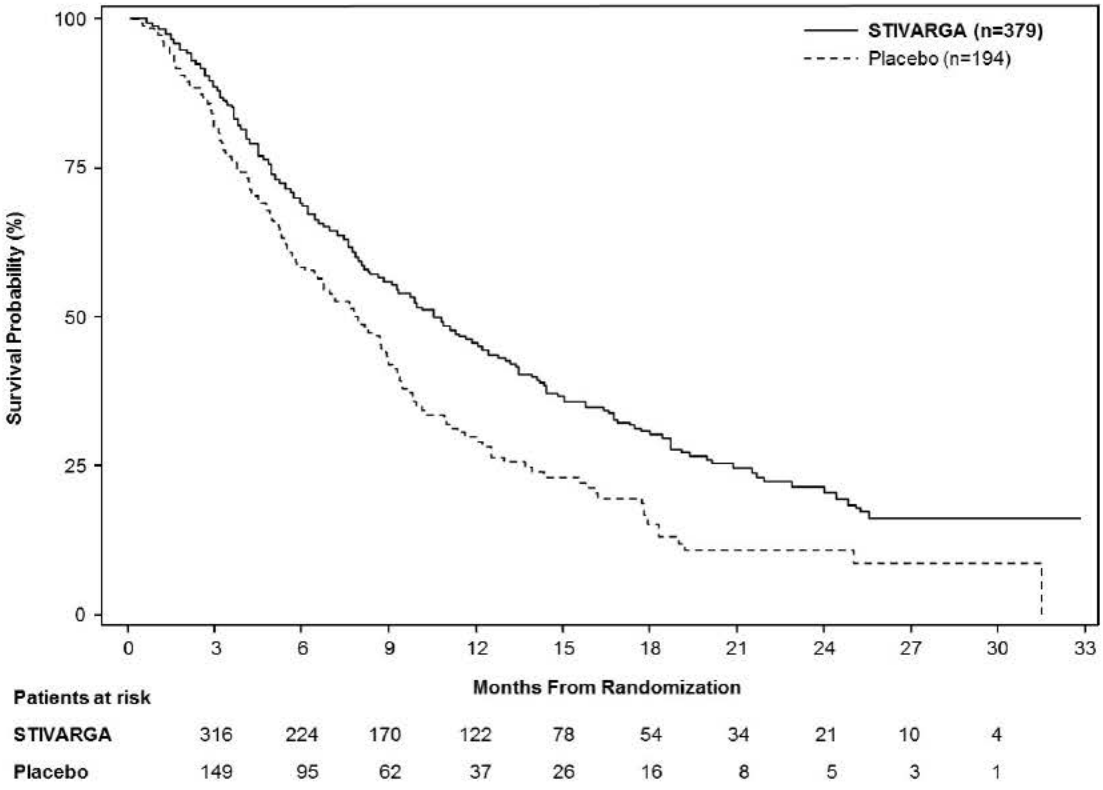
Efficacy Results (b) (4) RESORCE (b) (4)		
	(b) (4) n=379	Placebo n=194
Overall Survival		
Number of Deaths (%)	233 (62)	140 (72)
Median OS in months (95% CI[a])	10.6 (9.1, 12.1)	7.8 (6.3, 8.8)
Hazard Ratio[b] (95% CI[a])	0.63 (0.50, 0.79)	
p-value[c]	<0.0001	
Progression-free Survival (mRECIST)		
Number of Events (%)	293 (77)	181(93)
Progressive Disease	274 (72)	173 (89)
Death	19 (5)	8 (4)
Median PFS in months (95% CI[a])	3.1 (2.8, 4.2)	1.5 (1.4, 1.6)
Hazard Ratio[b] (95% CI[a])	0.46 (0.37, 0.56)	
p-value[c]	<0.0001	
Progression-free Survival (RECIST 1.1)		
Number of Events (%)	288 (76)	184 (95)
Progressive Disease	270 (71)	175 (90)
Death	18 (5)	9 (5)
Median PFS in months (95% CI[a])	3.4 (2.9, 4.2)	1.5 (1.4, 1.5)
Hazard Ratio[b] (95% CI[a])	0.43 (0.35, 0.52)	
Overall Response (mRECIST)		
Overall Response Rate	11%	4%
95% CI[a]	(8%, 14%)	(2%, 8%)
Complete Response	0.5%	0
Partial Response	10%	4%
Overall Response (RECIST 1.1)		
Overall Response Rate	7%	3%
95% CI[a]	(4%, 10%)	(1%, 6%)
Complete Response	0	0
Partial Response	7%	3%

CI=confidence interval.

[b] Estimated with Cox proportional hazard model stratified by geographic region, ECOG performance status, Alpha-fetoprotein level, presence versus absence of extrahepatic disease, and presence versus absence of macrovascular invasion.

[c] Log rank test stratified by geographic region, ECOG performance status, alpha-fetoprotein level, presence versus absence of extrahepatic disease, and presence versus absence of macrovascular invasion.

Kaplan-Meier Curve (b) (4) Overall Survival (b) (4) RESORCE (b) (4)



A substantive data issue that occurred during review of this application was the submission of modified databases based on audits of clinical study sites in China, which raised concerns regarding the reliability of these "cleaned and locked" datasets. These audits resulted in changes to the efficacy results in a small percentage of patients. The statistical reviewer conducted a sensitivity analysis for overall survival that excluded the 137 patients enrolled across 27 clinical study sites in China. The results of this sensitivity analysis are summarized in the table below.

Sensitivity Analysis Excluding Patients Enrolled in China		
	Regorafenib (n=291)	Placebo (n=145)
Number of Event (%)	183	108
Number of Censored (%)	108	37
Median OS in months (95% CI)	10.9 (9.1, 13.2)	8.3 (6.8.9.3)
Hazard ratio (95%CI)	0.62 (0.48, 0.80)	

Based on comparisons of the results in the original dataset, the revised dataset, and the sensitivity analysis (above), the results were not substantially altered with the revised dataset. Based on Bayer's statements that the revised dataset is a more accurate reflection of the data and analyses with this revised dataset resulted in a slightly smaller treatment effect (based on the hazard ratio) than that provided in the original submission, the clinical and statistical review staff agreed that the results presented in the product labeling should be based on the revised datasets.

8. Safety

Size of the database
The size of the safety database (374 regorafenib-treated patients) was sufficient to make a risk: benefit assessment in the indicated population of patients receiving second-line treatment for unresectable or metastatic hepatocellular carcinoma). The toxicity of regorafenib in this patient population was similar to that observed in prior approvals and there was no increase in hepatotoxicity among patients with HCC as compared to those with metastatic colorectal cancer or GIST.

Among the 374 patients who received at least one dose of regorafenib in the RESORCE trial, 33% were exposed for ≥6 months and 14% were exposed for ≥ 12 months. Dose interruptions for adverse events were required in 58% of regorafenib-treated patients and 48% of patients had their dose reduced. The most common adverse reactions requiring dose modification (interruption or dose reduction) were hand-foot skin reactions (HFSR; also referred to as palmar-plantar erythrodysesthesia syndrome (PPES)) in 20.6%, hyperbilirubinemia in 5.9%, fatigue in 5.1%; and diarrhea in 5.3%. Adverse reactions that resulted in treatment discontinuation were reported in 10.4% of regorafenib-treated patients compared to 3.6% of placebo-treated patients; the most common adverse reactions requiring discontinuation of regorafenib were HFSR/PPES (1.9%) and increased AST (1.6%).

Major safety concerns related to labeling
The toxicity of regorafenib in this setting was similar to that observed in prior approvals. Pooled analyses to better assess the incidence of serious adverse reactions were conducted among the following populations: 1142 regorafenib-treated patients enrolled in one of four placebo-controlled trials; 4518 regorafenib-treated patients across all clinical trials; and 4800 regorafenib-treated patients enrolled in clinical trials or expanded access programs. These included hepatotoxicity (ranging from 0 to 1.6% incidence); ≥ Grade 3 infection (9%); ≥ Grade 3 hemorrhage (3%); gastrointestinal perforation (0.6%); gastrointestinal fistula (0.8%); ≥Grade 3 hand-foot skin reaction (HFSR) (16%); ≥Grade 3 rash (3%); Stevens Johnson syndrome and erythema multiforme (<0.1% each) and toxic epidermal necrolysis (<0.02%); hypertensive crisis (0.2%); myocardial ischemia and infarction (0.9%); r reversible posterior leukoencephalopathy syndrome (RPLS) (0.02%). In addition, the regorafenib can cause embryo-fetal toxicity and, based on effects in the class of vascular endothelial growth factor inhibitors, is expected to impair wound healing.

REMS

I concur with the clinical review team that no new safety issues were identified and that the risks of regorafenib in this patient population are acceptable in light of the life-threatening stage of disease and lack of alternative therapy. I concur that REMS (risk mitigation and evaluation strategies) are not required to ensure safe use of this marketed drug in the indication population (patients with HCC with disease progression following sorafenib).

PMRs and PMCs
The review team did not identify the need for post-marketing requirements under 505(o) and there were no post-marketing commitments requested by FDA for this development program.

9. Advisory Committee Meeting

This efficacy supplement was not referred for review to the Oncologic Drugs Advisory Committee because this is not the first approval for this drug, the safety profile is acceptable for this indication, the clinical trial design is similar to other products approved for this indication, and outside expertise was not necessary since there were no controversial issues that would benefit from advisory committee discussion.

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10. Pediatrics

On June 4, 2015, FDA designed regorafenib as an orphan drug for the "treatment of hepatocellular carcinoma." Based on this action, this efficacy supplement is exempt for the requirements of the Pediatric Research Equity Act (PREA) for the proposed indication.

11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.

12. Labeling

- Physician labeling
  - Across all labeling sections, the references to clinical studies now identify the study acronym (and in section 14, refer to the NCT numeric designation at www.clinicaltrials.gov). This change is based on feedback from external users who had difficulty determining the study being cited in the USPI.
  - Indications and Usage: The proposed indication (treatment of patients with hepatocellular carcinoma (HCC) *who have been previously treated with* (b) (4) was revised to more accurately reflect the patient population studied (previously treated with sorafenib).

- Dosage and Administration: modified to clarify the directions for dosing after/following a low fat meal (similar edits to Patient Counseling and Patient Package Insert); modified for consistency and clarity regarding dose modifications in patients with infections.
- Warnings and Precautions: The Warnings and Precautions section was updated by Bayer to include a new subsection on Infections, identified based on the pooled analysis of adverse reactions among 1142 regorafenib-treated patients enrolled in randomized, placebo-controlled studies. The incidence of adverse reactions, including ≥ Grade 3 adverse reactions was updated to reflect the incidence across the pooled analysis (with the exception of hepatotoxicity) to provide a more precise estimation of these uncommon serious adverse reactions. The risks of hepatotoxicity were provided by indication rather than as a pooled analysis, since such risks may differ based on the extent of underlying pathology in the liver and that this would be of concern to prescribers. It is noted, however, that the incidence of hepatotoxicity was actually not substantially different across the indicated patient populations. Finally, subsection on Gastrointestinal Perforation and Fistula moved to increase prominence given the severity (fatal events) of these adverse reactions.
- Adverse Reactions: This section was updated to include the characterization of the safety population (as treated) and adverse reactions and clinical laboratory abnormalities observed in the RESORCE trial. Change to the incidence of "pain" in the GRID and CORRECT trials based on re-analysis using multiple preferred terms in this composite endpoint and for consistency with results reported for RESORCE.
- Use in Specific Populations: Geriatrics subsection updated to reflect data in the pooled analysis of 1142 regorafenib-treated patients and to describe the apparent increased in risk of Grades 3-4 hypertension in elderly patients as compared to younger patients (relative to placebo-treated patients) observed in the RESORCE trial. Edits to Renal Impairment subsection (b) (4) and revisions to subsection on Hepatic Impairment for clarity and consistency with data reviewed in the updated population PK analyses.
- Clinical Pharmacology: Section 12.1 was updated to include CSF1R as a target of regorafenib, tumor immunity as a potential mechanism of action, and the results of pharmacology studies characterizing anti-tumor activity. Section 12.3 was updated to describe the pharmacokinetics of regorafenib and its major active metabolite in patients with hepatic impairment.
- Nonclinical Pharmacology/Toxicology
- Clinical Studies: Updated to include the results of the RESORCE trial. Results were expanded to provide additional details on the clinical trial design and characteristics for the study population. The results for tumor-based endpoints based on both mRECIST for HCC and RECIST v1.1 as prescribers may be interested in the differences (if any) according to the response criteria used, however based on the FDA's interpretation of the protocol and analysis plan (which were not explicit) the primary analysis of tumor-based endpoint was to be based on mRECIST and statistical tests were limited to PFS were limited to this analysis (there was no adjustment for testing of ORR).
- Patient Counseling: Edited for conformance with current labeling practices and applicable guidances and to reflect re-ordering of the Warnings and Precautions section of product labeling.

- Patient labeling/Medication guide: Patient labeling was revised to reflect the new indication and description of adverse reactions observed in the RESORCE trial, as reflected in the full prescribing information. .

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action: Approval

- Risk Benefit Assessment
  Hepatocellular carcinoma is a serious and life-threatening disease with a 5-year survival rate of 3% in patients with metastatic disease, not amenable to local therapy. There is only one drug (sorafenib) that is FDA-approved for this population; the RESORCE trial enrolled patients who were no longer responding to sorafenib. Thus, this population has a clear, unmet medical need.

  The RESORCE trial demonstrated a statistically robust and clinically important improvement in overall survival, as characterized by an increase in median survival of approximately 3 months (10.6 months compared with 7.8 months) supported by a statistically robust doubling in progression-free survival (3.1 months compared with 1.5 months). The toxicity profile of regorafenib was similar to that observed in the previously approved indications, with the most common adverse reactions resulting in treatment modification being HFSR, fatigue, diarrhea, and hepatic laboratory abnormalities. While regorafenib can results in serious and fatal adverse reactions, the improvement in survival indicates that the benefits of tumor control outweighs these serious risks, which are considered acceptable by the patient and medical oncology community in light of the serious and fatal nature of metastatic/ unresectable HCC.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies
  There were no new safety signals identified during review of this efficacy supplement that required Risk Evaluation and Mitigation Strategies under 505(o) to ensure safe and effective use.

- Recommendation for other Postmarketing Requirements and Commitments
  I concur that there are no safety signals that require post-marketing assessment and no post-marketing commitments were requested by FDA based on the information provided in this supplement.

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/s/

PATRICIA KEEGAN
04/27/2017

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203085Orig1s007

OFFICER/EMPLOYEE LIST

Officer/Employee List
Application: sNDA 203085/ Supplement 007

The following officers or employees of the FDA participated in the decision to approve this application and consented to be identified on this list:

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203085Orig1s007

MEDICAL REVIEW(S)

CLINICAL REVIEW- ADDENDUM

Application Type	sNDA
Application Number(s)	203085/155, 156
Priority or Standard	Priority
Submit Date(s)	October 6, 2016 October 30, 2016
Received Date(s)	October 6, 2016 October 31, 2016
PDUFA Goal Date	April 28, 2017
Division / Office	DOP2/OHOP
Reviewer Name(s)	Lorraine Pelosof
Review Completion Date	April 28, 2017
Established Name	Regorafenib
(Proposed) Trade Name	Stivarga
Therapeutic Class	small molecule kinase inhibitor
Applicant	Bayer HealthCare Pharmaceuticals Inc.
Formulation(s)	40 mg tablets
Dosing Regimen	4 x 40 mg tablets every day; 3 weeks on/1 week off in each 4 week cycle
Indication(s)	for the treatment of patients with hepatocellular carcinoma (HCC) who have been previously treated with (b) (4)
Intended Population(s)	patients with hepatocellular carcinoma (HCC) who have been previously treated with (b) (4)

This review addendum addresses and updates various review issues that arose after the completion of the Clinical Review document dated 4/7/17.

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

After further discussions and review, the indication was revised to:

> Approval is recommended, pending agreement on final labeling, for the use of regorafenib for the treatment of patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib.

This decision was based on the fact that a (b) (4) did not reflect the data submitted and could lead to (b) (4)

6 Review of Efficacy

6.1.4 Analysis of Primary Endpoint

On April 20, 2017, Bayer informed FDA about an internal audit of some of their clinical sites in China that resulted in Bayer updating survival data. According to Bayer, inclusion of the updated data would have resulted in a result slightly more favorable to regorafenib. A different sensitivity analysis was performed by the Office of Biostatistics (removing data from clinical sites that enrolled patients in China) that did not reveal a significant impact due to this update (hazard ratio for overall survival decreased from 0.63 to 0.62 favoring the regorafenib arm). Given the magnitude and direction of the difference, the label will reflect the analysis based on the original data.

7 Review of Safety

On page 39 of the clinical review, 3rd paragraph, the text should state "On *March* 23, 2017" instead of "May 23, 2017".

7.3.3 Dropouts and/or Discontinuations

After further clarifications regarding the data included within the datasets, FDA agreed with Bayer's incidence numbers for regorafenib dose interruptions (58%), reductions (48%), and discontinuations (10%) due to adverse events.

9 Appendices

9.1 Labeling Recommendations

The following summarizes key labeling updates made since the time of submission of the Clinical Review on 4/7/17.

1 INDICATIONS AND USAGE
1.3 Hepatocellular Carcinoma

As indicated above, the indication agreed upon is "for the treatment of patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib".

5 WARNINGS AND PRECAUTIONS

The following populations were defined in the label:

4,518 = The number of patients treated with single- agent regorafenib across all the clinical trials.

4,800 = The number of patients treated with regorafenib across all the clinic trials or in an expanded access program.

6 ADVERSE REACTIONS
6.1 Clinical Trials Experience

The list of the most common adverse drug reactions (≥20%) in patients receiving regorafenib in randomized, placebo-controlled trials was confirmed as: pain (including gastrointestinal and abdominal pain), HFSR, asthenia/fatigue, diarrhea, decreased appetite/food intake, hypertension, infection, dysphonia, hyperbilirubinemia, fever, mucositis, weight loss, rash, and nausea.

8 USE IN SPECIFIC POPULATIONS
8.5 Geriatric Use

Regarding the incidence of hypertension in patients ≥ 65 years of age who received regorafenib, Bayer agreed to examine this issue further in the pooled population from its randomized, placebo-controlled trials and the following was added to the label: "There was an increased incidence of Grade 3 hypertension (18% versus 9%) in the placebo-controlled trials among STIVARGA-treated patients 65 years of age and older as compared to younger patients. In addition, one Grade 4 hypertension event has been reported in the 65 years and older age group and none in the younger age group."

14 CLINICAL STUDIES
14.3 Hepatocellular Carcinoma (HCC)

Section 14 of the label was updated to reflect data from the RESORCE trial.

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/s/

LORRAINE C PELOSOF
05/01/2017

STEVEN J LEMERY
05/01/2017

CLINICAL REVIEW

Application Type	sNDA
Application Number(s)	203085/155, 156
Priority or Standard	Priority
Submit Date(s)	October 6, 2016 October 30, 2016
Received Date(s)	October 6, 2016 October 31, 2016
PDUFA Goal Date	April 28, 2017
Division / Office	DOP2/OHOP
Reviewer Name(s)	Lorraine Pelosof
Review Completion Date	April 6, 2017
Established Name	Regorafenib
(Proposed) Trade Name	Stivarga
Therapeutic Class	small molecule kinase inhibitor
Applicant	Bayer HealthCare Pharmaceuticals Inc.
Formulation(s)	40 mg tablets
Dosing Regimen	4 x 40 mg tablets every day; 3 weeks on/1 week off in each 4 week cycle
Indication(s)	for the treatment of patients with hepatocellular carcinoma (HCC) who have been previously treated with (b) (4)
Intended Population(s)	patients with hepatocellular carcinoma (HCC) who have been previously treated with (b) (4)

APPEARS THIS WAY ON ORIGINAL

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Approval is recommended, pending agreement on final labeling, for the use of regorafenib for the treatment of patients with hepatocellular carcinoma (HCC) who have been previously treated with (b) (4)

The applicant provided data establishing the safety and effectiveness of the product for the proposed indication as described under 21CFR 314.70.

1.2 Risk Benefit Assessment

Benefit-risk summary and assessment

Regorafenib is a small-molecule tyrosine kinase inhibitor that targets multiple kinases including VEGFR-2 and VEGFR-3. Regorafenib currently has indications in CRC and GIST and is being proposed for the treatment of patients with hepatocellular carcinoma (HCC) who have been previously treated with (b) (4)

HCC is associated with high morbidity and mortality. The 5-year OS for patients with advanced HCC in the U.S. is only approximately 12%. The only approved systemic therapy for the treatment of advanced HCC is sorafenib, a multikinase inhibitor with multiple targets including VEGF pathways. Based on prior studies, sorafenib improves median survival by approximately 2-3 months when compared to placebo. After HCC has progressed on sorafenib, the median OS is approximately 8 months and there are no approved systemic therapies for HCC after progression on sorafenib.

The efficacy of regorafenib for the treatment of patients with advanced HCC was demonstrated in Study 15982, a multicenter, randomized, placebo-controlled trial comparing once daily regorafenib to placebo in patients with HCC that had progressed on sorafenib. A total of 573 patients were randomized, 379 in the regorafenib arm and 194 in the placebo arm. Median overall survival was 10.6 months in the regorafenib arm and 7.8 months in the placebo arm with a hazard ratio of 0.63 (95% CI: 0.50, 0.79) and an unstratified log-rank p-value of 0.0002.

The safety profile from Study 15982 was consistent with what is known about regorafenib for the treatment of metastatic CRC and GIST and was consistent with regorafenib being an oral VEGF-targeting tyrosine kinase inhibitor. Although adverse events were frequent in Study 15982, only about 10% of patients permanently discontinued regorafenib with the primary reason being an adverse event.

The proposed indication for regorafenib following progression of HCC [redacted] indication for regorafenib, which is supported by Study 15982, is for the treatment of patients with [redacted]

In summary, the approval is recommended based on a prolongation of overall survival with an acceptable toxicity profile, with which the oncology community has experience in managing.

Analysis of condition

Summary

Regorafenib is an oral tyrosine kinase inhibitor that is proposed for the treatment of patients with hepatocellular carcinoma (HCC) who have been previously treated with [redacted]

In the U.S. in 2016, an estimated 39,230 new diagnoses and 27,170 deaths due to liver and intrahepatic bile duct cancers will have occurred, with the majority of these being HCC.[1] In the U.S., the 5-year survival rate for HCC is approximately 12%.[2]

Advanced HCC is generally considered to be incurable and the goal of therapy is to prolong survival and improve quality of life. Systemic treatment is generally administered until disease progression or the toxicity of the therapy is deemed to be intolerable or detrimental to the quality of life. The only systemic therapy approved for the treatment of advanced HCC is the oral multikinase inhibitor sorafenib.

Conclusion

Advanced HCC is a progressive disease with a fatal outcome. The oral multikinase inhibitor sorafenib is the only approved systemic therapy for advanced HCC.

Current Treatment Options

Summary of evidence

In 2007, sorafenib received regular FDA approval for the treatment of patients with advanced HCC. The median overall survival for patients with HCC that has progressed on sorafenib, is approximately 7-9 months.[3-6] There are no systemic therapies approved to treat advanced HCC that has progressed on sorafenib.

Conclusion

There are no approved systemic therapy options to treat advanced HCC that has progressed on sorafenib. Therefore, regorafenib addresses an unmet medical need.

Clinical benefit

Summary of evidence

The efficacy of regorafenib for the treatment of patients with advanced HCC that has progressed on sorafenib was demonstrated in one multicenter, randomized, placebo-controlled trial, Study 15982.

In Study 15982, patients with advanced HCC that had progressed on sorafenib were randomized 2:1 to receive regorafenib or placebo. The efficacy analysis of regorafenib was based on the ITT population of 573 patients with 379 patients in the regorafenib arm and 194 patients in the placebo arm. Patients were administered 160 mg of regorafenib or a matching placebo once daily.

Patient demographics were balanced between the two arms. The median age at randomization was 63 years and 66% of the patients had an ECOG performance status of 0 while 34% had an ECOG performance status of 1. Eighty eight percent of the patients were men. Forty one percent of the patients were Asian. Ninety eight percent of the patients had Child-Pugh class A cirrhosis and 2% had Child-Pugh class B. All patients had HCC that had progressed on sorafenib.

At the time of data cutoff, 233 (61%) of the patients in the regorafenib arm had died while 140 (72%) of the patients in the placebo arm had died. Sixty five patients (17.2%) in the regorafenib arm and 10 patients (5.2%) in the placebo arm were ongoing with study drug at the time of data cut off.

The primary endpoint of OS from randomization was met as median OS was 10.6 months in the regorafenib arm and 7.8 months in the placebo arm with a HR of 0.63 [95% CI: 0.50, 0.79; p-value (unstratified log rank test) = 0.0002]. Subgroup analyses for OS were, in general, consistent with the OS in the ITT population.

The secondary endpoint of PFS was met based on both mRECIST for HCC and standard RECIST criteria. Using mRECIST, median time to disease progression was 3.1 months in the regorafenib arm compared to 1.5 months in the placebo arm [HR of 0.46 (95% CI: 0.37, 0.56; $p < 0.0001$]. Using standard RECIST criteria, median time to disease progression was 3.4 months in the regorafenib arm compared to 1.5 months in the placebo arm [HR of 0.43 (95% CI: 0.35, 0.52; $p < 0.0001$].

The secondary endpoint of ORR was met based on both mRECIST for HCC and standard RECIST criteria. Using mRECIST criteria, the ORR was 10.6% in the regorafenib arm compared to 4.1% in the placebo arm ($p = 0.005$) while using standard RECIST criteria, the ORR was 6.6% in the regorafenib arm compared to 2.6% in the placebo arm ($p = 0.02$).

Conclusion

Study 15982 was an adequate and well-controlled study that demonstrated that regorafenib for the treatment of advanced HCC in the 2nd-line setting resulted in a modest survival benefit. The use of regorafenib resulted in a median prolongation of survival of 2.8 months with median OS of 10.6 months and 7.8 months in the regorafenib and placebo arms, respectively.

Risk

Summary of evidence

The safety analysis was based on the safety population of Study 15982 with 374

patients in the regorafenib arm and 193 patients in the placebo arm. Overall, the incidence rates of adverse events of any grade were 100% in the regorafenib arm and 93% in the placebo arm which were comparable. The incidence rates of Grade 3-4 adverse events were 79% in the regorafenib arm compared to 56% in the placebo arm while the incidence rates of SAEs were 44% in the regorafenib arm compared to 47% in the placebo arm.

The most frequently reported (> 5%) Grades 3-4 adverse events in either arm were hypertension (15% and 5% in the regorafenib and placebo arms, respectively), palmar-plantar erythrodysesthesia syndrome (12% and 1% in the regorafenib and placebo arms, respectively),increased AST (11% in each arm), hypophosphatemia (8% and 2% in the regorafenib and placebo arms, respectively), increased blood bilirubin (7% and 9%, in the regorafenib and placebo arms, respectively), increased lipase (7% and 2% in the regorafenib and placebo arms, respectively), and fatigue (6% and 4% in the regorafenib and placebo arms, respectively).

Grade 3-4 adverse events associated with VEGF inhibition and/or TKIs were increased in the regorafenib arm and included hypertension (15% and 5% in the regorafenib and placebo arms, respectively), hemorrhagic shock (1% and 0% in the regorafenib and placebo arms, respectively), and palmar-plantar erythrodysesthesia syndrome (12% and 1% in the regorafenib and placebo arms, respectively). The incidence of Grade 3-5 hypertension among regorafenib-treated patients was higher in patients ≥ 65 years of age compared to younger patients (21% in regorafenib-treated patients ≥ 65 years compared to 9% in regorafenib-treated patients < 65 years).

Eighty eight deaths occurred during the treatment emergent adverse event period, 50 (13%) in the regorafenib arm and 38 (20%) in the placebo arm. The two arms were generally balanced with respect to the causes and, based on a focused review of narratives and brief case summaries, many of these deaths appeared to occur in the setting of clinical progression of disease.

The proportion of patients who discontinued study drug primarily due to an adverse event was similar between arms (10% and 9% in the regorafenib and placebo arms, respectively).

Conclusion

In summary, there were no new safety signals in Study 15982 and the safety profile was within what was expected for a regorafenib and for tyrosine kinase VEGF inhibitors, in general. Regorafenib appears to have a reasonable safety profile in this population and adverse events were generally manageable with supportive care or dose modification.

Risk management

The risks of regorafenib use in the treatment of advanced HCC are well known to prescribers and managed through product labeling. Additionally, this drug will be prescribed by oncologists who have specific training in the administration of anti-neoplastic drugs and in the management of toxicities related to these drugs.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

No REMS were identified as necessary to approve this efficacy supplement.

1.4 Recommendations for Postmarket Requirements and Commitments

No new post-marketing commitments or requirements are recommended.

2 Introduction and Regulatory Background

Stivarga® (regorafenib) was approved in the U.S. on September 27, 2012, for the treatment of patients with metastatic CRC who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF therapy, and, if KRAS wild type, an anti-EGFR therapy. On May 29, 2013, the U.S. package insert was expanded to include patients with locally advanced, unresectable or metastatic gastrointestinal stromal tumor (GIST) who have previously been treated with imatinib mesylate and sunitinib malate.

In this submission, the Applicant seeks approval for the following indication "the treatment of patients with hepatocellular carcinoma (HCC) who have been previously treated with (b) (4)

This application was submitted on October 30, 2016 (final sNDA rolling submission date) and the PDUFA goal date (priority review) is April 28, 2017. This review describes the efficacy and safety data supporting approval and the recommendation of the clinical reviewer.

2.1 Product Information

Stivarga® (regorafenib) is an oral bi-aryl urea compound that targets different receptor tyrosine kinases including vascular endothelial growth factor receptor 2 (VEGFR-2), vascular endothelial growth factor receptor (VEGFR-3), platelet-derived growth factor receptor (PDGFR), fibroblast growth factor receptor (FGFR), KIT proto-oncogene receptor tyrosine kinase (c-Kit), Raf-1 proto-oncogene, serine/threonine kinase (RAF1), and both wild-type and V600E-mutated B-Raf proto-oncogene, serine/threonine kinase (BRAF).[7] These various kinases function in cellular metabolism, growth, and proliferation and are often inappropriately activated in tumor cells. Because of this, they are common targets of anti-cancer agents.

Stivarga is supplied as a 40mg tablet.

2.2 Currently Available Treatments for Proposed Indications

In its earlier, localized stages, HCC is often treated with locoregional therapies such as surgery (resection or orthotopic liver transplant), radiofrequency ablation (RFA), or transarterial chemoembolization (TACE). For patients with advanced or metastatic HCC and Child-Pugh A cirrhosis, first-line systemic treatment consists of sorafenib, an oral multikinase inhibitor, at 400 mg twice daily, based on results of the SHARP study[8]. In that study, 602 patients with advanced HCC were randomized to receive sorafenib 400 mg twice daily or placebo. The primary outcome was overall survival (OS) and this endpoint was met with a median OS of 10.7 months in the sorafenib arm versus 7.9 months in the placebo arm (hazard ratio of 0.69, 95% confidence interval 0.55 to 0.87, $p < 0.001$). In addition to the SHARP study, the effects of sorafenib for the treatment of patients with advanced HCC were assessed in 271 patients in a clinical trial conducted in China, South Korea, and Taiwan. In this trial, the median OS was 6.5 months compared to 4.2 months in the sorafenib and placebo arms, respectively (HR of 0.68, 95% confidence interval 0.50,0.93, p=0.014).[9]

There are currently no approved agents for the treatment of advanced or metastatic HCC that has progressed on sorafenib.

2.3 Availability of Proposed Active Ingredient in the United States

Stivarga® (regorafenib) was approved in the U.S. on September 27, 2012, for the treatment of patients with metastatic CRC who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF therapy, and, if KRAS wild type, an anti-EGFR therapy. On May 29, 2013, the U.S. package insert was expanded to include patients with locally advanced, unresectable or metastatic gastrointestinal stromal tumor (GIST) who have been previously treated with imatinib mesylate and sunitinib malate.

2.4 Important Safety Issues With Consideration to Related Drugs

Though the exact adverse event profile varies among the different agents and also depends on patient- and disease-specific factors, the oral tyrosine kinase inhibitors (TKIs) generally have a characteristic pattern of toxicity that includes hypertension, proteinuria, skin reactions, thromboemboli, and diarrhea. Some of these effects are considered to be “on-target” effects of inhibiting particular pathways such as the VEGF (hypertension, proteinuria, thromboemboli) or EGFR (skin reactions) pathways.[10] Similarly, drugs that predominantly target the VEGF pathway, regardless of whether they are small molecule TKIs or monoclonal antibodies, generally have a characteristic adverse event profile that includes hypertension, proteinuria, hemorrhage, thrombosis, fistula formation, and gastrointestinal perforation.[11]

2.5 Summary of Presubmission Regulatory Activity Related to Submission

On December 12, 2012, the Applicant submitted a new protocol for Study 15982: "Randomized, double-blind, placebo-controlled, multicenter phase III study of regorafenib in patients with hepatocellular carcinoma (HCC) after sorafenib" under IND 75642. On March 31, 2015, a request for Orphan Drug Designation (ODD) was submitted for the treatment of patients with HCC and was granted on June 4, 2015.

On December 23, 2015, the Applicant requested a Type C meeting to discuss plans to submit a supplemental new drug application (sNDA) for Study 15982. On March 4, 2016, FDA issued Type C meeting written responses. The main issues addressed included FDA's recommendation that worse case imputation be used for OS analysis in the event of missing data. FDA also stated [(b) (4)] Additionally, FDA stated that the determination of Priority Review would be made at the time of sNDA filing.

On March 23, 2106, FDA issued an Advice/Information Request in response to the Applicant's March 18, 2016, letter requesting additional clarification regarding the statistical analysis plan. In FDA's March 23, 2016, letter, FDA recommended that Bayer use day 1 for the treatment arm and day 30 for the control arm as the worst case imputation approach for the OS analysis when data are missing. FDA also stated that the Applicant's plan to order the secondary endpoints for hierarchical testing using PFS followed by TTP was acceptable.

On July 21, 2016, a Type B pre-sNDA meeting between the Applicant and FDA was held to discuss the efficacy and safety results of Study 15982 and to discuss the proposed indication for regorafenib. The Applicant proposed the following indication: "Stivarga is indicated for the treatment of patients with hepatocellular carcinoma (HCC) who have been previously treated with [(b) (4)]". FDA stated that if the Fast Track designation is granted, it would need to incorporate prior sorafenib treatment in the indication statement [(b) (4)] FDA also stated that the Applicant could propose the [(b) (4)] ("previously treated with [(b) (4)]") with justification at the time of original sNDA submission. At this meeting, it was also agreed that analyses regarding treatment post-progression would be considered exploratory. Discussions regarding the format of the summaries, safety updates, and the contents of the supplement were held, and the present submission follows the agreements reached during the meeting.

Fast Track designation was granted for the HCC development plan on July 28, 2016.

2.6 Other Relevant Background Information

HCC

An estimated 39,230 new diagnoses and 27,170 deaths due to liver and intrahepatic bile duct cancers occurred in the U.S. in 2016 with a male to female ratio of new diagnoses of 3:1 and of deaths of 2:1.[1] The majority of these new cases and deaths are due to HCC, the most common primary cancer of the liver worldwide.[12] Overall for HCC in the U.S., the 5-year survival rate is approximately 12%.[2] Even when diagnosed and resected in its earlier stages, HCC carries a poor prognosis with a 5-year survival rate of approximately 50%.[12] Additionally, the incidence of liver cancer has been increasing in both males and females in the U.S[1] and, worldwide, liver cancer is one of the most common causes of cancer deaths and led to approximately 700,000 deaths in 2008 alone.[13] Eastern and Southeastern Asia, Middle and Western Africa, Melanesia, and Micronesia/Polynesia have the highest incidence of liver cancer.[13]

The main risk factor for developing HCC is liver cirrhosis, found in 80-90% of patients with HCC.[2,14] Causes of cirrhosis include hepatitis B virus (HBV) infection, hepatitis C virus (HCV) infection, alcohol use, non-alcoholic steatohepatitis, and, rarely, inherited metabolism disorders.[14] In Asia and Africa, chronic HBV infection is the leading cause of HCC while in North America, Europe, and Japan, HCV infection is the leading cause.[2,15]

The Barcelona Clinic Liver Cancer (BCLC) staging system is widely used for HCC and is outlined below.[16,17]

BCLC Stage	Tumor Characteristics	Child-Pugh Score
A (Early)	Single tumor or 3 tumors all < 3 cm	A-B
B (Intermediate)	Multinodular	A-B
C (Advanced)	Vascular invasion or extrahepatic spread	A-B
D (End-Stage)	Any	C

Treatment Options in HCC

Regarding treatment options for HCC, locoregional modalities include surgical resection and orthotopic liver transplantation. Surgical resection is often limited to patients without cirrhosis and who have early stage HCC. When surgical resection is attempted in patients with cirrhosis, good prognostic markers include small tumor (< 3 cm in diameter), normal total bilirubin level, and no portal hypertension (PH).[2] Nevertheless, the overall 5-year risk of recurrence of HCC after resection is up to 70%.[2] Orthotopic liver transplantation using the Milan criteria[18] for patient selection typically has a 4-year overall survival (OS) rate of 85% and a 4-year recurrence free survival (RFS) rate of 92%[2]. Other local therapies, for disease confined to the liver, include radiofrequency ablation (RFA), transarterial chemoembolization (TACE), and radioembolization with yttrium-90.[2,12]

For more advanced HCC, the only approved standard systemic therapy is with the oral tyrosine kinase inhibitor (TKI) sorafenib, as discussed above in Section 2.2. There are currently no standard systemic therapy options available for patients with HCC that has progressed on sorafenib therapy. Based on the placebo arm of published reports of trials examining second-line agents for the treatment of HCC, the estimated median overall survival for patients with HCC that has progressed on sorafenib is approximately 7-9 months.[3-6]

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission was of adequate quality for the clinical review.

3.2 Compliance with Good Clinical Practices

The study reports contained in this sNDA included statements that the trials were conducted in accordance with the Declaration of Helsinki and The International Conference on Harmonization (ICH) GuidelineE6: Good Clinical Practice (GCP).

3.3 Financial Disclosures

Financial disclosure information was collected based on participation in Study 15982. Bayer stated that financial disclosure information was collected or due diligence was exercised to obtain the information and that each listed clinical investigator that was required to disclose if he/she had a proprietary interest in this product or significant equity in Bayer as defined in 21 CFR 54.2(b) did not disclose any such interests. Bayer also stated that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

A total of 971 principal investigators (PIs) and sub-investigators (Sub-Is) signed financial disclosure forms. Of these 971 PIs and Sub-Is, 781 signed both initial and interim/end-of-study (EOS) forms and 190 signed only the initial forms because he or she left the trial site (118) or did not randomize any patients to the study (72). Six PIs and Sub-Is did not sign any forms and did not participate in the study. Additionally, Bayer provided Form 3455 for 4 PIs and Sub-Is who had disclosable information:

Two investigators at site (b) (6), received approximately $91,000 for research grants, speaking fees, educational programs, or consulting from Bayer between 2013-2016. This site consented (b) (6) patients, (b) (6) of which received treatment.

Reviewer's Comment: *The number of patients treated at this site constituted approximately (b) (6)% of the total patients treated. Additionally, Bayer examined the data from that site and did not find evidence of unusual outliers.*

One investigator at site (b) (6) received approximately $36,000 in speaking and consulting fees and $50,000 in institutional grants from Bayer between 2014-2016. (b) (6) patients were consented at this site and (b) (6) received treatment.

Reviewer's Comment: *The number of patients treated at this site constituted approximately (b) (6)% of the total patients treated. Additionally, Bayer examined the data from that site and did not find evidence of unusual outliers.*

One investigator at site (b) (6) received approximately $185,200 from Bayer for consulting between 2013-2016. (b) (6) patients were consented and (b) (6) received treatment.

Reviewer's Comment: *Bayer states that, although the details of the above payments to the investigator were not initially disclosed, the information from patients enrolled at this site was reviewed at the conclusion of the trial and no outliers in terms of safety or efficacy were identified. The number of patients treated at this site constituted approximately (b) (6)% of the total patients treated.*

The Clinical Investigator Financial Disclosure Review Form is attached to this review.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Not applicable for this supplement.

4.2 Clinical Microbiology

Not applicable for this supplement.

4.3 Preclinical Pharmacology/Toxicology

Not applicable for this supplement.

4.4 Clinical Pharmacology

In addition to the clinical pharmacology information provided in previous regorafenib applications, Bayer provided data from three clinical pharmacology studies in this

application: Study 16653 (a pharmacokinetic study in cancer patients with renal impairment), Study 16674 (a drug-drug interaction study in cancer patients), and Study 16675 (a drug-drug interaction study in healthy volunteers). New clinical pharmacology information is also provided from Study 15982 (the RESORCE study). Sections 4.4.1, 4.4.2, and 4.4.3 briefly summarize clinical pharmacology information. Refer to the Office of Clinical Pharmacology review for additional analyses and conclusions regarding the data.

4.4.1 Mechanism of Action

In the application, Bayer stated that in *in-vitro* and *in-vivo* pre-clinical studies, regorafenib inhibits the growth, migration, and invasion of HCC cells and also induces apoptosis in HCC cells.

4.4.2 Pharmacokinetics

In the application, Bayer states that regorafenib is metabolized by multiple mechanisms, including glucuronidation and oxidation, to form two pharmacologically active metabolites, M-2 and M-5. Thus, this application includes data on unchanged regorafenib, M-2, and M-5.

Based on studies of patients with different races and ethnicities, Bayer states that dose adjustments based on race and ethnicity are not needed. Regarding liver function, Bayer states that the regorafenib exposure is similar between patients with normal liver function and patients with Child-Pugh class A liver impairment. There are limited data available regarding patients with Child-Pugh class B liver impairment and pharmacokinetic studies have not been performed on patients with Child-Pugh class C liver impairment. Based on renal impairment studies, Bayer states that patients with mild or moderate renal impairment demonstrated similar exposure of regorafenib compared to patients with normal renal function.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

One adequate and well-controlled study was used to support the expansion of the label in second line HCC, Study 15982 (PH-38451).

5.2 Review Strategy

The safety and efficacy analyses were based on the evaluation of Study 15982, “A randomized, double blind, placebo-controlled, multicenter phase III study

of regorafenib in patients with hepatocellular carcinoma (HCC) after sorafenib."

The first subject's first visit (FSFV) was on May 14, 2013, and the last subject's last visit (LSLV) on or before the data cutoff was on February 29, 2016. End of Study follow up is ongoing. The study enrolled patients from 152 clinical investigator sites in 21 countries in the U.S., South America, Europe, Asia, and Australia. A total of 843 patients were enrolled. Twenty four centers in China, Spain, France, the United Kingdom, Hungary, Italy, Japan, South Korea, Russia, Taiwan, and the United States enrolled ten or more patients each (328, 39%). Due to screen failures, a total of 573 patients were randomized. Of these, nine centers in China, France, Hungary, Italy, Japan, Russia, and Taiwan randomized ten or more patients each (127 patients, or 22%). Efficacy and safety analyses were conducted using the clinical database with a data cutoff date of February 29, 2016.

5.3 Discussion of Study 15982

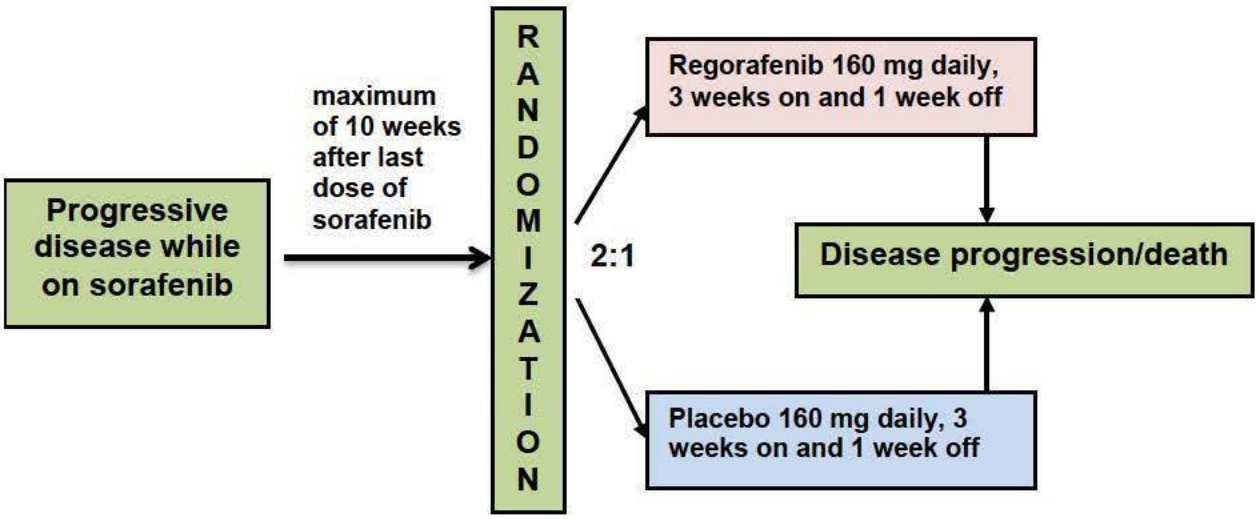
Study 15982, "A randomized, double blind, placebo-controlled, multicenter phase III study of regorafenib in patients with hepatocellular carcinoma (HCC) after sorafenib"

The following protocol synopsis is based on the latest version of the protocol. Amendment #5 was approved December 1, 2015. Table 1 at the end of the protocol review summarizes major changes to the protocol since it was initiated.

Study Design
Study 15982 was an international, randomized, double blind, placebo-controlled study. The study was managed by Bayer HealthCare AG.

The study compared the efficacy and safety of second-line regorafenib versus placebo in patients with HCC that had progressed on sorafenib.
The following figure shows the study design.

Figure 1- 15982 Study Design



Patients were randomized in a 2:1 ratio to receive either regorafenib or placebo using a computer-generated randomization list. The randomization number for each eligible patient was then provided to the investigator through an interactive voice response system (IVRS). Patients were stratified based on geographical region (Asia versus rest of world), ECOG performance status (0 versus 1), AFP level (< 400 ng/mL versus ≥ 400 ng/mL) extrahepatic disease (presence vs absence), and macrovascular invasion (presence versus absence). Study treatment was administered until progressive disease (PD) based on RECIST v1.1 or based on mRECIST for HCC patients, clinical progression (worsening ECOG performance status to ≥ 3 or symptomatic deterioration including increasing LFTs), death, unacceptable toxicity, or decision by patient or treating physician. Of note, the protocol allowed for continuation of treatment beyond PD if the treating physician felt the treatment was providing clinical benefit.

Objectives

The ***primary objective*** of this study was to determine overall survival (OS).

Secondary objectives were analyses of time to progression (TTP), progression free survival (PFS), objective tumor response rate (ORR), and disease control rate (DCR) defined as complete response (CR) + partial response (PR) + stable disease (SD).

Tertiary objectives were analyses of duration of response (DoR), duration of stable disease, health related quality of life and utility values, pharmacokinetics (PK), and biomarker evaluation.

Safety objectives were the analysis of adverse events, physical examination and vital signs, laboratory assessments, 12-lead electrocardiograms (ECG), Child-Pugh status, and ECOG performance status.

Study Population (modified for brevity)

Inclusion Criteria:

1. Patients with histological confirmation of HCC or with non-invasive diagnosis of HCC based on the American Association for the Study of Liver Diseases (AASLD) criteria in patients with confirmed cirrhosis.
2. Patients must have HCC that has progressed on prior treatment with sorafenib. Progression on sorafenib was defined as radiologic progression based on the radiology charter. Patients must have tolerated treatment with sorafenib (defined as not less than 20 days on at least 400 mg daily within the last 28 days prior to stopping the sorafenib). Patients had to be randomized within 10 weeks after the last dose of sorafenib.

3. BCLC stage category B or C that cannot benefit from treatments with established efficacy.
4. Liver function status Child-Pugh class A as calculated during the screening period.
5. Any local or locoregional therapy of intrahepatic tumors must have been completed ≥ 4 weeks before 1st dose of study medication.
6. Adequate organ function including:
    a. Total bilirubin ≤ 2 mg/dL
    b. ALT and AST ≤ 5 X upper limit of normal (ULN)
    c. Serum creatinine ≤ 1.5 X ULN
    d. Glomerular filtration rate (GFR) ≥30 mL/min/1.73 m^2
    e. Platelet count ≥ 60,000/mm^3
7. ECOG performance status 0-1.
8. Age ≥ 18 years.
9. Signed written informed consent.
10. Agreement for men and women to use adequate contraception methods.

Exclusion Criteria:

1. Prior systemic treatment for HCC except sorafenib.
2. Sorafenib treatment within 2 weeks of randomization.
3. Permanent discontinuation of sorafenib therapy due to sorafenib-related toxicity.
4. Candidate for liver transplantation.
5. Patients with large esophageal varices at risk for bleeding and that were not being treated with standard medical treatment.
6. Ascites not controlled with diuretic or paracenteses.
7. Ascites or pleural effusion causing respiratory compromise.
8. Clinically significant bleeding event ≥ Grade 3 within 30 days of randomization.
9. Uncontrolled hypertension defined as systolic blood pressure >150 mmHg or diastolic pressure >90 mmHg despite optimal medical management.
10. Arterial or venous thrombotic or embolic events within 6 months before 1st dose of study medication.
11. Persistent proteinuria ≥ Grade 3.
12. Non-healing wound, ulcer, or bone fracture.
13. Hepatitis B infection unless no active viral replication is present.
14. Hepatitis C infection that requires antiviral treatment.
15. NYHA CHF Class ≥ 2.
16. Unstable angina or myocardial infarction within 6 months of randomization.
17. Cardiac arrhythmias requiring anti-arrhythmic medication, excluding beta-blockers and digoxin.
18. Interstitial lung disease with ongoing symptoms at screening.
19. Known history of or presence of a symptomatic CNS tumor.
20. Known history of HIV infection.

21. Known hypersensitivity to any of the study drugs, study drug classes, or excipients in the formulation.
22. Inability to swallow or any malabsorption condition.
23. Pregnancy or breast feeding.

Reviewer's Comment: *The protocol adequately selected for a patient population with mild cirrhosis (98% of the patients had Child-Pugh A class cirrhosis) but did not enroll patients with Child-Pugh class B or C cirrhosis (except for the 2% of patients with class B cirrhosis). Thus, the safety and efficacy in these groups of patients is unknown. The primary objective of overall survival is appropriate for this population of patients.*

Treatment Plan

Patients randomized to receive regorafenib received 160 mg (4 x 40-mg tablets) orally daily for 3 weeks of every 4 week cycle and also received best supportive care (BSC). Patients randomized to receive placebo received 160 mg (4 x 40-mg) of matching placebo tablets on the same schedule as the patients receiving regorafenib and also received BSC. Study medication was delayed or reduced based on adverse events graded using NCI CTCAE v4.03, according to pre-defined guidelines. Dose levels were as follows:

Does Level 0: Standard dose, 160 mg orally daily
Dose Level -1: 120 mg orally daily
Dose Level -2: 80 mg orally daily

No more than 2 dose reductions were allowed. Intra-patient dose re-escalation was allowed.

Dose modifications and delays for Grade 3-4 AST and/or ALT increases related to study drug were as follows:

Grade 3, 1st occurrence: Interrupt treatment until ≤ Grade 2 or baseline and then resume at one dose level lower.

Grade 3, 2nd occurrence: Interrupt treatment until ≤ Grade 2 or baseline and then resume at a second dose level lower.

Grade 3, 3rd occurrence: Discontinue study drug.

Grade 3 with ALT or AST > 8 x ULN and a concomitant increase in total bilirubin level to any degree, 1st occurrence: Interrupt treatment until ≤ Grade 2 or baseline and then resume at one dose level lower *or* consider discontinuing study drug.

Grade 3 with ALT or AST > 8 x ULN and a concomitant increase in total bilirubin level to any degree, 2nd occurrence: Discontinue study drug.

Grade 4: Discontinue study drug.

Dose modifications and delays for Grade 2-3 palmar-plantar erythrodysesthesia syndrome (PPES)/hand-foot skin reaction (HFSR) related to study drug were as follows:

Grade 2, 1st occurrence: Institute supportive measures and consider decreasing dose by one level. If no improvement, interrupt study drug for at least seven days until resolves or improves to Grade 1.

Grade 2, no improvement after seven days interruption or 2nd occurrence: Interrupt study drug until resolves or improves to Grade 1 and then resume study drug at one dose level reduced.

Grade 2, 3rd occurrence: Interrupt study drug until resolves to Grade 1 and the resume study drug at 2 dose levels reduced total.

Grade 2, 4th occurrence: Discontinue study drug.

Grade 3, 1st occurrence: Institute supportive measures and interrupt study drug for at least seven days until resolves or improves to Grade 1 and then resume study drug at one dose level reduced.

Grade 3, 2nd occurrence: Institute supportive measures and interrupt study drug for at least seven days until resolves or improves to Grade 1 and then resume study drug at two dose levels reduced total.

Grade 3, 3rd occurrence: Discontinue study drug.

Dose modifications and delays for treatment-emergent hypertension were as follows:

Grade 1: Consider increasing blood pressure monitoring.

Grade 2: If not symptomatic, continue study drug but treat with anti-hypertensives for goal diastolic blood pressure (BP) ≤ 90 mmHg. If symptomatic, interrupt study drug until symptoms resolve and diastolic BP ≤ 90 mmHg.

Grade 3: Interrupt study drug until any symptoms resolve and goal diastolic BP ≤ 90 mmHg and then resume at the same dose level. If BP is not controlled with anti-hypertensive, reduce dose by one dose level. If Grade 3 recurs despite dose reduction and anti-hypertensive therapy, reduce study drug by another dose level.

Grade 4: Discontinue study drug.

Dose modifications and delays for all other Grade 3-4 adverse events related to study drug were as follows:

Grade 3: Interrupt study drug until ≤ Grade 2 and reduce dose by one dose level.
Grade 4: Interrupt study drug until ≤ Grade 2 and consider discontinuation of study drug.

Efficacy assessments

Tumor measurements, response, and disease progression were assessed using RECIST v1.1 and mRECIST for HCC criteria every 6 weeks +/- 7 days after baseline. All post-baseline imaging assessments were required to be performed using the same technique (including modality and slice thickness) as the baseline scan.

The study schedule of assessments is in the Appendices section (Table 30).

Safety

Adverse events were evaluated using CTCAE v4.03 and adverse events of all grades were collected, regardless of relationship to study drug or placebo. Hepatic failure, hepatobiliary disorders (Grades 4 and 5), and bleeding/hemorrhagic events (Grade ≥3) were considered adverse events of special interest (AESI). A treatment-emergent AE (TEAE) was defined as any event arising or worsening after initiation of study drug until 30 days after the last study drug intake. “Common” TEAEs were defined as AEs with at least a 5% total incidence rate of any grade.

The study schedule of assessments is in the Appendices section of this review (Table 30).

Withdrawal criteria:

- Patient request
- Investigator assessment that continuation would be harmful to patient
- Substantial non-compliance by patient
- Illicit drug use by the patient that could increase toxicity or confound assessments

- Severe allergic reaction or any other potential adverse reaction felt to warrant discontinuation
- Development of intercurrent illness or situation which would impact assessments and study endpoints
- Progressive disease (Of note, if an investigator felt that a patient could receive clinical benefit from continued treatment, the patient was allowed to remain on study.)
- Clinical progression
- Development of a second malignancy
- Loss of patient to follow up
- Interruption of study drug administration for more than 28 consecutive days
- Need for more than two dose reductions
- Pregnancy

Of note, if an investigator felt that a patient could receive clinical benefit from continued treatment, the patient was allowed to remain on study.

Reviewer's Comment: *The efficacy and safety monitoring plans were adequate for this population.*

Statistical Issues

Primary endpoint
The primary endpoint was overall survival (OS), performed on the intention to treat (ITT) population. OS was defined as the time from randomization to death due to any cause. Patients were stratified based on geographical region (Asia versus rest of world), ECOG performance status (0 versus 1), AFP level (< 400 ng/mL versus ≥ 400 ng/mL) extrahepatic disease (presence vs absence), and macrovascular invasion (presence versus absence).

Secondary endpoints
Secondary endpoints were:

Time to progression (TTP) was defined as the time in days from randomization to radiological or clinical progression. In this study, clinical progression was defined

as worsening of the ECOG performance status to ≥ 3 or symptomatic deterioration including an increase in liver function tests (LFTs).

Progression free survival (PFS) was defined as the time in days from randomization to progression (radiological or clinical) or death due to any cause.

Objective tumor response rate (ORR) was defined as the rate of patients with complete response (CR) or partial response (PR) over all randomized patients. Patients who discontinued without an assessment were considered non-responders for the analysis.

Disease control rate (DCR) was defined as the rate of patients with CR, PR, or stable disease (SD) over all treated patients.

Tumor response and disease progression were evaluated based on RECIST v1.1 and also mRECIST for HCC.

Tertiary endpoints
Tertiary endpoints were:

Duration of response was defined as the time from first documented objective response to disease progression or death and was evaluated using RECIST v1.1 and mRECIST for HCC criteria.

Duration of stable disease was defined as the time from randomization to the date that disease progression or death was first documented and was evaluated using RECIST v1.1 and mRECIST for HCC criteria.

Pharmacokinetics (PK) of regorafenib

Health related quality of life (HRQoL) using the FACT-Hep and the EQ-5D instruments.

Biomarker evaluation on patient blood samples and tumor tissue were planned to assess the mechanisms of action of regorafenib in patients with HCC.

For this study, the full analysis set (FAS) (i.e., the intent-to-treat analysis set) was defined as all randomized patients. The safety analysis set (SAF population) comprised all randomized patients who received at least one dose of study medication. Patients who were withdrawn from the study were not replaced.

Regarding interim analyses, one formal interim futility analysis was performed. A second formal interim analysis, for OS, was originally planned but this requirement was

removed in amendment 4 of the protocol and was not performed (see Protocol Amendment section, below).

The sample size was calculated based on the OS endpoint with a targeted improvement of a 43% increase in median OS compared to placebo and an associated hazard ratio (HR) of 0.7. Approximately 370 events, assuming a one-sided α of 0.025, were required to achieve a 43% improvement in median OS with a power of 90% and a randomization of 2:1 between regorafenib and placebo. Ultimately, 843 patients were enrolled and 573 patients were randomized.

Reviewer's Comment: *The primary endpoint of overall survival is an appropriate endpoint to establish benefit. There are currently no approved therapies for the treatment of patients with advanced or metastatic HCC that has progressed on sorafenib therapy.*

Protocol amendments

Study 15982 had 5 protocol amendments, all of which were in effect prior to the data cutoff for the report submitted to FDA for review. Table 1 summarizes the major changes in each protocol amendment.

Table 1- Study 15982: Protocol Amendments

Amendment 1 (2 May 2013) v 2.0
• Inclusion criteria were modified to allow patients who had demonstrated progression in previously-treated tumor lesions. • The requirement for the assessment of esophageal varices by endoscopy within 6 months and 12 months of the start of the study was modified to require that endoscopy be performed as per local standard of care. • Text was modified stipulating that patients should start treatment no later than 3 days after randomization. • The requirement for dose adjustments or interruptions in response to increasing bilirubin levels was removed because it was felt that isolated elevations of bilirubin levels without concomitantly elevated transaminases did not require strict dose modification. • Text was added stating that strong inhibitors of CYP3A4 activity should be avoided.
Amendment 2 (13 December 2013) v 3.0
• The time of randomization of patients was to take place within 10 weeks of a patient's last treatment with sorafenib (changed from 8 weeks to accommodate patients transferred from outside sites). • In the section on radiological assessment text was added clarifying how tumor evaluation for HCC should be conducted using RECIST 1.1 and mRECIST.

• A section entitled "Adverse events of special interest" was added.
Amendment 3 (11 November 2014) v 4.0
• The number of patients to be recruited into the study was increased from 530 to 560 to enable 150 patients from China to be recruited while maintaining the 40% cap for Asian patients. • A change was included so that patients who had had previous intrahepatic intraarterial chemotherapy with lipiodol could be enrolled in the study.
Amendment 4 (2 November 2015) v 5.0
• The requirement for the 2nd interim analysis was removed because slower than expected accrual in China would have led to it being conducted prior to full patient accrual.
Amendment 5 (1 December 2015), v 6.0
• Information was added regarding interactions between regorafenib and neomycin, breast cancer resistant protein (BCRP), UGT1A1, UGT1A9, P-glycoprotein substrates, and bile salt sequestering agents.

6 Review of Efficacy

Efficacy Summary

Efficacy analyses were based on the ITT population which consisted of 573 patients (379 patients in the regorafenib arm and 194 patients in the placebo arm).

Patient demographics were balanced between the two arms. The median age at randomization was 64 years in the regorafenib arm and 62 years in the placebo arm. Eighty eight percent of the patients were men in both arms. This percentage of men reflects the higher proportion of male patients in the HCC population although estimates described in literature range between 2:1 and 4:1 male:female.[14] Although data on race was missing for 20% and 23% of the patients in the regorafenib and placebo arms, respectively (due to laws prohibiting the collection of these data in particular countries), the two arms appeared balanced with respect to race and each arm had 38% of patients from Asia and 62% from the rest of the world (ROW).

At the time of data cutoff, 233 (61%) of patients in the regorafenib arm had died and 140 (72%) of patients in the placebo arm had died. The study met the primary endpoint of demonstrating an improvement in overall survival in the regorafenib arm. The median OS was 10.6 months in the regorafenib arm compared to 7.8 months in the placebo arm with a hazard ratio (HR) of 0.63 [95% CI: 0.50, 0.79; p-value (unstratified log-rank test) = 0.0002]. The median OS time was increased by 2.8 months. Subgroup analyses were exploratory but were, in general, consistent with the OS in the ITT population.

The secondary endpoints of PFS and ORR were also met when assessed by either modified RECIST for HCC criteria (mRECIST) or standard RECIST criteria. The

mRECIST for HCC criteria led to a more conservative estimation of PFS [HR = 0.46 (0.37, 0.56) using mRECIST and HR = 0.43 (0.35, 0.52) using RECIST] while standard RECIST criteria led to a more conservative estimate of ORR [point estimates of 10.6% and 4.1% in the regorafenib and placebo arms, respectively, using mRECIST and 6.6% and 2.6% for the regorafenib and placebo arms, respectively, using RECIST].

The mRECIST criteria for HCC were proposed in 2008 and aimed to improve the radiologic assessment of HCC, particularly in the setting of locoregional or molecularly-targeted therapies.[19] These modified criteria use the arterial uptake in contrast-enhanced imaging techniques to assess for viable (versus necrotic) tumor tissue.[19] Increasingly, clinical studies for patients with HCC are reporting results using mRECIST in addition to or instead of RECIST. Related to this concept, a modified version of mRECIST that specifically measures the change in arterial enhancement of HCC lesions also has been proposed.[20]

In Study 15982, the primary endpoint was OS and this endpoint was met. PFS and ORR were secondary endpoints although the Office of Biostatistics has recommended that ORR be exploratory because it was not included in the pre-specified hierarchical test order for secondary endpoints. For PFS, mRECIST criteria led to a more conservative estimation compared to the estimation by standard RECIST criteria though both were similar and both favored the regorafenib arm.

6.1 Indication

Currently, regorafenib is indicated for the treatment of patients with 1) metastatic colorectal cancer (CRC) who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF therapy, and, if RAS wild-type, an anti-EGFR therapy or 2) locally advanced, unresectable or metastatic gastrointestinal stromal tumor (GIST) who have been previously treated with imatinib mesylate and sunitinib malate.

This supplement aims to expand the indication by adding “for the treatment of patients with hepatocellular carcinoma (HCC) who have been previously treated with (b) (4) ”.

6.1.1 Methods

The safety and efficacy analyses were centered on the evaluation of one trial, Trial 15982 (PH-38451), “A randomized, double blind, placebo-controlled, multicenter phase III study of regorafenib in patients with hepatocellular carcinoma (HCC) after sorafenib.”

6.1.2 Demographics

Study 15982 enrolled 843 patients at 152 sites located in 21 countries in the U.S., South America, Europe, Asia, and Australia, 270 of which were screen failures. Thus, 573 patients were ultimately randomized. The first patient's first visit was in May 2013 and the last patient's last visit on or before the data cutoff was in February 2016. Nine centers in China, France, Hungary, Italy, Japan, Russia, and Taiwan randomized ten or more patients each (127 patients, or 22%). Efficacy and safety analyses were conducted using the clinical database with a data cutoff date of February 29, 2016.

Patient demographics were generally balanced between the two treatment arms (Table 2). Median age at randomization was 62 years in the placebo arm and 64 years in the regorafenib arm. Eighty eight percent of the patients were men in both arms which reflects the higher proportion of male patients in the HCC population although estimates described in literature range between 2:1 and 4:1 male:female.[14] Regarding race, not all of the participating countries require or allow reporting of race but of those that report, the two arms were generally balanced with 40.2% of the patients in the placebo arm being Asian and 41.2% of the patients in the regorafenib arm being Asian. A total of 38% of patients were enrolled from Asian study sites.

Table 2- Study 15982: Demographics (ITT population)

	no. of PL (% of N) N= 194	no. of Regorafenib (% of N) N=379
Gender		
Male	171 (88)	333 (88)
Female	23 (12)	46 (12)
Age (years)		
Range (years)	23-83	19-85
Mean (SD)	61.1 (11.6)	61.8 (12.4)
Median	62	64
Younger than 65 years	116 (60)	199 (53)
Race		
Asian	78 (40)	156 (41)
Black or African American	2 (1)	6 (2)
White	68 (35)	138 (36)
Multiple	1 (0.5)	2 (0.5)
Not reported	45 (23)	77 (20)
Region		
Asia	73 (38)	143 (38)
Rest of the world	121 (62)	236 (62)

Initial disease characteristics were similar and balanced between treatment arms (Table 3). Sixty six percent of patients had ECOG performance status of 0 in both arms. However, regarding randomization based on ECOG performance status, data input for randomization differed for 19 patients (3.3% of the 573 patient ITT population). A

sensitivity analysis performed by the Office of Biostatistics did not reveal a significant impact due to this difference.

The etiology of HCC was similar in both arms and was due to hepatitis B or C or alcohol use in the majority of patients in both arms. A patient could have more than one etiology so the sum of the individual etiologies is not identical to the total number of patients in a given treatment arm.

For Barcelona Clinic Liver Cancer (BCLC) classification and Child-Pugh score at study entry, the placebo and regorafenib arms were similar with 89% and 86% of patients classified as BCLC stage C and 97% and 98% of patients classified as Child-Pugh A, in the placebo and regorafenib arms, respectively. The eligibility criteria for Study 15982 stipulated that only patients with Child-Pugh A classification (and BCLC stages B or C) at baseline are eligible. The enrollment of patients with Child-Pugh score B or BCLC stage A are discussed in Section 6.1.3 Subject Disposition.

Alpha-fetoprotein (AFP) values for the two arms are also recorded in Table 3. Values were not available for 3 (1.5%) and 5 (1.3%) patients in the placebo and regorafenib arms, respectively. However, regarding randomization based on AFP group (≥ 400 ng/mL versus < 400 ng/mL), data input for randomization differed for those 8 patients with missing AFP values (1.4% of the 573 ITT population). A sensitivity analysis performed by the Office of Biostatistics did not reveal a significant impact due to this difference.

Regarding macrovascular invasion and/or extrahepatic disease, the placebo arm had a smaller percentage of patients with macrovascular invasion only but a larger percentage of patients with extrahepatic disease only compared to the regorafenib arm. Both conditions were present in 20% and 19% of the placebo and regorafenib arms, respectively while the placebo arm had a smaller percentage (16%) of patients with neither condition, compared to the regorafenib arm (20%).

Based on the medical history dataset, 429 patients had a medical history of cirrhosis (75% of the 573 patients in the ITT population). Of these 429 patients, 7% and 6% of the patients had documented ascites and 18% and 13% of the patients had documented esophageal varices at the time of study entry, in the placebo and regorafenib arms, respectively.

Table 3-Study 15982: Disease characteristics (ITT population)

	no. of PL (% of N) N= 194	**no. of Regorafenib (% of N) N=379**
ECOG PS		
0	129 (66)	251 (66)
1	65 (34)	128 (34)
Etiology of HCC		

	no. of PL (% of N) N= 194	no. of Regorafenib (% of N) N=379
Hepatitis B	73 (38)	143 (38)
Hepatitis C	41 (21)	78 (21)
Alcohol use	55 (28)	90 (24)
Other (not Hepatitis or Alcohol)	46	96
BCLC stage at study entry		
A (early)	0 (0)	1 (0.3)
B (intermediate)	22 (11)	53 (14)
C (advanced)	172 (89)	325 (86)
Child-Pugh score at study entry		
A5	118 (61)	244 (64)
A6	70 (36)	129 (34)
B7	5 (3)	5 (1)
B8	1 (0.5)	0 (0)
Missing data	0 (0)	1 (0.3)
Alpha-fetoprotein (AFP) group		
≥ 400 ng/mL	85 (44)	158 (42)
< 400 ng/mL	106 (55)	216 (57)
Missing data	3 (1.5)	5 (1.3)
Alpha-fetoprotein (AFP) ng/mL		
Mean ng/mL	12622	13508
Median ng/mL	234	183
Missing data (number of patients)	3	5
Macrovascular invasion		
Present	54 (28)	110 (29)
Absent	140 (72)	269 (71)
Extrahepatic disease		
Present	147 (76)	265 (70)
Absent	47 (24)	114 (30)
Macrovascular invasion and Extrahepatic disease		
Macrovascular invasion only	15 (8)	39 (10)
Extrahepatic disease only	108 (56)	194 (51)
Both present	39 (20)	71 (19)
Neither present	32 (16)	75 (20)
Presences of ascites at study entry	**no. of PL (% of N) N =144 (patients with cirrhosis)**	**no. of Regorafenib (% of N) N =285 (patients with cirrhosis)**
Yes	10 (7)	17 (6)
No	134 (93)	268 (94)
Presence of esophageal varices at study entry	**no. of PL (% of N) N = 144 (patients with cirrhosis)**	**no. of Regorafenib (% of N) N =285 (patients with cirrhosis)**
Yes	26 (18)	37 (13)
No	118 (82)	248 (87)

6.1.3 Subject Disposition

Of the randomized patients, 194 were assigned to the placebo (PL) arm and 379 were assigned to the regorafenib arm with 573 patients in the full analysis set (FAS). However, 5 patients randomized to regorafenib did not receive treatment and 1 patient randomized to placebo did not receive treatment. The safety population included the 567 patients who received at least one dose of study medication: 374 patients who received regorafenib and 193 patients who received placebo.

Of the 567 patients who started study drug, 65 patients (17.2% of the 379 randomized patients) in the regorafenib arm and 10 patients (5.2% of the 194 randomized) in the placebo arm were ongoing with study drug at the time of data cut off.

6.1.3.1 Protocol violations and deviations

Bayer reported 1 protocol violation in the regorafenib arm (0.3%) and 3 protocol violations in the placebo arm (1.5%) that led to termination of treatment.

The only major protocol deviation was defined as randomization of a patient who then does not receive treatment. As discussed above, 5 patients in the regorafenib group (1.3%) and 1 patient in the placebo group (0.5%) had major protocol deviations.

Minor protocol deviations were reported in 100% of the patients in both arms of the trial and those that were considered important largely involved excluded concomitant medication treatment, inclusion/exclusion criteria not met but patient received treatment, and patient met withdrawal criteria but remained in the treatment phase. Table 8-2 in the Clinical Study Report (CSR) summarizes these data and the two treatment arms were similar with respect to the reasons for minor protocol deviations. Regarding patients not meeting inclusion/exclusion criteria but still entering the treatment phase, 5 patients in the regorafenib arm (1.3%) and 6 patients in the placebo arm (3%) had Child-Pugh class B cirrhosis despite the protocol excluding patients with Child-Pugh class B or C. Additionally, 1 patient in the regorafenib arm (0.3%) had Child-Pugh class information missing. Similarly, 1 patient in the regorafenib arm (0.3%) had BCLC stage A disease despite the protocol excluding patients with stage A disease.

Despite these violations and deviations, their number and nature of the violations would not appear to invalidate the analysis of overall survival.

6.1.4 Analysis of Primary Endpoint

The primary endpoint of Study 15982 was overall survival (OS). Overall survival was defined as the time from randomization to death due to any cause. At the time of data cutoff, 233 (61%) of patients in the regorafenib arm had died and 140 (72%) of patients

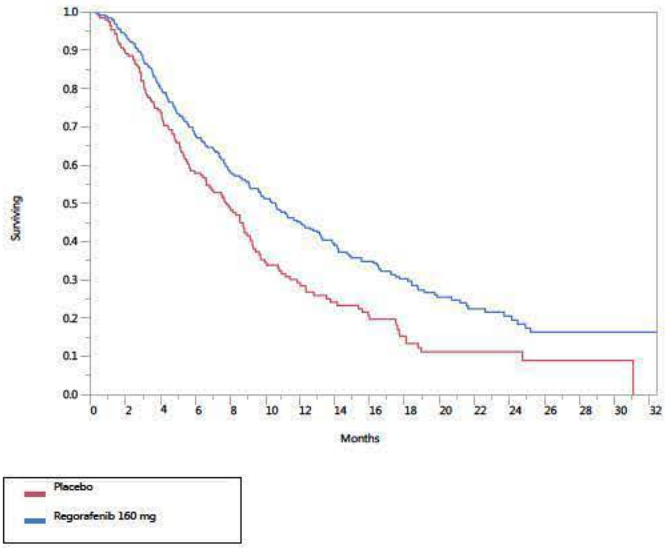
in the placebo arm had died. Table 4 summarizes the overall survival results in the ITT population. The median OS was 10.6 months in the regorafenib arm compared to 7.8 months in the placebo arm. The median time was increased by 2.8 months in the regorafenib arm.

Table 4- Study 15982: Overall survival results (ITT)

	PL; n(%) N= 194	Regorafenib; n (%) N=379
Alive	54 (28)	146 (39)
Death	140 (72)	233 (61)
Time to event (95% CI)	7.8 (6.3, 8.8)	10.6 (9.1, 12.1)
HR (95% CI)	0.63 (0.50, 0.79)	
p-value (unstratified log rank test)	0.0002	

The Kaplan-Meier plot (Figure 2) showed separation of the curves in favor of the regorafenib arm. The curves appeared to separate early and continued to be separate at two years.

Figure 2- Study 15982: Kaplan Meier curve, overall survival (ITT)



6.1.5 Analysis of Secondary Endpoints

Secondary endpoints in this study were analyses TTP, PFS, ORR, and DCR (b) (4) ORR and PFS, assessed by both mRECIST for HCC and RECIST, were analyzed in the Office of Biostatistics review and a summary of their analyses are summarized below (Table 5

and Table 6). The Office of Biostatistics recommends that the ORR endpoint be considered exploratory because ORR testing was not included in the pre-specified hierarchical test order for secondary endpoints.

Table 5- Study 15982: PFS results (ITT population)

PFS by mRECIST	**PL; n(%) N= 194**	**Regorafenib; n (%) N=379**
# PFS events	181 (93)	293(77)
# progressive disease	173	274
# deaths	8	19
mPFS (95% CI) in months	1.5 (1.4, 1.6)	3.1 (2.8, 4.2)
HR (95% CI)	0.46 (0.37, 0.56)	
p-value	< 0.0001	
PFS by RECIST	**PL; n(%) N= 194**	**Regorafenib; n (%) N=379**
# PFS events	184 (95)	288 (76)
# progressive disease	175	270
# deaths	9	18
mPFS (95% CI) in months	1.5 (1.4, 1.5)	3.4 (2.9, 4.2)
HR (95% CI)	0.43 (0.35, 0.52)	
p-value	< 0.0001	

Table 6- Study 15982: ORR results (ITT population)

ORR by mRECIST	**PL; n(%) N= 194**	**Regorafenib; n (%) N=379**
Response Rate (95% CI)	4.1 % (1.8%, 8.0%)	10.6% (7.6%, 14.1%)
Responders (CR+PR)	8	40
CR	0	2
PR	8	38
p-value	0.004728	
Median duration of response (months)	2.7 (1.9, NE)	3.5 (1.9, 4.5)
ORR by RECIST	**PL; n(%) N= 194**	**Regorafenib; n (%) N=379**
Response Rate (95% CI)	2.6% (0.8%, 5.9%)	6.6% (4.3%, 9.6%)
Responders (CR+PR)	8	25
CR	0	0
PR	8	25
p-value	0.019991	
Median duration of response (months)	5.6 (2.3, NE)	5.9 (1.4, 8.4)

6.1.6 Other Endpoints

Duration of response analyses are included in Table 6.

FACT-Hep and EQ-5D patient-reported outcomes (PRO) instruments were administered to patients during the trial. These instruments were self-administered at Cycle 1-Day 1, at every cycle, and then at the end-of-study visit. FACT-Hep scores range from 0 to 180 with higher scores correlating with higher quality of life. EQ-5D scores range from -0.59 to 1.0 with higher scores correlating with higher health states.

Figure 3- Study 15982: FACT-Hep- means with 95% CI, Full Analysis Set (copied from submission)

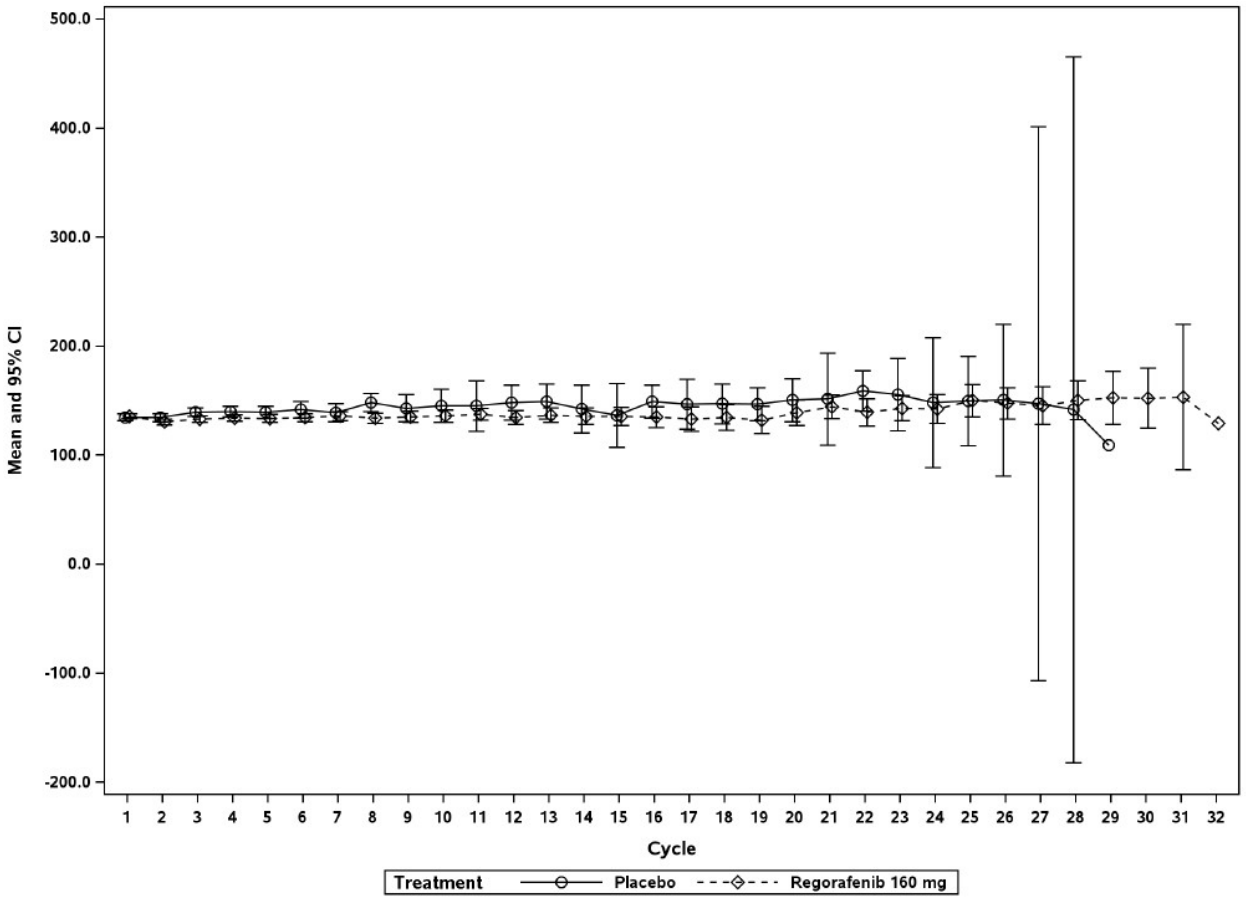
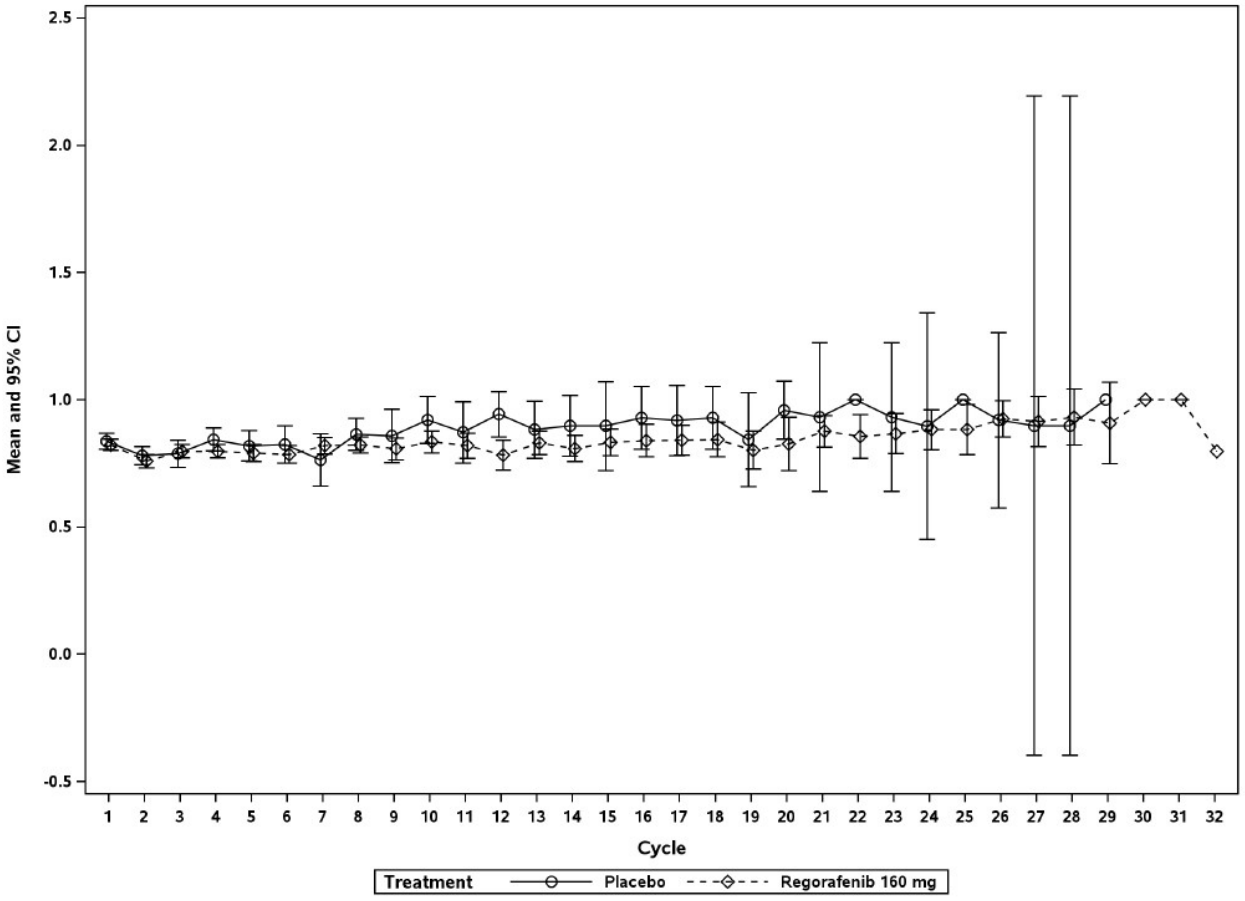


Figure 4- Study 15982: EQ-5D index score - means with 95% CI, Full Analysis Set (copied from submission)



As demonstrated in Figure 3 and Figure 4, differences between arms using the FACT-Hep and EQ-5D did not meet minimally important difference thresholds and, thus, did not identify any clinically meaningful differences between the two arms.

6.1.7 Subpopulations

Patients were stratified based on geographical region (Asia versus rest of world), ECOG performance status (0 versus 1), AFP level (< 400 ng/mL versus ≥ 400 ng/mL) extrahepatic disease (presence vs absence), and macrovascular invasion (presence versus absence). The Office of Biostatistics analyzed OS based on these subgroups and most of the OS analyses for these subgroups were consistent with the primary analysis. All of these subgroup analyses are considered exploratory.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Not applicable.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Not applicable.

6.1.10 Additional Efficacy Issues/Analyses

Not applicable.

7 Review of Safety

Safety Summary

The safety analysis was conducted based on data from the safety population of Study 15982 (374 patients in the regorafenib arm and 193 patients in the placebo arm). Overall, incidence rates of adverse events of any grade (100% in the regorafenib arm and 93% in the placebo arm) were comparable between the treatment arms. The high incidence of adverse events in the placebo arm reflects the morbidity of advanced HCC. The incidence of Grade 3-4 adverse events was higher in the regorafenib arm compared to the placebo arm (79% compared to 56%).

The reported incidence of death related to adverse events was lower in the regorafenib arm (13% compared to 20%). The most frequently reported causes of Grade 5 events were general physical health deterioration (23 in the regorafenib arm and 16 in the placebo arm) and hepatic failure (3 in the regorafenib arm and 5 in the placebo arm).

The most frequently reported (> 5%) Grades 3-4 adverse events in either arm were hypertension (15% and 5% in the regorafenib and placebo arms, respectively), PPES (12% and 1% in the regorafenib and placebo arms, respectively), increased AST (11% in each arm), hypophosphatemia (8% and 2% in the regorafenib and placebo arms, respectively), increased blood bilirubin (7% and 9%, in the regorafenib and placebo arms, respectively), increased lipase (7% and 2% in the regorafenib and placebo arms, respectively), and fatigue (6% and 4% in the regorafenib and placebo arms, respectively).

Grade 3-4 adverse events associated with VEGF inhibition and/or TKIs were increased in the regorafenib arm and included hypertension (15% and 5% in the regorafenib and placebo arms, respectively), hemorrhagic shock (1% and 0% in the regorafenib and placebo arms, respectively), and PPES (12% and 1% in the regorafenib and placebo arms, respectively). The incidence of Grade 3-5 hypertension among regorafenib-

treated patients was higher in patients ≥ 65 years of age compared to younger patients (21% in regorafenib-treated patients ≥ 65 years compared to 9% in regorafenib-treated patients < 65 years).

The proportion of patients who discontinued study drug primarily due to an adverse event was similar between arms (10% and 9% in the regorafenib and placebo arms, respectively).

On May 23, 2017, Bayer informed FDA of updated safety data for some of their patients, largely from 1 investigator site in China and 1 investigator site in Taiwan that were the result of data audits performed by Bayer. Most of the new data that impacted AE reporting were Grade 1 events and affected the incidence rate of a limited number of adverse events described in labeling by 1% or less. Due to the limited scope of these changes, the label was not updated to reflect these changes.

In summary, based on these data from Study 15982, the overall safety profile was within what was expected for regorafenib in this patient population although patients ≥ 65 years appear to be at an increased risk for moderate to severe hypertension.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The safety and efficacy analyses were primarily based on the evaluation of one trial, 15982 (PH-38451), “A randomized, double blind, placebo-controlled, multicenter phase III study of regorafenib in patients with hepatocellular carcinoma (HCC) after sorafenib.”

7.1.2 Categorization of Adverse Events

The severity of adverse events was documented using NCI-CTCAE version 4.0. The MedDRA 19.0 dictionary was used to code adverse event data.

Verbatim terms in the adverse event dataset were reviewed to determine whether MedDRA preferred terms were appropriately coded. Overall the coding of adverse events appeared to be adequate.

A subset of the CRFs was examined to assess the accuracy transfer of the data from the CRFs to the datasets. The data transfer was determined to be appropriate.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Not applicable.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

All safety analyses were based on the safety population, which included all randomized patients who received any amount of study treatment, and were analyzed according to actual treatment received. Five patients randomized to regorafenib did not receive treatment and 1 patient randomized to placebo did not receive placebo. Thus, the safety population included the 573 randomized patients minus the above 6 patients for a total of 567 patients.

7.2.2 Explorations for Dose Response

Not applicable.

7.2.3 Special Animal and/or In Vitro Testing

Not applicable.

7.2.4 Routine Clinical Testing

Routine clinical testing and monitoring were analyzed, and the results of these analyses are described in the Laboratory and Safety Sections of this review (Sections 7.3 and 7.4).

7.2.5 Metabolic, Clearance, and Interaction Workup

Not applicable.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The safety profile of anti-VEGF agents was characterized by assessing the occurrence of hypertension, proteinuria, arterial and venous thromboembolic events, hemorrhagic events (e.g., gastrointestinal bleeding, hemoptysis, epistaxis), compromised wound healing, reversible posterior leukoencephalopathy syndrome, gastrointestinal perforation and fistula, and cardiac dysfunction. The safety of small molecule TKIs was

characterized assessing the occurrence of hypertension, proteinuria, skin reactions, thromboemboli, and diarrhea.

7.3 Major Safety Results

The following analyses in the safety section of this review are based on adverse events that occurred between the first administration of regorafenib or placebo and 30 days after the last administration using the treatment-emergent adverse event (TEAE) flag for data set analyses. Importantly, the protocol-specified window for the safety follow up period is 30+4 days and is, thus, not identical to the population used for the main safety summary analyses in the clinical study report which used the applicant's treatment-emergent adverse flag. The safety population includes the 573 randomized patients minus the 6 patients who did not receive study medication for a total of 567 patients, 193 who received placebo and 374 who received regorafenib. Table 7 summarizes the major safety results that occurred using the TEAE flag for selection. Almost all (93%) patients in the placebo arm experienced an AE compared to 100% of the patients in the regorafenib arm. The percentage of patients who experienced a Grade 3-4 AE was higher in the regorafenib arm, with 79% compared to 56% in the placebo arm. Of note, Bayer calculated the incidence of Grade 3 and 4 TEAEs differently, likely excluding from their Grade 3-4 list those patients who also had a Grade 5 event. Thus, in Bayer's Table 10-2, the Grade 3-4 numbers are 75 (38.9%) and 248 (66.3%) for the placebo and regorafenib arms, respectively (the patients who experienced a Grade 5 event were described separately). The trend remains the same using either calculation method. In contrast to AEs, the percentage of patients who experienced either an SAE or a Grade 5 AE was higher in the placebo arm compared to the regorafenib arm.

Table 7-Study 15982: Major safety results summary

	no. of PL (% of N) N= 193	**no. of Regorafenib (% of N) N=374**
Subjects who experienced an AE	179 (93)	374 (100)
Subjects who experienced an AE Grade 3-4	109 (56)	295 (79)
Subjects who experienced a SAE	90 (47)	166 (44)
Deaths related to an AE	38 (20)	50 (13)

At the SOC level, Table 8, the most frequently affected systems of all Grades (≥ 20% incidence) were Gastrointestinal disorders (78% and 59% in the regorafenib and placebo arms, respectively), General disorders and administration site conditions (70% and 55% in the regorafenib and placebo arms respectively), Skin and subcutaneous tissue disorders (66% and 31% in the regorafenib and placebo arms, respectively), Investigations (58% and 37% in the regorafenib and placebo arms, respectively), Metabolism and nutrition disorders (53% and 34% in the regorafenib and placebo arms, respectively), Respiratory, thoracic and mediastinal disorders (41% and 22% in the

regorafenib and placebo arms, respectively), Vascular disorders (36% and 13% in the regorafenib and placebo arms, respectively), Musculoskeletal and connective tissue disorders (35% and 28% in the regorafenib and placebo arms, respectively), and Infections and infestations (31% and 18% in the regorafenib and placebo arms, respectively).

Table 8- Study 15982: AEs by SOC

SOC	no. of PL (% of N) N= 193		no. of Regorafenib (% of N) N=374	
	All Grades	Grades 3-5	All Grades	Grades 3-5
Gastrointestinal disorders	114 (59)	29 (15)	290 (78)	65 (17)
General disorders and administration site conditions	106 (55)	31 (16)	260 (70)	71 (19)
Skin and subcutaneous tissue disorders	59 (31)	2 (1)	245 (66)	51 (14)
Investigations	72 (37)	40 (21)	217 (58)	117 (31)
Metabolism and nutrition disorders	66 (34)	22 (11)	199 (53)	75 (20)
Respiratory, thoracic and mediastinal disorders	43 (22)	11 (6)	153 (41)	17 (5)
Vascular disorders	26 (13)	11 (6)	134 (36)	60 (16)
Musculoskeletal and connective tissue disorders	55 (28)	8 (4)	132 (35)	17 (5)
Infections and infestations	35 (18)	11 (6)	117 (31)	30 (8)
Nervous system disorders	49 (25)	8 (4)	91 (24)	22 (6)
Blood and lymphatic system disorders	30 (16)	12 (6)	65 (17)	25 (7)
Renal and urinary disorders	18 (9)	4 (2)	63 (17)	13 (3)
Hepatobiliary disorders	31 (16)	26 (13)	55 (15)	32 (9)
Psychiatric disorders	17 (9)	2 (1)	45 (12)	4 (1)
Endocrine disorders	0 (0)	0 (0)	29 (8)	0 (0)
Cardiac disorders	9 (5)	1 (1)	27 (7)	7 (2)
Injury, poisoning and procedural complications	14 (7)	3 (2)	24 (6)	4 (1)
Ear and labyrinth disorders	5 (3)	0 (0)	19 (5)	0 (0)
Reproductive system and breast disorders	10 (5)	2 (1)	18 (5)	0 (0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	8 (4)	2 (1)	15 (4)	10 (3)
Eye disorders	5 (3)	0 (0)	9 (2)	1 (0)
Surgical and medical procedures	0 (0)	0 (0)	2 (1)	2 (1)
Immune system disorders	0 (0)	0 (0)	1 (0)	0 (0)

At the preferred term (PT) level,

Table 9, the most frequently reported adverse events of all Grades (≥ 20% incidence) were palmar-plantar erythrodysaesthesia syndrome (PPES) (51% and 7% in the

regorafenib and placebo arms, respectively), diarrhea (41% and 15% in the regorafenib and placebo arms, respectively), hypertension (31% and 6% in the regorafenib and placebo arms, respectively), decreased appetite (30% and 14% in the regorafenib and placebo arms, respectively), fatigue 28% and 24% in the regorafenib and placebo arms, respectively), increased aspartate aminotransferase (AST) (25% and 20% in the regorafenib and placebo arms, respectively), increased blood bilirubin (24% and 16% in the regorafenib and placebo arms, respectively), abdominal pain (21% and 16% in the regorafenib and placebo arms, respectively), and pyrexia (20% and 7% in the regorafenib and placebo arms, respectively).

The complete list of AEs (all grades) by PT can be found in Table 31. FDA's analysis concurs with Bayer's reported incidence rates of TEAEs in their clinical study report.

Table 9- Study 15982: AEs by PT with ≥ 5% incidence in regorafenib arm and with a ≥ 3% difference between arms

PT	no. of PL	% of PL N = 193	no. of Regorafenib	% of Regorafenib N = 374
Palmar-plantar erythrodysaesthesia syndrome (PPES)	13	7	192	51
Diarrhoea	29	15	153	41
Hypertension	12	6	115	31
Decreased appetite	27	14	114	30
Fatigue	47	24	106	28
Aspartate aminotransferase (AST) increased	38	20	92	25
Blood bilirubin increased	31	16	91	24
Abdominal pain	30	16	79	21
Pyrexia	13	7	74	20
Dysphonia	3	2	66	18
Constipation	21	11	65	17
Nausea	26	13	64	17
Asthenia	18	9	56	15
Alanine aminotransferase increased	21	11	54	14
Hypoalbuminaemia	14	7	52	14
Anaemia	21	11	51	14
Weight decreased	8	4	50	13
Abdominal pain upper	17	9	47	13
Vomiting	13	7	47	13
Back pain	17	9	45	12
Cough	13	7	41	11
Muscle spasms	4	2	38	10
Hypophosphataemia	4	2	36	10
Platelet count decreased	2	1	34	9
Proteinuria	2	1	32	9
Stomatitis	4	2	31	8
Lipase increased	6	3	27	7
Alopecia	5	3	26	7

PT	no. of PL	% of PL N = 193	no. of Regorafenib	% of Regorafenib N = 374
Hypokalaemia	5	3	26	7
Pain in extremity	6	3	26	7
Hypothyroidism	0	0	24	6
Malaise	5	3	22	6
Hyponatraemia	6	3	21	6
White blood cell count decreased	2	1	17	5

When grouped by high level term (HLT), Table 10, the most frequent AEs (≥ 20%) were skin and subcutaneous conditions, asthenic conditions, diarrhea, liver function analyses, gastrointestinal and abdominal pain, appetite disorders, vascular hypertensive disorders, musculoskeletal and connective tissue pain and discomfort, nausea and vomiting symptoms, upper respiratory tract signs and symptoms, and febrile disorders.

Table 10- Study 15982: AEs by HLT (incidence ≥ 5%)

HLT	no. PL	% of PL N= 193	no. Regorafenib	% of Regorafenib N=374
Skin and subcutaneous conditions NEC	13	7	192	51
Asthenic conditions	67	35	174	47
Diarrhoea (excl infective)	29	15	154	41
Liver function analyses	57	30	141	38
Gastrointestinal and abdominal pains (excl oral and throat)	47	24	121	32
Appetite disorders	28	15	115	31
Vascular hypertensive disorders NEC	12	6	115	31
Musculoskeletal and connective tissue pain and discomfort	35	18	91	24
Nausea and vomiting symptoms	32	17	83	22
Upper respiratory tract signs and symptoms	8	4	77	21
Febrile disorders	13	7	74	20
Gastrointestinal atonic and hypomotility disorders NEC	24	12	66	18
Oedema NEC	26	13	62	17
Peritoneal and retroperitoneal disorders	31	16	58	16
Physical examination procedures and organ system status	9	5	56	15
General signs and symptoms NEC	35	18	55	15
Protein metabolism disorders NEC	15	8	54	14
Anaemias NEC	21	11	51	14

HLT	no. PL	% of PL N= 193	no. Regorafenib	% of Regorafenib N=374
Coughing and associated symptoms	17	9	45	12
Muscle related signs and symptoms NEC	4	2	39	10
Urinary abnormalities	6	3	39	10
Potassium imbalance	12	6	37	10
Phosphorus metabolism disorders	4	2	36	10
Platelet analyses	2	1	36	10
Stomatitis and ulceration	6	3	36	10
Breathing abnormalities	17	9	32	9
White blood cell analyses	5	3	32	9
Tissue enzyme analyses NEC	11	6	30	8
Digestive enzymes	6	3	29	8
Lower respiratory tract and lung infections	5	3	28	7
Upper respiratory tract infections	5	3	27	7
Alopecias	5	3	26	7
Rashes, eruptions and exanthems NEC	15	8	26	7
Headaches NEC	12	6	24	6
Pain and discomfort NEC	9	5	24	6
Thyroid hypofunction disorders	0	0	24	6
Cholestasis and jaundice	8	4	23	6
Flatulence, bloating and distension	12	6	22	6
Oral dryness and saliva altered	9	5	22	6
Sodium imbalance	7	4	21	6
Pruritus NEC	15	8	20	5
Dermal and epidermal conditions NEC	10	5	18	5
Nasal disorders NEC	2	1	18	5

7.3.1 Deaths

Eighty eight deaths occurred during the TEAE (30 day) period, 50 (13%) in the regorafenib arm and 38 (20%) in the placebo arm. Table 11 details the causes of death by PT in each arm during the TEAE period. The two arms are generally balanced with respect to the causes and, based on a focused review of narratives and brief case summaries, many of these deaths appeared to occur in the setting of clinical progression of disease.

Table 11- Study 15982: Causes of Grade 5 events by PT

	no. of PL	no. of Regorafenib
Deaths	**38**	**50**
Causes by PT	**39***	**50**
Acute hepatic failure	0	1
Ascites	1	2
Blood pressure decreased	0	1
Bronchial obstruction	0	1
Cardiac arrest	1	0
Craniocerebral injury	0	1
Death	0	1
Duodenal perforation	0	1
Dyspnoea	1	2
Encephalopathy	1	0
General physical health deterioration	16	23
Haemorrhage intracranial	0	1
Hepatic encephalopathy	1	1
Hepatic failure	5	3
Hepatic haemorrhage	2	0
Hepatorenal syndrome	1	1
Hypovolaemic shock	0	1
Intra-abdominal haemorrhage	1	0
Lung infection	0	1
Meningorrhagia	0	1
Multiple organ dysfunction syndrome	1	0
Myocardial infarction	0	1
Oesophageal varices haemorrhage	1	0
Peritonitis bacterial	0	1
Pleural effusion	1	0
Pneumonia	0	1
Respiratory failure	3	1
Sepsis	0	1
Septic shock	0	1
Shock haemorrhagic	0	2
Tumour haemorrhage	1	0
Upper gastrointestinal haemorrhage	2	0

Note: 39 different Grade 5 events were attributed to 38 individual patients in the placebo arm. One patient in the placebo arm had two Grade 5 events attributed, one each in Gastrointestinal disorders (ascites) and Nervous system disorders (hepatic encephalopathy).

Of these 88 deaths, the SOC groups (Table 12) that differed the most between the two arms and for which the regorafenib arm had a higher incidence were Infections and infestations (1.3% and 0% in the regorafenib and placebo arms, respectively) and Vascular disorders (0.8% and 0% in the regorafenib and placebo arms, respectively). Review of these narratives did not reveal any emerging patterns. One patient died from

meningorrhagia in the setting of regorafenib and therapeutic low molecular weight heparin (LMWH) but in the absence of CNS lesions. This event is consistent with prior regorafenib adverse event data.

Table 12- Causes of Grade 5 events by SOC

SOC	no. of PL (% of N) N = 193	no. of Regorafenib (% of N) N = 374
Cardiac disorders	1 (0.5)	1 (0.3)
Gastrointestinal disorders	5 (2.6)	3 (0.8)
General disorders and administration site conditions	17 (8.8)	24 (6.4)
Hepatobiliary disorders	8 (4.1)	5 (1.3)
Infections and infestations	0 (0)	5 (1.3)
Injury, poisoning and procedural complications	0 (0)	1 (0.3)
Investigations	0 (0)	1 (0.3)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.5)	0 (0)
Nervous system disorders	2 (1.0)	3 (0.8)
Respiratory, thoracic and mediastinal disorders	5 (2.6)	4 (1.1)
Vascular disorders	0 (0)	3 (0.8)

Note: One patient in the placebo arm had two Grade 5 events attributed, one each in Gastrointestinal disorders (ascites) and Nervous system disorders (hepatic encephalopathy).

Of the nine deaths attributed by investigators to study drug, two occurred in the placebo arm (both with PT of hepatic failure) and seven occurred in the regorafenib arm (with PTs of duodenal perforation, meningorrhagia, shock hemorrhagic, hepatic encephalopathy, death (NOS), myocardial infarction, and general physical health deterioration). Review of these narratives did not reveal unexpected patterns for this drug class in this population of patients.

7.3.2 Nonfatal Serious Adverse Events

During the 30-day TEAE period, the incidence of SAEs was 44% in the regorafenib arm and 47% in the placebo arm. Table 13 lists the incidences of non-fatal SAEs by PT and Table 14 lists the incidence of Grade 3 and 4 SAEs by SOC that occurred in the two arms. These incidence rates are comparable between the two arms.

Table 13- Study 15982: Non-fatal (Grades 1-4) SAEs (incidence ≥1%) by PT

PT	no. of PL (% of N) N= 193	no. of Regorafenib (% of N) N=374
General physical health deterioration	13 (7)	29 (8)
Ascites	6 (3)	9 (2)
Hepatic failure	8 (4)	9 (2)
Hepatic encephalopathy	2 (1)	7 (2)
Back pain	2 (1)	6 (2)
Pneumonia	1 (1)	6 (2)
Dyspnoea	2 (1)	5 (1)
Pyrexia	1 (1)	5 (1)
Oesophageal varices haemorrhage	1 (1)	4 (1)
Pleural effusion	1 (1)	4 (1)
Tumour pain	0 (0)	4 (1)
Acute coronary syndrome	0 (0)	3 (1)
Anaemia	1 (1)	3 (1)
Asthenia	0 (0)	3 (1)
Dehydration	0 (0)	3 (1)
Diarrhoea	0 (0)	3 (1)
Encephalopathy	3 (2)	3 (1)
Haemoptysis	2 (1)	3 (1)
Pancreatitis	0 (0)	3 (1)
Shock haemorrhagic	0 (0)	3 (1)
Upper gastrointestinal haemorrhage	3 (2)	3 (1)
Abdominal infection	0 (0)	2 (1)
Abdominal pain	4 (2)	2 (1)
Abdominal pain lower	0 (0)	2 (1)
Atrial fibrillation	0 (0)	2 (1)
Fatigue	0 (0)	2 (1)
Hepatic cirrhosis	0 (0)	2 (1)
Hepatic function abnormal	3 (2)	2 (1)
Hepatic haemorrhage	2 (1)	2 (1)
Hypoglycaemia	0 (0)	2 (1)
Hyponatraemia	0 (0)	2 (1)
Jaundice cholestatic	1 (1)	2 (1)
Liver abscess	2 (1)	2 (1)
Lung infection	0 (0)	2 (1)
Pneumonitis	0 (0)	2 (1)
Renal failure	1 (1)	2 (1)
Seizure	0 (0)	2 (1)
Sepsis	0 (0)	2 (1)

Table 14- Study 15982: Grade 3-4 SAEs by SOC

SOC	no. of PL (% of N) N= 193	no. of Regorafenib (% of N) N=374
General disorders and administration	14 (7)	31 (8)

SOC	no. of PL (% of N) N= 193	no. of Regorafenib (% of N) N=374
site conditions		
Gastrointestinal disorders	17 (9)	27 (7)
Infections and infestations	5 (3)	25 (7)
Hepatobiliary disorders	20 (10)	21 (6)
Nervous system disorders	4 (2)	18 (5)
Respiratory, thoracic and mediastinal disorders	8 (4)	14 (4)
Musculoskeletal and connective tissue disorders	4 (2)	10 (3)
Metabolism and nutrition disorders	4 (2)	8 (2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (1)	8 (2)
Cardiac disorders	1 (1)	6 (2)
Vascular disorders	2 (1)	6 (2)
Blood and lymphatic system disorders	2 (1)	4 (1)
Injury, poisoning and procedural complications	3 (2)	4 (1)
Investigations	2 (1)	4 (1)
Renal and urinary disorders	2 (1)	4 (1)
Skin and subcutaneous tissue disorders	0 (0)	2 (1)
Eye disorders	0 (0)	1 (0)
Psychiatric disorders	0 (0)	1 (0)
Reproductive system and breast disorders	1 (1)	0 (0)

7.3.3 Dropouts and/or Discontinuations

Dose reductions and interruptions occurred more often in the regorafenib arm compared to the placebo arm while both arms had similar incidence rates of discontinuations (Table 15). Of note, a patient could have more than one dose reduction or interruption. The most frequent AEs leading to study drug withdrawal in the regorafenib arm were general physical health deterioration/abnormal general physical health condition (6 events), hepatic failure (5 events), increased AST (3 events), hepatic encephalopathy (3 events), increased blood bilirubin/increased conjugated bilirubin/hyperbilirubinemia (3 events), fatigue/asthenia (3 events), and PPES (2 events).

Table 15- Study 15982: Study drug dose reduced, interrupted, or withdrawn

Event	no. of PL patients	% of PL N = 193	no. of Regorafenib patients	% of Regorafenib N = 374
Total reduced, interrupted, or withdrawn	**46**	**24**	**225**	**60**
Reduced	9	5	105	28
Interrupted	29	15	172	46
Withdrawn (discontinued)	18	9	37	10

This analysis differs from that of Bayer with their analysis concluding that dose interruptions and dose reductions occurred in (b)(4)% and 48% of regorafenib-treated patients, respectively. This issue (and reasons for discrepancies) is currently under review as part of labeling.

7.3.4 Significant Adverse Events- Non-Fatal Grade 3-4 AEs

This section focuses on Grade 3-4 AEs. Adverse events that are known to be related to VEGF inhibition will be further discussed in Section 7.3.5 Submission Specific Primary Safety Concerns. Table 16 summarizes the incidence of all Grade 3-4 AEs by SOC.

Table 16- Study 15982: Grade 3-4 AEs by SOC

SOC	no. of Gr 3-4 PL	% of PL N = 193	no. of Gr 3-4 Regorafenib	% of Regorafenib N = 374
Investigations	40	21	116	31
Metabolism and nutrition disorders	22	11	75	20
Gastrointestinal disorders	24	12	62	17
Vascular disorders	11	6	57	15
Skin and subcutaneous tissue disorders	2	1	51	14
General disorders and administration site conditions	14	7	47	13
Hepatobiliary disorders	18	9	27	7
Blood and lymphatic system disorders	12	6	25	7
Infections and infestations	11	6	25	7
Nervous system disorders	6	3	19	5
Musculoskeletal and connective tissue disorders	8	4	17	5
Renal and urinary disorders	4	2	13	3
Respiratory, thoracic and mediastinal	6	3	13	3

SOC	no. of Gr 3-4 PL	% of PL N = 193	no. of Gr 3-4 Regorafenib	% of Regorafenib N = 374
disorders				
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1	1	10	3
Cardiac disorders	0	0	6	2
Psychiatric disorders	2	1	4	1
Injury, poisoning and procedural complications	3	2	3	1
Surgical and medical procedures	0	0	2	1
Eye disorders	0	0	1	0
Reproductive system and breast disorders	2	1	0	0

Table 17 summarizes the most frequent Grade 3-4 AEs by PT, regardless of outcome, which occurred with an incidence rate of 2% or more. Of these, hypertension (15% and 5% in the regorafenib and placebo arms, respectively), PPES (12% and 1% in the regorafenib and placebo arms, respectively), hypophosphatemia (8% and 2% in the regorafenib and placebo arms, respectively), and increased lipase (7% and 2% in the regorafenib and placebo arms, respectively) were the most common. Increased AST and increased blood bilirubin were also among the most common Grade 3-4 AEs but were not increased in the regorafenib arm compared to the placebo arm.

Table 17- Study 15982: Grade 3-4 AEs by PT (incidence ≥ 2%)

PT	no. of Gr 3-4 PL N= 193	% of PL N= 193	no. of Gr 3-4 Regorafenib N=374	% of Regorafenib N=374
Hypertension	9	5	55	15
Palmar-plantar erythrodysaesthesia syndrome	1	1	46	12
Aspartate aminotransferase increased	22	11	41	11
Hypophosphataemia	3	2	31	8
Blood bilirubin increased	18	9	28	7
Lipase increased	3	2	25	7
Fatigue	7	4	22	6
Ascites	11	6	16	4
Anaemia	11	6	15	4
General physical health deterioration	9	5	15	4
Hyponatraemia	6	3	15	4
Asthenia	2	1	14	4
Diarrhoea	0	0	12	3
Gamma-glutamyltransferase increased	5	3	12	3

PT	no. of Gr 3-4 PL N= 193	% of PL N= 193	no. of Gr 3-4 Regorafenib N=374	% of Regorafenib N=374
Alanine aminotransferase increased	5	3	11	3
Abdominal pain	5	3	10	3
Decreased appetite	3	2	10	3
Platelet count decreased	0	0	10	3
Hypokalaemia	2	1	9	2
Back pain	2	1	8	2
Blood alkaline phosphatase increased	4	2	7	2
Hyperbilirubinaemia	3	2	7	2
Proteinuria	1	1	7	2
Weight decreased	0	0	7	2
Amylase increased	0	0	6	2
Hepatic encephalopathy	1	1	6	2
Hepatic failure	4	2	6	2
Hypoalbuminaemia	1	1	6	2

Adverse events with an increased incidence of 2% or more in the regorafenib arm compared to the placebo arm were hypertension, palmar-plantar erythrodysaesthesia syndrome (PPES), hypophosphatemia, increased lipase, fatigue, asthenia, diarrhea, decreased platelet count, decreased weight, and increased amylase.

As discussed above, FDA's analysis of the overall incidence of Grade 3-4 TEAEs differed from that of Bayer though the trends were the same.

Investigations

As an SOC, Investigations were the most frequently observed Grade 3-4 TEAEs in Study 15982 and Table 18 summarizes the individual PTs under this SOC. Events with a higher incidence in the regorafenib arm were increased lipase, decreased platelet count, decreased weight, increased amylase, decreased white blood cell count, decreased hemoglobin, and decreased lymphocytes. A higher incidence rate of Grade 3-4 blood bilirubin levels was observed in the placebo arm.

Table 18- Study 15982: Grade 3-4 Investigations AEs by PT (and incidence ≥1% in regorafenib arm)

PT	no. of Gr 3-4 PL N= 193	% of PL N= 193	no. of Gr 3-4 Regorafenib N=374	% of Regorafenib N=374
Aspartate aminotransferase increased	22	11	41	11
Blood bilirubin increased	18	9	28	7
Lipase increased	3	2	25	7
Gamma-glutamyltransferase increased	5	3	12	3

Alanine aminotransferase increased	5	3	11	3
Platelet count decreased	0	0	10	3
Blood alkaline phosphatase increased	4	2	7	2
Weight decreased	0	0	7	2
Amylase increased	0	0	6	2
Bilirubin conjugated increased	1	1	5	1
Neutrophil count decreased	1	1	4	1
White blood cell count decreased	0	0	4	1
Haemoglobin decreased	0	0	3	1
Lymphocyte count decreased	0	0	3	1

Metabolism and nutrition disorders

Metabolism and nutrition disorders was the next most frequent SOC in terms of Grade 3-4 TEAEs observed and the individual PTs are summarized in Table 19. Hypophosphatemia occurred at an increased incidence in the regorafenib arm.

Table 19- Study 15982: Grade 3-4 Metabolism and Nutrition Disorder AEs by PT (and incidence ≥1% in regorafenib arm)

PT	no. of Gr 3-4 PL N= 193	% of PL N= 193	no. of Gr 3-4 Regorafenib N=374	% of Regorafenib N=374
Hypophosphataemia	3	2	31	8
Hyponatraemia	6	3	15	4
Decreased appetite	3	2	10	3
Hypokalaemia	2	1	9	2
Hypoalbuminaemia	1	1	6	2
Dehydration	0	0	5	1
Hyperglycaemia	4	2	5	1
Hyperkalaemia	2	1	4	1
Hypoglycaemia	0	0	4	1
Hyperuricaemia	0	0	2	1
Hypocalcaemia	0	0	2	1

Gastrointestinal disorders

Gastrointestinal disorders are of particular interest in this HCC population and Table 20 summarizes the Grade 3-4 events in this SOC. Diarrhea occurred at an incidence of 3% in the regorafenib arm compared to 0% in the placebo arm while the other PTs were similar between the two arms.

Table 20- Study 15982: Grade 3-4 Gastrointestinal Disorder AEs by PT (and incidence ≥1% in regorafenib arm)

PT	no. of Gr 3-4 PL N= 193	% of PL N= 193	no. of Gr 3-4 Regorafenib N=374	% of Regorafenib N=374
Ascites	11	6	18	5
Diarrhoea	0	0	12	3
Abdominal pain	5	3	10	3
Abdominal pain lower	0	0	3	1
Oesophageal varices haemorrhage	1	1	3	1
Stomatitis	0	0	3	1
Upper gastrointestinal haemorrhage	3	2	3	1
Vomiting	1	1	3	1
Abdominal pain upper	2	1	2	1
Dysphagia	0	0	2	1
Gastritis	1	1	2	1
Nausea	0	0	2	1

Vascular disorders

Vascular disorders are also of particular interest in the HCC population and in patients taking VEGF-inhibitors and are summarized in Table 21. The incidence rate of hypertension was higher in the regorafenib arm as was the incidence rate of Grade 3 hypertension.

Table 21- Study 15982: Grade 3-4 Vascular Disorder AEs by PT (and incidence ≥1% in regorafenib arm)

PT	no. of Gr 3-4* PL N= 193	% of PL N= 193	no. of Gr 3-4 Regorafenib N=374	% of Regorafenib N=374
Hypertension	9	5	55	15
Shock haemorrhagic	0	0	3	1

Skin and subcutaneous tissue disorders

The increased incidence of Grade 3-4 skin and subcutaneous tissue disorders (in Table 16) in the regorafenib arm compared to the placebo arm is largely due to the increased incidence of PPES as shown in Table 22. No Grade 4 Skin and subcutaneous tissue disorder adverse events were reported in either arm.

Table 22- Study 15982: Grade 3-4 Skin and subcutaneous tissue disorder AEs by PT (and incidence ≥1% in regorafenib arm)

PT	no. of Gr 3-4 PL N= 193	% of PL N= 193	no. of Gr 3-4 Regorafenib N=374	% of Regorafenib N=374
Palmar-plantar erythrodysaesthesia syndrome	1	1	46	12
Skin ulcer	0	0	2	1

General disorders and administration site conditions

While general physical health deterioration events of all Grades occurred at an increased incidence in the placebo arm compared to the regorafenib arm (14% compared to 12%, Table 31), Grade 3-4 general physical health deterioration events occurred at a similar incidence between the two arms (Table 23) while Grade 3-4 events of asthenia and fatigue occurred at an increased incidence in the regorafenib arm compared to the placebo arm.

Table 23- Study 15982: Grade 3-4 General disorders and administration site condition AEs by PT (and incidence ≥1% in regorafenib arm)

PT	no. of Gr 3-4 PL N= 193	% of PL N= 193	no. of Gr 3-4 Regorafenib N=374	% of Regorafenib N=374
General physical health deterioration	14	7	28	7
Fatigue	7	4	22	6
Asthenia	2	1	14	4

Hepatobiliary disorders

Although not increased in incidence in the regorafenib arm, because of their particular relevance to this population, the Grade 3-4 hepatobiliary disorder PTs are summarized in Table 24. There was an increased incidence of hepatic failure in the placebo arm compared to the regorafenib arm which likely reflects the increased incidence of progression of disease in the placebo arm.

Table 24- Study 15982: Grade 3-4 Hepatobiliary disorder AEs by PT

PT	no. of Gr 3-4 PL N= 193	% of PL N= 193	no. of Gr 3-4 Regorafenib N=374	% of Regorafenib N=374
Hepatic failure	8	4	9	2
Hyperbilirubinaemia	3	2	7	2
Hepatic function abnormal	4	2	2	1

Hepatic haemorrhage	2	1	2	1
Hepatorenal syndrome	2	1	2	1
Jaundice	3	2	2	1
Jaundice cholestatic	1	1	2	1
Acute hepatic failure	0	0	1	0
Bile duct stone	0	0	1	0
Cholangitis	1	1	1	0
Cholecystitis	0	0	1	0
Gallbladder obstruction	0	0	1	0
Hepatic cirrhosis	1	1	1	0
Hepatic ischaemia	0	0	1	0
Hepatitis acute	0	0	1	0
Hepatobiliary disease	0	0	1	0
Portal vein thrombosis	1	1	1	0
Bile duct stenosis	4	2	0	0
Cholestasis	1	1	0	0

Infections and infestations
Grade 3-4 infections and infestation PTs are summarized in Table 25. Based on HLTs for AEs of all grades (Table 10), lower respiratory tract and lung infections and upper respiratory tract infections occurred at an increased incidence in the regorafenib arm compared to the placebo arm and Table 25 reflects this trend as well. To address the increased incidence rate of infections, the applicant proposed a Warning describing the overall increased rate of infections in the pooled randomized trials (HCC trial plus previously reviewed colorectal cancer and GIST trials).

Table 25- Study 15982: Grade 3-4 Infections and infestation AEs by PT (and incidence ≥1% in regorafenib arm)

PT	no. of Gr 3-4 PL N= 193	% of PL N= 193	no. of Gr 3-4 Regorafenib N=374	% of Regorafenib N=374
Pneumonia	1	1	6	2
Abdominal infection	2	1	3	1
Sepsis	0	0	3	1
Lung infection	1	1	2	1
Peritonitis bacterial	1	1	2	1
Urinary tract infection	0	0	2	1

7.3.5 Submission Specific Primary Safety Concerns

Safety issues with particular relevance to this anti-VEGF TKI, were hypertension, proteinuria, gastrointestinal fistulas and perforation, wound healing difficulty,

thromboemboli, and cardiac events. Adverse event, laboratory, and vital sign data were examined and do not reveal any new safety findings with the exception of the magnitude of the incidence of Grade 3-5 hypertension in patients older than 65 years old (Section 7.5.3, below).

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Table 26 summarizes Grade 1-2 events.

Table 26- Study 15982: Grade 1-2 AEs by PT (incidence > 5%)

PT	no. of Gr 1-2 PL N= 193	% of PL N= 193	no. of Gr 1-2 Regorafenib N=374	% of Regorafenib N=374
Palmar-plantar erythrodysaesthesia syndrome	13	7	187	50
Diarrhoea	29	15	151	40
Decreased appetite	25	13	111	30
Fatigue	42	22	102	27
Hypertension	9	5	94	25
Blood bilirubin increased	24	12	79	21
Abdominal pain	26	13	75	20
Aspartate aminotransferase increased	30	16	75	20
Pyrexia	13	7	74	20
Dysphonia	3	2	66	18
Constipation	20	10	64	17
Nausea	26	13	64	17
Oedema peripheral	26	13	56	15
Asthenia	18	9	53	14
Hypoalbuminaemia	13	7	50	13
Weight decreased	8	4	50	13
Ascites	27	14	49	13
Alanine aminotransferase increased	19	10	48	13
Abdominal pain upper	16	8	47	13
Anaemia	17	9	47	13
Vomiting	12	6	46	12
Back pain	15	8	43	11
Cough	13	7	41	11
Muscle spasms	4	2	38	10
Platelet count decreased	2	1	32	9
Stomatitis	4	2	31	8

Proteinuria	2	1	29	8
Alopecia	5	3	26	7
Dyspnoea	12	6	26	7
Pain in extremity	6	3	26	7
Hypothyroidism	0	0	24	6
Headache	12	6	23	6
Insomnia	8	4	23	6
Malaise	5	3	22	6
Dry mouth	9	5	21	6
Hypokalaemia	4	2	21	6

7.4.2 Laboratory Findings

Analysis of selected hematologic, metabolic, gastrointestinal, renal, and endocrine laboratory data are displayed in Table 27 and are consistent with data provided in the submission. Clinically relevant findings in the regorafenib arm compared to the placebo arm were reported for neutropenia (Grade 3), thrombocytopenia, hypocalcemia, hypokalemia, hypophosphatemia, hyperbilirubinemia, increased alkaline phosphatase, increased ALT, increased AST, increased INR, increased lipase, proteinuria, and hypoglycemia. These findings are consistent with this class of drugs and with prior experience with regorafenib. Although the incidence of the hypothyroidism AE is increased in the regorafenib arm compared to placebo (6% versus 0%, Table 9), there was less of a difference in the laboratory parameter of decreased free T4 between the two arms (5% versus 3%). The incidence of increased creatinine was lower in the regorafenib arm compared to the placebo arm (77% versus 86%).

Table 27- Study 15982: Laboratory data

Table 27	no. of PL (% of N) N= 193*			no. of Regorafenib (% of N) N=374*		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Anemia	134 (71)	9 (5)	0 (0)	266 (72)	22 (6)	0 (0)
Lymphopenia	110 (59)	21(11)	1 (0.5)	249 (68)	57 (16)	7 (2)
Neutropenia	28 (15)	1 (0.5)	1 (0.5)	50 (14)	11 (3)	0 (0)
Thrombocytopenia	94 (50)	0 (0)	0 (0)	231 (63)	17 (5)	3 (0.8)
Hypocalcemia	19 (10)	0 (0)	0 (0)	86 (23)	1 (0.3)	0 (0)
Hypokalemia	17 (9)	4 (2)	0 (0)	113 (31)	14 (4)	2 (0.5)
Hypophosphatemia	59 (31)	13 (7)	0 (0)	259 (70)	119 (32)	6 (2)
Hyperbilirubinemia	104 (54)	21 (11)	9 (5)	290 (78)	48 (13)	11 (3)
Increased alkaline phosphatase	137 (73)	19 (10)	1 (0.5)	290 (79)	35 (10)	0 (0)
Increased ALT	112 (59)	9 (5)	0 (0)	261 (70)	21 (6)	2 (0.5)
Increased amylase	35 (19)	4 (2)	1 (0.5)	84 (23)	9 (2)	1 (0.3)
Increased AST	161 (84)	33 (17)	5 (3)	344 (93)	60 (16)	6 (2)
Increased GGT	168 (89)	76 (40)	5 (3)	325 (88)	128 (35)	13 (4)
Increased INR	51 (35)	3(2)	0 (0)	125 (44)	2 (0.7)	0 (0)
Increased lipase	50 (27)	14 (8)	2 (1)	148 (41)	41 (11)	11 (3)
Increased creatinine	161 (86)	4 (2)	1 (0.5)	282 (77)	7 (2)	0 (0)
Proteinuria	58 (37)	5 (3)	0 (0)	152 (51)	50 (17)	0 (0)
Decreased Free T4	6 (3)	-	-	19 (5)	-	-
Hypoglycemia	15 (8)	1 (0.5)	1 (0.5)	61 (17)	5 (1)	1 (0.3)

all grades = Gr 1-5
* = Based on patients with post-baseline laboratory samples.

7.4.3 Vital Signs

In addition to reviewing hypertension as an AE, the vital sign data set was reviewed for elevations in blood pressure. Grade 2 or higher hypertension was reported in 62% of patients in the regorafenib arm compared to 40% of the patients in the placebo arm and Grade 3 or higher hypertension was reported in 21% of patients in the regorafenib arm compared to 9% of patients in the placebo arm. These results are consistent with the mechanism of action of regorafenib and with its reported adverse event profile.

7.4.4 Electrocardiograms (ECGs)

No ECG monitoring data were submitted.

7.4.5 Special Safety Studies/Clinical Trials

Not applicable.

7.4.6 Immunogenicity

Not applicable.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

The mean daily dose of regorafenib administered during this study was 144 mg and the median dose was 159 mg. The dose dependency for adverse events was not submitted in this application as all patients received the same starting dose in the clinical trial.

7.5.2 Time Dependency for Adverse Events

Regarding the development of PPES, 76% of regorafenib-treated patients who developed PPES, developed it during the first cycle of treatment which is consistent with the findings from patients with CRC and GIST who received regorafenib. Similarly, most of the patients treated with regorafenib who develop hypertension developed it during the first cycle of treatment.

7.5.3 Drug-Demographic Interactions

Race
Table 28 summarizes selected laboratory assessments based on race. The incidence of PPES was higher in Asian regorafenib-treated patients compared to white regorafenib-treated patients (14% versus 8%) and this finding is consistent with the data reported in trials of regorafenib in patients with CRC and GIST. The incidence of increased ALT was also higher in Asian patients compared to white patients though the overall incidence was only 5%. In white patients, there was a higher incidence of increased blood bilirubin in the regorafenib-treated arm compared to the placebo arm. Due to the small number of patients, conclusions regarding Black/African American patients cannot be made. Additionally, for 20% and 23% of patients in the regorafenib and placebo arms, respectively, data on race was not reported in accordance with laws governing study sites in particular countries. In part, because of this lack of reporting, conclusions regarding the differences in ALT and bilirubin levels described above also cannot be considered conclusive.

Table 28- Study 15982: Race/Ethnicity and laboratory assessments

PT				
Asian	**no. of Gr 3-4 PL**	**% of Gr 3-4 PL N= 78**	**no. of Gr 3-4 Regorafenib**	**% of Regorafenib N=155**
Alanine aminotransferase increased	1	1	7	5
Aspartate aminotransferase increased	13	17	24	15
Blood bilirubin increased	11	14	10	6
Hypertension	2	3	13	8
Hypophosphataemia	2	3	13	8
Palmar-plantar erythrodysaesthesia syndrome (PPES)	0	0	21	14
Black/African American	**no. of Gr 3-4 PL**	**% of PL N = 2**	**no. of Gr 3-4 Regorafenib**	**% of Regorafenib N=6**
Alanine aminotransferase increased	0	0	0	0
Aspartate aminotransferase increased	0	0	1	17
Blood bilirubin increased	0	0	0	0
Hypertension	0	0	0	0
Hypophosphataemia	0	0	0	0
Palmar-plantar erythrodysaesthesia syndrome (PPES)	0	0	0	0
White	**no. of Gr 3-4 PL**	**% of PL N= 68**	**no. of Gr 3-4 Regorafenib**	**% of Regorafenib N=135**
Alanine aminotransferase increased	3	4	3	2
Aspartate aminotransferase increased	5	7	8	6
Blood bilirubin increased	3	4	13	10
Hypertension	5	7	23	17
Hypophosphataemia	1	1	9	7
Palmar-plantar erythrodysaesthesia syndrome (PPES)	1	1	11	8

Age
Table 29 shows the incidence of Grades 1-5 and Grades 3-5 selected adverse events in the regorafenib and placebo arms based on age < 65 years or ≥ 65 years. Of the 193 patients in the placebo arm, 115 were < 65 years (60%) and 78 were ≥ 65 years (40%). Of the 374 patients in the regorafenib arm, 195 were < 65 years (52%) and 179 were ≥ 65 years (48%). Among patients ≥ 65 years, the incidence of Grades 3-5 hypertension and hypophosphatemia appeared higher compared to younger patients.

Table 29- Study 15982: Age and laboratory assessments

	Placebo				Regorafenib			
	age < 65 years N = 115		age ≥ 65 years N = 78		age < 65 years N = 195		age ≥ 65 years N = 179	
PT	% Grades 1-5	*% Grades 3-5*	% Grades 1-5	*% Grades 3-5*	% Grades 1-5	*% Grades 3-5*	% Grades 1-5	*% Grades 3-5*
Hypertension	5	*3*	8	*6*	26	*9*	36	*21*
Hypokalaemia	3	*2*	1	*0*	7	*1*	7	*4*
Hyponatraemia	4	*4*	1	*1*	6	*3*	6	*5*
Hypophosphataemia	3	*3*	1	*0*	5	*5*	15	*12*
Palmar-plantar erythrodysaesthesia syndrome (PPES)	9	*0*	4	*1*	57	*13*	45	*11*

7.5.6 90-Day Safety Update

On January 23, 2017, Bayer submitted a 90-day safety update (as previously agreed to by the FDA). The new SAE reports from this update covered twenty five patients in Study 15982, twenty of whom were in the regorafenib arm. These reports did not reveal any new safety information.

8 Postmarket Experience

No new information pertinent to this application.

9 Appendices

9.1 Labeling Recommendations

The following table summarizes the significant recommended changes to the regorafenib label. As this review will be completed prior to the PDUFA goal date, some changes to the labeling may occur subsequent to the completion of this review that may

be addressed in an amendment to the clinical review. Rows in dark grey indicate the sections of the label with changes, rows in light grey indicate Bayer's proposal, and rows with no filling summarize FDA proposed changes to Bayer's proposal in bold type.

1 Indications and Usage, 1.3
Addition of "Hepatocellular carcinoma (HCC) who have been previously treated with (b) (4) "
The indication in regards to prior therapy is currently being negotiated at this time.
2.2 Recommended doses and schedules
Addition of "(b) (4)"
FDA concurred.
Addition of "(b) (4) "
FDA proposed removing this sentence as insufficient information was provided to support the safety of this recommendation.
5 Warnings and Precautions
Bayer pooled data from the four placebo-controlled trials of regorafenib [CORRECT for mCRC, GRID for GIST, CONCUR for mCRC, and RESORCE (Study 15982)]
FDA concurred (b) (4)
"4800 patients treated with STIVARGA across all clinical trials;"
FDA has asked for justification regarding the specific number of patients in all four trials.
6 Adverse Reactions
"reactions (≥20%) in patients receiving STIVARGA are pain (including gastrointestinal and abdominal pain), HFSR, asthenia/fatigue, (b) (4) diarrhea, decreased appetite/food intake, hypertension, infection, (b) (4) dysphonia, (b) (4) hyperbilirubinemia, fever, mucositis, (b) (4) weight loss, (b) (4) rash, (b) (4) and nausea."
FDA proposed "Pain, Asthenia/fatigue, PPES, Diarrhea, Decreased appetite, HTN, Infection and infestations, Dysphonia, Mucositis, Pyrexia, Weight decrease, Constipation, Rash, Nausea, Hyperbilirubinemia" ***This change reflects FDA's calculations of adverse events; however, FDA will wait to receive Bayer's response (i.e., if FDA agrees to the Bayer's methodology regarding the calculation of adverse events).***
6.1 Clinical Trials Experience
Bayer updated some of their adverse event incidence numbers for Colorectal Cancer and GIST. Additionally, a Hepatocellular Carcinoma subsection was added to the label.
FDA agrees with the updated adverse event incidence numbers based on tables in the ADR JD with the exception of Colorectal cancer/Pain/Placebo/Grade ≥ 3. Regarding the Hepatocellular Carcinoma section, labeling review is ongoing.
8.5 Geriatric Use
FDA requested that Bayer analyze hypertension for all grades and Grades ≥ 3 for the pooled

data from the 4 randomized, placebo-controlled trials.
14 Clinical Studies **(b) (4) Hepatocellular Carcinoma (HCC)**
Addition of a new subsection
Labeling review is ongoing.

9.2 Advisory Committee Meeting

No advisory committee meeting was held for this application.

9.3 Additional Tables

Table 30-Study 15982: Schedule of assessments (copied from submission)

	Screening Visits could be combined as long as assessments were completed within the time frames.			Cycle 1 (4 weeks)		Cycle 2+ (4 weeks)		End of treatment	Safety follow-up + 4 days	Follow-up
	Within 28 days	Within 14 days	Within 7 days	Day 1 ± 3 days	Day 15 ± 3 days	Day 1 ± 3 days	Day 15[a] ± 3 days[a]	Within 14 days	Within 30 days	Every month
Initiation procedures										
Informed consent	X									
Inclusion/exclusion Criteria Checked		X		X						
Demographics	X									
Diagnosis confirmation	X									
Hepatitis B and C testing [a]	X									
BCLC stage/ TNM stage	X									
Prior anti-cancer chemotherapy, radiotherapy and surgery	X									
Complete medical history incl. HCC etiology	X									
Head CT/MRI (if brain metastases are suspected)	X									
Bone scan (if metastases are suspected)	X									
Radiology review (according to the radiology charter)	X									
Study treatment										
Randomization				X						
Drug dispensing and accountability				X		X		X		
Efficacy assessments										
Tumor assessment (CT or MRI) [b]	X					X[b]		X		X[b]
Child-Pugh			X	X[n]		X		X		
Anti-cancer therapies									X	X
Survival assessment										X[f]
Safety assessments										
12-lead ECG [c]	X			X[c]		X		X		
Adverse events & toxicities					X[d]					
Prior and concomitant medications					X					
Archived biopsy - Biomarker sampling	X[e]									
Whole blood - Biomarker sampling [e]			X[e]	X[e]	X[e]					

(continued)

	Screening Visits could be combined as long as assessments were completed within the time frames.			Cycle 1 (4 weeks)		Cycle 2+ (4 weeks)		End of treatment	Safety follow-up +4 days	Follow-up
	Within 28 days	Within 14 days	Within 7 days	Day 1 ± 3 days	Day 15 ± 3 days	Day 1 ± 3 days	Day 15[k] ± 3 days[k]	Within 14 days	Within 30 days	Every month
Plasma for genetic biomarkers [e]			X[e]	X[e]						
Plasma for non-genetic biomarkers [d]			X[e]	X[e]	X[e]	X[e]	X[e]	X[e]		
ECOG Performance Status		X		X		X		X		
Physical examination		X		X		X		X		
Vital signs		X		X	X	X	X	X		
Blood pressure monitoring		X			X[l]			X		
CBC with differential [f]			X	X[f]	X	X	X[k]	X		
Chemistry & electrolyte panel [f]			X	X[f]	X	X	X[k]	X		
Urinalysis [f]			X	X[f]	X	X	X[k]	X		
Thyroid function test (TSH, free T3, free T4)			X	X[f]		X		X		
Coagulation panel (PT-INR, PTT, aPTT) [g, f]			X	X[g, h]		X		X		
Pregnancy test (if applicable)			X	X[m]		X[m]		X[m]		
GFR assessment			X							
Alpha-Fetoprotein (AFP)			X	X		X		X		
Other										
Pharmacokinetic sampling [h]					X	X	X			
Patient-reported Quality of Life (EQ-5D and FACT-Hep) [i]				X		X		X		

Abbreviations: AFP = alfa fetoprotein; aPTT = activated partial thromboplastin time; BCLC = Barcelona Clinic Liver Cancer; C = cycle; CBC = complete blood count; CT = computed tomography scan; D = day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EQ-5D = quality of life questionnaire; FACT-Hep = Functional Assessment of Cancer Therapy-Hepatobiliary; HCC = hepatocellular carcinoma; MRI = magnetic resonance imaging; PT-INR = prothrombin time – international normalized ratio; PTT = partial thromboplastin time; TNM = Tumor, node, metastasis; TSH = Thyroid-stimulating hormone.

a Hepatitis B surface antigen and anti-Hepatitis C Virus (HCV) antibody testing to be performed at baseline unless pre-study results are available.

b Tumor measurements (CT/MRI scans) to be conducted every 6 weeks ± 7 days until PD. After 8 cycles of treatment, these assessments should be done every 12 weeks ± 14 days. If tumor assessments are available during the follow up period for subjects who discontinued study treatment and have not experienced PD, they should be recorded in the CRF.

c After 6 cycles, ECG can be performed based on the investigator's discretion. ECG is not required on Day 1 of Cycle 1 if done within 7 days of starting study drug treatment.

d Adverse event (AE) assessment to be started after signing of IC until 30 days after last study treatment (excluding survival assessment)

e Archival Biopsy for Biomarkers: Archival FFPE tumor tissue may be supplied as a block or as precut slides. Precut slides should be freshly prepared, unstained, and cut to a thickness of 5 microns (n=12, if possible) and 10 microns (n=5, if possible). Tumor tissue should be collected from subjects who did or did not provide genetic consent. Whole Blood for Biomarkers: A whole blood sample (~5 mL) will be obtained at screening, C1D1 or C1D15 only from subjects who provide genetic consent. Plasma for Biomarkers: For subjects who have not provided genetic consent, ~10 mL of blood will be taken at each time point for plasma preparation. For subjects who have provided genetic consent, an additional ~10 mL of blood will be taken at the screening and C1/D1 time points. On treatment days, blood for plasma preparation should be taken prior to drug administration.

f The laboratory evaluations are not required at Day 1 of Cycle1 if these were completed within 7 days of starting study drug treatment. In addition, weekly checks of ALT, AST and bilirubin are required during the first two cycles of study treatment (See Table 7–6).

g If a subject is on warfarin with stable PT-INR at baseline, the PT-INR should be assessed on Day 5 (+/- 3 days). If value is above the therapeutic61 range, the dose should be modified and the assessment should be repeated weekly until it is stable. This information will be recorded in the CRF.

h In all subjects, a pre-dose blood sample will be collected on Day 15 of Cycle 1, and on Days 1 and 15 of Cycle 2. In at least 80 subjects additional blood samples were to be collected (see separate Lab Manual for sample collection and processing procedure) at Cycle 1 Day 15, Cycle 2 Day 1 and Cycle 2 Day 15 between 2 and 4 hours postdose.

I Weekly for first 6 weeks of treatment. Please see Table 7–6. The blood pressure can be recorded by qualified site staff, e.g. a study nurse, treating investigator, nurse practitioner, etc. and entered onto the CRF on the required visits.

j The FACT-Hep (Version 4), and the EQ-5D were to be self-administered by the subject at the start of the visit, before the subject sees the investigator and before any study related procedures are done, so that any interaction between the subjects and investigator or other health care provider will not influence the responses to the questionnaires. Questionnaires should be administered at baseline (C1D1), at every cycle, and at the end of treatment visit. The site personnel should complete the Subject Reported Outcomes Information Sheet.

k After 6 cycles, Day 15 assessments can be done at the discretion of the investigator

l Additional phone contacts will be required for formal survival sweeps at the time of the interim and primary analyses. Monthly survival assessments will continue until the approximate date of unblinding for primary completion. If deemed necessary, survival assessments via additional phone contacts might continue past the primary analysis until end of study

m If required by national /institutional regulations, pregnancy test should be performed for women of child bearing potential prior to the study drug administration at day one of each cycle

n Child-Pugh is not required at Cycle 1 Day 1 if it was assessed within 7 days of starting study drug treatment and if laboratory evaluations (bilirubin, albumin, and PT prolonged or INR) were not completed at Cycle 1 Day 1.

Table 31- Study 15982: AEs by PT (sorted by frequency, then alphabetical order)

PT	no. of PL Grades 1-5	% of PL N = 193	no. of Regorafenib Grades 1-5	% of Regorafenib N = 374
Palmar-plantar erythrodysaesthesia	13	7	192	51

PT	no. of PL Grades 1-5	% of PL N = 193	no. of Regorafenib Grades 1-5	% of Regorafenib N = 374
syndrome				
Diarrhoea	29	15	153	41
Hypertension	12	6	115	31
Decreased appetite	27	14	114	30
Fatigue	47	24	106	28
Aspartate aminotransferase increased	38	20	92	25
Blood bilirubin increased	31	16	91	24
Abdominal pain	30	16	79	21
Pyrexia	13	7	74	20
Dysphonia	3	2	66	18
Constipation	21	11	65	17
Nausea	26	13	64	17
Ascites	31	16	58	16
Asthenia	18	9	56	15
Oedema peripheral	26	13	56	15
Alanine aminotransferase increased	21	11	54	14
Hypoalbuminaemia	14	7	52	14
Anaemia	21	11	51	14
Weight decreased	8	4	50	13
Abdominal pain upper	17	9	47	13
Vomiting	13	7	47	13
Back pain	17	9	45	12
General physical health deterioration	27	14	44	12
Cough	13	7	41	11
Muscle spasms	4	2	38	10
Hypophosphataemia	4	2	36	10
Platelet count decreased	2	1	34	9
Proteinuria	2	1	32	9
Stomatitis	4	2	31	8
Dyspnoea	15	8	28	7
Lipase increased	6	3	27	7
Alopecia	5	3	26	7
Hypokalaemia	5	3	26	7
Pain in extremity	6	3	26	7
Hypothyroidism	0	0	24	6
Insomnia	8	4	24	6
Headache	12	6	23	6
Blood alkaline phosphatase increased	8	4	22	6

PT	no. of PL Grades 1-5	% of PL N = 193	no. of Regorafenib Grades 1-5	% of Regorafenib N = 374
Gamma-glutamyltransferase increased	12	6	22	6
Malaise	5	3	22	6
Dry mouth	9	5	21	6
Hyponatraemia	6	3	21	6
Rash	14	7	20	5
Pruritus	14	7	19	5
Abdominal distension	10	5	18	5
Musculoskeletal pain	11	6	17	5
White blood cell count decreased	2	1	17	5
Chest pain	4	2	16	4
Epistaxis	2	1	16	4
Pleural effusion	11	6	15	4
Arthralgia	11	6	14	4
Bronchitis	1	1	14	4
Dyspepsia	4	2	14	4
Hyperbilirubinaemia	3	2	14	4
Blood thyroid stimulating hormone increased	3	2	13	3
Dizziness	8	4	13	3
Nasopharyngitis	2	1	13	3
Urinary tract infection	3	2	13	3
Anxiety	4	2	12	3
Blood lactate dehydrogenase increased	4	2	12	3
Hepatic encephalopathy	7	4	12	3
Hyperkalaemia	7	4	12	3
Hypomagnesaemia	0	0	12	3
Myalgia	2	1	12	3
Amylase increased	0	0	11	3
Dysgeusia	1	1	11	3
Influenza like illness	6	3	11	3
Mucosal inflammation	0	0	11	3
Neutrophil count decreased	2	1	11	3
Haemorrhoids	0	0	10	3
Oropharyngeal pain	1	1	10	3
Erythema	1	1	9	2
Fall	4	2	9	2
Gastritis	3	2	9	2
Haematuria	2	1	9	2

PT	no. of PL Grades 1-5	% of PL N = 193	no. of Regorafenib Grades 1-5	% of Regorafenib N = 374
Hepatic failure	9	5	9	2
Hyperkeratosis	1	1	9	2
Hypocalcaemia	0	0	9	2
Hypoglycaemia	0	0	9	2
Pneumonia	2	1	9	2
Tinnitus	2	1	9	2
Urine bilirubin increased	1	1	9	2
Abdominal pain lower	0	0	8	2
Blood creatinine increased	5	3	8	2
Dry skin	5	3	8	2
Hyperglycaemia	5	3	8	2
Jaundice	3	2	8	2
Lymphocyte count decreased	2	1	8	2
Musculoskeletal chest pain	2	1	8	2
Thrombocytopenia	4	2	8	2
Upper respiratory tract infection	2	1	8	2
Bilirubin conjugated increased	1	1	7	2
Chills	0	0	7	2
Dehydration	0	0	7	2
Depression	4	2	7	2
Haemoglobin decreased	0	0	7	2
Haemoptysis	3	2	7	2
Hypotension	4	2	7	2
Oral candidiasis	0	0	7	2
Tumour pain	3	2	7	2
Bone pain	4	2	6	2
Dermatitis acneiform	4	2	6	2
Influenza	1	1	6	2
Leukocytosis	1	1	6	2
Muscular weakness	2	1	6	2
Pancreatitis	0	0	6	2
Paraesthesia	4	2	6	2
Pollakiuria	2	1	6	2
Atrial fibrillation	0	0	5	1
Blood albumin decreased	1	1	5	1
Cheilitis	0	0	5	1
C-reactive protein increased	1	1	5	1
Dysphagia	2	1	5	1
Gastrointestinal pain	1	1	5	1
Glossodynia	0	0	5	1

PT	no. of PL Grades 1-5	% of PL N = 193	no. of Regorafenib Grades 1-5	% of Regorafenib N = 374
Hepatic function abnormal	5	3	5	1
Mouth ulceration	2	1	5	1
Peripheral sensory neuropathy	1	1	5	1
Skin lesion	2	1	5	1
Tremor	0	0	5	1
Urticaria	0	0	5	1
Vertigo	3	2	5	1
Weight increased	0	0	5	1
White blood cell count increased	0	0	5	1
Wound	0	0	5	1
Activated partial thromboplastin time prolonged	1	1	4	1
Blood urea increased	1	1	4	1
Dysuria	1	1	4	1
Encephalopathy	6	3	4	1
Flank pain	2	1	4	1
Flatulence	2	1	4	1
Gingival pain	0	0	4	1
Hepatic pain	2	1	4	1
Hyperhidrosis	0	0	4	1
Hyperuricaemia	2	1	4	1
Lung infection	2	1	4	1
Monocyte count increased	0	0	4	1
Oedema	0	0	4	1
Oesophageal varices haemorrhage	1	1	4	1
Pharyngitis	1	1	4	1
Pneumonitis	0	0	4	1
Portal vein thrombosis	2	1	4	1
Rash pustular	1	1	4	1
Rectal haemorrhage	0	0	4	1
Respiratory tract infection	0	0	4	1
Skin exfoliation	0	0	4	1
Skin ulcer	0	0	4	1
Tachycardia	0	0	4	1
Tooth infection	0	0	4	1
Upper gastrointestinal haemorrhage	4	2	4	1
Varices oesophageal	0	0	4	1
Abdominal infection	2	1	3	1
Acute coronary syndrome	0	0	3	1
Acute kidney injury	3	2	3	1

PT	no. of PL Grades 1-5	% of PL N = 193	no. of Regorafenib Grades 1-5	% of Regorafenib N = 374
Alpha 1 foetoprotein increased	1	1	3	1
Angina pectoris	0	0	3	1
Blood glucose increased	0	0	3	1
Candida infection	0	0	3	1
Cellulitis	1	1	3	1
Chest discomfort	1	1	3	1
Chronic gastritis	0	0	3	1
Dyspnoea exertional	2	1	3	1
Ear discomfort	0	0	3	1
Erythema multiforme	0	0	3	1
Gastrointestinal infection	0	0	3	1
Gastrooesophageal reflux disease	3	2	3	1
Gingival bleeding	0	0	3	1
Gynaecomastia	1	1	3	1
Haematoma	1	1	3	1
Haemorrhoidal haemorrhage	0	0	3	1
Hepatic cirrhosis	2	1	3	1
Hyperaesthesia	0	0	3	1
Hyperammonaemia	0	0	3	1
Hyperthyroidism	0	0	3	1
Hypertriglyceridaemia	2	1	3	1
Lymphopenia	1	1	3	1
Neck pain	2	1	3	1
Neutropenia	0	0	3	1
Neutrophil count increased	0	0	3	1
Nocturia	0	0	3	1
Oral fungal infection	0	0	3	1
Pain	3	2	3	1
Prothrombin time prolonged	2	1	3	1
Rales	1	1	3	1
Rash maculo-papular	1	1	3	1
Rectal tenesmus	0	0	3	1
Scrotal erythema	0	0	3	1
Sepsis	0	0	3	1
Shock haemorrhagic	0	0	3	1
Sleep disorder	2	1	3	1
Somnolence	4	2	3	1
Spinal pain	1	1	3	1
White blood cells urine positive	1	1	3	1
Abdominal discomfort	4	2	2	1

PT	no. of PL Grades 1-5	% of PL N = 193	no. of Regorafenib Grades 1-5	% of Regorafenib N = 374
Anal erosion	0	0	2	1
Aphonia	1	1	2	1
Asterixis	0	0	2	1
Atrial flutter	0	0	2	1
Autoimmune thyroiditis	0	0	2	1
Bacterial test positive	0	0	2	1
Blood potassium decreased	0	0	2	1
Blood uric acid decreased	0	0	2	1
Cholangitis	1	1	2	1
Chronic kidney disease	0	0	2	1
Contusion	3	2	2	1
Crepitations	0	0	2	1
Cystitis	2	1	2	1
Decubitus ulcer	0	0	2	1
Dental caries	0	0	2	1
Depressed mood	1	1	2	1
Dermal cyst	0	0	2	1
Dermatitis	0	0	2	1
Diabetes mellitus	2	1	2	1
Diverticulum intestinal	0	0	2	1
Duodenal ulcer	0	0	2	1
Eczema	0	0	2	1
Electrocardiogram QT prolonged	0	0	2	1
Electrocardiogram T wave inversion	0	0	2	1
Flushing	0	0	2	1
Gait disturbance	1	1	2	1
Gastritis erosive	1	1	2	1
Gastroenteritis	0	0	2	1
Gastrointestinal haemorrhage	4	2	2	1
General physical condition abnormal	0	0	2	1
Genital rash	1	1	2	1
Glossitis	0	0	2	1
Haematemesis	1	1	2	1
Haematochezia	0	0	2	1
Hepatic haemorrhage	2	1	2	1
Hepatomegaly	1	1	2	1
Hepatorenal syndrome	2	1	2	1
Hiccups	2	1	2	1
Hypoacusis	0	0	2	1
Hypophagia	1	1	2	1

PT	no. of PL Grades 1-5	% of PL N = 193	no. of Regorafenib Grades 1-5	% of Regorafenib N = 374
Hypoproteinaemia	1	1	2	1
Iron deficiency	2	1	2	1
Jaundice cholestatic	1	1	2	1
Lethargy	2	1	2	1
Liver abscess	2	1	2	1
Malnutrition	1	1	2	1
Memory impairment	0	0	2	1
Nasal dryness	0	0	2	1
Nitrite urine present	0	0	2	1
Oral pain	0	0	2	1
Osteoporosis	0	0	2	1
Palpitations	2	1	2	1
Penile erythema	0	0	2	1
Peritonitis bacterial	1	1	2	1
Platelet count increased	0	0	2	1
Proctalgia	1	1	2	1
Productive cough	2	1	2	1
Rash erythematous	0	0	2	1
Rash papular	0	0	2	1
Red blood cell count decreased	1	1	2	1
Renal failure	5	3	2	1
Rhinitis	0	0	2	1
Seizure	0	0	2	1
Sinus tachycardia	2	1	2	1
Spinal osteoarthritis	0	0	2	1
Subcutaneous abscess	0	0	2	1
Syncope	0	0	2	1
Thirst	0	0	2	1
Thyroxine free increased	0	0	2	1
Tinea pedis	1	1	2	1
Toothache	1	1	2	1
Tri-iodothyronine free increased	0	0	2	1
Urine analysis abnormal	0	0	2	1
Urine ketone body present	0	0	2	1
Urobilinogen urine increased	0	0	2	1
Vision blurred	2	1	2	1
Acne	0	0	1	0
Acute hepatic failure	0	0	1	0
Acute sinusitis	0	0	1	0
Adenocarcinoma gastric	0	0	1	0

PT	no. of PL Grades 1-5	% of PL N = 193	no. of Regorafenib Grades 1-5	% of Regorafenib N = 374
Ammonia increased	0	0	1	0
Amnesia	0	0	1	0
Anal fissure	0	0	1	0
Anal fistula	0	0	1	0
Anal haemorrhage	0	0	1	0
Angular cheilitis	0	0	1	0
Anorectal discomfort	0	0	1	0
Anorectal infection	0	0	1	0
Aphasia	2	1	1	0
Aphthous ulcer	0	0	1	0
Aptyalism	0	0	1	0
Arrhythmia	1	1	1	0
Astigmatism	0	0	1	0
Atrioventricular block first degree	0	0	1	0
Bacteriuria	0	0	1	0
Benign neoplasm of thyroid gland	0	0	1	0
Benign prostatic hyperplasia	1	1	1	0
Bile duct stone	0	0	1	0
Blepharitis	0	0	1	0
Blister	1	1	1	0
Blood chloride increased	0	0	1	0
Blood phosphorus decreased	0	0	1	0
Blood pressure decreased	0	0	1	0
Blood pressure diastolic increased	0	0	1	0
Blood pressure increased	0	0	1	0
Blood sodium decreased	0	0	1	0
Blood thyroid stimulating hormone decreased	0	0	1	0
Bone marrow failure	0	0	1	0
Bradycardia	2	1	1	0
Brain neoplasm	0	0	1	0
Brain oedema	0	0	1	0
Breast mass	1	1	1	0
Breath sounds abnormal	0	0	1	0
Bronchial obstruction	0	0	1	0
Calculus urinary	0	0	1	0
Cancer pain	1	1	1	0
Cardiac failure	0	0	1	0
Cataract operation	0	0	1	0
Cerebrovascular accident	0	0	1	0

PT	no. of PL Grades 1-5	% of PL N = 193	no. of Regorafenib Grades 1-5	% of Regorafenib N = 374
Cholecystitis	0	0	1	0
Circadian rhythm sleep disorder	0	0	1	0
Clostridium difficile colitis	0	0	1	0
Clostridium difficile infection	0	0	1	0
Coccydynia	1	1	1	0
Cold sweat	0	0	1	0
Colitis	0	0	1	0
Concussion	0	0	1	0
Conduction disorder	0	0	1	0
Confusional state	1	1	1	0
Conjunctival haemorrhage	0	0	1	0
Craniocerebral injury	0	0	1	0
Cystitis noninfective	0	0	1	0
Death	0	0	1	0
Depressive symptom	0	0	1	0
Dermatitis allergic	0	0	1	0
Dermatitis atopic	0	0	1	0
Dermatitis bullous	0	0	1	0
Dermatitis exfoliative	0	0	1	0
Dermatitis psoriasiform	0	0	1	0
Device related infection	0	0	1	0
Diarrhoea haemorrhagic	0	0	1	0
Dislocation of vertebra	0	0	1	0
Disorientation	1	1	1	0
Diverticulum	0	0	1	0
Drug eruption	0	0	1	0
Dry eye	0	0	1	0
Dry throat	0	0	1	0
Duodenal perforation	0	0	1	0
Duodenitis	0	0	1	0
Dysaesthesia	0	0	1	0
Eczema asteatotic	0	0	1	0
Electrocardiogram abnormal	0	0	1	0
Embolism	0	0	1	0
Emotional disorder	0	0	1	0
Epidemic pleurodynia	0	0	1	0
Epigastric discomfort	1	1	1	0
Epilepsy	0	0	1	0
Erectile dysfunction	1	1	1	0
Escherichia sepsis	0	0	1	0

PT	no. of PL Grades 1-5	% of PL N = 193	no. of Regorafenib Grades 1-5	% of Regorafenib N = 374
Eyelid oedema	0	0	1	0
Face oedema	0	0	1	0
Facial wasting	0	0	1	0
Febrile infection	0	0	1	0
Feeling abnormal	0	0	1	0
Feeling cold	1	1	1	0
Femur fracture	1	1	1	0
Fine motor skill dysfunction	0	0	1	0
Folliculitis	0	0	1	0
Food poisoning	0	0	1	0
Fungal skin infection	1	1	1	0
Furuncle	0	0	1	0
Gallbladder obstruction	0	0	1	0
Gallbladder pain	0	0	1	0
Gastritis haemorrhagic	0	0	1	0
Genital candidiasis	0	0	1	0
Genital herpes	0	0	1	0
Gingival oedema	0	0	1	0
Gingival ulceration	0	0	1	0
Gingivitis	0	0	1	0
Gout	2	1	1	0
Gravitational oedema	0	0	1	0
Groin pain	2	1	1	0
Haemobilia	0	0	1	0
Haemoglobin increased	0	0	1	0
Haemorrhage intracranial	0	0	1	0
Hepatic ischaemia	0	0	1	0
Hepatitis acute	0	0	1	0
Hepatobiliary disease	0	0	1	0
Hernia pain	0	0	1	0
Herpes zoster	0	0	1	0
Hot flush	3	2	1	0
Hypercalcaemia	3	2	1	0
Hypermetropia	0	0	1	0
Hypersensitivity	0	0	1	0
Hypersomnia	0	0	1	0
Hypertensive crisis	0	0	1	0
Hypertensive heart disease	0	0	1	0
Hyperventilation	0	0	1	0
Hypoaesthesia	1	1	1	0

PT	no. of PL Grades 1-5	% of PL N = 193	no. of Regorafenib Grades 1-5	% of Regorafenib N = 374
Hypogeusia	0	0	1	0
Hypoventilation	0	0	1	0
Hypovolaemic shock	0	0	1	0
Incontinence	0	0	1	0
Increased bronchial secretion	0	0	1	0
Infected neoplasm	0	0	1	0
Infection	4	2	1	0
Inflammation	0	0	1	0
Inguinal hernia	1	1	1	0
International normalised ratio increased	1	1	1	0
Interstitial lung disease	0	0	1	0
Intervertebral disc protrusion	0	0	1	0
Irritable bowel syndrome	0	0	1	0
Joint swelling	1	1	1	0
Jugular vein thrombosis	0	0	1	0
Lacrimation increased	0	0	1	0
Large intestine benign neoplasm	0	0	1	0
Laryngeal pain	0	0	1	0
Leukopenia	1	1	1	0
Ligament sprain	0	0	1	0
Lip pain	0	0	1	0
Lower respiratory tract infection	0	0	1	0
Lung abscess	0	0	1	0
Lung hypoinflation	0	0	1	0
Melaena	1	1	1	0
Meningorrhagia	0	0	1	0
Menorrhagia	0	0	1	0
Migraine	0	0	1	0
Mouth haemorrhage	0	0	1	0
Muscle fatigue	0	0	1	0
Myasthenia gravis	0	0	1	0
Myocardial infarction	0	0	1	0
Nail disorder	0	0	1	0
Nasal congestion	0	0	1	0
Nasal herpes	0	0	1	0
Nephrolithiasis	0	0	1	0
Nephrotic syndrome	0	0	1	0
Nervous system disorder	0	0	1	0
Neuralgia	0	0	1	0

PT	no. of PL Grades 1-5	% of PL N = 193	no. of Regorafenib Grades 1-5	% of Regorafenib N = 374
Neuropathy peripheral	1	1	1	0
Night sweats	1	1	1	0
Nipple pain	1	1	1	0
Non-cardiac chest pain	1	1	1	0
Ocular icterus	0	0	1	0
Odynophagia	1	1	1	0
Oesophageal candidiasis	1	1	1	0
Oesophagitis	0	0	1	0
Oliguria	0	0	1	0
Oral discomfort	0	0	1	0
Otitis externa	1	1	1	0
Otitis media	0	0	1	0
Pain of skin	0	0	1	0
Painful defaecation	0	0	1	0
Pallor	0	0	1	0
Pancreatitis acute	0	0	1	0
Pancytopenia	0	0	1	0
Paronychia	0	0	1	0
Parosmia	0	0	1	0
Pathological fracture	1	1	1	0
Pelvic fluid collection	1	1	1	0
Pelvic fracture	0	0	1	0
Pelvic pain	3	2	1	0
Periarthritis	0	0	1	0
Periodontal disease	0	0	1	0
Periodontitis	0	0	1	0
Peripheral artery stenosis	1	1	1	0
Peripheral coldness	0	0	1	0
Peripheral motor neuropathy	0	0	1	0
Peripheral swelling	2	1	1	0
Periphlebitis	0	0	1	0
Peritonitis	2	1	1	0
Pharyngeal inflammation	0	0	1	0
Photopsia	0	0	1	0
Plantar erythema	0	0	1	0
Pneumonia aspiration	0	0	1	0
Polydipsia	0	0	1	0
Poor quality sleep	1	1	1	0
Portal hypertensive gastropathy	0	0	1	0
Post-traumatic pain	0	0	1	0

PT	no. of PL Grades 1-5	% of PL N = 193	no. of Regorafenib Grades 1-5	% of Regorafenib N = 374
Presbyopia	0	0	1	0
Procedural pain	0	0	1	0
Protein total increased	1	1	1	0
Protein urine present	1	1	1	0
Prothrombin time shortened	0	0	1	0
Pruritus generalised	1	1	1	0
Pubic pain	0	0	1	0
Pulmonary congestion	0	0	1	0
Pulmonary embolism	1	1	1	0
Pulmonary oedema	0	0	1	0
Pulmonary venous thrombosis	0	0	1	0
Punctate keratitis	0	0	1	0
Purpura	1	1	1	0
Purulent discharge	0	0	1	0
Quadriparesis	0	0	1	0
Rash generalised	0	0	1	0
Red blood cells urine	0	0	1	0
Red blood cells urine positive	1	1	1	0
Reflux gastritis	0	0	1	0
Renal impairment	0	0	1	0
Renal pain	0	0	1	0
Respiratory distress	0	0	1	0
Respiratory failure	3	2	1	0
Respiratory tract infection viral	0	0	1	0
Restlessness	0	0	1	0
Retinal artery occlusion	0	0	1	0
Rhinorrhoea	4	2	1	0
Rib fracture	1	1	1	0
Scab	0	0	1	0
Scrotal swelling	0	0	1	0
Scrotal ulcer	0	0	1	0
Sebaceous hyperplasia	0	0	1	0
Septic shock	0	0	1	0
Skin fissures	0	0	1	0
Skin hyperpigmentation	0	0	1	0
Skin infection	0	0	1	0
Skin irritation	0	0	1	0
Skin reaction	1	1	1	0
Skin swelling	0	0	1	0
Spider naevus	0	0	1	0

PT	no. of PL Grades 1-5	% of PL N = 193	no. of Regorafenib Grades 1-5	% of Regorafenib N = 374
Spinal column injury	0	0	1	0
Spinal compression fracture	1	1	1	0
Squamous cell carcinoma of skin	0	0	1	0
Staphylococcal bacteraemia	0	0	1	0
Staphylococcus test positive	0	0	1	0
Status epilepticus	0	0	1	0
Stoma site haemorrhage	0	0	1	0
Streptococcal bacteraemia	0	0	1	0
Streptococcal infection	0	0	1	0
Subcutaneous haematoma	0	0	1	0
Supraventricular extrasystoles	1	1	1	0
Supraventricular tachycardia	0	0	1	0
Therapeutic embolisation	0	0	1	0
Thrombocytosis	0	0	1	0
Thrombosis	0	0	1	0
Thyroid neoplasm	0	0	1	0
Thyroxine increased	0	0	1	0
Tinea cruris	0	0	1	0
Tongue discolouration	0	0	1	0
Tooth abscess	0	0	1	0
Tooth loss	0	0	1	0
Tracheal disorder	0	0	1	0
Tracheitis	0	0	1	0
Traumatic haemorrhage	0	0	1	0
Tri-iodothyronine free decreased	0	0	1	0
Tumour associated fever	0	0	1	0
Umbilical hernia	0	0	1	0
Upper extremity mass	0	0	1	0
Ureterolithiasis	0	0	1	0
Urinary incontinence	1	1	1	0
Urine output decreased	0	0	1	0
Urine transitional cells present	0	0	1	0
Urosepsis	0	0	1	0
Vasculitis	1	1	1	0
Venous thrombosis limb	0	0	1	0
Viral infection	0	0	1	0
Visual field defect	0	0	1	0
Wolff-Parkinson-White syndrome	0	0	1	0
Wound infection	0	0	1	0
Accident	1	1	0	0

PT	no. of PL Grades 1-5	% of PL N = 193	no. of Regorafenib Grades 1-5	% of Regorafenib N = 374
Ageusia	1	1	0	0
Arthritis	2	1	0	0
Atelectasis	1	1	0	0
Bile duct stenosis	4	2	0	0
Blood creatine phosphokinase increased	1	1	0	0
Blood triglycerides increased	1	1	0	0
Blood uric acid increased	1	1	0	0
Breast pain	1	1	0	0
Burning sensation	1	1	0	0
Cardiac arrest	1	1	0	0
Cerebral haematoma	1	1	0	0
Change of bowel habit	1	1	0	0
Cholestasis	2	1	0	0
Conjunctivitis	2	1	0	0
Deep vein thrombosis	2	1	0	0
Dyskinesia	1	1	0	0
Eating disorder	1	1	0	0
Eye haemorrhage	1	1	0	0
Eye pain	1	1	0	0
Fibrin D dimer increased	1	1	0	0
Gastric disorder	1	1	0	0
Gastric haemorrhage	1	1	0	0
Genital cyst	1	1	0	0
Glycosuria	1	1	0	0
Haemarthrosis	1	1	0	0
Haemoglobinuria	1	1	0	0
Haemorrhagic anaemia	1	1	0	0
Hemiparesis	1	1	0	0
Hepatitis B	1	1	0	0
Hepatocellular injury	1	1	0	0
Hordeolum	1	1	0	0
Hypernatraemia	1	1	0	0
Hyperthermia	1	1	0	0
Ileus	1	1	0	0
Infusion related reaction	1	1	0	0
Ingrown hair	1	1	0	0
Intermittent claudication	1	1	0	0
Intestinal obstruction	1	1	0	0
Intra-abdominal haemorrhage	2	1	0	0

PT	no. of PL Grades 1-5	% of PL N = 193	no. of Regorafenib Grades 1-5	% of Regorafenib N = 374
Iron deficiency anaemia	1	1	0	0
Limb discomfort	1	1	0	0
Lower gastrointestinal haemorrhage	1	1	0	0
Lymph node pain	2	1	0	0
Lymphadenitis	1	1	0	0
Metastases to lung	1	1	0	0
Multiple organ dysfunction syndrome	1	1	0	0
Musculoskeletal discomfort	1	1	0	0
Musculoskeletal stiffness	3	2	0	0
Nodule	1	1	0	0
Obstruction gastric	1	1	0	0
Oesophageal carcinoma	1	1	0	0
Oesophageal haemorrhage	1	1	0	0
Oesophageal stenosis	1	1	0	0
Oesophageal ulcer	1	1	0	0
Onychomalacia	1	1	0	0
Oropharyngeal candidiasis	1	1	0	0
Orthostatic hypotension	1	1	0	0
Overdose	1	1	0	0
Palmar erythema	1	1	0	0
Papule	1	1	0	0
Periorbital haematoma	1	1	0	0
Petechiae	2	1	0	0
Plantar fasciitis	1	1	0	0
Pleural infection bacterial	1	1	0	0
Pubis fracture	1	1	0	0
Pulmonary thrombosis	1	1	0	0
Renal artery arteriosclerosis	1	1	0	0
Sciatica	2	1	0	0
Sinus congestion	1	1	0	0
Skin disorder	1	1	0	0
Tendonitis	1	1	0	0
Thermal burn	1	1	0	0
Tumour haemorrhage	1	1	0	0
Urinary retention	1	1	0	0
Uterine leiomyoma	1	1	0	0
Vena cava embolism	1	1	0	0
Visual acuity reduced	1	1	0	0
Vitamin D deficiency	1	1	0	0

PT	no. of PL Grades 1-5	% of PL N = 193	no. of Regorafenib Grades 1-5	% of Regorafenib N = 374
Vocal cord paralysis	1	1	0	0
Vulvitis	1	1	0	0
Waist circumference increased	1	1	0	0
Wound infection bacterial	1	1	0	0

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Clinical Investigator Financial Disclosure
Review Template

Application Number: sNDA 203085

Submission Date(s): October 6, 2016; October 30, 2016

Applicant: Bayer HealthCare Pharmaceuticals Inc.

Product: regorafenib

Reviewer: Lorraine Pelosof

Date of Review: April 6, 2017

Covered Clinical Study (Name and/or Number): Study 15982 "A randomized, double blind, placebo-controlled, multicenter phase III study of regorafenib in patients with hepatocellular carcinoma (HCC) after sorafenib"

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 971		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 4		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 4 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 971		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from applicant)

Discuss whether the applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*.[1] Also discuss whether these interests/arrangements, investigators who are sponsor employees, or lack of disclosure despite due diligence raise questions about the integrity of the data:

- If not, why not (e.g., study design (randomized, blinded, objective endpoints), clinical investigator provided minimal contribution to study data)
- If yes, what steps were taken to address the financial interests/arrangements (e.g., statistical analysis excluding data from clinical investigators with such interests/arrangements)

Briefly summarize whether the disclosed financial interests/arrangements, the inclusion of investigators who are sponsor employees, or lack of disclosure despite due diligence affect the approvability of the application.

Please refer to Section 3 of the Clinical Review.

[1] See [web address].

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LORRAINE C PELOSOF
04/06/2017

STEVEN J LEMERY
04/07/2017

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203085Orig1s007

CHEMISTRY REVIEW(S)

Office of Lifecycle Drug Products
Division of Post-Marketing Activities I
Review of Chemistry, Manufacturing, and Controls

1. **NDA Efficacy Supplement No.:** 203085/S007

2. **Submission(s) Being Reviewed**:

Submission	Type	Submission Date	CDER Stamp Date	Assigned Date	PDUFA Goal Date	Review Date
Original Supplement	PA	06-Oct-2016* 31-Oct-2016**	30-Oct-2016	07-Nov-2016	22-Feb-2017	25-Jan-2017

*Part1 of 2 Rolling Submission date; **Part2 of 2 Rolling Submission date

3. **(a) Provides For From Cover Letter:**
   - A new indication for Stivarga (regorafenib) Tablet, 40mg for the treatment of patients with hepatocellular carcinoma (HCC) who have been previously treated with (b) (4)

   (b) Additional Change(s) Proposed in the Supplement: none

4. **Review #**: 1

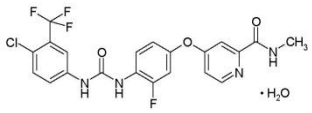
5. **Clinical Review Division**: Division of Oncology Products 2 (DOP2)

6. **Name and Address of Applicant**:
   Bayer HealthCare Pharmaceuticals Inc.
   100 Bayer Blvd.
   P.O. Box 915
   Whippany, NJ 07981-09151

7. **Drug Product**:

Drug Name	Dosage Form	Strength	Route of Administration	Rx or OTC	Special Product
Stivarga®	Tablet, Film coated	40mg	oral	Rx	No

8. **Chemical Name and Structure of Drug Substance**:

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

9. **Indication**:
   Stivarga is a kinase inhibitor indicated for the treatment of patients with metastatic colorectal cancer (CRC) who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF therapy, and, if RAS wild- type, an anti-EGFR therapy.

10. **Supporting/Relating Documents**: none

11. **Consults**: none

12. **Executive Summary**:
    The Efficacy sNDA 203085/S007 seeks to include data for regorfenib tables 40mg for the treatment of patients with hepatocellular carcinoma (HCC) who have been previously treated with (b) (4) The data supporting this efficacy was derived from Study 15982 (also known as "RESORCE"), a randomized, double-blind, placebo-controlled, multicenter global Phase 3 study of regorafenib in patients with hepatocellular carcinoma (HCC) following sorafenib treatment. Patients who have progressed on sorafenib (documented radiological progression according to the radiology

charter) are treated with regorafenib or placebo using a 2:1 randomization scheme. Patients are randomized to receive either regorafenib 160mg once daily for 3wks of every 4wk (28 day) cycle (i.e., 3wks on/1wk off) plus best supportive care (BSC) or identical placebo tablets plus BSC. For study 15982 there is no change to the approved dp (160mg as 4 tablets of 40 mg, orally). The placebo tablet is identical to the approved drug, thus assuring blinding. **Study 15982 (RESORCE) Final Study Report**, and Electronic Datasets and Case Report Forms is provided in Module 5 section **5.3.5.1**.

Efficacy sNDA 203085/S007 is further supported by data from Study 14596, an uncontrolled open label, multicenter, Phase 2 safety study in patients with hepatocellular carcinoma (HCC). For study 14596 there is no change to the approved dp (160mg as 4 tablets of 40 mg, orally) & no placebo (no blinding). **Study 14596 Addendum Study Report,** and Electronic Datasets Forms are provided in Module 5 section **5.3.5.2**.

The proposed updated package insert for regorafenib tablets is provided in accordance with the physician's labeling rule (PLR), 21 CFR 201.56-57. The PI is provided as both a draft, clean and annotated file, and in Structured Product Labeling (SPL) format. The SPL format follows the guidance set forth in Guidance for Industry, Providing Regulatory Submissions in Electronic Format – Content of Labeling, issued by the Center for Drug Evaluation and Research in April 2005. The updated PI does not change CMC relevant sections ((**2**),(**3**) & (**11**)). Sections **16.1** & **16.2** have been combined under section **16 How Supplied/Storage and Handling**. No changes have been made to the current approved text in sections **16.1** & **16.2**. The updated PI for efficacy sNDA 203085/S007is acceptable for CMC.

A request for categorical exclusion from the environmental assessment (EA) requirement in accordance with 21 CFR 25.31(b) & the FDA Guidance for Industry, dated July 1998 & entitled "Environmental Assessment of Human Drug and Biologics Applications," is provided in section **1.12.14** of Rolling Submission #1 (Seq0092/**SDN155)**. Bayer requests categorical exclusion from EA under the basis that the Expected Introduction Concentration (EIC) of the active moiety in the aquatic environment is below the threshold of 1.0ppb. Furthermore, it is anticipated that this proposed action would not significantly affect the quality of human environment. Bayer's request for a categorical exclusion is acceptable.

Based on the supporting data provided, Efficacy sNDA 203085/S007is recommended for approval from a CMC standpoint.

13. **Conclusions & Recommendations**:
This efficacy supplement is recommended for approval from a CMC perspective.

14. **Comments/Deficiencies to be Conveyed to Applicant**: none

15. **Primary Reviewer**:
Lorenzo Rocca, CMC Reviewer, Branch 1, Division of Post-Marketing Activities I, Office of Lifecycle Drug Products (OLDP), Office of Pharmaceutical Quality (OPQ)

Lorenzo A. Rocca -S
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DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300136530, cn=Lorenzo A. Rocca -S
Date: 2017.01.25 22:51:41 -05'00'

16. **Secondary Reviewer**:
Ramesh Raghavachari, Branch Chief, Branch 1, Division of Post-Marketing Activities I, OLDP, OPQ

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Date: 2017.01.26 09:40:17 -05'00'

CMC Assessment

I. Background Information

The Efficacy sNDA 203085/S007 has been prepared in accordance with agreements reached with DOP2 from the Type C Meeting (Written Responses Only) on 04-Mar-2016 and the Pre-sNDA Type B meeting on 21-Jul-2016.

On 28-Jul-2016, FDA granted **Fast Track Designation** for regorafenib for the "treatment of patients with (b) (4) hepatocellular carcinoma (HCC) who have been previously treated with sorafenib," and on 04-June-2016 FDA granted **Orphan Drug Designation** for regorafenib for the "treatment of hepatocellular carcinoma."

Bayer submitted **Request for Submission of Portions of an Application to IND 75,642** on 01-Sep-2016 & **Grant Rolling Review Letter** dated 04-Oct-2016. Bayer submitted Rolling Submission #1 (Seq092/**SDN155**) on 6-Oct-2016 & Rolling Submission #2 (Seq093/**SDN156**) on 31-Oct-2016.

II. Proposed Changes

- A new indication for Stivarga (regorafenib) Tablet, 40mg for the treatment of patients with hepatocellular carcinoma (HCC) who have been previously treated with (b) (4)

III. Data Submitted to Support the Proposed Changes

Rolling Submission #2 (31-Oct-2016) of 203085/S007 includes a hyperlink to the Cumulative Reviewer's Guide (**1.2**) to Rolling Submission #1 & #2. The Table of Contents of the Cumulative Reviewer's Guide lists the cumulative contents of Rolling Submission #1 (06-Oct-2016) & Rolling Submission #2 (31-Oct-2016), & includes hyperlinks to the following sections of Rolling Submission #1 & Rolling Submission #2:

- **3.1.9** Module 1.12.14: Environmental Analysis (Rolling Submission #1)
- **3.1.11** Module 1.14: Labeling
- **3.3.7** Module 5.3.5.1: Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication[HCC]
- **3.3.8** Module 5.3.5.2: Study Reports of Uncontrolled Clinical Studies

The sections listed above adequately support the approval of efficacy sNDA 203085/S007 from a CMC perspective. For brevity the supporting CMC date is not reproduced here but is available in Rolling Submission #1 (06-Oct-2016) & Rolling Submission #2 (31-Oct-2016).

Overall Evaluation: Acceptable

IV. Risk Associated with the Proposed Changes and Impact to Product Quality and Patient Safety

The applicant has provided sufficient and adequate data to conclude there are no CMC issues associated with recommending approval of Efficacy sNDA 203085/S007 from a CMC perspective.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203085Orig1s007

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

ADDENDUM

NDA/BLA #:	203085
Serial #:	007
Drug Name:	Stivarga (Regorafenib)
Indication:	The treatment of patients with hepatocellular carcinoma (HCC) who have been previously treated with (b) (4)
Applicant:	Bayer HealthCare Pharmaceuticals
Received Date:	October 6, 2016; October 31, 2016
PDUFA Date:	April 30, 2017
Review Type:	Priority
Biometrics Division:	Division of Biometrics V
Statistical Reviewer:	Xiaoping (Janet) Jiang, Ph.D.
Concurring Reviewers:	Lisa Rodriguez, Ph.D., Team Leader
	Kun He, Ph.D., Associate Director
Medical Division:	Division of Oncology Products 2
Clinical Team:	Lorraine Pelosof, M.D., Ph.D., Clinical Reviewer
	Steven Lemery, M.D., Clinical Team Leader
	Patricia Keegan, M.D., Division Director
Project Manager:	Anuja Patel, M.P.H.

Keywords: Stratified log-rank test, Kaplan-Merier method, Cox regression

Table of Contents

TABLE 1 RESULT OF OS PRIMARY ANALYSIS 3
TABLE 2 RESULT OF OS SENSITIVITY ANALYSIS (EXCLUDING PATIENTS FROM ALL SITES IN CHINA) 4

This addendum is to Dr. Xiaoping (Janet) Jiang's statistical review for efficacy supplement of New Drug Application 203085S007 (dated on April 6, 2017). This addendum contains an exploratory sensitivity analysis of OS excluding sites in China.

On October 6, and October 31, 2016, the applicant submitted a sNDA to seek an approval of regorafenib for the proposed indication 'treatment of patients with hepatocellular carcinoma (HCC) who have been previously treated with (b) (4)'. In the submissions, the applicant provided clinical data and results from Study 15982 (RESORCE) entitled 'A randomized, double blind, placebo-controlled, multicenter phase III study of regorafenib in patients with hepatocellular carcinoma (HCC) after sorafenib', and other studies.

In Study RESORCE, a total of 573 eligible patients were randomized in a 2:1 ratio to receive regorafenib plus best supportive care (BSC) or match placebo plus BSC. The randomization was stratified by geographical region (Asia versus rest of world), Eastern Cooperative Oncology Group (ECOG) performance status (0 versus 1), Alpha-fetoprotein level (<400 ng/mL versus ≥400 ng/mL), extrahepatic disease (presence versus absence), and macrovascular invasion (presence versus absence). The primary endpoint was overall survival (OS). The primary analysis was a stratified log-rank test. For details regarding the design, data analyses, and results of Study RESORCE, please refer to Dr. Xiaoping (Janet) Jiang's statistical review (dated on April 6, 2017).

On April 12, 2017, the applicant submitted an amendment to the supplemental new drug application (NDA203085S007). In the submission, the applicant provided some additional findings that were not included in the clinical study report (CSR) for the pivotal clinical study RESORCE. The majority of the findings (data corrections or data additions) were from sites in China and Taiwan. On April 20, 2017, in the Teleconference with FDA, the applicant informed FDA that there was a small efficacy difference due to the data from one or two sites in China. There are 27 sites from China in RESORCE with a total of 137 patients. Based on the review team's internal discussion, this statistical reviewer conducted an exploratory OS sensitivity analysis by excluding 137 patients from all 27 sites in China. Table 1 summarizes OS primary analysis that was presented in Dr. Xiaoping (Janet) Jiang's April 6, 2017 statistical review.

Table 1 Result of OS primary Analysis

	Placebo + BSC n=194	**Regorafenib + BSC n=379**
Number of Event (%)	140 (72.2)	233 (61.5)
Median OS in Months (95% CI)	7.8 (6.3, 8.8)	10.6 (9.1, 12.1)
Hazard Ratio[a] (95%CI)	0.63 (0.50, 0.79)	
P-value[a]	<0.0001	

[a] stratified by line of therapy (3rd-line vs. 4th-line or beyond), geographical region (Asia vs. rest of world (ROW)), ECOG-PS (0 vs. 1), Alpha-fetoprotein level (<400 ng/mL vs. ≥400 ng/mL), presence vs. absence of extrahepatic disease, and presence vs. absence of macrovascular invasion.

Table 2 summarizes the exploratory OS sensitivity analysis.

Table 2 Result of OS Sensitivity Analysis (Excluding patients from all sites in China)

	Placebo + BSC n=145	**Regorafenib + BSC n=291**
Number of Events (%)	108 (37.1)	183 (62.9)
Number of Censored (%)	37 (25.5)	108 (37.1)
Median OS in months (95% CI)	8.3 (6.8, 9.3)	10.9 (9.1, 13.2)
Hazard ratio[a] (95%CI)	0.62 (0.48, 0.80)	

[a] *stratified by line of therapy (3rd-line vs. 4th-line or beyond), geographical region (Asia vs. rest of world (ROW)), ECOG-PS (0 vs. 1), Alpha-fetoprotein level (<400 ng/mL vs. ≥400 ng/mL), presence vs. absence of extrahepatic disease, and presence vs. absence of macrovascular invasion.*

Reviewer's Comment:

1. *As shown in Table 2, the results of the OS sensitivity analyses are consistent with the results of the OS primary analysis.*

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/s/

XIAOPING JIANG
04/27/2017

LISA R RODRIGUEZ
04/27/2017

KUN HE
04/27/2017

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA #:	203085
Supplement #:	007
Drug Name:	Stivarga (Regorafenib)
Indication:	The treatment of patients with hepatocellular carcinoma (HCC) who have been previously treated with (b) (4)
Applicant:	Bayer HealthCare Pharmaceuticals
Received Dates:	October 6, 2016; October 31, 2017
PDUFA Date:	April 30, 2017
Review Type:	Priority
Biometrics Division:	Division of Biometrics V
Statistical Reviewer:	Xiaoping (Janet) Jiang, Ph.D.
Concurring Reviewers:	Lisa Rodriguez, Ph.D., Team Leader
	Rajeshwari Sridhara, Ph.D., Division Director
Medical Division:	Division of Oncology Products 2
Clinical Team:	Lorraine Pelosof, M.D., Ph.D., Clinical Reviewer
	Steven Lemery, M.D., Clinical Team Leader
	Patricia Keegan, M.D., Division Director
Project Manager:	Anuja Patel, M.P.H.

Keywords: Stratified log-rank test, Kaplan-Meier method, Cox regression

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1 EXECUTIVE SUMMARY

The applicant submitted an efficacy supplement of New Drug Application (sNDA) with results and data from Study 15982 (also known as "RESORCE") entitled 'A randomized, double blind, placebo-controlled, multicenter phase III study of regorafenib in patients with hepatocellular carcinoma (HCC) after sorafenib' and other studies to seek an approval of regorafenib for the proposed indication: '*treatment of patients with hepatocellular carcinoma (HCC) who have been previously treated with* (b) (4)

In Study RESORCE, a total of 573 eligible patients were randomized in a 2:1 ratio to receive regorafenib plus best supportive care (BSC) or match placebo plus BSC. The randomization was stratified by geographical region (Asia versus rest of world), Eastern Cooperative Oncology Group (ECOG) performance status (0 versus 1), Alpha-fetoprotein level (<400 ng/mL versus ≥400 ng/mL), extrahepatic disease (presence versus absence), and macrovascular invasion (presence versus absence).

The primary endpoint was overall survival (OS). The primary analysis was a stratified log-rank test on the intent-to-treat population, consisting of all randomized patients. Based on 373 death events, the OS result demonstrated that the patients had statistically significant improvement in survival time when treated with regorafenib plus BSC compared to the patients treated with BSC alone (stratified log-rank p-value <0.0001). The estimated hazards ratio (HR) of OS was 0.63 with 95% confidence interval (CI) (0.50, 0.79) in favor of the treatment with regorafenib plus BSC. The estimated median OS was 10.6 months (95% CI: 9.1, 12.1) for patients in the regorafenib arm plus BSC versus 7.8 months (95% CI: 6.3, 8.8) for the patients in the placebo plus BSC arm.

The results of the secondary endpoint progression-free survival (PFS) assessed using modified Response Evaluation Criteria in Solid Tumors (mRECIST) also showed that treatment with regorafenib plus BSC statistically significantly delayed time to progression/death for patients compared to the treatment with BSC alone (stratified log-rank p-value <0.0001) with an estimated HR of 0.46 (95% CI: 0.37, 0.56). The results of PFS assessed using RECIST and the results of PFS assessed using mRECIST are similar (RECIST PFS: stratified log-rank p-value <0.0001 with an estimated HR of 0.43 and 95% CI: [0.35, 0.52]). The observed objective tumor response rate (ORR) per mRECIST (RECIST) was 10.6% (6.6%) in patients treated with regorafenib plus BSC versus 4.1% (2.6%) in patients treated with BSC alone. Whether to include results of PFS and ORR based on mRECIST or based on RECIST to the label of regorafenib is deferred to the clinical review team.

Whether the results from Study RESORCE provide a favorable benefit to risk ratio to support an approval of regorafenib for the proposed indication will be determined by the clinical review team.

2 INTRODUCTION

2.1 Overview

Stivarga (regorafenib) is a bi-aryl urea that inhibits multiple kinases involved in tumor cell proliferation and neo-angiogenesis. On September 27, 2012, FDA approved Stivarga for *"the treatment of patients with metastatic colorectal cancer (CRC) who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF therapy, and, if KRAS wild type, an anti-EGFR therapy"* On February 25, 2013, FDA approved Stivarga for the second indication *'locally advanced, unresectable or metastatic gastrointestinal stromal tumor (GIST) who have been previously treated with imatinib mesylate and sunitinib malate.'* On October 6, 2016, the applicant submitted data and results from efficacy study 15982 (RESORCE) and human pharmacokinetic studies to seek an approval of regorafenib for a proposed indication for patients with hepatocellular carcinoma (HCC) who have been previously treated with (b) (4).

Study RESORCE was a phase 3, randomized, double-blind, placebo-controlled, and multicenter study of regorafenib in patients with hepatocellular carcinoma (HCC) after failed prior systemic treatment with sorafenib. The primary objective of the study was to evaluate efficacy and safety of regorafenib in patients with HCC in terms of overall survival (OS). Among 573 eligible patients, 379 patients were randomized to receive regorafenib plus BSC and 194 patients were randomized to receive match placebo plus BSC. The first visit of the first patient was on May 14, 2013 and the last visit of the last patient was on February 29, 2016. The primary completion date for the study was February 29, 2016. Study RESORCE was conducted at 152 study centers from Australia, the United States, and some countries in Europe and Asia.

The secondary study objectives included evaluating efficacy of regorafenib in terms of time to progression (TTP), progression-free survival (PFS) and objective tumor response rate (ORR).

2.2 Data Sources

Data used for this review were from the electronic submission received on October 6, 2016. The link was "\\CDSESUB1\evsprod\NDA203085\203085.enx"

3 STATISTICAL EVALUATION

This section focuses on efficacy evaluation for the efficacy study RESORCE.

3.1 Data and Analysis Quality

The quality of submitted data allowed this reviewer to reproduce the results of the primary analysis and other major submitted efficacy analyses. Also, the statistical analysis plan (SAP) was provided in the sNDA submission.

Reviewer's Comments:

1. *During the review process, several information requests were sent to the applicant to request the SAS programs that were used to conduct major efficacy results and for clarification regarding the issues in the submitted SAS programs. The issues were resolved based on the applicant's submitted responses.*

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

RESORCE was designed as a randomized, double-blind, placebo-controlled, multi-center phase III study to evaluate efficacy and safety of regorafenib in patients with HCC who had failed prior systemic treatment with sorafenib. The inclusion criterion included histological or cytological confirmation of HCC or non-invasive diagnosis of HCC per American Association for the Study of Liver Diseases (AASLD) criteria in patients with a confirmed diagnosis of cirrhosis; failure to prior treatment with sorafenib (defined as documented radiological progression according to the radiology charter); Barcelona Clinic Liver Cancer (BCLC) stage Category B or C that could not benefit from treatments of established efficacy with higher priority such as resection, local ablation, chemoembolization, or systemic sorafenib.

Eligible patients who progressed on sorafenib were randomized in a 2:1 ratio, using a telephone Interactive Voice Response System (IVRS), to receive one of the two following treatments:

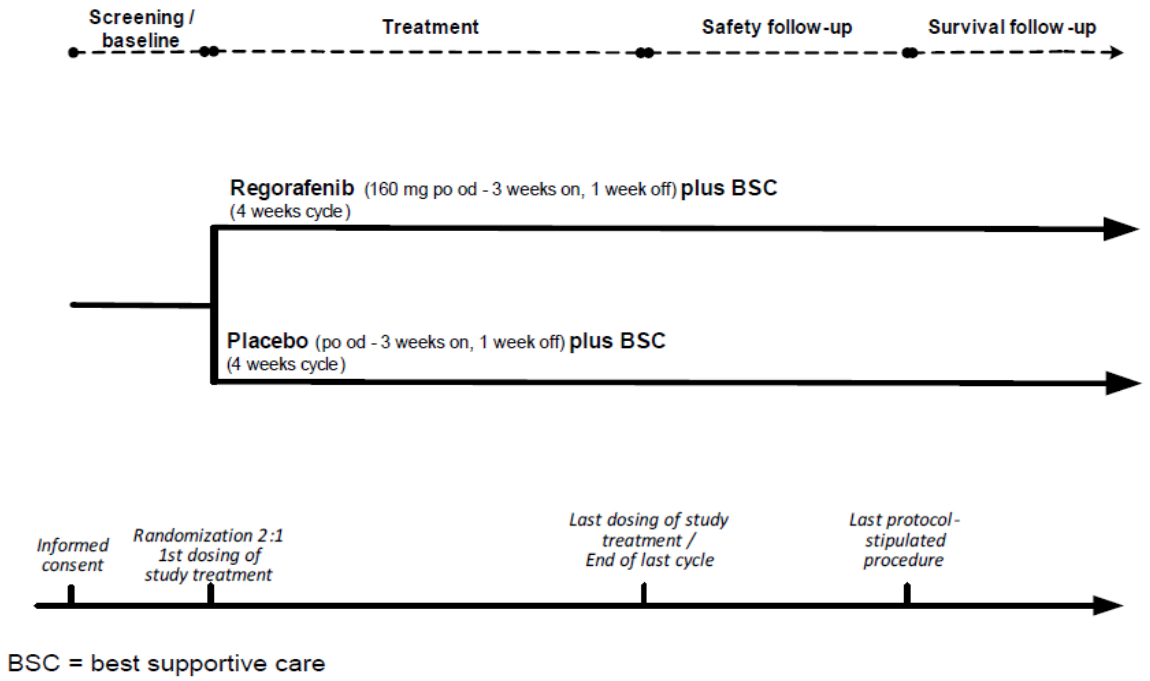
Experimental Arm: 160 mg (4 x 40 mg tablets) every day; 3 weeks on/1 week off in each 4 week cycle plus BSC (best supportive care)

Control Arm: Matching 4 x 40 mg placebo tablets every day; 3 weeks on/1 week off in each 4 week cycle plus BSC

The randomization was stratified by geographical region (Asia vs. rest of world (ROW)), ECOG performance status (0 vs. 1), AFP levels (<400 ng/mL vs. ≥400 ng/mL), extrahepatic disease (presence vs. absence), and macrovascular invasion (presence vs. absence).

Figure 3.1 shows the overall study design of RESORCE.

Figure 3.1 Overall Study Design



[Source: Clinical Study Report Figure 7.1]

Per the protocol, the treatment continued until disease progression defined by modified Response Evaluation Criteria in Solid Tumors (mRECIST) for Hepatocellular Carcinoma, unacceptable treatment-related toxicity, or patient or physician decision to discontinue. The standard solid tumor response evaluation criterion RECIST 1.1 measures just the diameter of a lesion, irrespective of viability or necrosis. In contrast to RECIST, mRECIST does not include necrotic tissue into the measurement, only viable parts of tumor lesions. For more details regarding the difference of the two criteria, refer to Dr. Pelosof's clinical review. All patients entered the follow-up period upon discontinuation of study treatments (regorafenib or placebo) for survival until death was documented, except for those patients who specifically withdrew consent to follow-up.

The primary endpoint was OS. OS was defined as the time from date of randomization to death due to any cause. OS for patients who were not known to have died were censored at their last date of being known alive or at the database cutoff date, whichever came first. The assessment of survival status was performed every month until death, consent withdrawal, lost to follow up, or study end.

Assuming that the true OS hazard ratio was 0.70 with 8 months in the placebo arm and 11.4 months in the regorafenib arm, a total of 370 events could provide 90% power to detect statistically significant difference in OS between two arms at a 2-sided significance level of 0.05. A sample size of 560 patients would provide 370 events in approximately 33 months of study

duration, assumed accrual time was 22 months and accrual rate 25 patients/month ramp-up 3 months.

The secondary endpoints in the study included TTP, PFS and ORR. Per the protocol and the SAP, TTP was defined as the time from randomization to radiological or clinical disease progression. TTP for patients without radiological or clinical tumor progression at the time of analysis were censored at their last date of tumor evaluation. PFS was defined as the time from randomization to disease progression (radiological or clinical) or death due to any cause, if death occurs before progression is documented. For the patient who did not have radiological or clinical tumor progression or death at the time of analysis, PFS was censored at the last date of tumor evaluation.

Tumor measurements (via CT or MRI scans) were conducted every 6 weeks ± 7 days until PD. After 8 cycles of treatment these assessments should be done every 12 weeks ± 14 days. Tumor response and disease progression were evaluated based on RECIST 1.1 criteria and the mRECIST criteria for HCC regarding the definition of Progressive Disease.

The following censoring rules for PFS were specified in the SAP.

- For the patient who did not have tumor assessments after baseline, and
  - did not die, PFS was censored at day 1
  - died within
    - the first 12+1 weeks after randomization for patients who discontinued treatment prior to cycle8
    - the first 24+2 weeks after randomization for patients who discontinued treatment after to cycle8,

    death was not considered as a PFS event
  - died later than
    - 12+1 weeks after randomization for patients who discontinued treatment prior to cycle8,
    - 24+2 weeks after randomization for patients who discontinued treatment after to cycle8,

    death was not considered as a PFS event and PFS will be censored at day 1.

- For the patient who changed therapy to something other than the study medication prior to observing progression, PFS was censored at the date of the last scan performed prior to the change of therapy.
- For the patient who had progression after 2 consecutive missed or non-evaluable assessments (i.e., up to cycle 8 progression later than the last evaluable scan + 12 weeks + 1 week, after cycles 8 the last evaluable scan + 24 weeks + 2 weeks), PFS was censored at the date of the last evaluable scan before the 2 missing assessments.
- For the patient who discontinued or withdrew early from the study without documented progression, PFS was censored on the date of the last evaluable tumor assessment unless the patient died within
  - 12+1 weeks after the last evaluable assessment for subjects who discontinued treatment prior to cycle8,

- 24+2 weeks after the last evaluable assessment for subjects who discontinued treatment after to cycle8

In these cases, death was considered a PFS event.

ORR was defined as the rate of patients with complete response (CR) or partial response (PR) over all randomized patients. Patients prematurely discontinuing without an assessment were considered non-responders.

In Study RESORCE, Health-Related Quality of Life (HRQoL) for patients was assessed as a tertiary objective. HRQoL was measured by using the instrument FACT-Hep (Functional Assessment of Cancer Therapy-Hepatobiliary) and the instrument EQ-5D (EuroQoL-5 Dimensions questionnaire) on the same visit schedule.

EQ-5D contains a descriptive system which measures 5 health dimensions: mobility, self-care, usual activity, pain/discomfort, and anxiety/depression. Each dimension contains 3 levels of response to reflect the degree of problems patients have experienced: no problem (level 1), some problems (level 2), and extreme problems (level 3). These five health dimensions are summarized into a single score, the EQ-5D index score according to EQ-5D scoring information. The EQ-5D index score ranges -0.59 to 1 with higher scores representing better health states. The EQ-5D also contains a visual analog scale (EQ-VAS), which records the respondents' self-rated health status on a vertical graduated visual analogue scale ranging from 0 (worst imaginable health state) to 100 (best imaginable health state).

FACT-Hep consists of five subscales: (1) physical well-being (PWB); (2) social/family well-being (SWB); (3) emotional well-being (EWB); (4) functional well-being (FWB); and the hepatobiliary cancer subscale (HCS). The PWB, FWB, SWB and EWB are summed to form the FACT-General (FACT-G) total score. The FACT-G and HCS score are summed to form the FACT-Hep total score.

In Study RESORCE, the FACT-Hep and EQ-5D were both self-administrated by the patients at Cycle 1, Day 1, (i.e. baseline for patient report outcomes [PRO]), at every cycle, and end-of-study visit at the start of the visit before seeing the physician.

3.2.2 Statistical Methodologies

Per the SAP, the primary analysis of OS was a log-rank test stratified by five randomized stratified factors at one-sided significance level of 0.025. The primary analysis was performed according to treatment groups as randomized, with stratification strata as recorded in the IVRS. The Kaplan-Meier method was used to provide OS curves for each treatment arm. Hazard ratio and its 95% confidence interval were estimated using the Cox proportional hazards model stratified by the stratification factors that were used in the primary analysis of OS.

The same statistical analysis methods were applied to the secondary endpoints TTP and PFS analyses. In order to control type I error rate (alpha), a hierarchical order for testing the secondary endpoints TTP and PFS was specified in the SAP, i.e. after the primary analysis of OS

shows statistically significant improvement in favor of Regorafenib, TTP was tested first and then PFS was tested. There were two planned OS interim analyses: when 30% and 75% of 370 required death events were observed. The first OS interim analysis was for futility purposes. An O'Brien-Fleming alpha spending function approach was used to determine the significance thresholds based on the actual number of events by the time of the analyses.

ORR was compared between treatment groups using the Cochran-Mantel-Haenszel (CMH) test, adjusting for the same stratification factors as for the primary analysis of OS. Estimates and their 95% confidence intervals were computed for each treatment group. The difference in ORR between the regorafenib and placebo group and the corresponding 95% confidence intervals were also calculated.

Per SAP, HRQoL measures as evaluated by EQ-5D and FACT-Hep instruments were analyzed as tertiary endpoints. Descriptive statistics were provided for the FACT-Hep questionnaire (each domain score including the HCS and the FACT-Hep total score) and for the EQ-5D index score (obtained by summarizing the five health dimensions) and visual analog scale score (VAS) at each assessment time and for change from baseline by treatment group.

Reviewer's Comments:

2. *During the communication between FDA and the applicant before the sNDA submission, FDA had conveyed to the sponsor that FDA didn't agree* (b) (4) [redacted]

3. *Per the protocol and SAP, disease progression in the PFS definition was assessed based on RECIST 1.1 and the mRECIST, respectively. However, SAP did not specify which criteria should be used as the primary analysis of PFS.*

4. *Per the SAP, ORR would be compared between treatment groups using the CMH test. Because testing ORR was not included in the pre-specified hierarchical test order for the secondary endpoints, the comparison should be considered exploratory analysis.*

5. *The data monitoring committee (DMC) recommended the study to be continued after reviewing the first interim analysis of OS. Also DMC recommended to remove the second interim analysis of OS. The applicant followed the DMC recommendation as indicated in the protocol Amendment 4. According to O'Brien-Fleming spending function, a very small alpha (0.00000696) was allocated to the first interim analysis.*

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

There were 843 patients screened to Study RESORCE. Among the 843 patients, 270 patients (32%) failed screening, and 573 patients (68%) were eligible to be randomized to the study.

Table 3.1 summarizes the disposition for all randomized patients as of August 05, 2016, the date for database locked for the clinical study report (CSR).

Table 3.1 Patient Disposition

	Placebo + BSC	Regorafenib + BSC
Randomized, n (%)	194 (100.0)	379 (100.0)
Never treated	1(0.5)	5 (1.3)
Started treatment	193(99.5)	374 (98.7)
Ongoing with treatment (as of LPLV)	10 (5.2)	65 (17.2)
Terminated treatment	183 (94.3)	309 (81.5)
Primary reason for terminating treatment		
Progression disease	131 (68)	170 (45)
Withdrawal by subject	5 (2.6)	26 (6.9)
AE associated with clinical disease progression	28 (14.4)	56 (14.8)
AE not associated with clinical disease progression	12 (6.2)	47 (12.4)
Death	0	5 (1.3)
Other	5 (2.6)	2 (0.5)

[Source: Clinical Study Report Table 8-1]

Reviewer's Comments:

6. *Note that there are more patients who withdrew treatment by themselves in regorafenib arm (6.9%) than placebo arm (2.6%).*

Table 3.2 summarizes this reviewer's results of the patients' demographics.

Table 3.2 Demographics for All Randomized Patients

	Placebo + BSC (n=194)	Regorafenib + BSC (n=379)	Total (n=573)
Gender, n (%)			
Male	171 (88.1)	333 (87.9)	504 (88.0)
Female	23 (11.9)	46 (12.1)	69 (12.0)
Age, year			
Median (range)	62 (23 - 83)	64(19 - 85)	63 (19 - 85)
Age Group n (%)			
<65	116 (59.8)	199 (52.5)	315 (55.0)
>=65	78 (40.2)	180 (47.5)	258 (45.0)
Region			
Asia	73 (37.6)	143 (37.7)	216 (37.7)
Rest of the world	121 (62.4)	236 (62.3)	357 (62.3)
Race/ethnic group, n (%)			
White	68 (35.1)	138 (36.4)	206 (36.0)
Asian	78 (40.2)	156 (41.2)	234 (40.8)
Other	3 (1.5)	8 (2.1)	11 (1.9)
Not reported	45 (23.2)	77 (20.3)	122 (21.3)

Some major baseline disease characteristics are summarized in Table 3.3**.**

Table 3.3 Baseline Disease Characteristics for All Randomized Patients

	Placebo + BSC (n=194)	Regorafenib + BSC (n=379)
ECOG performance status (CRF*), n (%)		
0	130 (67.0)	247 (65.2)
1	64 (33.0)	132 (34.8)
Etiology of HCC, n (%)		
Hepatitis B	73 (37.6)	143 (37.7)
Hepatitis C	41 (21.1)	78 (20.6)
Alcohol use	55 (28.4)	90 (23.7)
Genetic / Metabolic	6 (3.1)	16 (4.2)
Non-Alcoholic steatohepatitis (NASH)	13 (6.7)	25 (6.6)
Unknown	32 (16.5)	66 (17.4)
Other	4 (2.1)	12 (3.2)
BCLC stage at study entry, n (%)		
A (Early Stage)	0	1 (0.3)
B (Intermediate Stage)	22 (11.3)	53 (14.0)
C (Advanced Stage)	172 (88.7)	325 (85.8)
Child-Pugh score, n (%)		
5	118 (60.8)	244 (64.4)
6	70 (36.1)	129 (34.0)
7	5 (2.6)	5 (1.3)
8 or missing	1 (0.5)	1 (0.3)

*[Source: Clinical Study Report Table 8-5] *based on data collected in case report form (CRF)*

Reviewer's Comments:

7. *As shown in Table 3.2 and Table 3.3, the demographic and major baseline disease characteristics appear balanced between the two treatment arms.*

3.2.4 Results and Conclusions

3.2.4.1 Results of Primary Endpoint

As August 05, 2016, a total of 373 death events were observed, 3 more events than the requirement for conducting the final overall survival analysis. Table 3.4 summaries the applicant's analyses of OS.

Table 3.4 Primary Analysis of Overall Survival

	Placebo + BSC n=194	Regorafenib + BSC n=379
Number of Event (%)	140 (72.2)	233 (61.5)
Median OS in Months (95% CI)	7.8 (6.3, 8.8)	10.6 (9.1, 12.1)
Hazard Ratio (95%CI)	0.63 (0.50, 0.79)	
P-value[a]	<0.0001	

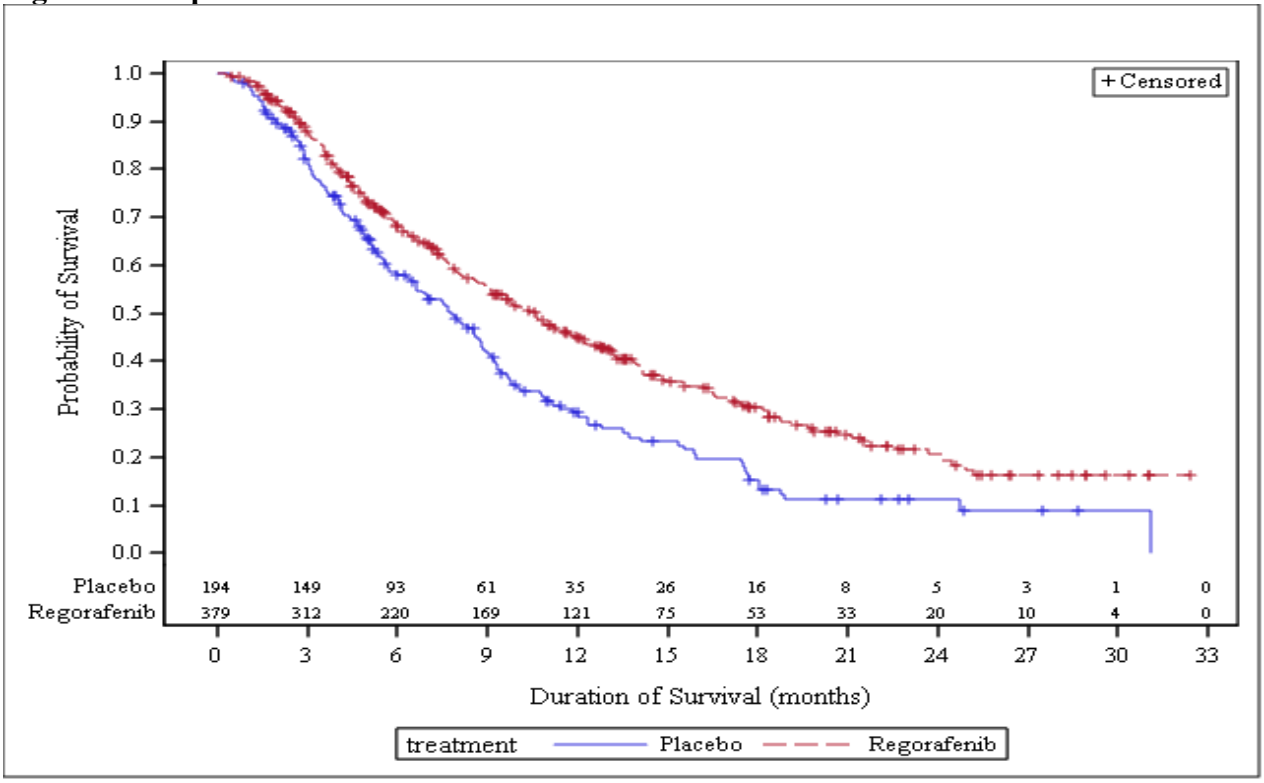
[a]*log-rank test stratified by line of therapy (3rd-line vs. 4th-line or beyond), geographical region (Asia vs. rest of world (ROW)), ECOG-PS (0 vs. 1), Alpha-fetoprotein level (<400 ng/mL vs. ≥400 ng/mL), presence vs. absence of extrahepatic disease, and presence vs. absence of macrovascular invasion.*

Reviewer's Comments:

8. *This reviewer has verified the applicant's OS result shown in Table 3.4. Taking account a very small alpha (0.00000696 according to O'Brien-Fleming spending function) that was spent on the first interim analysis, the alpha available for the primary analysis was approximately 0.05. The OS primary analysis result in Table 3.4 demonstrated that the patients treated with regorafenib plus BSC had statistically significant improvement in survival time compared to the patients treated with placebo plus BSC.*

Figure 3.2 displays the reviewer's Kaplan-Meier curves of OS.

Figure 3.2 Kaplan-Meier curves of OS



Reviewer's Comments:

9. *The primary analysis of OS shown in Table 3.4 was conducted using stratification values as recorded in the IVRS. The applicant also conducted sensitivity analyses such as stratified analysis using strata recorded in case report form (CRF) and unstratified analysis to evaluate the robustness of the OS primary analysis result. Table 3.5 summarizes the sensitivity analyses.*

Table 3.5 Sensitivity Analyses of Overall Survival

	Placebo + BSC n=194	Regorafenib + BSC n=379
Number of Event (%)	140 (72.2)	233 (61.5)
Median OS in Months (95%CI)	7.8 (6.3, 8.8)	10.6 (9.1, 12.1)
Stratified Analysis using strata recorded from CRF		
Hazard Ratio (95%CI)	0.66 (0.53, 0.83)	
P-value[a]	0.0003	
Unstratified analysis		
Hazard Ratio(95%CI)	0.67 (0.55, 0.83)	
P-value[a]	0.0002	

[a]log-rank test stratified by line of therapy (3rd-line vs. 4th-line or beyond), geographical region (Asia vs. rest of world (ROW)), ECOG-PS (0 vs. 1), Alpha-fetoprotein level (<400 ng/mL vs. ≥400 ng/mL), presence vs. absence of extrahepatic disease, and presence vs. absence of macrovascular invasion.

Reviewer's Comments:

10. This reviewer has verified the two sensitivity analyses. As shown in Table 3.5, the results of OS sensitivity analyses are consistent with the result of the OS primary analysis.

3.2.4.2 Results of Secondary Endpoints

Progression-free survival (PFS) and objective response rate (ORR) were the secondary endpoints evaluated in the study. Table 3.6 summaries the applicant's and this reviewer's PFS analyses based on mRECIST and RECIST, respectively.

Table 3.6 Analyses of Progression Free Survival

	Placebo + BSC n=194	**Regorafenib + BSC n=379**
PFS assessed by using mRECIST		
Number of Events (%)	181 (93.3)	293 (77.3)
progression	173	274
death	8	19
Median PFS in months (95% CI)	1.5 (1.4, 1.6)	3.1 (2.8, 4.2)
Hazard Ratio (95% CI)	0.46 (0.37, 0.56)	
P-value[a]	<0.0001	
PFS assessed by using RECIST		
Number of Events (%)	184 (94.8)	288 (76.0)
progression	175	270
death	9	18
Median PFS in months (95% CI)	1.5 (1.4, 1.5)	3.4 (2.9, 4.2)
Hazard Ratio (95% CI)	0.43 (0.35, 0.52)	
P-value[a]	<0.0001	

[Source: Clinical Study Report Table 9-1] [a]Log-rank test stratified by line of therapy (3rd-line vs. 4th-line or beyond), geographical region (Asia vs. rest of world (ROW)), ECOG-PS (0 vs. 1), Alpha-fetoprotein level (<400 ng/mL vs. ≥400 ng/mL), presence vs. absence of extrahepatic disease, and presence vs. absence of macrovascular invasion.

Figure 3.3 displays Kaplan-Meier curves of PFS assessed using mRECIST.

Figure 3.3 Kaplan-Meier curves of PFS (per mRECIST)

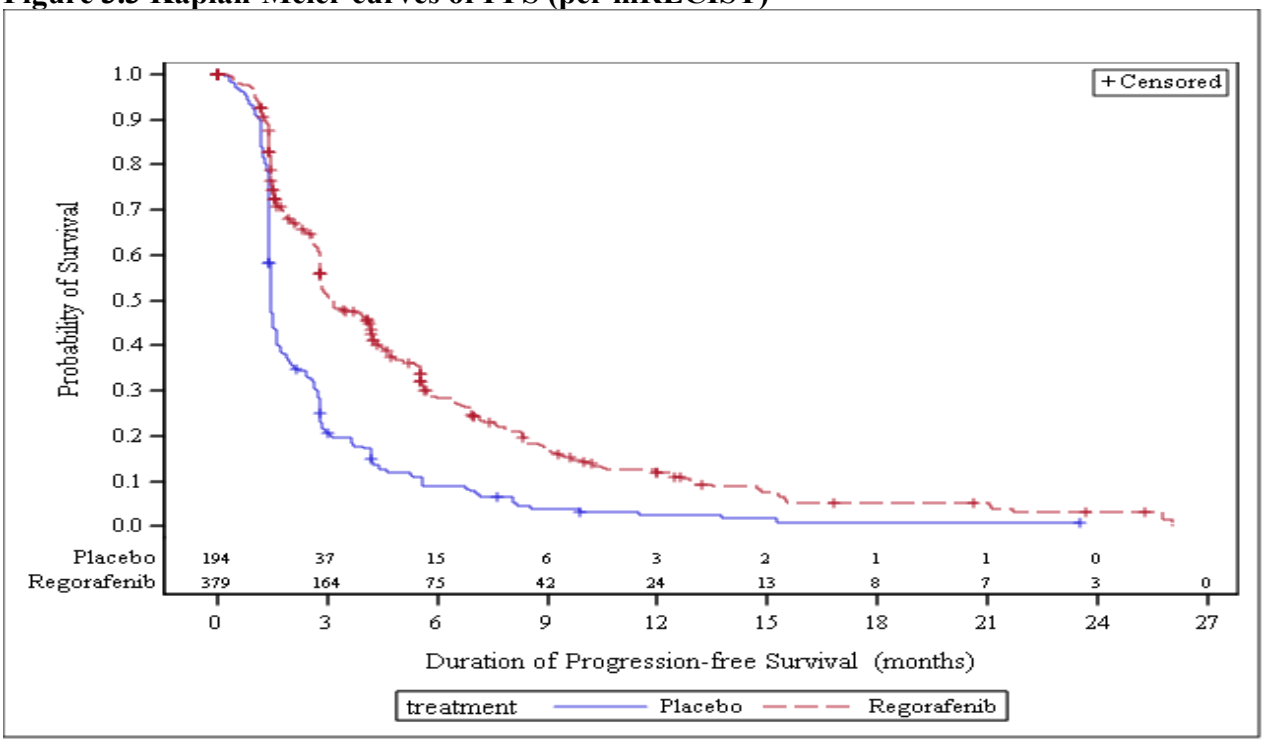
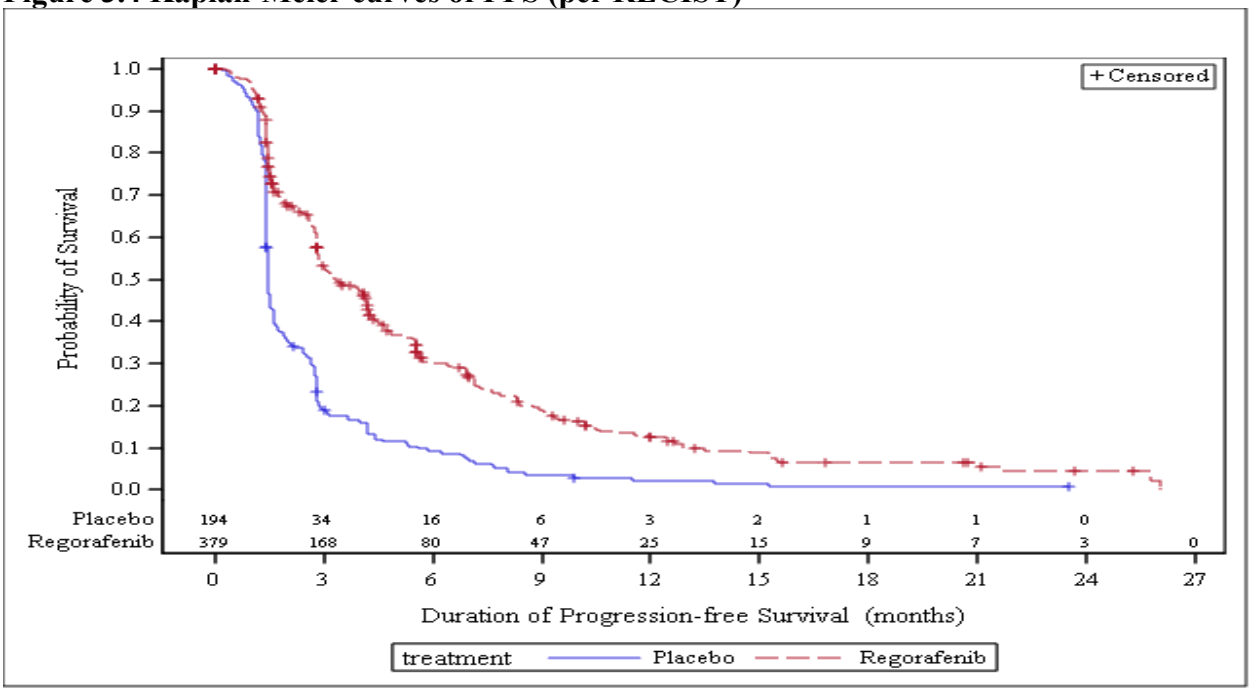


Figure 3.4 displays Kaplan-Meier curves of PFS assessed using RECIST.

Figure 3.4 Kaplan-Meier curves of PFS (per RECIST)



Reviewer's Comments:

11. *As mentioned in one of the previous reviewer's comments, FDA had conveyed to the applicant that FDA didn't agree* (b) (4) [redacted]

12. *As shown in Table 3.6, treatment with regorafenib plus BSC statistically significantly delayed time to progression/death compared to treatment with BSC alone.*

13. *The SAP did not specify which criteria (RECIST or mRECIST) would be used for the primary analysis of PFS. It is deferred to the clinical review team to determine which PFS result (based on mRECIST or RECIST) should be included to the product label.*

14. *There are 12 patients who had different status of progression disease (PD) determined by using mRECIST. Among these 12 patients, 7 patients had PD determined by mRECIST and did not have PD determined by RECIST. The PFS using RECIST for those patients was censored at the date of the first PD assessed by using mRECIST which is the date of last evaluable tumor assessment before treatment change or before death. Table 3.7 summaries this reviewer's concordance analysis of PD assessment using mRECIST or RECIST.*

Table 3.7 Concordance of mRECIST and RECIST

	Using RECIST, n (%)			
	Placebo + BSC n=194		Regorafenib + Placebo n=379	
Using mRECSIT, n (%)	PD	No PD	PD	No PD
PD	173 (89.2)	0 (0.0)	267 (70.4)	7 (1.8)
No PD	3 (1.5)	10 (5.2)	2 (0.5)	84 (22.2)

Reviewer's Comments:

15. *As shown in Table 3.7, the concordance rate of using mRECIST and using RECIST in placebo arm (94.4%) is similar as the one (92.6%) in regorafenib arm.*

Table 3.8 summarizes the applicant's and this reviewer's ORR analyses based on ORR data using mRECIST and RECIST, respectively.

Table 3.8 Results of Objective Response Rate and Duration of Response

	Placebo + BSC n=194	Regorafenib + BSC n=379
Using mRECIST		
Response rate (95%CI)	4.1% (1.8%, 8.0%)	10.6% (7.6%, 14.1%)
Responders (CR+PR)	8	40
Complete response	0	2
Partial response	8	38
p-value (CMH[a])	0.004728	
Median of Duration of Response (months)	2.7 (1.9, NE[b])	3.5 (1.9, 4.5)
Using RECIST		
Response rate (95%CI)	2.6% (0.8%, 5.9%)	6.6% (4.3%, 9.6%)
Responders (CR+PR)	8	25
Complete response	0	0
Partial response	8	25
p-value (CMH[a])	0.019991	
Median of Duration of Response (months)	5.6 (2.3, NE[b])	5.9 (1.4, 8.4)

[a]CMH=Cochran–Mantel–Haenszel test. [b]NE=not estimable due to few events.

Reviewer's Comments:

16. *Because the secondary endpoint ORR was not included in the pre-specified hierarchical order for testing the secondary endpoints, the p-values in the ORR results should be considered exploratory. Also, because the SAP did not specify whether ORR data using mRECIST or using RECIST should be used in the ORR primary analysis, it is deferred to the clinical review team to determine which ORR result should be included in the product label. Higher response rates are observed in bother arms using mRECIST correspond to using RECIST.*

3.2.4.3 Results of Health-related Quality of Life (HRQL)

As a tertiary objective of the study, Health-Related Quality of Life (HRQoL) was evaluated by using instruments FACT-Hep and the EQ-5D.

EQ-5D

During the treatment, among the patients who were expected to report to EQ-5D questionnaires in each visit (cycle) and the end of treatment visit, 95% versus 78% of the patients provided the questionnaires at the visit through all cycles versus the end of treatment visit. More than 93% versus 77% of the expected questionnaires were all answered through all cycles versus the end of treatment visit. Table 3.9 shows this reviewer's extract from the applicant's summary of EQ-5D questionnaire completion analysis through cycle 10 and the end of treatment visit.

Table 3.9: EQ-5D Questionnaire Completion Rate by Visit

	#Patients Expected to Answer Questionnaires		Completion Rate*	
Visit	**Placebo + BSC**	**Regorafenib + BSC**	**Placebo + BSC**	**Regorafenib + BSC**
Cycle 1	193	376	95.3%	97.1%
Cycle2	176	340	95.5%	96.8%
Cycle 3	97	269	96.9%	94.8%
Cycle 4	66	220	98.5%	97.3%
Cycle 5	51	184	96.1%	98.4%
Cycle 6	34	157	97.1%	96.8%
Cycle 7	29	128	86.2%	95.3%
Cycle 8	19	116	100.0%	94.8%
Cycle 9	14	93	93.3%	98.9%
Cycle 10	11	85	90.9%	98.8%
End of Treatment	144	236	79.2%	76.7%

*[Source: Clinical Study Report Table 14.2.4 / 1] *Completion Rate=#patients who answered all questions/#patients expected to answer questionnaires.*

Table 3.10 summarizes the applicant's descriptive statistics and changes from baseline for the EQ-5D index and EQ-VAS scores.

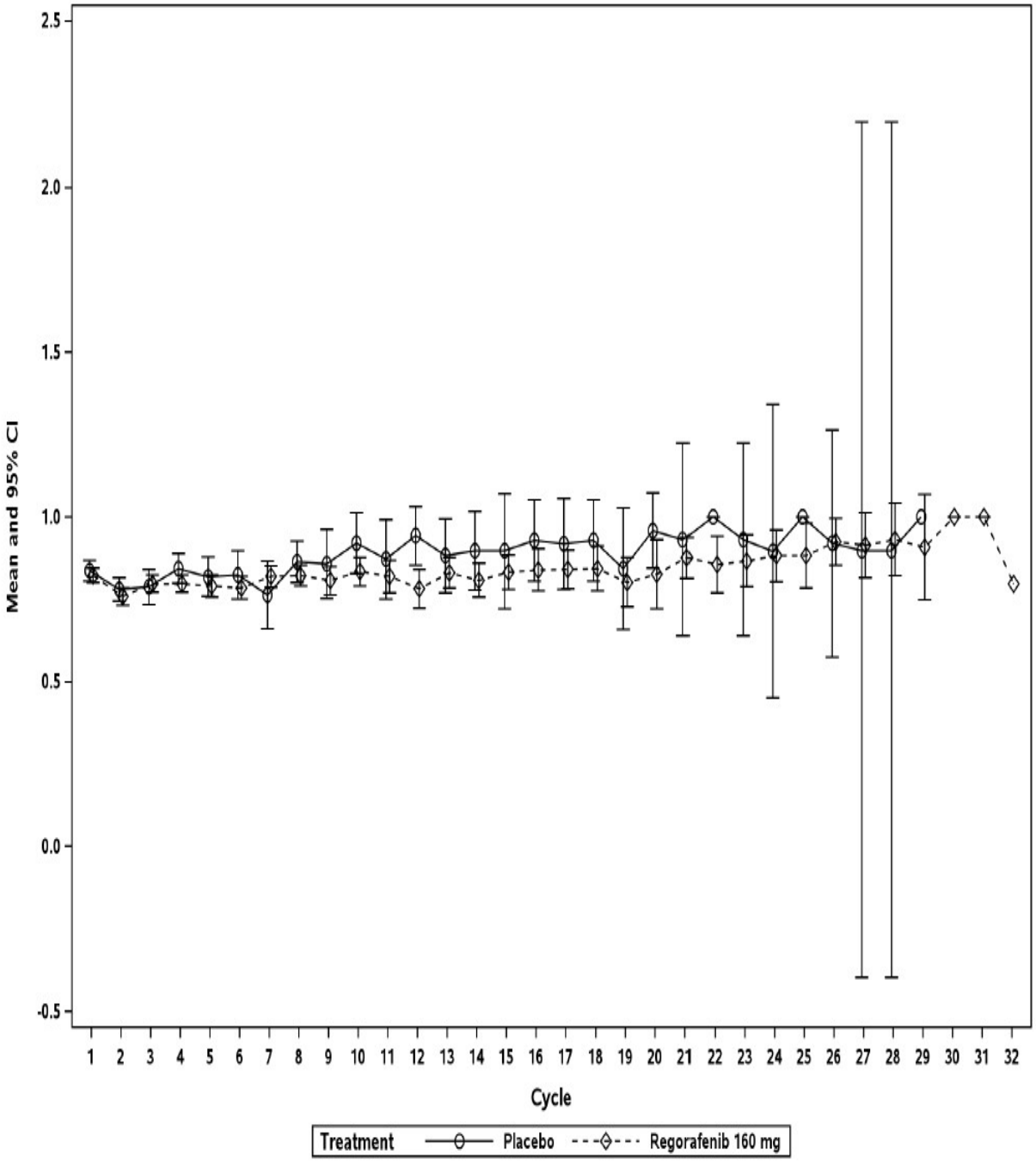
Table 3.10: Mean EQ-5D index and VAS scores through Cycle 16

	Placebo					Regorafenib				
EQ-5D	n	Mean	StD	Change from baseline	StD	n	Mean	StD	Change from baseline	StD
C1, Day 1	184	0.84	0.22	.	.	366	0.82	0.21	.	.
C2, Day 1	166	0.78	0.23	-0.06	0.19	324	0.76	0.24	-0.07	0.21
C3, Day 1	92	0.79	0.26	-0.07	0.20	249	0.80	0.21	-0.05	0.20
C4, Day 1	64	0.84	0.18	-0.02	0.19	210	0.80	0.20	-0.05	0.18
C4, Day 15 [a]	-	-	-	-	-	1	0.76	.	-0.24	.
C5, Day 1	48	0.82	0.21	-0.04	0.21	177	0.79	0.22	-0.06	0.21
C6, Day 1	33	0.82	0.21	-0.05	0.22	153	0.79	0.21	-0.07	0.20
C7, Day 1	27	0.76	0.26	-0.10	0.28	124	0.82	0.18	-0.05	0.17
C8, Day 1	19	0.86	0.13	-0.01	0.22	109	0.82	0.16	-0.05	0.18
C9, Day 1	14	0.86	0.18	-0.04	0.15	91	0.81	0.21	-0.06	0.21
C10, Day 1	10	0.92	0.13	0.07	0.14	82	0.83	0.20	-0.04	0.20
C11, Day 1	8	0.87	0.14	-0.04	0.05	75	0.82	0.21	-0.05	0.20
C12, Day 1	9	0.94	0.12	0.03	0.06	63	0.78	0.23	-0.07	0.23
C13, Day 1	9	0.88	0.15	-0.04	0.06	56	0.83	0.17	-0.03	0.18
C14, Day 1	8	0.90	0.14	-0.01	0.07	45	0.81	0.17	-0.08	0.16
C15 Day 1	6	0.90	0.17	-0.00	0.07	43	0.83	0.17	-0.07	0.13
C16 Day 1	5	0.93	0.10	-0.01	0.10	36	0.84	0.19	-0.07	0.16
EOT	110	0.67	0.32	-0.20	0.30	178	0.65	0.31	-0.17	0.30
EQ-VAS										
C1, Day 1	185	73.51	18.90	.	.	367	74.35	17.81	.	.
C2, Day 1	166	73.63	16.93	-0.85	17.13	326	71.93	17.87	-2.93	14.74
C3, Day 1	90	75.43	18.90	1.00	20.23	253	73.31	17.06	-1.93	15.43
C4, Day 1	63	77.10	16.77	0.67	16.07	213	73.64	16.66	-1.88	15.26
C4, Day 15 [a]	-	-	-	-	-	1	50.00	.	-35.00	.
C5, Day 1	47	76.49	17.50	1.79	17.28	179	74.82	15.84	-1.65	15.15
C6, Day 1	32	76.28	16.95	0.25	15.68	153	74.93	16.06	-1.68	16.09
C7, Day 1	26	76.35	19.65	1.04	16.81	123	75.80	17.60	-1.67	17.35
C8, Day 1	19	81.11	12.41	4.63	12.00	110	76.90	14.74	-2.30	14.84
C9, Day 1	13	82.46	14.30	9.54	15.27	92	74.57	16.73	-3.66	15.83
C10, Day 1	10	81.50	19.87	5.00	10.45	83	77.17	15.80	-0.90	15.39
C11, Day 1	8	84.38	12.04	11.25	12.33	75	76.17	16.30	-2.12	17.89
C12, Day 1	9	80.56	19.17	4.44	5.27	65	73.65	18.53	-3.59	19.15
C13, Day 1	8	80.13	17.04	6.38	4.90	57	74.54	16.97	-2.30	19.77
C14, Day 1	8	83.88	14.77	10.75	11.59	46	74.67	18.58	-1.94	21.10
C15, Day 1	6	79.00	19.95	10.67	12.61	44	76.96	13.94	-0.30	15.06
C16 Day 1	5	82.20	13.97	6.20	15.90	37	78.51	14.75	-2.16	12.12
EOT	112	67.39	20.20	-7.60	18.90	180	65.36	19.86	-9.26	18.88

[Source: Clinical Study Report Table 9-16] [a] first unscheduled Abbreviations: C = cycle number; EOT = End of Treatment; StD = standard deviation;

Figures 3.5 displays mean scores with 95% CIs for the EQ-5D index score by treatment arm over the course of the study.

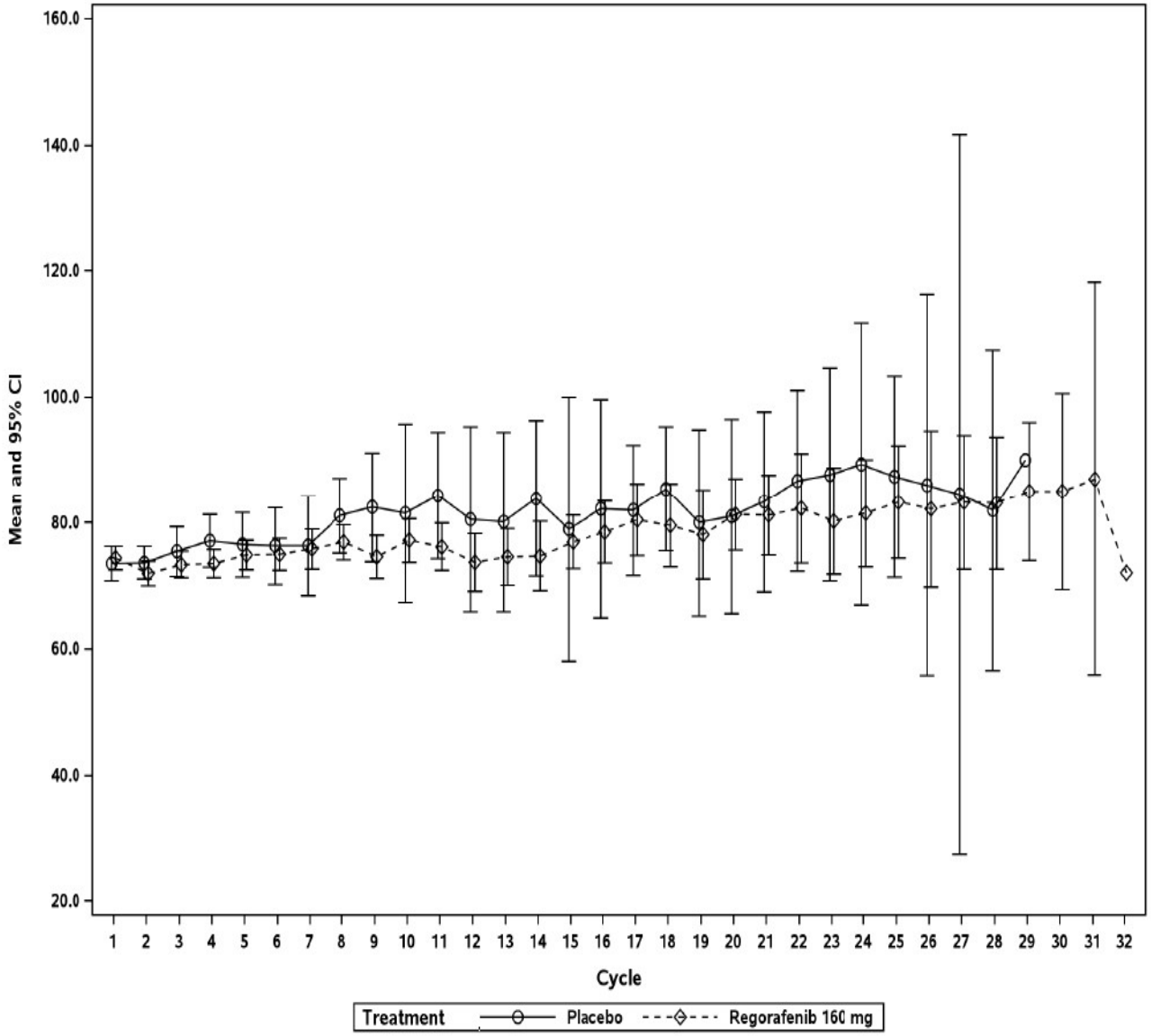
Figure 3.5 Mean Scores of EQ-5D index with 95% CIs by Treatment over the Study



[Source: Clinical Study Report Figure 9-13]

Figures 3.6 displays mean scores with 95% CIs for the EQ-5D VAS by treatment arm over the course of the study.

Figure 3.6 Mean Scores of EQ-5D VAS with 95% CIs by Treatment over the Study



[Source: Clinical Study Report Figure 9-14]

Reviewer's Comments:

17. The analyses of EQ-5D and FACT-Hep are exploratory descriptive analyses and no inference should be drawn.

FACT-Hep

Among the patients who were expected to provide FACT-Hep questionnaires in each visit (cycle) and the end of treatment visit, 95% versus 80% provided the questionnaires at the visit through all cycles versus the end of treatment visit. More than 86% versus 70% of the questionnaires were all answered through all cycles versus the end of treatment visit. Table 3.11

shows this reviewer's extract from the applicant's summary of FACT-Hep questionnaire completion analysis through cycle 10 and the end of treatment visit.

Table 3.11: FACT--Hep Questionnaire Completion Rate by Visit

	#Patients Expected to Answer Questionnaires		Completion Rate*	
Visit	**Placebo + BSC**	**Regorafenib + BSC**	**Placebo + BSC**	**Regorafenib + BSC**
Cycle 1	193	376	87.6%	88.8%
Cycle2	176	340	89.2%	87.4%
Cycle 3	97	269	90.7%	87.7%
Cycle 4	66	220	89.4%	86.8%
Cycle 5	51	184	86.3%	89.7%
Cycle 6	34	157	82.4%	93.0%
Cycle 7	29	128	79.3%	89.8%
Cycle 8	19	116	89.5%	90.5%
Cycle 9	15	94	80.0%	90.4%
Cycle 10	11	85	81.8%	90.6%
End of Treatment	144	236	71.5%	70.3%

*[Source: Clinical Study Report Table 14.2.4 / 10] *Completion Rate=#patients who answered all questions/#patients expected to answer questionnaires.*

Table 3.12 summarizes the applicant's descriptive statistics and changes from baseline for the FACT-Hep total scores through Cycle 16.

Table 3.12: FACT-Hep Total Score and Change from Baseline through Cycle 16

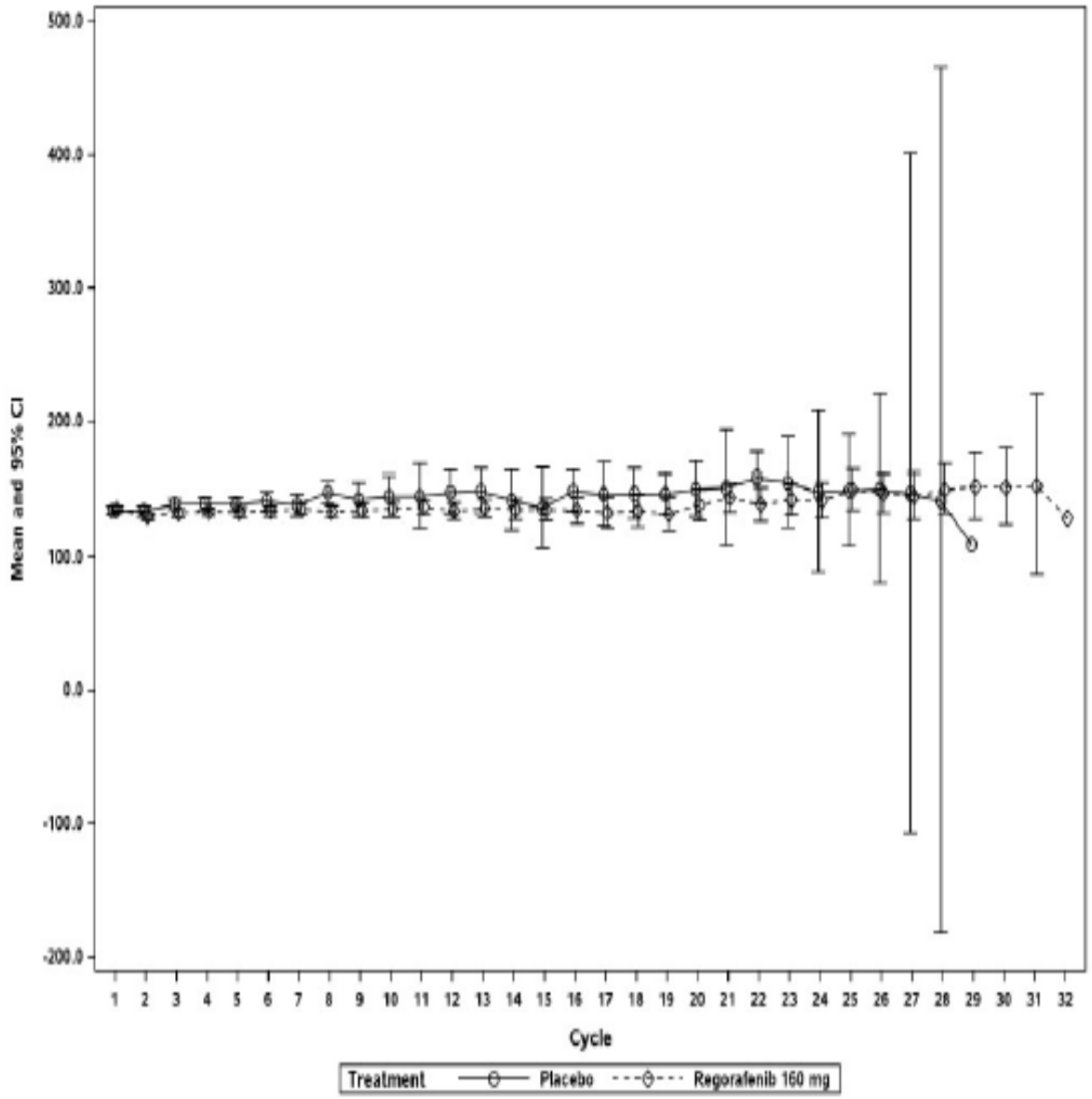
	Placebo					Regorafenib				
Cycle on Day 1	n	Mean	StD	Change from baseline	StD	n	Mean	StD	Change from baseline	StD
C1	185	134.4	21.7			367	135.5	22.9		
C2	164	134.0	23.6	-0.9	16.2	324	130.7	23.7	-6.0	17.1
C3	93	139.1	20.2	0.9	17.6	253	133.0	23.5	-5.2	16.0
C4	65	139.7	20.2	-0.3	19.3	212	134.0	23.2	-5.1	17.3
C5	49	139.3	20.6	-0.6	20.6	177	133.6	25.3	-6.3	21.2
C6	33	141.6	20.9	-2.0	18.4	153	134.3	23.0	-5.0	18.7
C7	28	138.9	21.4	-3.1	17.9	124	135.6	24.2	-4.8	18.4
C8	19	147.9	17.4	5.6	19.7	110	133.8	24.7	-7.3	21.1
C9	14	142.8	21.5	5.7	17.4	90	134.9	24.7	-5.4	19.7
C10	10	145.2	21.1	5.9	15.1	82	135.7	26.4	-2.4	18.6
C11	6	145.0	22.0	5.5	8.2	75	137.9	24.1	-3.0	19.4
C12	9	148.0	21.0	5.2	11.9	64	134.5	26.7	-5.8	23.9
C13	8	148.9	19.2	3.8	10.0	57	136.8	25.1	-2.8	19.8
C14	7	142.2	23.6	4.8	10.1	46	135.6	26.3	-3.8	21.0
C15	6	136.3	28.0	-3.6	15.2	44	135.4	27.6	-5.2	19.1
C16	5	149.1	12.3	0.6	15.3	37	134.7	29.3	-6.2	19.3
EOT Visit	111	122.9	26.3	-13.0	21.7	178	121.2	24.7	-15.0	22.1

Abbreviations: C = cycle number; D = day; EOT=End of treatment; MID = minimally important difference; N = number of subjects; StD = standard deviation.

[Source: Clinical Study Report Table 9-17]

Figure 3.7 displays mean FACT-Hep total scores with 95% CIs by treatment arm over the course of the study.

Figure 3.7: FACT-Hep Mean with 95% CIs by Treatment over the Study



[Source: Clinical Study Report Figure 9-15]

3.3 Evaluation of Safety

Please refer to Dr. Pelosof's clinical review for safety evaluation of regorafenib.

3.4 Benefit-Risk Assessment

The results of Study RESORCE show statistically significant improvement in overall survival and reducing time to progression/death in patients with HCC who had failed prior systemic treatment with sorafenib when treated with regorafenib plus BSC instead of BSC alone.

Whether the results from RESORCE provide a favorable benefit to risk ratio to support an approval of regorafenib for the proposed indication is deferred to the clinical review team.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

This reviewer has conducted OS analyses in the subgroups defined by age (greater than 65, less than or equal to 65 years), gender (male, female), and region (Asia vs. Rest of World; US vs. non-US). Table 4.1 summarizes this reviewer's OS analyses in the demographic subgroups.

Table 4.1: OS Analyses in Demographics Subgroups

Subgroup	#Events/#Patients	HR* (95%CI*)
Age		
<65	205/305	0.65 (0.49, 0.87)
>=65	168/258	0.74 (0.54, 1.02)
Gender		
Male	327/504	0.65 (0.52, 0.82)
Female	69/89	0.88 (0.48, 1.61)
Region		
Asia	142/216	0.65 (0.46, 0.92)
Rest of World	231/357	0.68 (0.52, 0.90)
US	22/31	0.90 (0.35, 2.33)
Non_US	351/542	0.67 (0.54, 0.83)

**Hazard ratio and CIs are based on an unstratified Cox Regression Model.*

Reviewer's Comments:

18. As shown in the Table 4.1, there was no outlier subgroup observed. The subgroup analyses results are considered exploratory.

4.2 Other Special/Subgroup Populations

This reviewer has conducted OS analyses in the subgroups defined by major baseline disease characteristics. The major baseline characteristics used to define the subgroups are ECOG performance status (0 vs. 1) at baseline, alpha fetoprotein (<400 ng/mL vs. ≥400 ng/mL), extrahepatic disease (presence vs. absence), macrovascular invasion (presence vs. absence), and etiology (Hepatitis B, Hepatitis C, alcohol use) based on the CRF. Table 4.2 summarizes this reviewer's OS analyses in the subgroups based on major baseline characteristics.

Table 4.2: OS Analyses in Baseline Characteristics Subgroups

Subgroup	#Events/#Patients	HR* (95%CI*)
ECOG Performance Status		
0	231/377	0.61 (0.47, 0.80)
1	142/196	0.78 (0.55, 1.11)
Alpha-Fetoprotein (CRF)		
<400ngml	194/324	0.67 (0.50, 0.90)
>=400ngml	179/249	0.68 (0.50, 0.92)
Extrahepatic Disease (CRF)		
absent	103/161	0.97 (0.63, 1.48)
present	270/412	0.61 (0.47, 0.77)
Macrovascular Invasion (CRF)		
absent	259/409	0.67 (0.52, 0.86)
present	114/164	0.67 (0.46, 0.98)
Etiology Hepatitis B		
No	238/357	0.73 (0.56, 0.95)
Yes	135/216	0.58 (0.41, 0.82)
Etiology Hepatitis C		
No	295/454	0.65 (0.51, 0.82)
Yes	78/119	0.79 (0.49, 1.26)
Etiology Alcohol Use		
No	273/428	0.59 (0.46, 0.76)
Yes	100/145	0.92 (0.61, 1.38)
Child-Pugh Status		
A5	222/362	0.59 (0.46, 0.79)
A6	141/199	0.80 (0.57, 1.13)

** Hazard ratio and CIs are based on an unstratified Cox Regression Model.*

Reviewer's Comments:

19. As shown in the Table 4.2, there was no outlier subgroup observed. The results of the baseline disease characteristic subgroup analyses are considered exploratory.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

This reviewer found no major statistical issue that impacted the overall conclusions.

5.2 Collective Evidence

Based on the data from Study RESORCE, the result of the OS primary analysis demonstrated that patients with hepatocellular carcinoma (HCC) after treatment with sorafenib had statistically significant improvement in survival time when treated with regorafenib plus BSC instead of BSC alone (stratified log-rank p-value <0.0001) with an estimated HR of 0.63 (95% CI 0.50, 0.79). The estimated median survival time was 10.6 months (95% CI: 9.1, 12.1) for the patients treated with regorafenib plus BSC versus 7.8 months (95% CI: 6.3, 8.8) for the patients treated with

BSC alone. The result of the secondary endpoint PFS assessed using mRECIST also showed that treatment with regorafenib plus BSC statistically significantly delayed time to progression /death (stratified log-rank p-value <0.0001) with an estimated HR of 0.46 (95% CI 0.37, 0.56) compared to treatment of BSC alone. The estimated median PFS assessed using mRECIST was 3.1 months (95% CI: 2.8, 4.2) for the patients treated with regorafenib plus BSC versus 1.5 months (95% CI: 1.4, 1.6) for the patients treated with BSC alone. The result of PFS assessed using RECIST is similar to the result of PFS assessed using mRECIST. The results of another secondary endpoint ORR are supportive with the observed ORR per mRECIST (RECIST) of 10.6% (6.6%) in patients treated with regorafenib plus BSC versus 4.1% (2.6%) in patients treated with BSC alone.

5.3 Conclusions and Recommendations

Based on analyses of OS and pre-specified key secondary endpoints from Study RESORCE, this reviewer concludes that treatment with regorafenib plus BSC statistically significantly prolongs survival time and delays time to progression/death for patients with HCC after treatment with sorafenib compared to the treatment with BSC alone. Whether the results from RESORCE provide a favorable benefit to risk ratio to support an approval of regorafenib for the proposed indication will be determined by the clinical review team.

5.4 Labeling Recommendations

This reviewer recommends result of the OS primary analysis to be included in the product label of regorafenib. Whether to include results of PFS and ORR based on mRECIST or based on RECIST in the label of regorafenib is deferred to the clinical review team. (b) (4)

[redacted]

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/s/

XIAOPING JIANG
04/06/2017

LISA R RODRIGUEZ
04/06/2017

RAJESHWARI SRIDHARA
04/07/2017

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203085Orig1s007

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Office of Clinical Pharmacology Review (Amendment)

NDA or BLA Number	NDA 203085
Link to EDR	\\CDSESUB1\evsprod\NDA203085
Submission Date	October 30, 2016
Submission Type	Priority
Brand Name	Stivarga
Generic Name	Regorafenib
Dosage Form and Strength	40 mg tablets
Route of Administration	Oral
Proposed Indication	Treatment of patients with Hepatocellular carcinoma (HCC) who have been previously treated with (b) (4)
Applicant	Bayer
Associated IND	IND 075642, (b) (4)
OCP Review Team	Youwei Bi, Ph.D.; Vadryn Pierre, Ph.D.; Jiang Liu, Ph.D.; Jeanne Fourie Zirkelbach, Ph.D.
OCP Final Signatory	

This review is an amendment to the OCP review for efficacy supplement of NDA 203085 regorafenib for the treatment of patients with hepatocellular carcinoma (HCC) which was submitted into DARRTS on April 6th, 2017. The section below is an amended version which corrects the number of patients with various degrees of hepatic impairment in section 2.4 Summary of Labeling Recommendations in the original OCP review.

2.4 Summary of Labeling Recommendations (Amended)

The office of Clinical Pharmacology recommends the following labeling language with regard to hepatic impairment in section 12:

"Based on a population pharmacokinetic analysis, no clinically important differences in the mean total exposure of regorafenib, including M-2 and M-5, were noted amongst patients with normal liver function (total bilirubin and AST ≤ ULN, n=744), mild hepatic impairment (total bilirubin ≤ ULN and AST >ULN or total bilirubin >ULN to ≤1.5x ULN, n=437), and moderate hepatic impairment (total bilirubin >1.5x to ≤3x ULN and any AST, n=36). The pooled analysis included 391 patients with HCC of whom 116, 249, and 26 were categorized as having normal liver function, mild, and moderate hepatic impairment, respectively. The pharmacokinetics of regorafenib were not evaluated in patients with severe hepatic impairment (total bilirubin >3x ULN)."

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/s/

YOUWEI N BI
05/15/2017

VADRYN PIERRE
05/15/2017

JIANG LIU
05/15/2017

JEANNE FOURIE ZIRKELBACH
05/16/2017

Office of Clinical Pharmacology Review

NDA or BLA Number	NDA 203085
Link to EDR	\\CDSESUB1\evsprod\NDA203085
Submission Date	October 30, 2016
Submission Type	Priority
Brand Name	Stivarga
Generic Name	Regorafenib
Dosage Form and Strength	40 mg tablets
Route of Administration	Oral
Proposed Indication	Treatment of patients with Hepatocellular carcinoma (HCC) who have been previously treated with (b) (4)
Applicant	Bayer
Associated IND	IND 075642, (b) (4)
OCP Review Team	Youwei Bi, Ph.D.; Vadryn Pierre, Ph.D.; Jiang Liu, Ph.D.; Jeanne Fourie Zirkelbach, Ph.D.
OCP Final Signatory	

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1. EXECUTIVE SUMMARY

The applicant submitted an efficacy supplement to support the approval of regorafenib for the treatment of patients with hepatocellular carcinoma (HCC) who have been previously treated with (b) (4)

To support the efficacy of regorafenib in the proposed HCC indication the applicant submitted results from trial 15982, entitled: "A randomized, double-blind, placebo-controlled, multicenter study to evaluate efficacy and safety of regorafenib in HCC patients who had previously failed sorafenib". The trial included 573 subjects stratified by geographical region [Asia, ROW (rest of the world)], ECOG status [0 vs 1], AFP levels (<400 ng/mL vs ≥400 ng/mL), presence of extrahepatic disease, and presence of macrovascular invasion). Patients were randomized in a 2:1 ratio to treatment with regorafenib (n=379) or placebo (n=194). The study met its primary endpoint as demonstrated by a statically significant improvement in median overall survival (OS) for patients treated with regorafenib, 10.1 months (95% CI: 9.1, 12.1) compared to those treated with placebo 7.8 months (95% CI: 6.3, 8.3); [Hazard Ratio (HR) 0.63 (95% CI: 0.50, 0.79) (p-value=0.000020)]. Notably, the proposed dosage regimen for the proposed indication is acceptable based on the clinical pharmacology properties of regorafenib and efficacy data from trial 15982.

Based on the population pharmacokinetic post-hoc analysis, no clinically important differences in the mean total exposure of regorafenib, including M2 and M5, were noted amongst patients with mild tomoderate hepatic impairment, or those with normal liver function according to NCI criteria for organ impairment. Regorafenib is not recommended for use in patients with severe hepatic impairment defined by total bilirubin >3x ULN or Child-Pugh C as it has not been studied in this population. No conclusive exposure-response relationships were identified between regorafenib exposure and relevant efficacy and safety data.

1.1 Recommendations

The Office of Clinical Pharmacology Divisions of Clinical Pharmacology V and Pharmacometrics have reviewed the information contained in this supplement for NDA 203085. This supplement is approvable from a clinical pharmacology perspective. The key review issues with specific recommendations/ comments are summarized below:

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	The primary evidence of effectiveness comes from a randomized, double-blind, placebo-controlled, multicenter trial (15982 [RESORCE]).
General dosing instructions	The recommended dose for regorafenib is 160 mg orally once daily with a light-fat meal for 21 consecutive days followed by 7 days off treatment in a complete cycle of 28 days.
Dosing in patient subgroups (intrinsic and extrinsic factors)	No dose individualization is recommended based on intrinsic factors. An appropriate dose has not been established for patients with severe hepatic impairment defined as total bilirubin >3x ULN or Child-Pugh C.

Labeling	Generally acceptable. The review team has specific content and formatting change recommendations.
Bridge between the to-be-marketed and clinical trial formulations	Not applicable. To-be-marketed formulation was used in clinical trials.
Other (specify)	Not applicable.

1.2 Post-Marketing Requirements and Commitments

Not applicable

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

Regorafenib is an oral multi-kinase inhibitor. An extensive summary of pharmacokinetics, relative bioavailability, food effect, dose-linearity, metabolism, excretion and drug interactions of regorafenib and its metabolites is provided in clinical pharmacology review for the original NDA 203085 submission (Reference ID: 3182650).

In brief, regorafenib undergoes extensive and complex biotransformation. The primary metabolism pathway of regorafenib involves both CYP3A4 and UGT1A9. Following a single oral administration of radiolabeled regorafenib, approximately 47% (24% as metabolite) and 19% (17% as glucuronides) of the dose was excreted as unchanged regorafenib in feces and urine, respectively. The active metabolites of regorafenib, M2 and M5, have demonstrated in vitro pharmacologic activity similar to that of parent regorafenib. The mean elimination $T_{1/2}$ for regorafenib, M2, and M5 was 28, 25, and 51 hrs, respectively.

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

The recommended dosing regimen for regorafenib is 160 mg orally once daily with a light-fat meal for 21 consecutive days followed by 7 days off treatment in a complete cycle of 28 days. Regorafenib is available as 40 mg film-coated tablets.

2.2.2 Therapeutic individualization

Hepatic Impairment

The pharmacokinetics of regorafenib, M-2, and M-5 were evaluated in 14 patients with hepatocellular carcinoma (HCC) and mild hepatic impairment (Child-Pugh A); 4 patients with HCC and moderate hepatic impairment (Child-Pugh B); and 10 patients with solid tumors and normal hepatic function after the administration of a single 100 mg dose of regorafenib. No clinically important differences in the mean

exposure of regorafenib, M-2, or M-5 were observed in patients with mild or moderate hepatic impairment compared to the patients with normal hepatic function.
Based on a population pharmacokinetic post-hoc analysis, no clinically important differences in the mean total exposure of regorafenib, including M2 and M5, were noted amongst patients with normal liver function (n=36), mild hepatic impairment (n=744), and moderate hepatic impairment (n=437) according to NCI criteria. The pharmacokinetics of regorafenib were not evaluated in patients with severe hepatic impairment defined as total bilirubin >3x ULN or Child-Pugh C.

Drug-Drug Interactions

In brief, the concomitant use of regorafenib with strong CYP3A4 inducers or strong CYP3A4 inhibitors should be avoided.

2.3 Outstanding Issues

Not applicable

2.4 Summary of Labeling Recommendations

The office of Clinical Pharmacology recommends the following labeling language with regard to hepatic impairment in section 12:

"Based on a population pharmacokinetic analysis, no clinically important differences in the mean total exposure of regorafenib, including M2 and M5, were noted amongst patients with normal liver function (total bilirubin and AST ≤ ULN, n=(b) (4)), mild hepatic impairment (total bilirubin ≤ ULN and AST >ULN, or total bilirubin >ULN to ≤1.5x ULN, n=(b) (4), and moderate hepatic impairment (total bilirubin >1.5x to ≤3x ULN, and any AST, n=(b) (4)). The pooled analysis included (b) (4) patients with HCC of which (b) (4) and (b) (4) were categorized as having normal liver function, mild, and moderate hepatic impairment, respectively. The pharmacokinetics of regorafenib were not evaluated in patients with hepatic impairment severity (total bilirubin >3x ULN)."

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

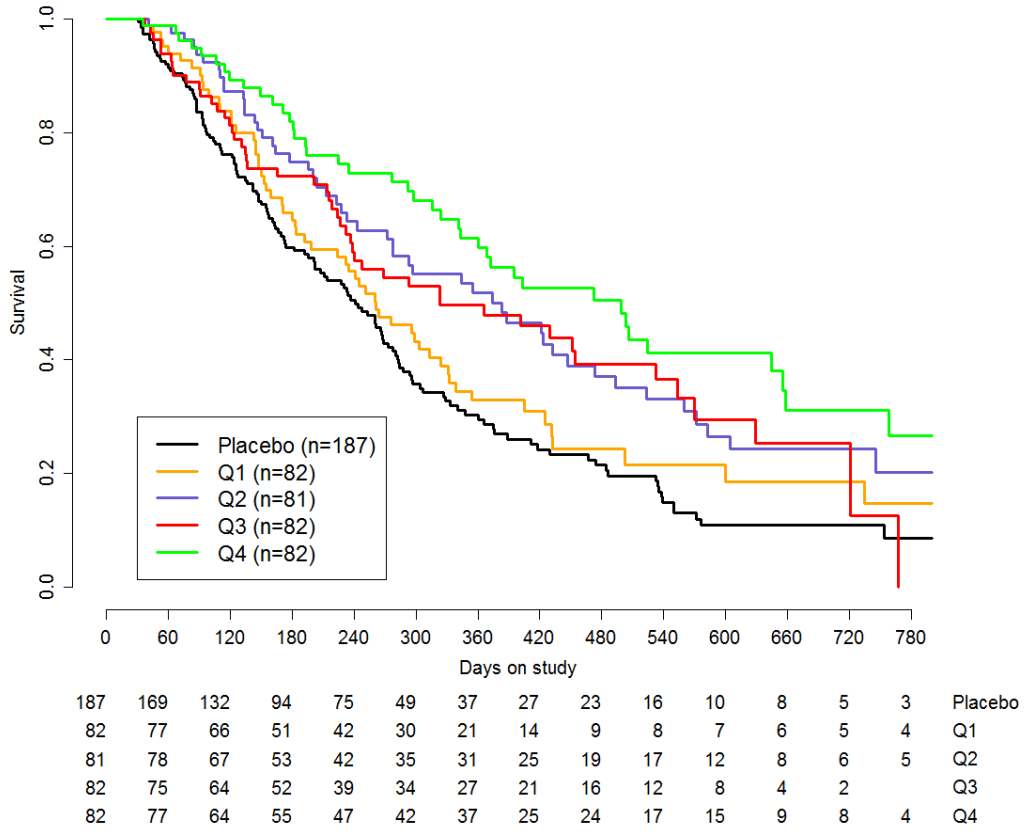
3.1 Clinical Pharmacology Review Questions

3.1.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

To support the efficacy of regorafenib in the proposed HCC indication the applicant submitted results from trial 15982. A statically significant OS benefit was identified for regorafenib with a HR of 0.63 (95% CI: 0.50, 0.79) (P-value=0.000020). The median OS was 10.6 months (95% CI 9.1, 12.1) in the regorafenib group compared to 7.8 months (95% CI 6.3, 8.8) in the placebo group. In addition, a treatment effect in favor of the regorafenib group with respect to the secondary endpoint of progression-free survival (PFS) was also identified with a HR of 0.46 (95% CI: 0.37. 0.56) (p-value<0.0001) using mRECIST criteria.

Exposure-response (E-R) relationships were explored between the selected exposure metric, average exposure of parent regorafenib in cycle 1 (CAVD28), and overall survival for study 15982. The univariate Kaplan Meier plot for the CAVD28 exposure quartiles and placebo for OS is shown in Figure 1. There appears to be a trend of shorter OS in patients with lower average exposure in cycle 1 (CAVD28) compared to patients with medium to high average exposure. Of note, the median overall survival in the low exposure group was numerically better when compared to patients receiving placebo. However, a strong association was not observed between OS and CAD28 in regorafenib-treated patients with a mortality HR equal to 0.984 (95%CI: 0.965, 1.004) based on a multivariate cox regression model adjusted for significant baseline covariates (ECOG status, baseline AFP value and baseline AST/ALT values). As a result, no evident and conclusive E-R relationship was identified between regorafenib exposure and overall survival.

Figure 1: (Univariate) Kaplan-Meier Curves for OS stratified by CAVD28 exposure quartiles and Placebo.



3.1.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

The proposed dosage of regorafenib is 160 mg once daily for 21 consecutive days followed by 7 days off treatment in a complete cycle of 28 days. As discussed in the section 3.3.1, according to trial 15982 the

proposed dosage appears to be effective with acceptable safety in patients with HCC who have been previously treated with [redacted] (b) (4).

Dose selection for regorafenib in the HCC patients was based on Phase 1, 2, and 3 data for mCRC and GIST indications as well as the Phase 2 study in HCC patients (A51601). The proposed dosage, 160 mg regorafenib once daily for 21 consecutive days followed by 7 days off treatment in a complete cycle of 28 days, was approved for the treatment of mCRC in 2012 and GIST in 2013, respectively. Regorafenib exposures are comparable across different trials and different indications.

The geometric mean average exposure to free aggregate, sum of the free molar concentrations of regorafenib and its metabolites M2 and M5, during first 2 cycles was about 20 nM, which is higher than the IC_{80} (16 nM) of regorafenib and M2 for VEGF receptors. The median exposure during cycle 1 in the low exposure group (<1st quartile) of free aggregate (13.4 nM) is only slightly lower than IC_{80} but still well above the IC_{50} (4 nM). The observed exposure data for regorafenib and its two metabolites suggest that a dose of 160 mg once daily result in systemic exposure of regorafenib that is able to inhibit the VEGF receptors in in vitro studies.

Exposure-safety reltionships for regorafenib were evaluated for incidence rate of overall TEAEs, incidence rate of TEAE of special interest (Hypertension, Diarrhea, Fatigue and HFSR) and laboratory abnormalities (AST, ALT, bilirubin and platelet). Overall, no consistent and conclusive exposure-dependent relationships were identified between regorafenib exposure and the above mentioned safety data explored in the E-R analysis.

In summary, the proposed dosage, 160 mg regorafenib once daily for 21 consecutive days followed by 7 days off treatment in a complete cycle of 28 days, appears to be appropriate in patients with HCC who have been previously treated with [redacted] (b) (4) based on the efficacy and safety data in a trial 15982. The selected dose was further supported by the evidence of effectiveness in the approved indications of mCRC and GIST. No evident and conclusive exposure-response relationships were identified for both efficacy and safety. However, there appears to be a trend for shorter OS in patients within the low exposure group.

3.2.3 Is an alternative dosing regimen and/or management strategy required for subpopulations based on intrinsic factors?

A post-hoc population PK analysis showed that there are no clinically relevant effects of intrinsic factors on the systematic exposure of regorafenib and its metabolites. No dose adjustment based on intrinsic factors is needed.

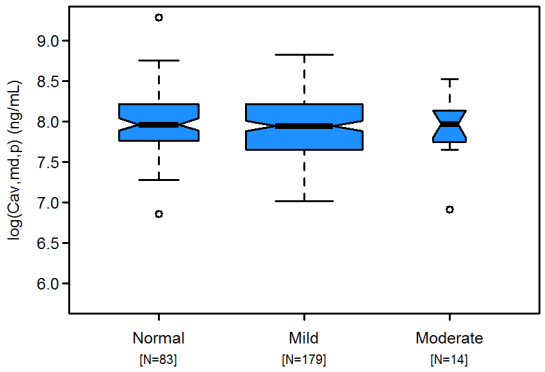
Hepatic impairment:

NCI criteria

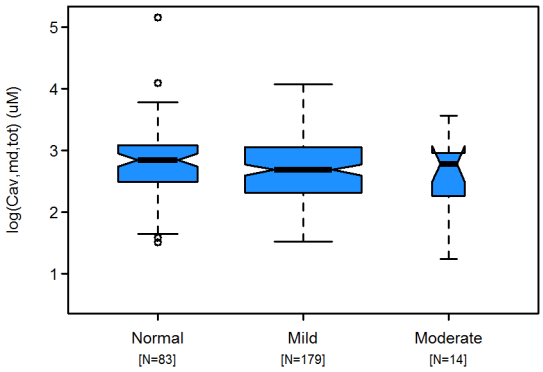
Among 1276 subjects from 16 clinical studies, 830, 413 and 33 subjects have normal, mild and moderate hepatic impairment based on NCI criteria [mild: total bilirubin less than or equal to upper limit of normal (ULN) and AST greater than ULN or total bilirubin between 1.0 to 1.5 times ULN and any AST, moderate: total bilirubin between 1.5 to 3 times ULN and any AST]. Overall, no influence of mild and moderate hepatic impairment at the start of treatment was observed on parent and total regorafenib exposure

(Figure 2). The pharmacokinetics of regorafenib have not been studied in patients with severe hepatic impairment [severe: total bilirubin greater than 3 times ULN and any AST].

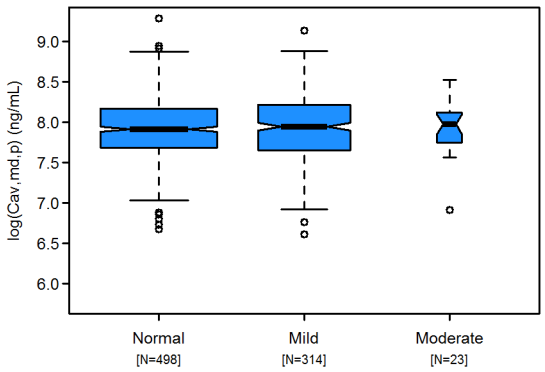
Figure 2: Comparison of Distribution of Parent Nominal Exposure (Cav,md,p) (Left) and Total Nominal Exposure (Cav,md,tot) (Right) across Different Levels of Liver Impairment (NCI criteria) at Start of Treatment within RESORCE (Top) ,Phase III Studies (Middle) and all studies (Bottom).



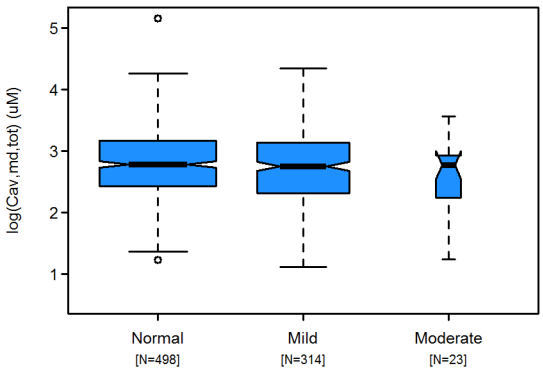
(**A**) Parent nominal exposure (*Cav,md,p*) in RESORCE



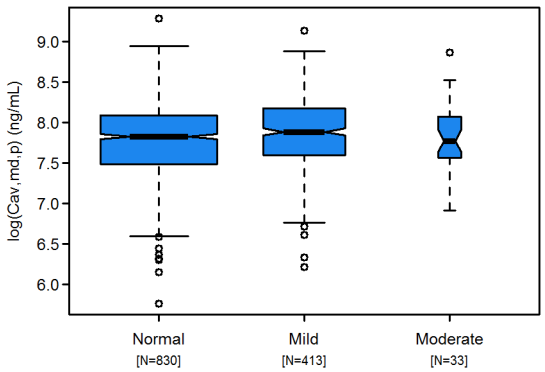
(**B**) Total nominal exposure (*Cav,md,tot*) in RESORCE



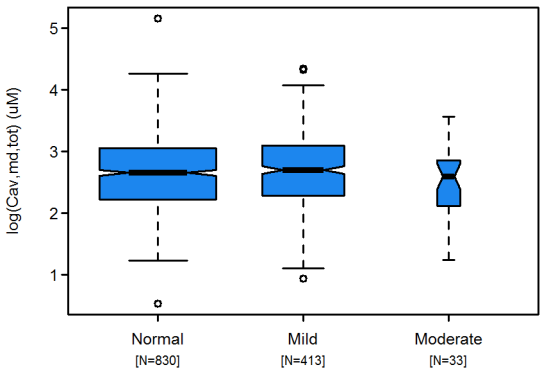
(**C**) Parent nominal exposure (*Cav,md,p*) in Phase III studies



(**D**) Total nominal exposure (*Cav,md,tot*) in Phase III studies



(**E**) Parent nominal exposure (*Cav,md,p*) in all studies

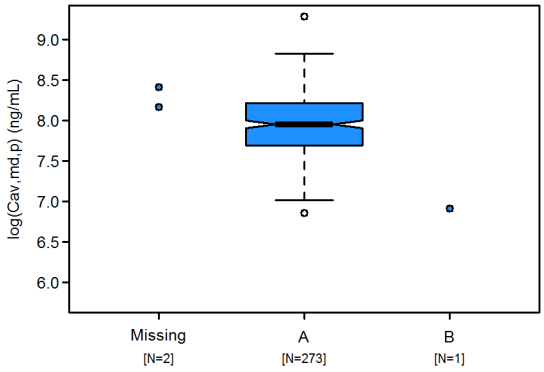


(**F**) Total nominal exposure (*Cav,md,tot*) in all studies

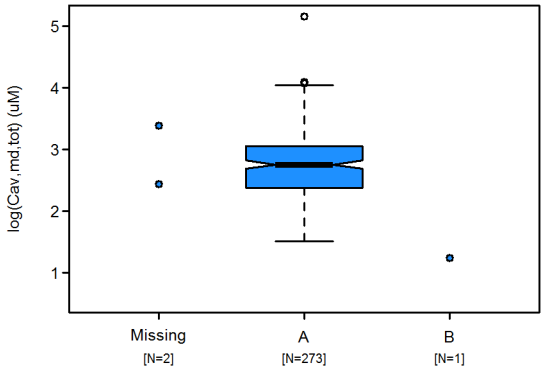
Child-Pugh score

The parent and total nominal exposures of subjects with Child-Pugh score level B are comparable to those with Child-Pugh score level A (Figure 3). However, this comparison is limited by the low number of subjects with Child-Pugh score B (n=1 in RESORCE study and n=5 in HCC studies). The pharmacokinetics of regorafenib have not been studied in patients with severe hepatic impairment (Child-Pugh C).

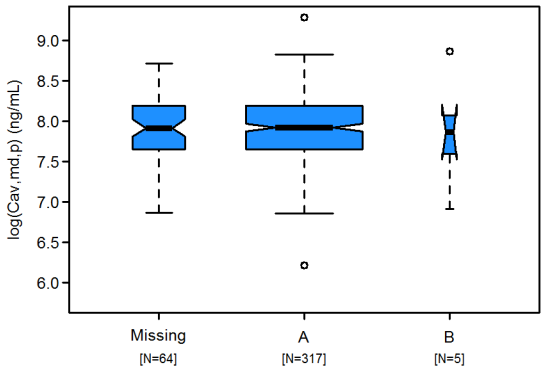
Figure 3: Comparison of Distribution of Parent Nominal Exposure (Cav,md,p) (Left) and Total Nominal Exposure (Cav,md,tot) (Right) across Different Levels of the Child Pugh Score at Start of Treatment within RESORCE (Top) and All HCC Studies (Bottom).



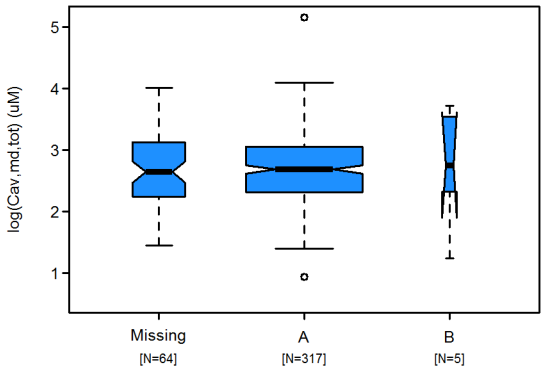
(**A**) Parent nominal exposure (*Cav,md,p*) in RESORCE



(**B**) Total nominal exposure (*Cav,md,tot*) in RESORCE



(**C**) Parent nominal exposure (*Cav,md,p*) in HCC studies



(**D**) Total nominal exposure (*Cav,md,tot*) in HCC studies

Source: Applicant's population pharmacokinetic report, Page 51, Figure 7.2:16

Ethnic groups:

In general, individual parent regorafenib and total exposures in patients with Asian race were comparable to exposures in patients with non-Asian race. No difference in exposure was observed among Japanese, Chinese and non-Asian patients. However, Asian patients being treated outside of Japan and China showed a trend of lower exposures compared to the other populations.

Other intrinsic factors:

The influence of covariates on the parent nominal exposure of regorafenib (Cav,md,p) was further investigated using a stepwise generalized additive modeling approach. The following covariates were

found to significantly influence regorafenib exposure: patient type, age, sex, BMI (body mass index), HB0 (baseline hemoglobin) and ALB0 (baseline albumin). However, the magnitude of the predicted changes in regorafenib exposure impacted by these significant covariates was considered small when compared to the overall observed variability, and no dose adjustment based on these covariates is needed.

4. APPENDICES

4.1 Population PK and/or PD Analyses

4.1.1 Introduction

Regorafenib is multi kinase inhibitor that inhibits tumor growth by suppressing tumor cell proliferation and tumor angiogenesis. Regorafenib has two active metabolites, M2 (BAY 75-7495) and M5 (BAY 81-8752), which were shown to have similar pharmacologic activity to parent drug in in vitro and in vivo studies.

In the previous submission for regorafenib, a population PK model was developed that described the concentration-time profiles of regorafenib, M-2, and M-5 in a pooled dataset of 14 sparsely and densely sampled Phase 1, 2 and 3 studies.

This established integrated PK model was applied to the sparsely sampled PK data from the RESORCE study (trial 15982 for HCC indication) in order to calculate the individual exposure estimates, and conduct a covariate analysis of parent and total nominal exposure in the combined dataset of 16 clinical trials.

4.1.1.1 Established Population PK Model for Regorafenib and its Metabolites

The final integrated model for regorafenib is characterized by first order absorption followed by a two compartmental disposition. M2 is formed in a concentration-dependent, non-linear manner from parent and follows a two-compartmental disposition. M5 is generated from M2 in a concentration-dependent, non-linear manner and also has a two-compartmental disposition. The structure for the final Pop-PK model is shown schematically in Figure 4.

Figure 4: Schematic Representation of the PK Models of Regorafenib, M2 and M5.

Source: Sponsor's Pop-PK report R-8931 page 77 Figure 8:1

4.1.2 Application and Results

4.1.2.1 Estimation of individual exposure of regorafenib and its metabolites - 80% dataset

The developed population PK model was applied to fit 2534 observations (846 parent, 828 M2 and 860 M5 observations, respectively) from 276 subjects available from an intermediate analysis dataset consisting of 80% of the total PK samples from Phase III study 15982 (RESORCE) in order to calculate the following individual exposure metrics:

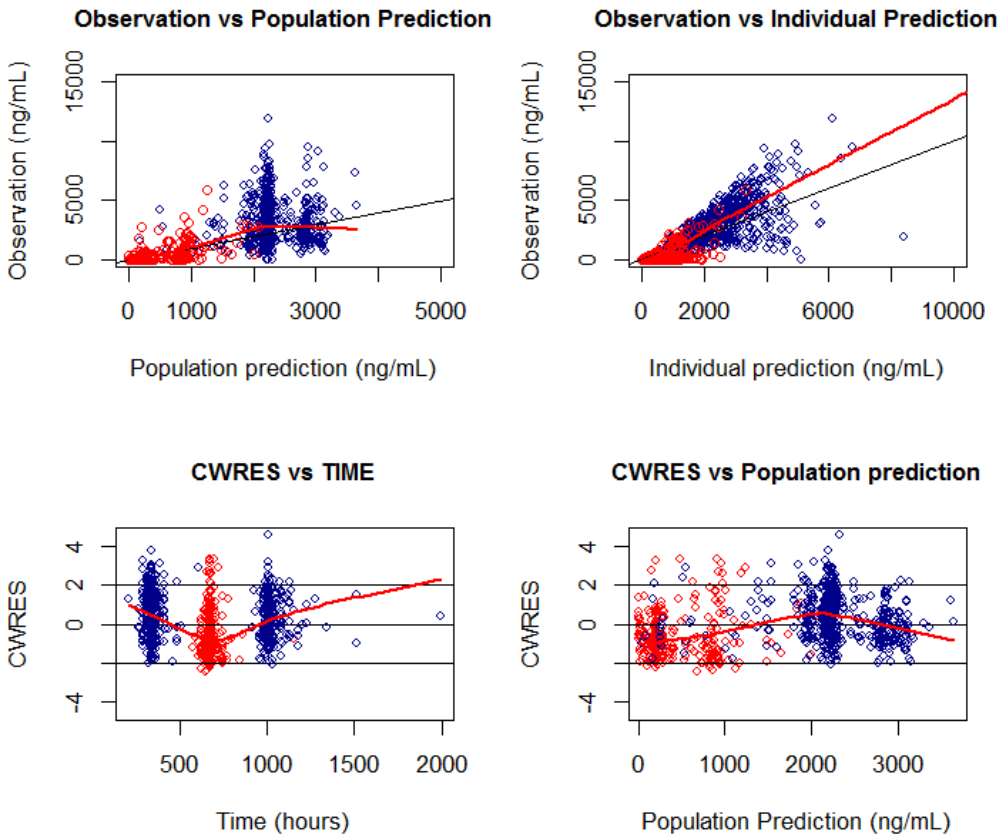
a) Parent, M2, M5, and total average concentration over the first 24 hours after treatment start following actual dosing (Cav(0-24h),sd,p, Cav(0-24h),sd,m2, Cav(0-24h),sd,m5, Cav(0-24h),sd,tot)
b) Parent, M2, M5, and total average concentration over 24 h after 21 days of nominal dosing (160 mg QD) (Cav,md,p, Cav,md,m2, Cav,md,m5, Cav,md,tot)
c) Parent, M-2, M-5, and total average concentration over the first 28 days after treatment start following actual dosing (3 weeks on/1 week off schedule) (Cav(0-28d),md,p, Cav(0-28d),md,m2, Cav(0-28d),md,m5, Cav(0-28d),md,tot)
d) Parent, M-2, M-5, and total average concentration over the first 56 days after treatment start following actual dosing (3 weeks on/1 week off schedule) (Cav(0-56d),md,p, Cav(0-56d),md,m2, Cav(0-56d),md,m5, Cav(0-56d),md,tot)

Goodness-of-fit plots (Figure 5 - Figure 7) and prediction-corrected visual predicted check (Figure 8) showed the previously developed model adequately described the steady-state concentrations of regorafenib and its two metabolites, but bias was shown in the predictions of non-steady-state concentrations such as observations sampled in cycle 2 day 1. The impact of biased predictions at cycle 2 day 1 visit on the calculation of individual exposure metrics was evaluated by fitting the integrated model to the data including and excluding those observations. The comparison of the parent and total nominal exposure (Cav,md,p and Cav,md,tot) obtained including and excluding cycle 2 day 1 observations was shown in Figure 9. In general, the observations in cycle 2 day 1 had no influential impact on the estimates of parent and total nominal exposure.

Reviewer's comments:

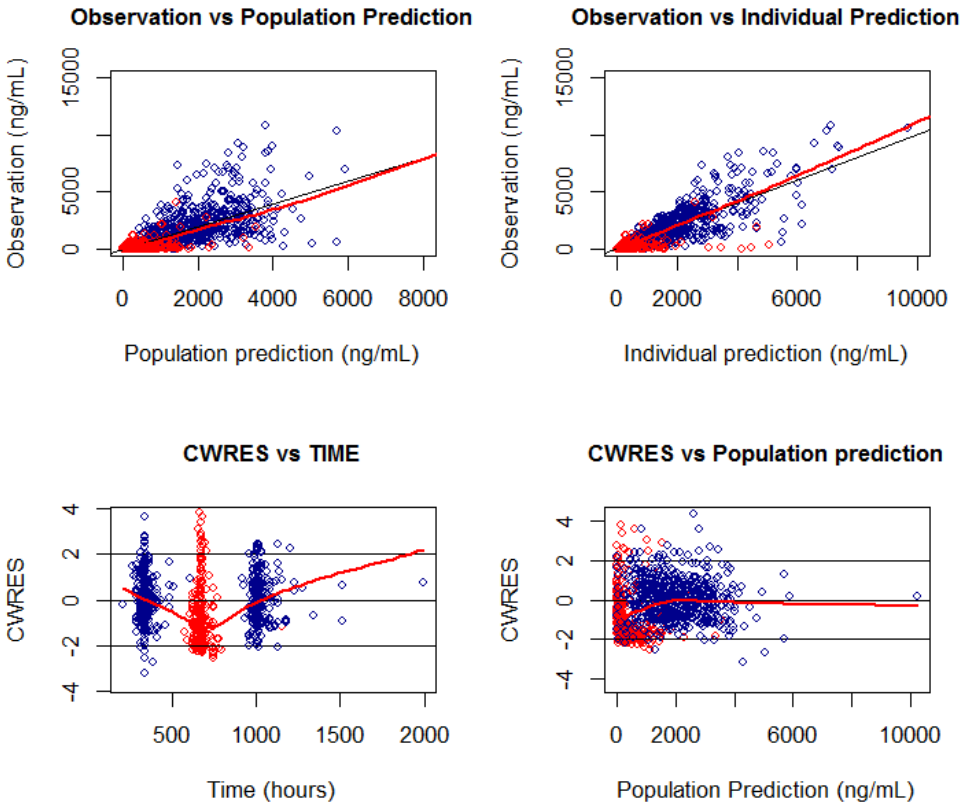
The reviewer agrees that goodness-of-fit plots and simulation-based diagnostics (pc-VPC) showed that the prior integrated Pop-PK model adequately described the steady-state concentrations of regorafenib and its two metabolites M2 and M5, and a bias was shown in the predictions of non-steady-state concentrations (e.g. Cycle 2 Day 1). However, by comparing the parent and total nominal exposure (Cav,md,p and Cav,md,tot) obtained including and excluding cycle 2 day 1 observations, the reviewer agrees that these observations had no influential impact on the estimates of individual exposure metrics.

Figure 5: Goodness-of-fit Plots of Regorafenib from Prior Pop-PK Model.



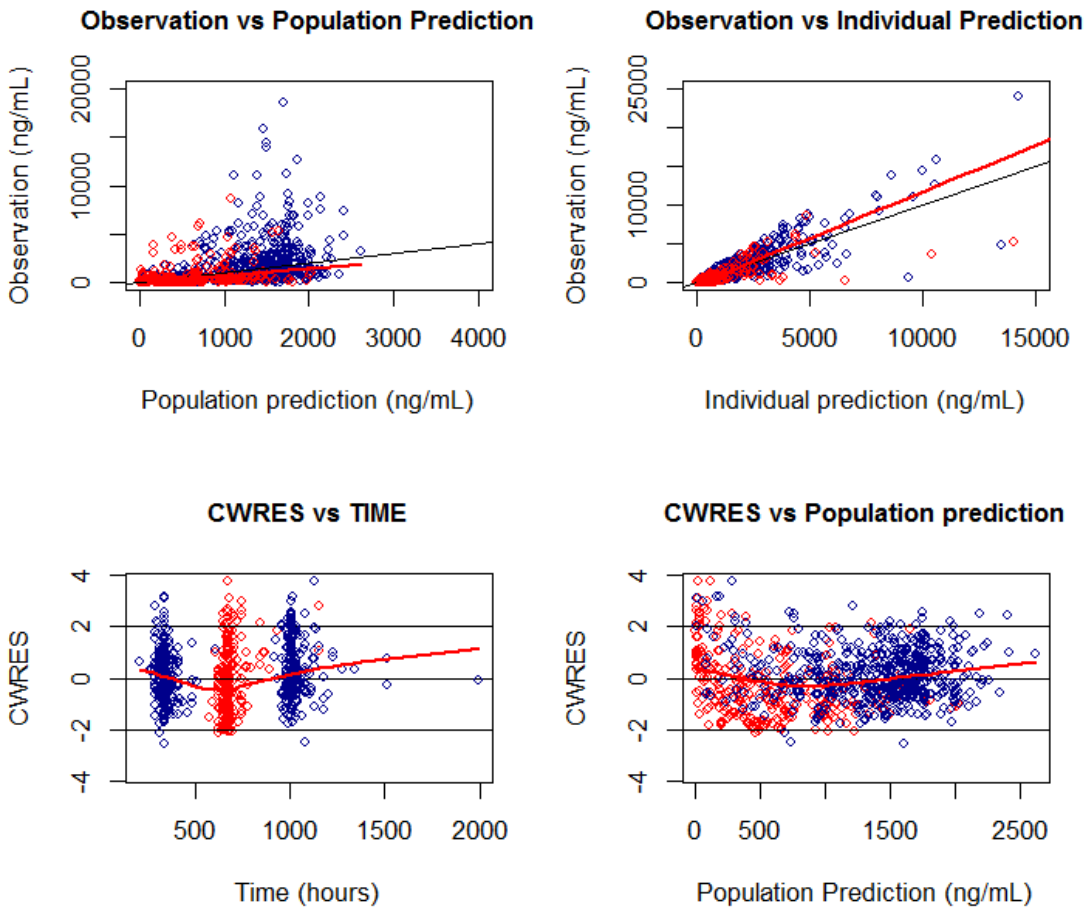
DV: Observations; PRED: Population Predictions; IPRED: Individual Predictions; CWRES: Conditional Weighted Residuals. Blue dots: steady-state concentrations. Red dots: non steady-state concentrations. Red solid line: Loess smooth through data.

Figure 6: Goodness-of-fit Plots of Metabolite M2 from Prior Pop-PK Model.



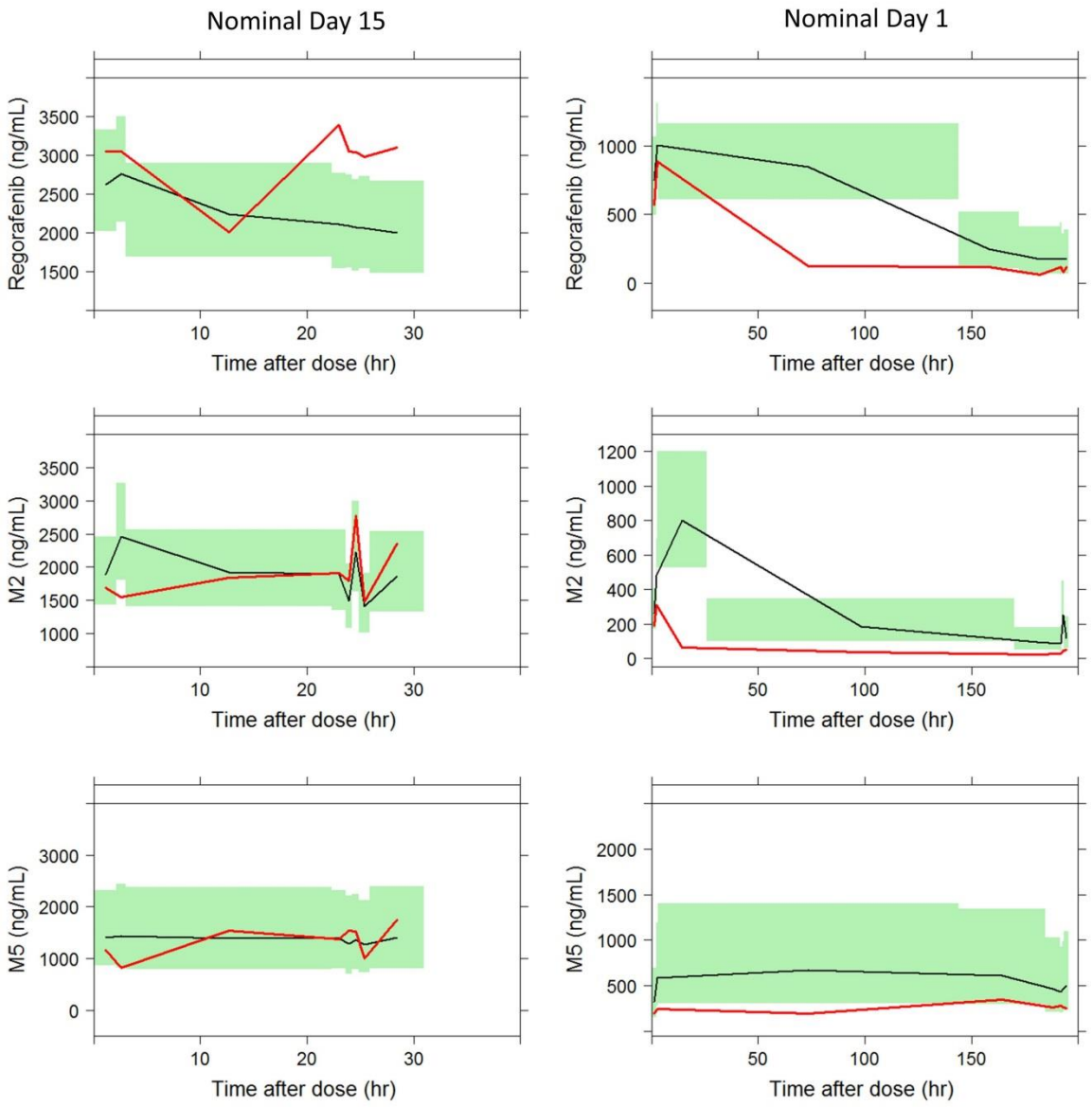
DV: Observations; PRED: Population Predictions; IPRED: Individual Predictions; CWRES: Conditional Weighted Residuals. Blue dots: steady-state concentrations. Red dots: non steady-state concentrations. Red solid line: Loess smooth through data.

Figure 7: Goodness-of-fit Plots of Metabolite M5 from Prior Pop-PK Model.



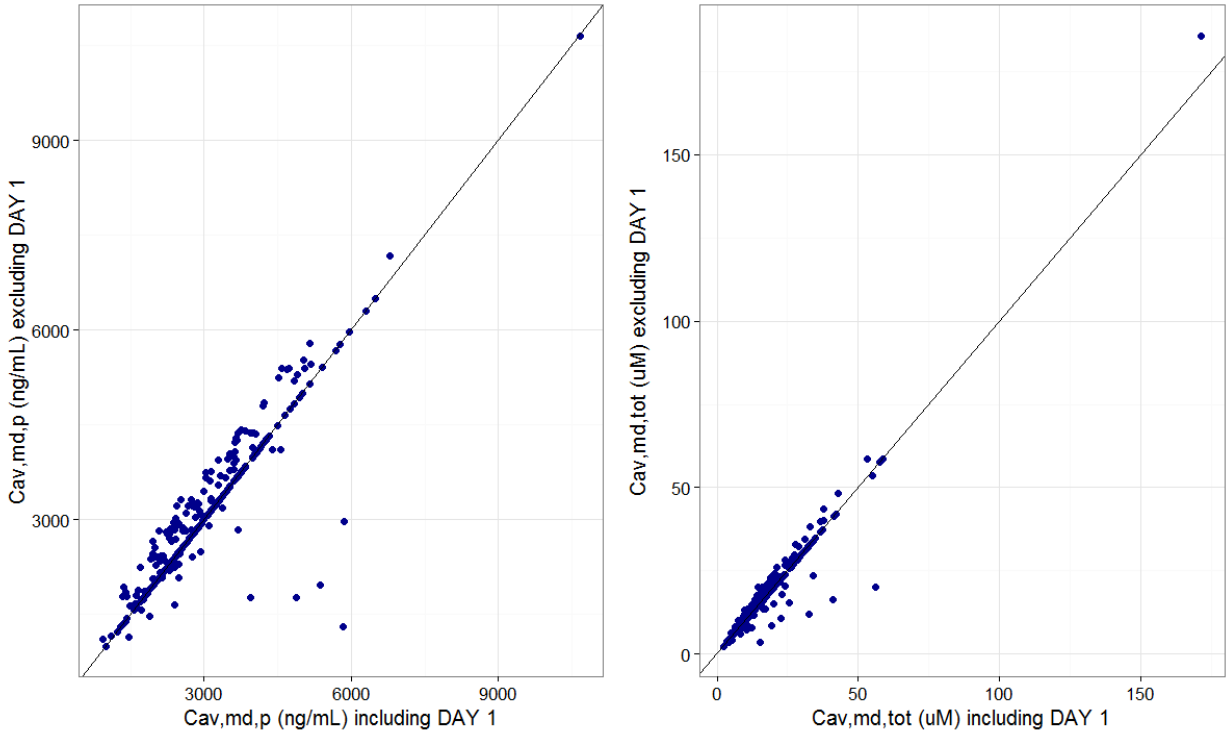
DV: Observations; PRED: Population Predictions; IPRED: Individual Predictions; CWRES: Conditional Weighted Residuals. Blue dots: steady-state concentrations. Red dots: non steady-state concentrations. Red solid line: Loess smooth through data.

Figure 8: Prediction-Corrected Visual Predictive Check for Regorafenib, M2 and M5 on Nominal Day 1 and 15



Red solid lines are median percentiles for observed data. Black solid lines are median percentiles for simulated data. Green area is the 95% confidence interval (CI) around the simulated median.

Figure 9: Comparison of Parent and Total Nominal Exposure (Cav,md,p and Cav,md,tot) obtained including and excluding cycle 2 day 1 visit observations.



4.1.2.2 Covariate analysis - 80% dataset

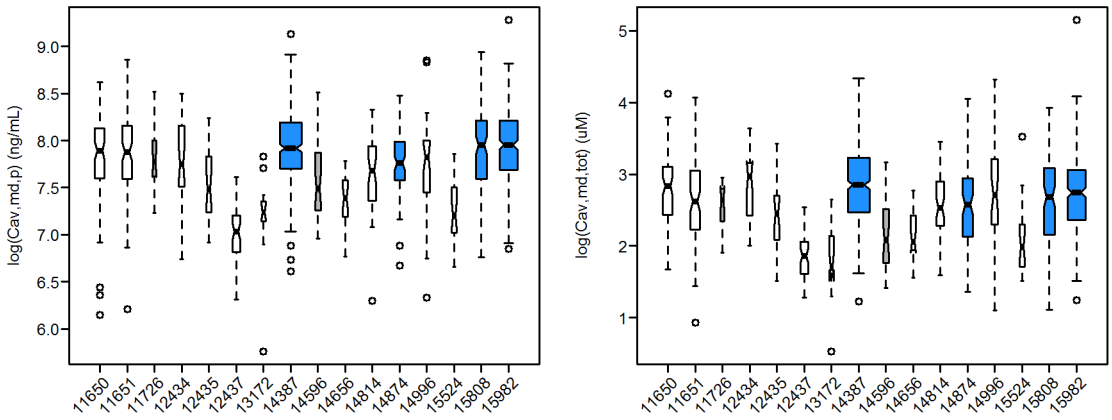
4.1.2.2.1 Graphical evaluation of individual exposure metrics

The dataset used for the covariate analysis consisted of parent and total nominal exposure (Cav,md,p and Cav,md,tot) and the covariates of 1276 subjects from 16 clinical regorafenib trials. The graphical exploration of covariates and subpopulations with respect to parent and total nominal exposure is described below.

Study population

Overall, the individual estimates of parent and total nominal exposure in study 15982 largely overlapped with those of the other studies including earlier Phase 3 studies (Figure 10). Among all studies there are no studies that stand out with clear higher than average exposure.

Figure 10: Distribution of Parent Nominal Exposure (Cav,md,p) (Left) and Total Nominal Exposure (Cav,md,tot) (Right) in All Studies.

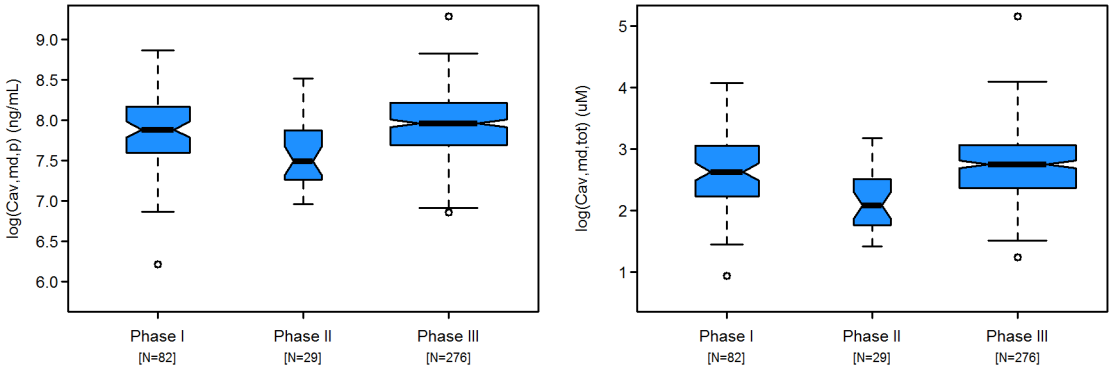


White: phase I studies, grey: phase II studies, blue: phase III; Whiskers (Black bars): Range between the lowest observation still within 1.5 x the interquartile range (IQR) of the lower quartile and the highest observation still within 1.5 x interquartile range (IQR) of the upper quartile. Box: Range between lower and upper quartile. Notches: 95% confidence interval of the median. Black horizontal line: Median. Grey dots: Outliers (individual values outside of whiskers), blue dots: individual observations.

Hepatocellular cancer (HCC)

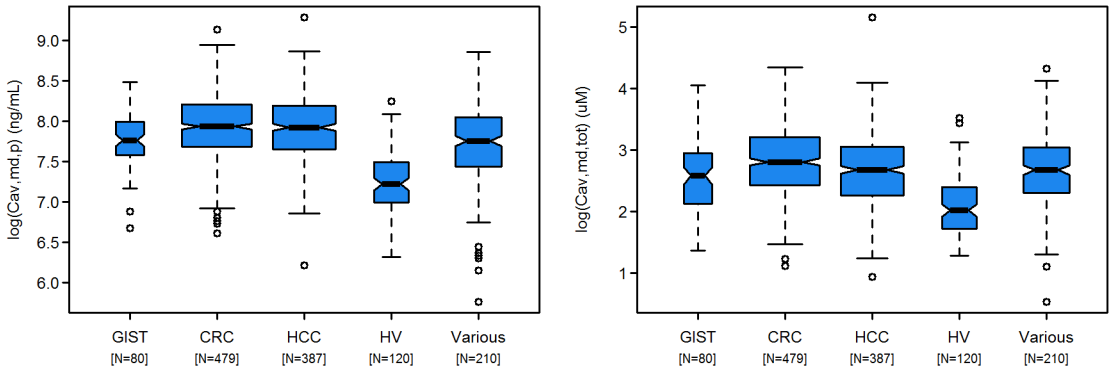
The individual estimates of parent and total nominal exposure is comparable in patients with HCC across Phase 1, 2 and 3 studies (Figure 11). Individual parent and total exposures in patients with HCC are comparable to those from patients with colorectal cancer (CRC), while they are slightly higher than those in patients with gastrointestinal solid tumor (GIST) as previously reported (Figure 12). Healthy volunteers were found to have lower predicted exposures for parent and total nominal exposure than patients.

Figure 11: Distribution of Cav,md,p (Left) and Cav,md,tot (Right) in HCC Patients across Phase I, Phase II and Phase III studies.



Source: Applicant's population pharmacokinetic report, Page 48, Figure 7.2:12

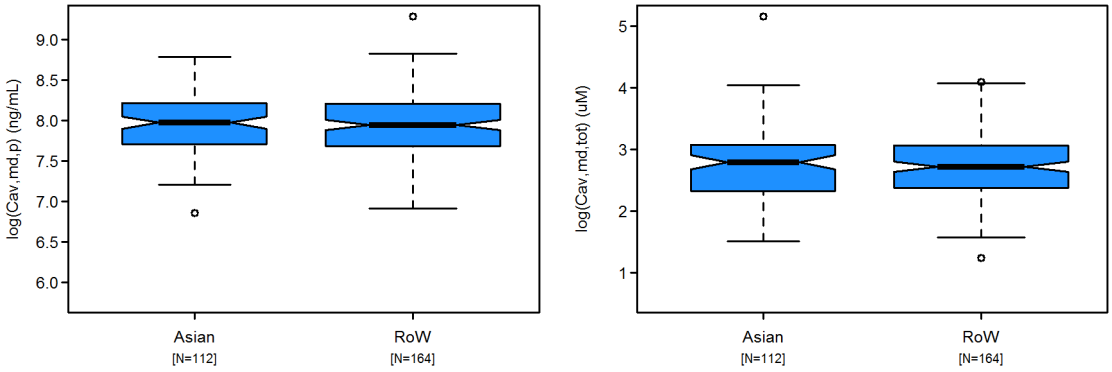
Figure 12: Distribution of Parent Nominal Exposure (Cav,md,p) (Left) and Total Nominal Exposure (Cav,md,tot) (Right) across patients with GIST, CRC, HCC and healthy volunteers.



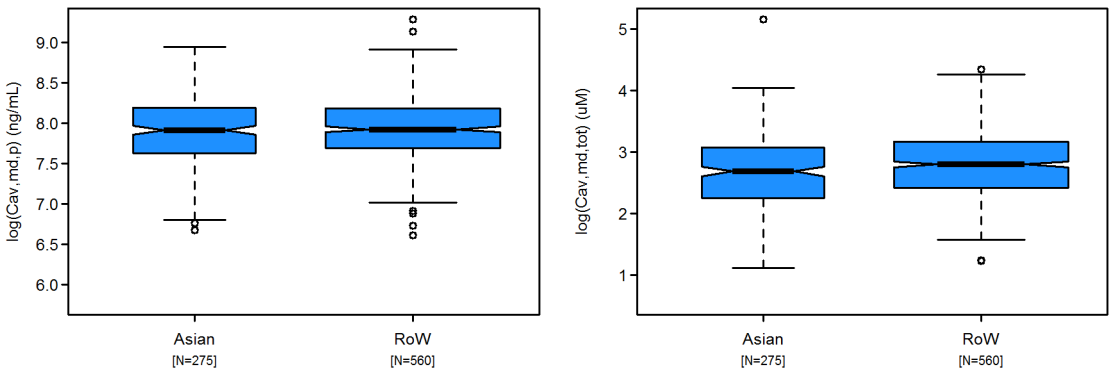
Ethnic groups

In general, individual parent and total exposures in patients with Asian race were comparable to exposures in patients with non-Asian race (Figure 13). No difference in exposure was observed among Japanese, Chinese and non-Asian patients (Figure 14). However, Asian patients being treated outside of Japan and China showed a trend of lower exposures compared to the other populations.

Figure 13: Distribution of Parent Nominal Exposure (Cav,md,p) (Left) and Total Nominal Exposure (Cav,md,tot) (Right) in Asian and non-Asian Subjects of RESORCE (top) and Phase III Studies (Bottom).



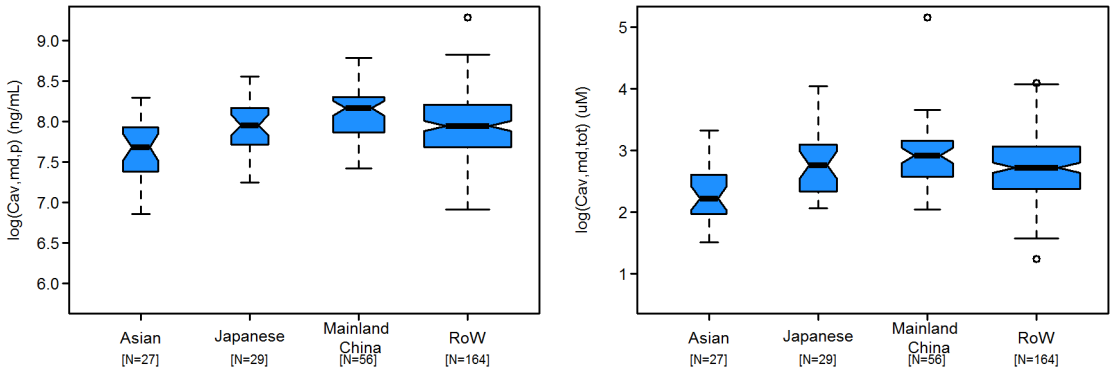
(**A**) Parent nominal exposure (*Cav,md,p*) in RESORCE (**B**) Total nominal exposure (*Cav,md,tot*) in RESORCE



(**C**) Parent nominal exposure (*Cav,md,p*) in phase III studies (**D**) Total nominal exposure (*Cav,md,tot*) in phase III studies

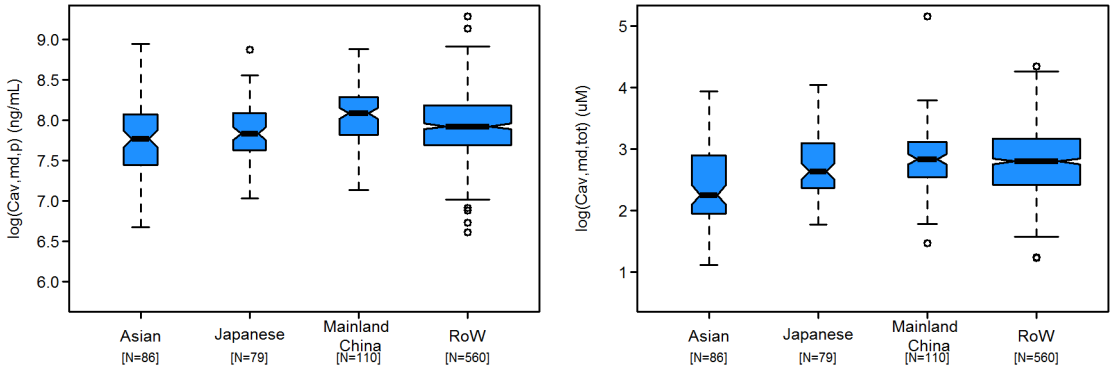
Source: Applicant's population pharmacokinetic report, Page 48, Figure 7.2:13

Figure 14: Distribution of Parent Nominal Exposure (Cav,md,p) (Left) and Total Nominal Exposure (Cav,md,tot) (Right) in Asian, Japanese, Chinese and Others of RESORCE (top) and phase III studies (bottom).



(**A**) Parent nominal exposure (*Cav,md,p*) in RESORCE

(**B**) Total nominal exposure (*Cav,md,tot*) in RESORCE



(**C**) Parent nominal exposure (*Cav,md,p*) in phase III studies (**D**) Total nominal exposure (*Cav,md,tot*) in phase III studies

Source: Applicant's population pharmacokinetic report, Page 49, Figure 7.2:14

Liver impairment

NCI Criteria

Among 1276 subjects from 16 clinical studies, 830 have normal liver funcition, while 413 and 33 subjects have mild and moderate hepatic impairment, respectively, based on NCI criteria [mild: total bilirubin less than or equal to upper limit of normal (ULN) and AST greater than ULN or total bilirubin between 1.0 to 1.5 times ULN and any AST, moderate: total bilirubin between 1.5 to 3 times ULN and any AST]. Overall, no influence of mild and moderate hepatic impairment at the start of treatment was observed on parent and total regorafenib exposures (Figure 2). The pharmacokinetics of regorafenib have not been studied in patients with severe hepatic impairment [severe: total bilirubin greater than 3 times ULN and any AST].

Child-Pugh score

The parent and total nominal exposure of subjects with Child-Pugh score level B is comparable to those with Child-Pugh score level A (Figure 3). However, this comparison is limited by the low number of subjects with Child-Pugh score B (n=1 in RESORCE study and n=5 in HCC studies). The pharmacokinetics of regorafenib have not been studied in patients with severe hepatic impairment (Child-Pugh C).

4.1.2.2.2 Stepwise generalized additive modeling (GAM)

The influence of covariates on the parent nominal exposures of regorafenib (Cav,md,p) were further investigated using a stepwise generalized additive modeling approach. Each potential covariate was first investigated by testing all the models of each individual covariate in the univariate manner. The covariates that resulted in decrease in AIC were carried forward to the stepwise multivariate GAM analysis. The backward deletion approach was then conducted to screen selected covariates. A covariate was kept in the multivariate model if its removal results in an increase in AIC. The following covariates were retained in the final statistical model: patient type, age, sex, BMI (body mass index), HB0 (baseline hemoglobin) and ALB0 (baseline albumin). The resulting parameter estimates are shown in Table 1. Similar modeling procedure was conducted to investigate the influence of covariates on the total nominal exposure (Cav,md,tot). The resulting parameter estimates are shown in Table 2.

Table 1: Parameter Estimates of the Covariate Model of the Log Transformed Parent Nominal Exposure (Cav,md,p)

[a]estimate
[b]estimate

Source: Applicant's population pharmacokinetic report, Page 53, Table 7.2:13

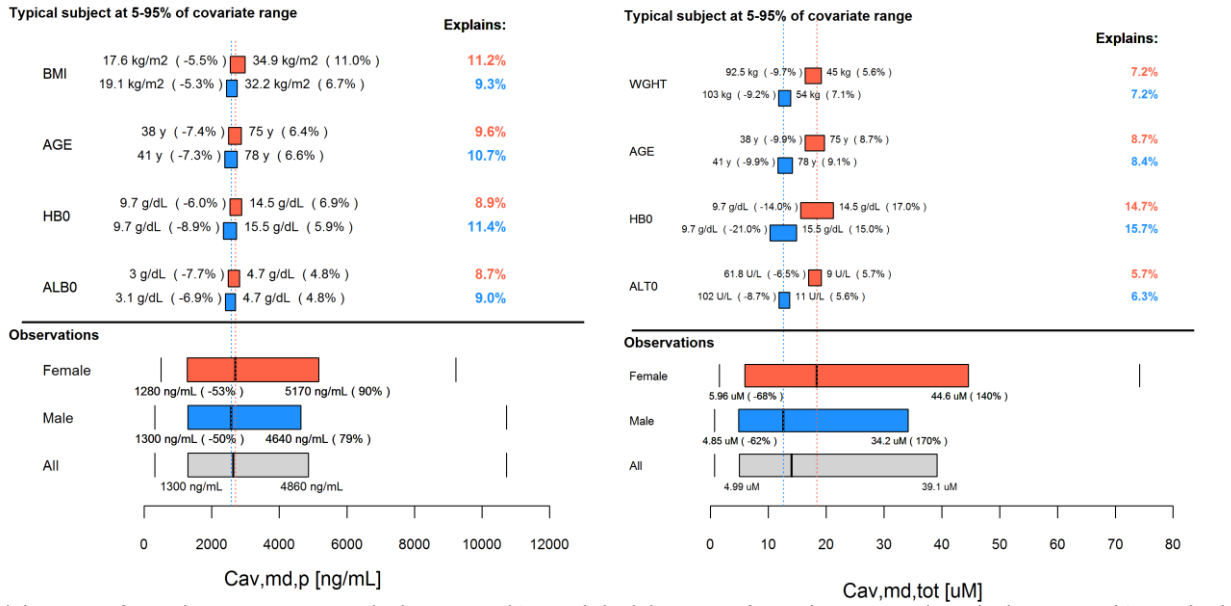
Table 2: Parameter Estimates of the Covariate Model of the Log Transformed Average Concentration over 24h for Parent, M-2 and M-5 (Cav,md,tot)

[a]esti
[b]esti

Source: Applicant's population pharmacokinetic report, Page 54, Table 7.2:14

The clinical relevance of the impact of significant covariates on parent and total nominal exposure was assessed by computing the predicted difference between the regorafenib exposure at the 5th to 95th percentile of the covariate and the exposure at the median of the covariate for males and females separately. The predicted difference was then compared to the overall observed variability in the regorafenib exposure. Simulation results showed that each significant covariate can only explain a small fraction of the exposure variability (up to 11.4% for Cav,md,p and 15.7% for Cav,md,tot) (Figure 15). Therefore, the clinical relevance of the significant covariates on the regorafenib exposure was considered small, and no dose adjustment based on these covariates is needed.

Figure 15: Impact of the Continuous Covariates on the Variability of Parent Nominal Exposure (Cav,md,p) (Left) and Total Nominal Exposure (Cav,md,tot) (right) for Males and Females Separately.



(**A**) Impact of covariates on parent nominal exposure (*Cav,md,p*) (**B**) Impact of covariates on total nominal exposure (*Cav,md,tot*)

Range bars show difference between the 5th to 95th percentile and the median of *Cav,md,p* and *Cav,md,tot* in all cancer patients. Covariate bars show the predicted difference between the *Cav,md,p* at the 5th to 95th percentile of the covariate and the *Cav,md,p* at the median of the covariate in all cancer patients.

Reviewer's comments:

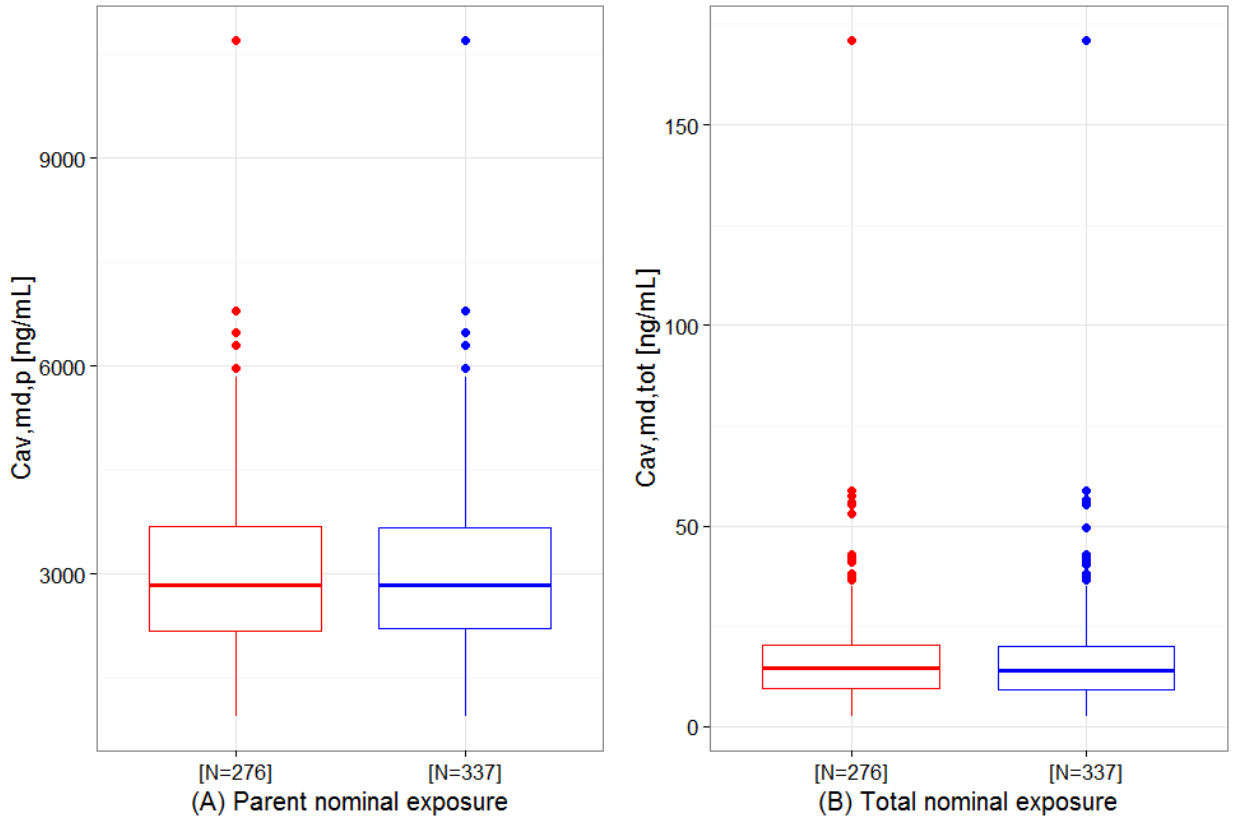
The reviewer agrees with the applicant in general. Graphical evaluation showed that parent or total nominal exposure appears to be comparable among patients with normal liver function, mild hepatic impairment and moderate hepatic impairment based on NCI criteria. The regorafenib exposure appears to be comparable between patients with Asian race and patients with non-Asian race.
Stepwise generalized additive modeling has further identified the following statistically significant covariates on parent nominal exposure: patient type, age, sex, BMI (body mass index), HB0 (baseline hemoglobin) and ALB0 (baseline albumin). However, the impact of these covariates on the regorafenib exposure was small compared to the observed overall variability, and no dose adjustment based on these covariates is needed.

4.1.2.3 Comparison of individual exposure of regorafenib between 80% and 100% dataset

4.1.2.3.1 Graphical Comparison

After obtaining 100% full dataset for study 15982, the applicant further compared the regorafenib parent and total nominal exposure between the interim and final dataset. In the final dataset, individual parent and total nominal exposure metrics were obtained from 337 patients based on 3210 observations (1073, 1049 and 1088 for parent, M2 and M5, respectively) in total. As illustrated in Figure 16, the distribution of parent and total nominal exposure in the full and interim dataset (80%) of study 15982 were very similar.

Figure 16: Distribution of Parent Nominal Exposure (Cav,md,p) (Left) and Total Nominal Exposure (Cav,md,tot) (Right) in RESORCE Study.



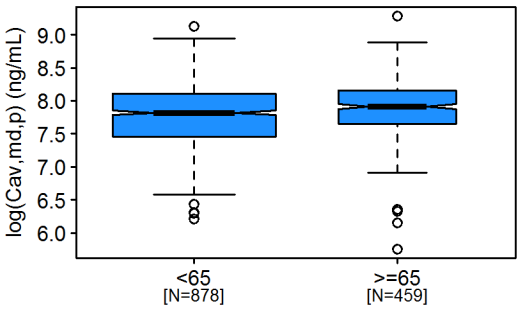
Red: based on dataset containing approximately 80% of RESORCE study data, Blue: based on dataset containing 100% of RESORCE study data.

Age

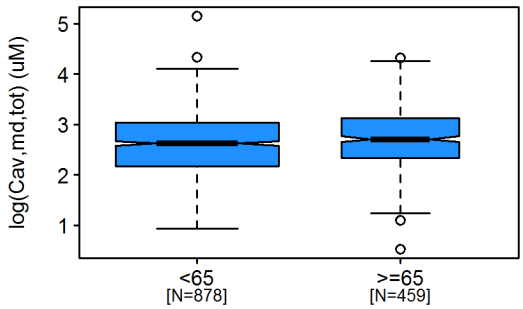
The parent and total nominal exposures were further compared graphically within different age categories; subjects < 65 years and ≥ 65 years and subjects < 65 years, 65-74 years, 75-84 years, and ≥ 85 years (Figure 17). The distribution of individual parent and total nominal exposures were comparable

among these age categories, although slightly higher exposures were observed in the older age groups numerically.

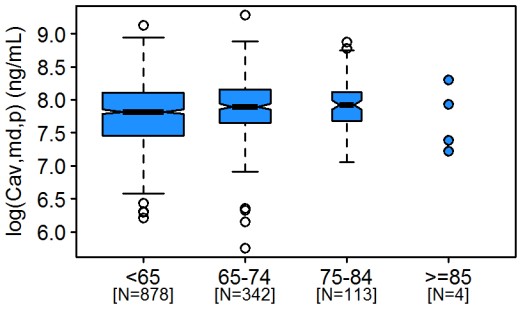
Figure 17: Distribution of Parent Nominal Exposure (Cav,md,p) (Left) and Total Nominal Exposure (Cav,md,tot) (Right) in Subjects within Different Age Categories.



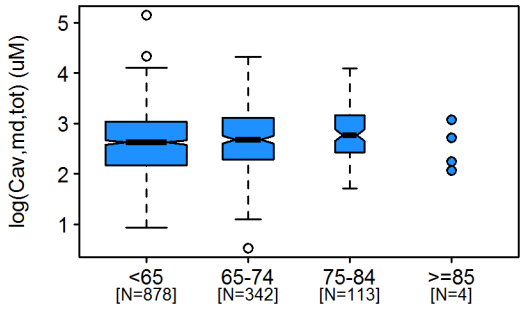
(**A**) Parent nominal exposure (*Cav,md,p*)



(**B**) Total nominal exposure (*Cav,md,tot*)



(**C**) Parent nominal exposure (*Cav,md,p*)

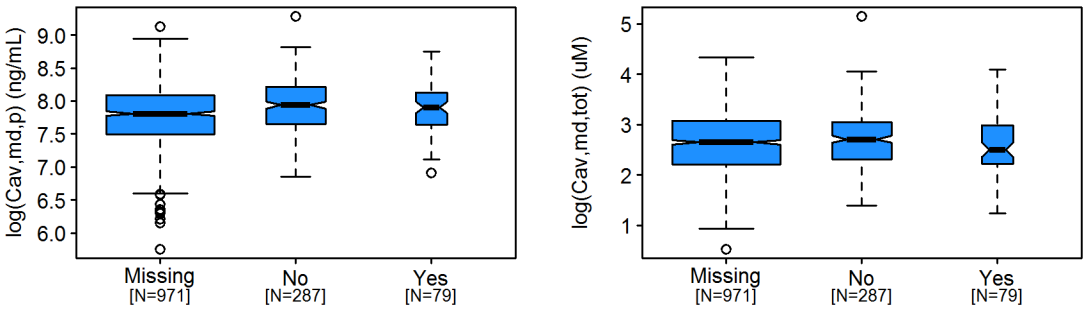


(**D**) Total nominal exposure (*Cav,md,tot*)

Alcohol Etiology

A possible effect of alcohol etiology (yes/no) on the regorafenib was also compared. As shown in the box plots in Figure 18, the distribution for individual parent and total nominal exposures of regorafenib were comparable in the univariate analysis of alcohol etiology.

Figure 18: Distribution of Parent Nominal Exposure (Cav,md,p) (Left) and Total Nominal Exposure (Cav,md,tot) (Right) in the Alcohol Etiology Categories.



(**A**) Parent nominal exposure (*Cav,md,p*) (**B**) Total nominal exposure (*Cav,md,tot*)

4.2 Exposure-Response Analyses

4.2.1 Exposure-Response for Efficacy

The purpose of this exploratory exposure-response (E-R) analysis was to evaluate the relationship between individual exposures of parent or free aggregate regorafenib and overall survival (OS) based on the data from a phase 3 study 15982.

Six different exposure metrics were evaluated in the E-R analysis, which include the average parent regorafenib and free aggregate concentration over cycle 1 day 1, over 28 days in cycle 1 and over 56 days in cycle 1 and 2. The free aggregate concentration of regorafenib was calculated as the sum of the free/unbound molar concentrations of regorafenib and its pharmacologically active metabolites M2 and M5. The average exposure of parent regorafenib in cycle 1 (CAVD28) was selected for the multivariate Cox regression analysis as it shows the strongest association with OS (lowest AIC) in the univariate analysis. It also shows a wider range of exposure compared to average exposure in day 1, and has a higher number of observations compared to average exposure in first 2 cycles.

The univariate Kaplan Meier plot for the CAVD28 exposure quartiles and placebo for OS is shown in Figure 1. It appears a trend of shorter OS is observed in patients with lower average exposure in cycle 1 (CAVD28). After removing the pre-specified baseline covariates in a backward manner from full Cox regression model, ECOG status, baseline AFP value and AST/ALT baseline values were found to be significant covariates and retained in the final reduced model. The CAVD28 quartiles were found to be significantly associated with the overall survival compared to placebo (Table 3). However, the strong association was not observed between OS and CAD28 in regorafenib-treated patients using cox regression analysis adjusted for the same baseline covariates (HR=0.984; 95%CI: 0.965, 1.004) (Table 4). As a result, no evident and conclusive E-R relationship was identified between regorafenib exposure and OS.

Table 3: Results of the Cox Regression Analysis of the Reduced Model for OS Including Placebo Data (n=514).

Covariate	Category	HR estimate	LLCI	ULCI	P-value of category	P-value of covariate
CAVD28	Placebo	1	na	na	Na	<0.001
	Q1	0.784	0.574	1.072	0.128	
	Q2	0.55	0.393	0.768	<0.001	
	Q3	0.652	0.468	0.908	0.011	
	Q4	0.453	0.317	0.647	<0.001	
ECOG stage	0	1	na	na	Na	<0.001
	>=1	1.577	1.253	1.985	<0.001	
AFP level	<400 ng/mL	1	na	na	Na	0
	>=400 ng/mL	2.022	1.617	2.528	<0.001	
Max of AST and ALT level	<= 1.5*ULN	1	na	na	na	<0.001
	>1.5*ULN, <=3*ULN	0.852	0.67	1.084	0.192	
	>3*ULN	1.83	1.233	2.716	0.003	

Table 4: Results of the Cox Regression Analysis of the Reduced Model for OS in Regorafeinb-Treated Patients (n=327).

Covariate	Category	HR estimate	LLCI	ULCI	P-value of category	P-value of covariate
CAVD28	100 ng/mL	0.984	0.965	1.004	0.127	0.121
ECOG stage	0	1	na	na	Na	0.002
	>=1	1.640	1.217	2.209	0.001	
AFP level	<400 ng/mL	1	na	na	Na	0
	>=400 ng/mL	1.986	1.488	2.649	<0.001	
Max of AST and ALT level	<= 1.5*ULN	1	na	na	Na	0.012
	>1.5*ULN, <=3*ULN	0.952	0.7	1.296	0.756	
	>3*ULN	2.084	1.270	3.422	0.004	

Similarly, no definite E-R relationship was observed between CAVD28 and Time to progression (TTP). Univariate K-M curve didn't show a trend of different survival across different exposure quartiles (Figure 19), nor did multivariate cox regression analysis identify a statistically significant relationship between CAVD28 and TTP after adjusting for significant baseline covariates (ECOG stage, Age category and AFP level) (Table 5).

Sensitivity analyses were conducted to assess the impact of excluded subjects due to missing data on the results. The sensitivity analysis resulted in similar parameter estimates, which indicated the analysis was robust with respect to the handling of missing data (i.e. exposure estimates, baseline covariates). This also held true for the selection of exposure metrics, as substituting CAVD28 with another exposure metric (CAVD1) did not result in different interpretations.

Figure 19: (Univariate) Kaplan-Meier Curves for TTP Stratified by CAVD28 Exposure Quartiles and Placebo.

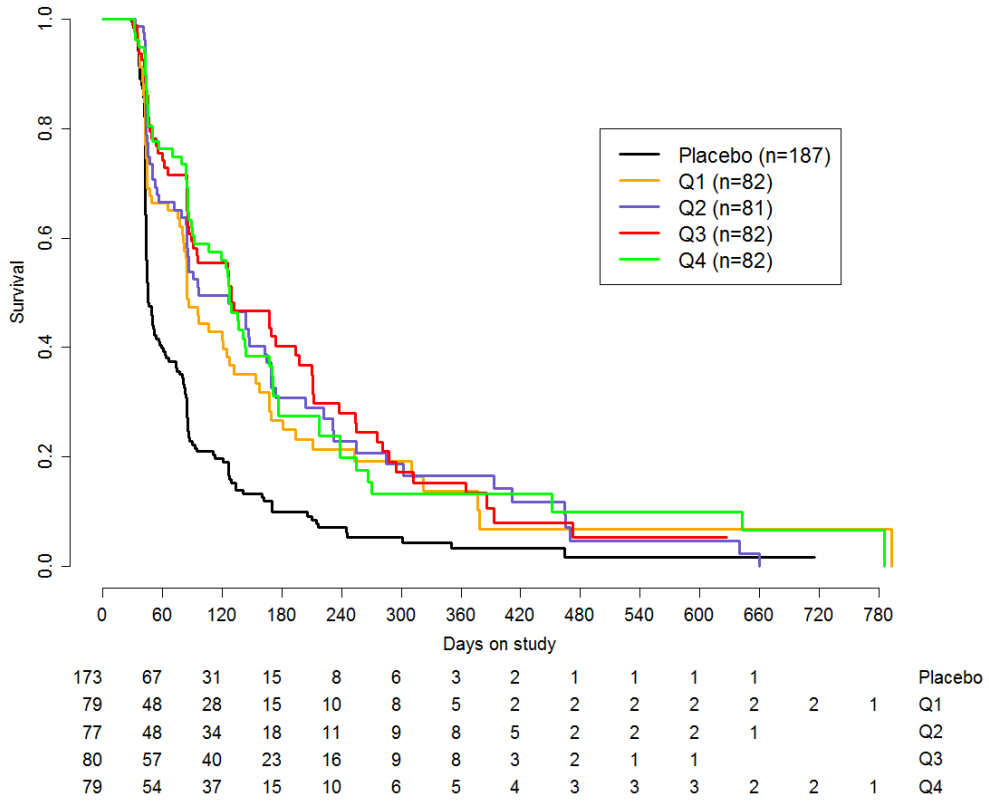


Table 5: Results of the Cox Regression Analysis of the Reduced Model for TTP in Regorafeinb-Treated Patients (n=315).

Covariate	Category	HR estimate	LLCI	ULCI	P-value of category	P-value of covariate
CAVD28	100 ng/mL	0.995	0.978	1.013	0.600	0.599
ECOG stage	0	1	na	na	Na	0.002
	>=1	1.577	1.198	2.075	0.001	
AFP level	<400 ng/mL	1	na	na	Na	0.018
	>=400 ng/mL	1.366	1.057	1.765	0.017	
Age	<65 years	1	na	na	na	0.009
	>=65 years	0.713	0.552	0.920	0.009	

Reviewer's comments:

Extensive analyses using K-M and multivariate cox proportional hazard regression analysis were conducted by the applicant to characterize the E-R relationship for OS and TTP. Although there appears to be a trend of lower overall survival in the low exposure group, no statistically significant relationship

was found between regorafenib exposure and OS or TTP after adjusting for baseline covariates. Thus, no evident and conclusive E-R relationship for efficacy was identified for regorafenib.

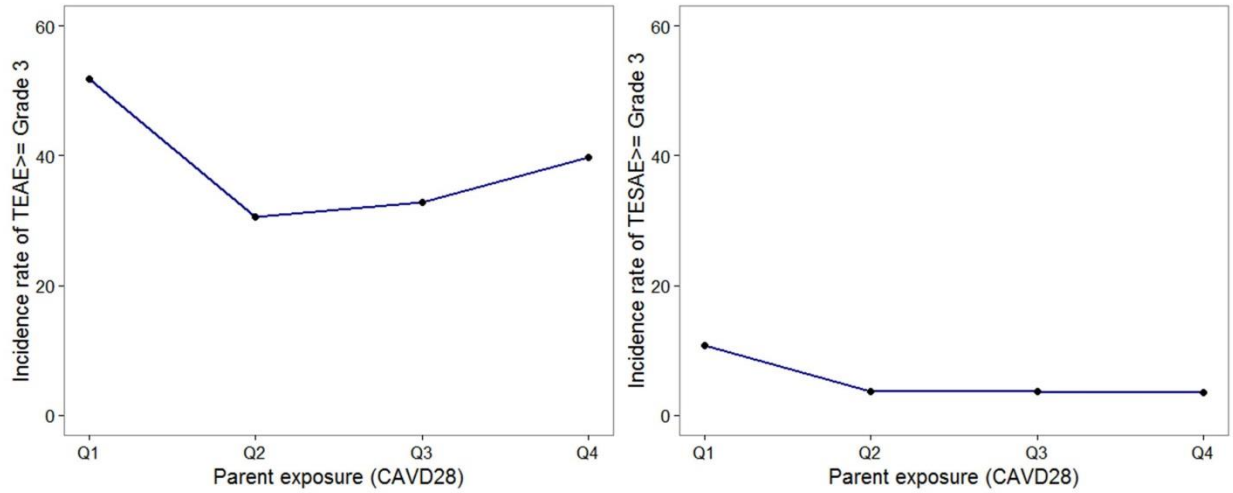
4.2.2 Exposure-Response for Safety

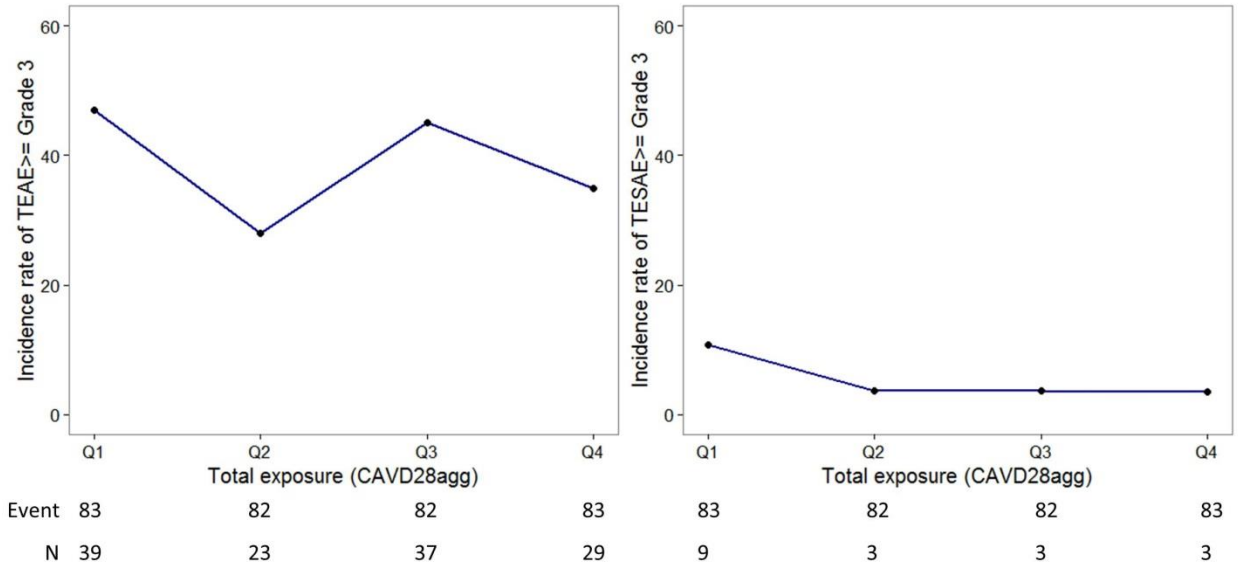
4.2.2.1 Overall treatment emergent AEs

The exposure-response for safety was first explored by evaluating the incidence rates of treatment-emergent adverse events (TEAEs) as a function of categories of estimated exposure metrics. Exposure metrics were derived from Pop-PK analysis and were described in section 4.4.1.

There was a trend of higher incidence rate of TEAEs ≥ Grade 3 during cycle 1 in the low regorafenib and free aggregate exposure groups (Figure 20). However, no statistically significant relationship between incidence rate of TEAEs ≥ Grade 3 and CAVD28 was identified in the logistic regression analysis (P-value = 0.074 and 0.292 for parent and free aggregate, respectively). It should also be noted that over the whole treatment period all of the patients experienced at least one TEAE. Similarly, no significant association was found between CAVD28 and incidence rate of ≥ grade 3 treatment-emergent serious adverse events (TESAEs) during cycle 1 by logistic regression (Figure 20) (P-value = 0.123 and 0.113 for parent and free aggregate, respectively).

Figure 20: Incidence Rate of TEAEs (Left)/TESAEs (Right) ≥ Grade 3 during Cycle 1 across Categories of Estimated Exposure of Regorafenib during Cycle 1



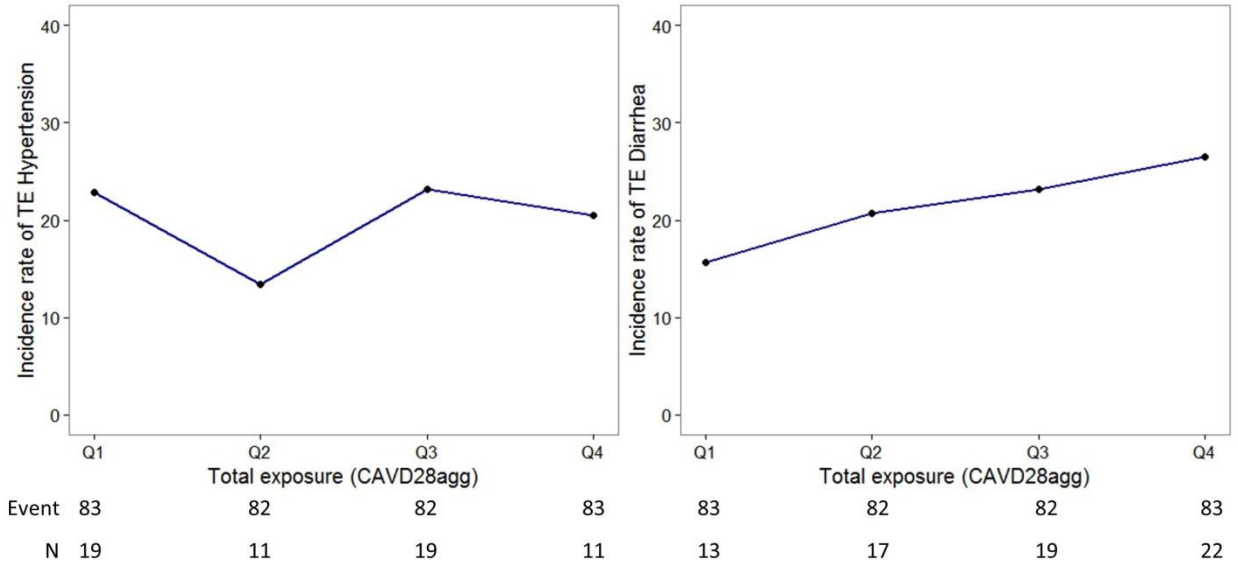


(A) TEAEs **(B)** TESAEs

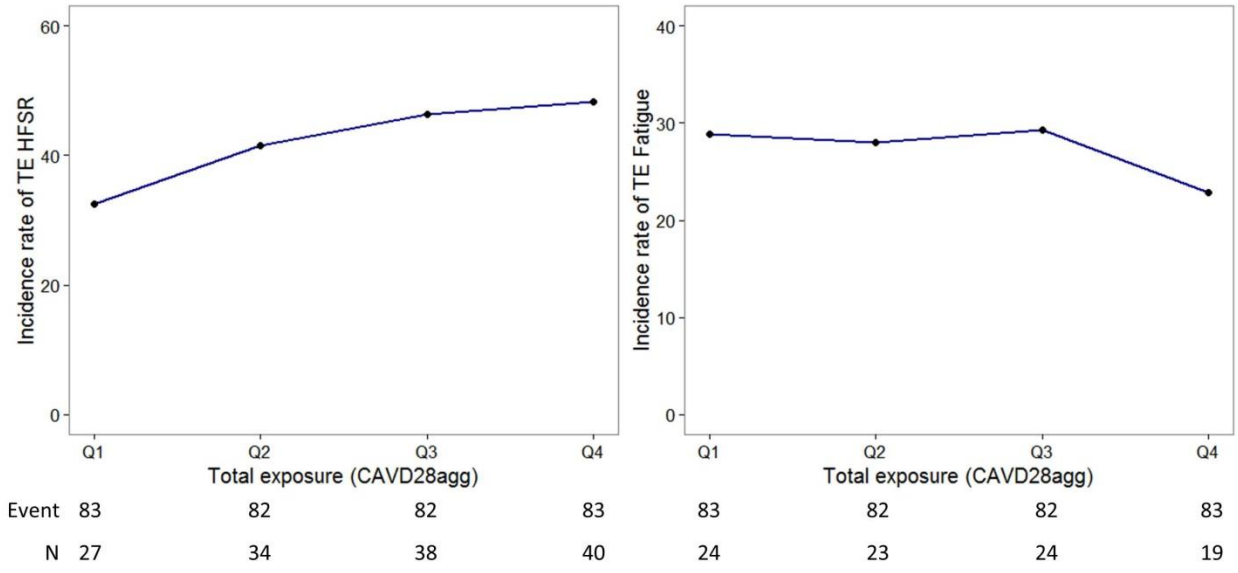
4.2.2 TEAEs of special interest

Exposure-response relationships were further investigated for TEAEs of special interest, namely hypertension, diarrhea, HFSR and asthenia/fatigue. There was no consistent exposure-dependent change in the overall incidence of any particular TEAE with increasing free aggregate exposure (Figure 21).

Figure 21: Incidence Rate of TEAEs of Special Interest (Hypertension, Diarrhea, HFSR and Fatigue) during Cycle 1 across Categories of Estimated Average Exposure of Free Aggregate in Cycle 1



(**A**) Hypertension (**B**) Diarrhea

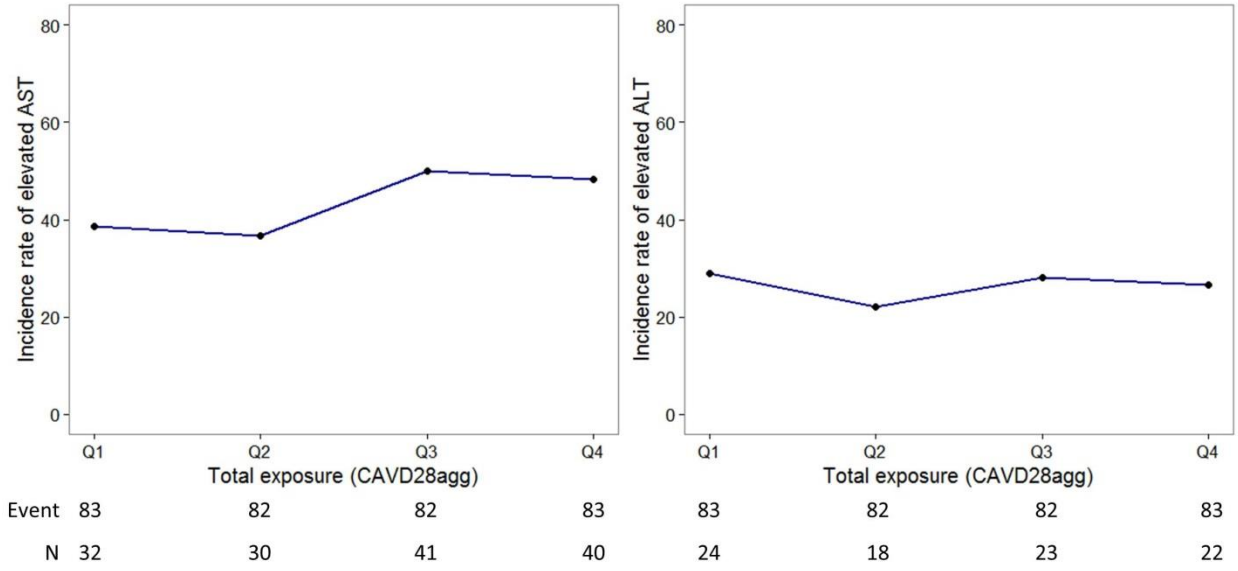


(**C**) HFSR (**D**) Fatigue

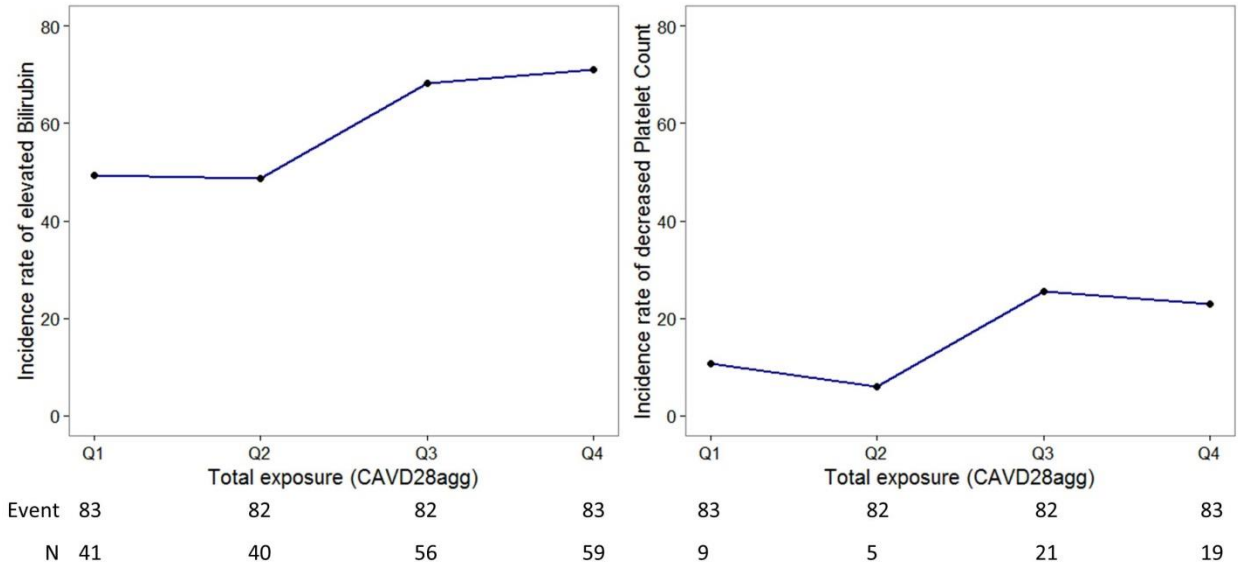
4.2.3 Laboratory data

The incidence rates of laboratory abnormalities of ALT, AST, platelet and total bilirubin (Grade ≥ 1) were compared across different categories of estimated average exposure of free aggregate in cycle 1 (Figure 22). There was no clear exposure-dependent increase in overall number of subjects with elevated AST or ALT with increasing free aggregate exposure of regorafenib. An increased incidence rate with number of subjects with elevated bilirubin or decreased platelet count was observed in higher exposure groups. Exploratory univariate logistic regression also identified a statically significant relationship between free aggregate exposure and occurrence of abnormal bilirubin (P-value=0.021) and platelet count (P-value=0.042). However, no exposure-dependent trend was observed in ≥ Grade 3 elevated bilirubin or decreased platelet count due to low number of observed events.

Figure 22: Incidence Rate of Laboratory Abnormalities (Grade ≥ 1) of ALT, AST, Platelet and Total Bilirubin during Cycle 1 across Categories of Estimated Average Exposure of Free Aggregate in Cycle 1



(**A**) AST (**B**) ALT



(**C**) Bilirubin (**B**) Platelet count

Reviewer's comments:

Exposure-safety evaluations were explored with relevant safety data such as the incidence rate of overall TEAEs, the incidence rates of TEAE of special interest (Hypertension, Diarrhea, Fatigue and HFSR) and laboratory abnormalities (AST, ALT, bilirubin and platelet). No consistent and conclusive exposure-dependent relationships were identified between regorafenib and free aggregate exposures and the abovementioned safety data.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

YOUWEI N BI
04/06/2017

VADRYN PIERRE
04/06/2017

JIANG LIU
04/06/2017

JEANNE FOURIE ZIRKELBACH
04/06/2017

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203085Orig1s007

OTHER REVIEW(S)

MEMORANDUM

Date: April 17, 2017
From: Whitney S. Helms, PhD
Pharmacology Supervisor
Division of Hematology Oncology Toxicology for Division of Oncology Products 2
To: File for NDA # 203085
STIVARGA (regorafenib)
Re: Labeling Supplement for Regorafenib (Supplment 7)

The Applicant provided references to support the inclusion of additional data in Section 12.1 (Mechanism of Action) of the label for regorafenib. Data to support the inclusion of CSFR1 as a clinically relevant target of regorafenib was previously reviewed during the original review of NDA 203085. In Study A58227 the Applicant showed that regorafenib was able to bind CSF1R with a K_D of 10 nM, within the range of binding for other kinases included in the label and a concentration that is clinically achievable at the recommended dose of 160 mg orally once daily for 21 days of a 28-day cycle. The originally reviewed xenograft data also specifically included studies using GIST and hepatocellular carcinoma tumors. Since these are the approved indications for regorafenib, the Applicant proposed naming these models in the label and FDA agreed.

The Applicant also submitted data from the literature describing the presence of tumor associated macrophages in syngeneic colorectal tumors orthotopically implanted in CD-1 mice. Beginning 4 days after orthotopic tumor implantation of a colorectal tumor model (CT26) in CD1-nude mice, animals were treated with regorafenib at a dose of 30 mg/kg for 10 days. The number of tumor associated macrophages, measured by staining with F4/80, decreased in regorafenib-treated mice compared to vehicle control or a VEGFR-2 antibody, DC101 (

Figure 1 A-B) [1] . More specifically, treatment with regorafenib resulted in lower levels of TIE2+ macrophages compared to the anti-VEGFR2 antibody (

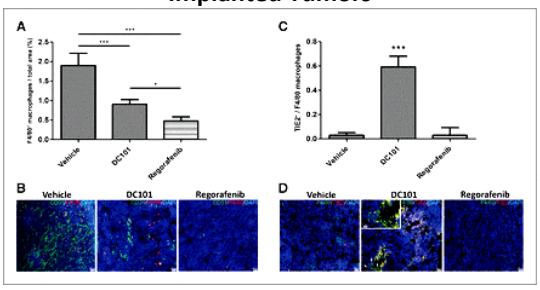
Figure 1 C-D). The authors cite data indicating a role for TIE2-expressing macrophages in promoting angiogenesis and tumor progression[2, 3].

[1] Abou-Elkacem L, Arns S, Brix G, Gremse F, Zopf D, Kiessling F, Lederle W. Regorafenib inhibits growth, angiogenesis, and metastasis in a highly aggressive, orthotopic colon cancer model. Mol Cancer Ther. 2013 Jul;12(7):1322-311

[2] Condeelis J, Pollard JW. Macrophages: obligate partners for tumor cell migration, invasion, and metastasis. Cell. 2006 Jan 27;124(2):263-6.

[3] De Palma M, Naldini L. Angiopoietin-2 TIEs up macrophages in tumor angiogenesis. Clin Cancer Res 2011;17:5226–32

Figure 1: Treatment with Regorafenib Reduces Macrophage, Including TIE2+ Macrophages, in Orthotopically Implanted Tumors

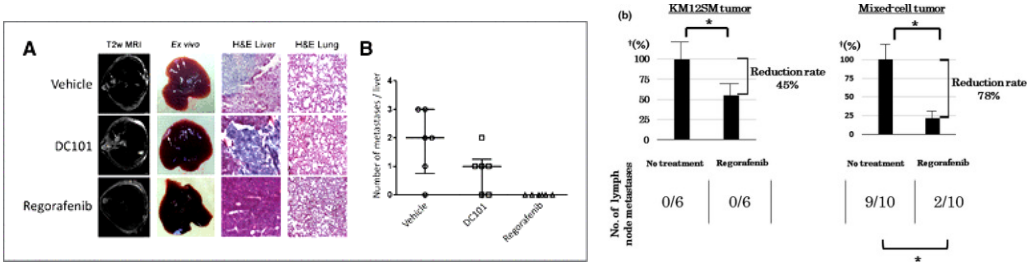


(Excerpted from Abou-Elkacem et. al)

This paper, thus, (b) (4) helps support the addition of a contribution of regorafenib to tumor immunity or maintenance of the tumor microenvironment, as stated in the originally approved label. The statement proposed by the Applicant, however, (b) (4)

The same study by Abou-Elkacem confirmed a decrease in metastatic lesions in mice treated with regorafenib compared to DC101 or vehicle control, similar to previous findings showing a decrease in metastatic activity in response to this drug. A second study using an orthotopic implantation model of tumor cells with mesenchymal stem cells also demonstrated a decrease in metastatic lesions in mice treated with regorafenib compared to control- treated animals[4].

Figure 2: Inhibition of Metastases by Regorafenib



(Left: Excerpted from Abou-Elkacem et. al. Right: Excerpted from Takigawa et. al.)

[4] Takigawa H, Kitadai Y, Shinagawa K, Yuge R, Higashi Y, Tanaka S, Yasui W, Chayama K. Multikinase inhibitor regorafenib inhibits the growth and metastasis of colon cancer with abundant stroma. Cancer Sci. 2016 May;107(5):601-8

Current	Proposed	FDA Recommends	Justification
Regorafenib is a small molecule inhibitor of multiple membrane-bound and intracellular kinases involved in normal cellular functions and in pathologic processes such as oncogenesis, tumor angiogenesis, and maintenance of the tumor microenvironment. In in vitro biochemical or cellular assays, regorafenib or its major human active metabolites M-2 and M-5 inhibited the activity of RET, VEGFR1, VEGFR2, VEGFR3, KIT, PDGFR-alpha, PDGFR-beta, FGFR1, FGFR2, TIE2, DDR2, TrkA, Eph2A, RAF-1, BRAF, BRAF V600E, SAPK2, PTK5, and Abl at concentrations of regorafenib that have been achieved clinically. In in vivo models, regorafenib demonstrated anti-angiogenic activity in a rat tumor model, and inhibition of tumor growth as well as anti-metastatic activity in several mouse xenograft models including some for human colorectal carcinoma.	Regorafenib is a small molecule inhibitor of multiple membrane-bound and intracellular kinases involved in normal cellular functions and in pathologic processes such as oncogenesis, tumor angiogenesis, metastasis and tumor immunity. In in vitro biochemical or cellular assays, regorafenib or its major human active metabolites M-2 and M-5 inhibited the activity of RET, VEGFR1, VEGFR2, VEGFR3, KIT, PDGFR-alpha, PDGFR-beta, FGFR1, FGFR2, TIE2, DDR2, TrkA, Eph2A, RAF-1, BRAF, BRAF V600E, SAPK2, PTK5, Abl and CSF1R) at concentrations of regorafenib that have been achieved clinically. In in vivo models, regorafenib demonstrated anti-angiogenic activity in a rat tumor model, inhibition of tumor growth in several mouse xenograft models including some for human colorectal carcinoma, gastrointestinal stromal and hepatocellular carcinoma, (b) (4)	Regorafenib is a small molecule inhibitor of multiple membrane-bound and intracellular kinases involved in normal cellular functions and in pathologic processes such as oncogenesis, tumor angiogenesis, metastasis and tumor immunity. In in vitro biochemical or cellular assays, regorafenib or its major human active metabolites M-2 and M-5 inhibited the activity of RET, VEGFR1, VEGFR2, VEGFR3, KIT, PDGFR-alpha, PDGFR-beta, FGFR1, FGFR2, TIE2, DDR2, TrkA, Eph2A, RAF-1, BRAF, BRAF V600E, SAPK2, PTK5, Abl and CSF1R) at concentrations of regorafenib that have been achieved clinically. In in vivo models, regorafenib demonstrated anti-angiogenic activity in a rat tumor model and inhibition of tumor growth in several mouse xenograft models including some for human colorectal carcinoma, gastrointestinal stromal and hepatocellular carcinoma. Regorafenib also demonstrated antimetstatic activity in a mouse xenograft model and two mouse orthotopic models of human colorectal carcinoma.	See Disscussion above. The Applicant submitted additional literature (b) (4)

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/s/

WHITNEY S HELMS
04/26/2017

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: April 26, 2017

To: Anuja Patel, MPH
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology & Oncology Products

From: Carole C. Broadnax, R.Ph., Pharm.D.
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: **Stivarga (regorafenib) tablets, for oral use**
NDA 203085 – 007
Addendum to OPDP Comments on proposed labeling

In response to the Division of Oncology Products 2's (DOP 2) December 12, 2016, consult request, OPDP provided initial comments on April 18, 2017, for proposed labeling (package insert (PI) and patient package insert (PPI)) for Stivarga (regorafenib) tablets, for oral use.

This addendum is for OPDP's additional comment (below) to DOP 2 for the Highlights section and for additional edits to Section 5.9 Wound Healing Complications of the proposed PI (attached) to further revise "regorafenib" to "STIVARGA" per the agreement reached during the April 24, 2017, tcon with Bayer. The additional Highlights comment and Section 5.9 edits were conveyed to DOP 2 via electronic mail and SharePoint on April 25, 2017.

> OPDP notes that Highlights is inconsistent with Section 2.1 Dosage and Administration and that Section 12.3 Pharmacokinetics, Absorption (last paragraph, last sentence) and Section 14.1 Colorectal Cancer (second paragraph, second sentence) are inconsistent with Section 2.1. Should the sentences in Highlights, 12.3, and 14.1 be revised to be consistent with 2.1? For example, Highlights states, "Take STIVARGA with a low-fat meal. (2.1, 12.3);" however, Section 2.1 states, "Swallow tablet whole with water after a low-fat meal that contains less than 600 calories and less than 30% fat [see Clinical Pharmacology (12.3)].

The version of the proposed PI used in this review was sent to OPDP (Carole Broadnax) from DOP-2 (Anuja Patel) via a link to Sharepoint contained in electronic mail dated April 24, 2017, and is titled, "stivarga-draft-uspi-ccds9-hcc-tracked-word-version.docx."

Thank you for the opportunity to provide comments on these proposed materials. If you have any questions regarding this consult review, please contact Carole Broadnax at 301-796-0575 or Carole.Broadnax@fda.hhs.gov.

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/s/

CAROLE C BROADNAX
04/26/2017

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs

PATIENT LABELING REVIEW

Date:	April 20, 2017
To:	Patricia Keegan, MD Director **Division of Oncology Products 2 (DOP2)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN, CWOCN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Morgan Walker, PharmD, MBA, CPH Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
Subject:	Focused Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	STIVARGA (regorafenib)
Dosage Form and Route:	tablets, for oral use
Application Type/Number/Supplement:	NDA 203085/S-007
Applicant:	Bayer HealthCare Pharmaceuticals Inc.

1 INTRODUCTION

On October 31, 2016, Bayer HealthCare Pharmaceuticals Inc. submitted for the Agency's review a Prior Approval Supplement to New Drug Application (NDA) 203085/S-007 for STIVARGA (regorafenib) tablets. This labeling supplement provides a proposed new indication for the treatment of patients with hepatocellular carcinoma (HCC) who have been previously treated with (b) (4).

STIVARGA (regorafenib) tablets was originally approved on September 27, 2012 with the indication for the treatment of patients with metastatic colorectal cancer (CRC) who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan based chemotherapy, an anti-VEGF therapy, and, if KRAS wild type, an anti-EGFR therapy. On February 25, 2013 STIVARGA (regorafenib) tablets was approved under NDA 204369 for the treatment of patients with locally advanced, unresectable or metastatic gastrointestinal stromal tumor (GIST) who have been previously treated with imatinib mesylate and sunitinib malate.

This focused review is written by the Division of Medical Policy Programs (DMPP) in response to a request by the Division of Oncology Products 2 (DOP2) on December 12, 2016 for DMPP to provide a focused review of the Applicant's proposed Patient Package Insert (PPI) for STIVARGA (regorafenib) tablets.

2 MATERIAL REVIEWED

- Draft STIVARGA (regorafenib) tablets PPI received on October 31, 2016, and received by DMPP on April 10, 2017.
- Draft STIVARGA (regorafenib) tablets Prescribing Information (PI) received on October 31, 2016, revised by the Review Division throughout the review cycle, and received by DMPP on April 10, 2017.

3 REVIEW METHODS

In our focused review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Our focused review of the PPI is appended to this memorandum. Consult DMPP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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/s/

MORGAN A WALKER
04/20/2017

BARBARA A FULLER
04/20/2017

LASHAWN M GRIFFITHS
04/20/2017

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: April 18, 2017

To: Anuja Patel, MPH
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology & Oncology Products

From: Carole C. Broadnax, R.Ph., Pharm.D.
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: **Stivarga (regorafenib) tablets, for oral use**
NDA 203085 – 007
OPDP Comments on proposed labeling

In response to the Division of Oncology Products 2's (DOP 2) December 12, 2016, consult request, OPDP has reviewed proposed labeling (package insert (PI) and patient package insert (PPI)) for Stivarga (regorafenib) tablets, for oral use.

This supplemental application proposes to revise the PI to:

- include a new indication for the treatment of patients with hepatocellular carcinoma (HCC) who have been previously treated with (b) (4);
- update Section 5 Warnings and Precautions, and Section 6 Adverse Reactions, with pooled data from four phase 3 trials (CORRECT (#14387), GRID (#14874), RESORCE (#15982), and CONCUR (#15808) following completion of RESORCE trial (#15982);
- add a new subsection, 5.2 Infections, under Warnings and Precautions based on data from the pooled phase 3 trials;
- update subsection 12.1 Mechanism of Action, to include language on metastasis and tumor immunity; and,
- revise the PPI for consistency with revisions proposed in the PI.

Comments on the proposed labeling are based on the substantially complete labeling dated April 10, 2017, entitled "sNDA 203085 S 007 FDA Preliminary edits to PI received 6 Jan 17.docx." OPDP's comments on the proposed labeling are provided directly on the marked version below.

If you have any questions regarding this consult review, please contact Carole Broadnax at 301-796-0575 or Carole.Broadnax@fda.hhs.gov.

Thank you for the opportunity to provide comments on these proposed materials.

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/s/

CAROLE C BROADNAX
04/18/2017

LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	December 30, 2016
Requesting Office or Division:	Division of Oncology Products 2 (DOP2)
Application Type and Number:	NDA 203085/S-007
Product Name and Strength:	Stivarga (regorafenib) Tablets, 40 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Bayer Health Care Pharmaceuticals Inc. (Bayer)
Submission Date:	October 31, 2016
OSE RCM #:	2016-2550
DMEPA Primary Reviewer:	Otto L. Townsend, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD, BCPS

1 REASON FOR REVIEW

This review responds to a request from the Division of Oncology Products 2 (DOP2) to evaluate Section 2 of the proposed Prescribing Information (PI) submitted by Bayer for areas of vulnerability that could lead to medication errors. The PI was submitted as part of an efficacy supplement which, if approved, would expand the indication of Stivarga to include the treatment of patients with hepatocellular carcinoma who have been previously treated with (b) (4).

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C – N/A
ISMP Newsletters	D
FDA Adverse Event Reporting System (FAERS)*	E
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

If approved, this efficacy supplement (S-007) will expand the indication of Stivarga (regorafenib) to include the treatment of patients with hepatocellular cancer using the same dosing recommendations as the currently approved indications. The submission included proposed changes to the prescribing information, but did not include any proposed changes to the container label or carton labeling. Bayer proposed to add the following introductory statements in Section 2.2 (Dose Modification) of the PI:

(b) (4)

Bayer provided the following rationale for the addition of these introductory statements:

> *<u>Rationale</u>* [redacted] *Sponsor believes it is appropriate to provide the prescriber with a general overview of the dose modification strategy for regorafenib, including mention of the dose modifications steps* [redacted] *prior to offering detailed guidance regarding the management of specific adverse events. Such an approach is expected to improve the readability and therefore the understanding of the dose modification guidance.*
>
> *Rationale* [redacted]

[redacted]

As part of our risk assessment, we also considered our recommendations and surveillance plan from our recent Postmarket Reviews that evaluated the potential overdose risk that is present when patients are prescribed 120 mg or 80 mg as dose reductions from the standard dose of 160 mg (see Appendix B for a summary or the referenced reviews for more details). Our gap search of FAERS and ISMP Newsletters did not identify any overdose medication errors associated with the availability of extra tablets when prescribed the 120 mg or 80 mg dose. We will continue to monitor medication error reports related to Stivarga.

4 CONCLUSION & RECOMMENDATIONS

The Applicant suggested [redacted]. We provide recommendations for consideration in Section 4.1 below.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information
   1. We defer the decision on the appropriateness of [redacted] to the review team. If the review team determines that [redacted] is appropriate, we recommend that the Applicant propose specific dosing guidelines in the Dosing and Administration section of the PI. For example, a new subsection [redacted]

[redacted]

APPEARS THIS WAY ON ORIGINAL

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Stivarga that Bayer submitted on October 31, 2016.

Table 2. Relevant Product Information for Stivarga	
Initial Approval Date	September 27, 2012
Active Ingredient	Regorafenib
Indication	Current: Colorectal Cancer and Gastrointestinal Stromal Tumors Proposed: treatment of patients with hepatocellular carcinoma who have been previously treated with (b) (4)
Route of Administration	Oral
Dosage Form	Tablets
Strength	40 mg
Dose and Frequency	160 mg (4 x 40 mg tablets) by mouth once daily for the first 21 days of each 28-day cycle.
How Supplied	Carton containing three bottles, with each bottle containing 28 tablets, for a total of 84 tablets per carton.
Storage	Store at 25°C (77°F); excursions are permitted from 15 to 30°C (59 to 86°F) [see USP Controlled Room Temperature]. Store tablets in the original bottle and do not remove the desiccant. Keep the bottle tightly closed after first opening. Discard any unused tablets 7 weeks after opening the bottle. Dispose of unused tablets in accordance with local requirements.
Container Closure	Plastic white opaque bottle with child-resistant closure.

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On December 6, 2016, we searched the L:drive and AIMS using the terms, "Stivarga" and "regorafenib" to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified 3 previous reviews[b,c,d].

The 2 most recent reviews were postmarket reviews that addressed a safety issue involving the potential overdose risk that is present when patients are prescribed 120 mg or 80 mg as dose reductions from the standard dose of 160 mg. A General Advise letter from DOP2 was issued to the Applicant requesting the following:

1. A summary of any medication errors or product complaints that Bayer has received that are associated with the package size of Stivarga.
2. A rationale for only supplying Stivarga in a 28-count bottle, which provides more tablets than the quantity required for dose modification.
3. Consideration for changing the package size if Stivarga to a 21- count bottle (carton containing 4 bottles).

In response to the General Advice letter from DOP2, Bayer determined there was not a need to change from a 28-count to 21-count bottle because they were not able to identify medication errors or product complaints that could be attributed to the availability of additional tablets when a patient is taking either a reduced dose of 120 mg or 80 mg. They proposed to continue monitoring this issue. In the absence of any medication errors related to package size, we found Bayer's proposal acceptable and we continue to monitor for medication errors related to Stivarga.

[b] Schlick, J. Label, Labeling, and Packaging Review for Stivarga (NDA 203085). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2012 JUL 25. RCM No.: 2012-1082.

[c] Townsend, O. Postmarket Medication Error Memorandum for Stivarga (NDA 203085). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 OCT 07. RCM No.: 2015-1809.

[d] Stewart, J. Postmarket Medication Error Memorandum for Stivarga (NDA 203085). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 MAY 24. RCM No.: 2016-998.

APPENDIX D. ISMP NEWSLETTERS

D.1 Methods

On December 6, 2016, we searched the Institute for Safe Medication Practices (ISMP) newsletters using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

ISMP Newsletters Search Strategy	
ISMP Newsletter(s)	Acute Care, Community and or Nursing
Search Strategy and Terms	Match Any of the Words: Stivarga, regorafenib

D.2 Results

Our search of the Institute for Safe Medication Practices (ISMP) newsletters did not yield any newsletters that described medication errors or actions possibly associated with the label and labeling of Stivarga.

APPENDIX E. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

E.1 Methods

We performed a gap search of the FDA Adverse Event Reporting System (FAERS) on December 6, 2016 using the criteria in Table 3, and then individually reviewed each case. We limited our analysis to cases that described errors possibly associated with the label and labeling. We used the NCC MERP Taxonomy of Medication Errors to code the type and factors contributing to the errors when sufficient information was provided by the reporter.[e]

Table 3: FAERS Search Strategy	
Initial FDA Receive Dates	May 1, 2016 to November 30, 2016
Product Name	Stivarga
Event (MedDRA Terms)	Medication errors SMQ (narrow)

E.2 Results

Our search retrieved 10 cases, but after further evaluation, we didn't identify any medication error cases that were relevant for this review and could be addressed by labels and labeling revisions.

E.3 Description of FAERS

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. FDA's Office of Surveillance and Epidemiology codes adverse events and medication errors to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm.

[e] The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website http://www.nccmerp.org/pdf/taxo2001-07-31.pdf.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[f] along with postmarket medication error data, we reviewed the following Stivarga labels and labeling submitted by Bayer on October 31, 2016.

- Prescribing Information

[f] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

OTTO L TOWNSEND
12/30/2016

CHI-MING TU
12/30/2016

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203085Orig1s007

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 075642

MEETING MINUTES

Bayer HealthCare Pharmaceuticals, Inc.
Attention: Lisa Chao, Ph.D.
Deputy Director, Regulatory Affairs
100 Bayer Boulevard, P.O. Box 915
Whippany, NJ 07981-0915

Dear Dr. Chao:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for regorafenib.

We also refer to the meeting between representatives of your firm and the FDA on July 21, 2016. The purpose of the meeting was to discuss the efficacy and safety results of Study 15982, entitled "A Randomized, Double-Blind, Placebo-Controlled, Multicenter Phase III Study of Regorafenib in Patients with Hepatocellular Carcinoma (HCC) After Sorafenib"; and to seek agreement on the contents of the sNDA and potential rolling review plan.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-3074.

Sincerely,

{See appended electronic signature page}

Idara Udoh, M.S.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-sNDA

Meeting Date and Time: July 21, 2016; 1:00 PM – 2:00 PM, EST
Meeting Location: White Oak Building 22, Conference Room: 1421

Application Number: IND 075642
Product Name: Regorafenib
Indication: Treatment of patients with hepatocellular carcinoma (HCC) who have been previously treated with (b) (4)
Sponsor/Applicant Name: Bayer HealthCare Pharmaceuticals, Inc.

Meeting Chair: Steven Lemery
Meeting Recorder: Idara Udoh

FDA ATTENDEES

Center for Drug Evaluation and Research, Division of Oncology Products 2 (DOP 2)
Martha Donoghue, Acting Associate Director
Steven Lemery, Clinical Team Leader
Damiette Smit, Clinical Reviewer
Lola Fashoyin-Aje, Clinical Reviewer
Monica Hughes, Chief, Project Management Staff
Idara Udoh, Senior Regulatory Health Project Manager

Center for Drug Evaluation and Research, Office of Clinical Pharmacology
Hong Zhao, Clinical Pharmacology Team Leader
Jeanne Fourie Zirkelbach, Clinical Pharmacology Team Leader
Jingyu Yu, Clinical Pharmacology Reviewer
Vadryn Pierre, Clinical Pharmacology Reviewer

Office of Pharmaceutical Quality (OPQ), Office of Lifecycle Drug Products
Zedong Dong, Quality Assessment Lead (Acting)

SPONSOR ATTENDEES

Bayer HealthCare Pharmaceuticals, Inc.
Gerold Meinhardt, Clinical Development
Mark Rutstein, Clinical Development
Adriaan Cleton, Clinical Pharmacology

Zuzana Jirakova Trnkova, Clinical Pharmacology
Christian Kappler, Clinical Statistics
Hui-Talia Zhang, Pharmacovigilance
Kathleen Schostack, Program Head
Lisa Chao, Regulatory Affairs
Birgit Wolf, Regulatory Affairs
Philip Johnson, Regulatory Affairs
Gerhard Schlueter, Regulatory Affairs
Marie-Aude Le Berre

MEETING PURPOSE

On May 20, 2016, Bayer HealthCare Pharmaceuticals, Inc. ("Bayer") requested a Type B pre-supplemental New Drug Application (sNDA) meeting to discuss the efficacy and safety results of Study 15982 (RESORCE), entitled "A Randomized, Double-Blind, Placebo-Controlled, Multicenter Phase III Study of Regorafenib in Patients with Hepatocellular Carcinoma (HCC) After Sorafenib" and to seek agreement on the contents of an sNDA and potential rolling review plan. Bayer plans to submit the sNDA in August/September 2016.

The meeting package was received on June 20, 2016. FDA sent Preliminary Comments to Bayer on July 18, 2016.

PROPOSED INDICATION

For the treatment of patients with hepatocellular carcinoma (HCC) who have been previously treated with (b) (4).

BACKGROUND

Regulatory History

Stivarga (regorafenib) is approved for the following indications:

- the treatment of patients with metastatic colorectal cancer (mCRC) who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF therapy, and, if KRAS wild type, an anti-EGFR therapy
- the treatment of patients with locally advanced, unresectable or metastatic gastrointestinal stromal tumor (GIST) who have been previously treated with imatinib mesylate and sunitinib malate.

On December 23, 2015, Bayer submitted a meeting request to obtain FDA feedback on the format and content of a planned sNDA based on the results of Study 15982, entitled "A Randomized, Double Blind, Placebo-Controlled, Multicenter Phase III Study of Regorafenib in Patients with Hepatocellular Carcinoma (HCC) after Sorafenib." A final written response (WRO) was issued on March 4, 2016.

[redacted]

On June 15, 2016, FDA received [redacted] request [redacted] Fast Track [redacted] for treatment of patients with hepatocellular carcinoma (HCC) who have been previously treated with [redacted]

Clinical

Bayer has conducted the following studies to support a marketing application for regorafenib in HCC:

- Study 11651 (an open-label, non-randomized, dose-escalating study)
- Study 14596 (a single-arm, multicenter, open-label safety study) and
- Study 15982 (a randomized, double blind, placebo-controlled, multicenter study).

Study 15982 will serve as the single pivotal clinical trial supporting the safety and efficacy evaluation of the proposed sNDA for the treatment of patients with HCC who have previously received sorafenib.

Study 14596 is a single-arm, multicenter safety study of regorafenib in patients with HCC (Child-Pugh A) after treatment with sorafenib. Thirty-six patients were enrolled. All patients experienced at least one treatment-emergent adverse event (TEAE). Three patients (8.3%) experienced a serious adverse event (SAE) determined to be drug-related (fatigue, diarrhea and hematoma). Five patients died with one cause of death determined to be drug-related (hematoma). The most frequent TEAE's included fatigue (69.4%), diarrhea (52.5%) and hand-foot skin reaction (HFSR; 60%). The most frequent TEAE's of Grade 3 or greater severity included fatigue (22.2%), HFSR (13.9%) and hyperbilirubinemia (11.1%). Median overall survival (OS) was 13.8 months (range of 1.4 – 28.9 months) and time to progression (TTP) was 4.3 months. Thirty-one patients were evaluable for response. One patient had a partial response and 25 patients had stable disease.

Study 15982 is a randomized, double-blind, multicenter, placebo-controlled trial that enrolled patients with HCC after they previously received sorafenib. A total of 560 patients were planned to be randomized. Randomization was stratified by region (Asian vs. rest of world), ECOG PS (0 vs. 1), AFP level (<400 ng/mL vs. ≥400 ng/mL), extrahepatic disease (presence vs. absence), and macrovascular invasion (presence vs. absence). A total of 573 patients were randomly assigned in a 2:1 ratio to two treatment arms:

- Experimental: regorafenib 160 mg orally, once daily, for 3 weeks of every 4 week (28-day) cycle (i.e. 3 weeks on/1 week off) plus best supportive care (BSC)
- Control: identical placebo tablets following the same treatment schedule plus BSC.

Treatment continued until disease progression, unacceptable treatment-related toxicity, or patient or physician decision to discontinue.

The primary endpoint was OS. Assuming that the median OS is 8 months in the control arm and 11.4 months in the experimental arm, a total of 370 events were needed to detect a hazard ratio (HR) of 0.70 with 90% power at a 1-sided alpha level of 2.5%. The primary analysis was a stratified log-rank test performed on the intent-to-treat population. One interim analysis of OS was planned after 111 (30%) events (for futility only). The futility stopping boundary was specified as non-binding. Major secondary endpoints included progression-free survival (PFS), TTP, and objective response rate (ORR). A hierarchical procedure was proposed to adjust for multiplicity in testing the secondary endpoints with the order of PFS→TTP.

The primary analysis of OS for Study 15982 was triggered after 372 events were observed. The efficacy results are: OS: HR 0.62 (95% CI: 0.5, 0.78), p<0.0001, median OS of 10.6 in the regorafenib arm and 7.8 months for placebo; PFS (mRECIST): HR 0.46 (95% CI: 0.37, 0.56), p<0.0001, median PFS 3.1 and 1.5 months; ORR (mRECIST): 10.6% and 4.1%, p=0.0047.

All patients treated with regorafenib and nearly all patients treated with placebo (92.7%) had at least one TEAE. Of these, 10.4% vs. 2.6% were determined to be both drug-related and serious in the regorafenib vs. placebo arms, respectively. Grade 5 events occurred in 13.4% of patients treated with regorafenib and in 19.7% of patients treated with placebo. The most common adverse events of Grade 3 or greater severity were HFSR (12.3% vs. 0.5% in the regorafenib vs. placebo group, respectively), diarrhea (3.2% vs. 0%), decreased appetite (2.7% vs. 1.6%), hypertension (14.7% vs. 4.7%), fatigue (5.9% vs. 3.6%), AST increased (11% vs. 11.4%), hyperbilirubinemia (7.5% vs. 9.3%), and abdominal pain (2.7% vs. 2.6%).

DISCUSSION OF FDA RESPONSES TO SPONSOR QUESTIONS

Question 1: Study 15982 to Support sNDA Filing
Bayer's position on Question #1 provided in Section 9.1 (page 35) of briefing package.

1. **Does the Division agree that the results from Study 15982, together with the results from the Phase 2 Study 14596, provide sufficient information for evaluation of the efficacy and safety of regorafenib in order to support an sNDA filing for the following indication: "Stivarga is indicated for the treatment of patients with hepatocellular carcinoma (HCC) who have been previously treated with [redacted (b) (4)]"?**

   FDA Response: FDA agrees that the results of both studies provide sufficient information to allow FDA to evaluate the efficacy and safety of regorafenib. However, FDA does not agree with the proposed indication. [redacted (b) (4)]

   Bayer's Response (Received via email on July 20, 2016): Bayer would like to discuss our rationale for the proposed indication. In that context, we would also like to discuss the

potential role of real-world evidence to support our proposed indication (b) (4)

Follow-up Question to FDA: Is our agreement to revise the indication as FDA has requested by email from Idara Udoh on July 12, 2016, a prerequisite for granting of Fast Track Designation? *FDA proposal: "For the treatment of patients with* (b) (4) *hepatocellular carcinoma (HCC) who have* ~~*been previously treated*~~ *with sorafenib* (b) (4)

Discussion During Meeting: FDA stated that the Fast Track designation (if granted) would need to incorporate prior sorafenib treatment in the indication statement (b) (4) FDA stated that Bayer could propose alternative labeling (with justification supporting their proposed approach) at the time of the original sNDA submission.

In regards to real-world evidence, FDA stated that Bayer could submit a proposal for review and feedback.

Question 2: Clinical Pharmacology

Bayer's position on Question #2 provided in Section 9.2 (page 36) of briefing package.

2. Does the Division agree with Bayer's planned exposure-response and dose modification analyses?

FDA Response: In general, the planned exposure-response and dose modification analyses are acceptable. FDA recommends that Bayer conduct multivariate Cox regression and/or logistic regression analyses, and includes the analysis report in the sNDA if the graphical exploration indicates any positive exposure-response relationship for efficacy.

Bayer's Response (Received via email on July 20, 2016): Analysis of the exposure-response is currently ongoing. Bayer would like to get an understanding from FDA of their definition of "any positive exposure-response relationship for efficacy".

Discussion During Meeting: FDA clarified that an exposure-response effect for efficacy may exist if there is a clinically relevant, visual separation between Kaplan-Meier survival curves in exposure groups for time-to-progression or overall survival. If such a separation is observed, a multivariate analysis would be recommended. Bayer asked for clarification regarding baseline characteristics of interest. FDA confirmed that the stratification factors should be considered for the exploratory post hoc analysis; however, other important prognostic factors could also be identified and incorporated into the analysis.

Question 3: Applicability of Data to US Population
Bayer's position on Question #3 provided in Section 9.3 (page 39) of briefing package.

3. **Does the Division concur with Bayer's analyses for US versus non-US subjects (outlined in the US-specific SAP), as well as for subjects from Asian vs Non-Asian countries (outlined in the global SAP for Study 15982) and agree that these analyses are adequate to demonstrate applicability of this study to the US population?**

   FDA Response: The proposed method is acceptable; however, whether the results are adequate to support the applicability to the US population will be determined during the review of the sNDA.

   Bayer's Response (Received via email on July 20, 2016): Bayer accepts FDA's responses and there is no further discussion.

   Discussion During Meeting: No discussion occurred.

Question 4: Clinical Benefit of Continued Treatment Past Progression
Bayer's position on Question #4 provided in Section 9.4 (page 41) of briefing package.

4. **Does the Division agree with Bayer's proposed approach to address the topic of treatment benefit post-progression?**

   FDA Response: Although we do not object to Bayer's proposed approach, we do not agree that the approach is sufficient to demonstrate that regorafenib provided clinical benefit in patients who experienced radiographic progression (e.g., based on absence of deterioration of ECOG performance status).

   Bayer's Response (Received via email on July 20, 2016): Since Bayer will not be seeking label claims of clinical benefit beyond progression, we would like to request additional understanding of FDA's feedback.

   Discussion During Meeting: FDA and Bayer agree that the analyses based on this information would be considered exploratory.

Question 5: Case Report Forms (CRFs) and Narratives
Bayer's position on Question #5 provided in Section 9.5 (page 42) of briefing package.

5. Does the Division agree with our planned submission of these CRFs and narratives?

FDA Response: No. Please also provide narrative summaries for patients who discontinued receiving regorafenib due to loss of follow-up, physician decision, or subject decision (or for administrative or other reasons not related to disease progression). Please also be prepared to submit any additional CRFs or narratives upon request.

Bayer's Response (Received via email on July 20, 2016): Bayer agrees to provide the additional narratives. Are these additional narrative summaries a new standard request for oncology applications?

Discussion During Meeting: FDA could not confirm that this is standard policy; however, additional CRFs or narratives are often requested as part of an NDA or sNDA submission to assist with the safety review.

Question 6: Rolling Review
Bayer's position on Question #6 provided in Section 9.6 (page 43) of briefing package.

6. Does the Division agree with this proposal of submitting the Module 2 and Module 5 clinical documents in a staggered manner in the context of the rolling submission?

FDA Response: If Bayer receives Fast Track (b) (4) based on the results of Study 15982, FDA agrees that Bayer can submit the clinical documents in a staggered manner in the context of a Rolling Review submission according to the following schedule proposed in the meeting package:

- August 2016:
  - Module 5: Study 15982 Final Study Report, Population PK Final Study Report, PK/PD Final Study Report, and Electronic Datasets.
  - Module 1 (except draft label)

- September 2016:
  - Module 5: Module 5.3.5.3 ISE and ISS, Electronic Datasets for Integrated Safety Analysis, Study 15982 US-Specific Report, and OSI requests.
  - Module 2: Module 2.7.2, 2.7.3, 2.7.4, and 2.6.
  - Module 1 (draft label).

If Bayer receives Fast Track (b) (4), please submit a formal request for Rolling Review with the agreed upon schedule as an amendment to the IND (with attached Form FDA 1571). Clearly identify the submission as a **REQUEST FOR SUBMISSION OF PORTIONS OF AN APPLICATION** in bold, uppercase letters.

Bayer's Response (Received via email on July 20, 2016): Bayer would like to inform FDA that we decided to reopen the database in order to address minor data issues that have no impact on the interpretation of the efficacy, safety and PK results, as well as on the benefit/risk profile of regorafenib. As a result, there will be a delay of approximately 1.5 months in the sNDA submission (for each wave of the rolling review) and the potential shifting of PK/PD and population PK reports into Wave 2. The revised rolling review strategy is as follows:

- **Wave 1 (approx. end Sept/beginning Oct 2016):**
  - Module 5: Study 15982 Final Study Report, ~~Population PK Final Study Report,~~ ~~PK/PD Final Study Report~~, and Electronic Datasets for Study 15982 and Population PK.
  - Module 1 (except draft label)
- **Wave 2 (approx. end of Oct/beginning Nov 2016):**
  - Module 5: Module 5.3.5.3 ISE and ISS, Electronic Datasets for Integrated Safety Analysis, **Population PK Final Study Report, PK/PD Final Study Report**, **Electronic data sets for PK/PD**, Study 15982 US-Specific Report, and OSI requests.
  - Module 2: Module 2.7.2, 2.7.3, 2.7.4, and 2.5.
  - Module 1 (draft label)

Does FDA agree with revised rolling review strategy?

Discussion During Meeting: FDA agrees that Bayer can submit the formal request for Rolling Review with the amended rolling submission strategy. FDA requested that Bayer document the data issues uncovered and how they were resolved.

Question 7: Applicant Orientation Meeting

7. **Given that Bayer will present the key efficacy and safety data from Study 15982 at the Pre-sNDA meeting, does the Division anticipate requesting an Applicant Orientation meeting for the HCC sNDA?**

FDA Response: No; however, FDA will contact Bayer if the Agency determines that the application would benefit from an Application Orientation meeting.

Bayer's Response (Received via email on July 20, 2016): Bayer accepts FDA's responses and there is no further discussion.

Discussion During Meeting: No discussion occurred.

ADDITIONAL FDA COMMENTS

Clinical Pharmacology

In the sNDA submission:

8. Provide a justification for the exposure metrics that are used in the exposure-response analyses. Drug exposure to be used in the analyses may include but not be limited to trough concentration at steady-state, maximum concentration at steady-state, average concentration at steady-state or trough concentration after the first dose. The use of either the parent drug exposure or metabolites exposure, or both, should be justified.

Bayer's Response (Received via email on July 20, 2016): Bayer accepts FDA's responses and there is no further discussion.

Discussion During Meeting: No discussion occurred.

9. Include the following in the exposure-response analysis reports:

a. A summary of baseline characteristics including but not limited to demographics, disease features and lab measurements, for all patients included in the analysis and subgroups based on drug exposures.

Bayer's Response (Received via email on July 20, 2016): Please see the following list of baseline characteristics that are planned to be incorporated in the analysis. This list can also be found in Section 6.1 of the Integrated Analysis SAP for the exposure-response analysis (Appendix 1 of the pre-sNDA Briefing Package). Bayer requests confirmation that this list is acceptable to FDA.

"Summary statistics (n, mean, SD, minimum, median, maximum) will be presented for the PKPD set for the variables age, weight, height, baseline body mass index (BMI), baseline ALT, baseline AST, baseline total bilirubin, and baseline platelets. If BMI is not available, it will be re-calculated if possible as baseline weight (kg) divided by height (m) squared. Frequency counts (n, %) will be presented for the variables sex, race group 1 (Asian vs Non-Asian), race group 2 (Japanese vs Chinese vs other Asian versus Non-Asian), ECOG performance status, baseline CTCAE grades for ALT, AST, total bilirubin, platelets, Child-Pugh score at baseline (A5 vs A6), hepatic function at baseline (maximum of baseline AST and baseline ALT ≤ 1.5*ULN vs > 1.5*ULN to ≤ 3* ULN vs > 3*ULN). 'Japanese' is defined as race = Asian and country = Japan, 'Chinese' is defined as race = Asian and country = mainland China."

Discussion During Meeting: FDA accepts Bayer's proposal and stated that additional information requests, if necessary, will be submitted during the sNDA review.

b. Distribution of drug exposure(s) for the full population used in the analysis.

Bayer's Response (Received via email on July 20, 2016): Bayer accepts FDA's responses and there is no further discussion.

Discussion During Meeting: No discussion occurred.

c. A summary table of final model parameters with their corresponding units.

Bayer's Response (Received via email on July 20, 2016): Bayer accepts FDA's responses and there is no further discussion.

Discussion During Meeting: No discussion occurred.

d. Any plots deemed appropriate to support the clinical interpretation of modeling results.

Bayer's Response (Received via email on July 20, 2016): Bayer accepts FDA's responses and there is no further discussion.

Discussion During Meeting: No discussion occurred.

e. A summary describing the clinical application of modeling results.

Bayer's Response (Received via email on July 20, 2016): Bayer accepts FDA's responses and there is no further discussion.

Discussion During Meeting: No discussion occurred.

10. Conduct graphical analysis of time to first dose modification in the overall population and by exposure groups.

Bayer's Response (Received via email on July 20, 2016): Bayer accepts FDA's responses and there is no further discussion.

Discussion During Meeting: No discussion occurred.

11. Please refer to the following guidance for general expectations on submitting pharmacometrics data and models: http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm.

Bayer's Response (Received via email on July 20, 2016): Bayer accepts FDA's responses and there is no further discussion.

Discussion During Meeting: No discussion occurred.

ADDITIONAL MEETING DISCUSSION

Labeling

Bayer inquired whether the safety data described in Section 5 of labeling could be consolidated across indications, rather than describing incidence rates separately for each indication. FDA stated that such an approach may be appropriate as long as the data pertaining to the specific Warnings are consistent in the different indications. FDA agreed that it could be appropriate to include the East Asian data in the pool if the data pertaining to the specific Warning are consistent with the data in the other populations, and providing the data are submitted in the sNDA.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions "shall be submitted in such electronic format as specified by [FDA]." FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog (Catalog) (See http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm).

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf). This guidance describes the submission types, the standardized study data

requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf), as well as email access to the eData Team (cder-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or after December 17, 2017. CDER has produced a *Study Data Standards Resources* web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that start before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

Additional information can be found at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm.

For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, CDER encourages sponsors to use Standards for the Exchange of Nonclinical Data (SEND) and submit sample or test data sets before implementation becomes required. CDER will provide feedback to sponsors on the suitability of these test data sets. Information about submitting a test submission can be found here: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm.

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled, Study Data Standards Resources and the

CDER/CBER Position on Use of SI Units for Lab Tests website found at http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm.

ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the draft guidance for industry, *Guidance for Industry Assessment of Abuse Potential of Drugs*, available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf.

Office of Scientific Investigations (OSI) Requests

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
   a. Site number
   b. Principal investigator
   c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
   d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a

clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.

2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
   a. Number of subjects screened at each site
   b. Number of subjects randomized at each site
   c. Number of subjects treated who prematurely discontinued for each site by site

3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
   a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
   b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
   c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

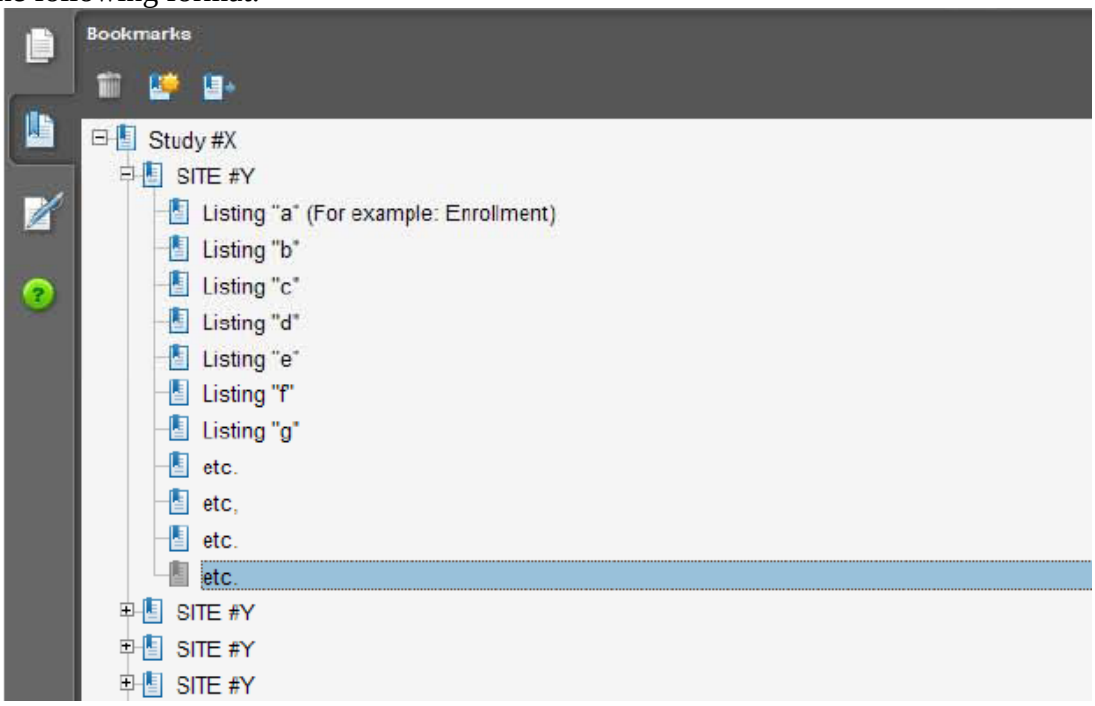
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
   a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
   b. Subject listing for treatment assignment (randomization)
   c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
   d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
   e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)

f. By subject listing, of AEs, SAEs, deaths and dates
g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring

2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER's Inspection Planning" (available at the following link http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf) for the structure and format of this data set.

Attachment 1

Technical Instructions:
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named "BIMO [list study ID, followed by brief description of file being submitted]." In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be "bimo." Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be "clinsite.xpt."

DSI Pre-NDA Request Item[1]	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:

C. It is recommended, but not required, that a Reviewer's Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be "BIMO Reviewer Guide." The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

[1] Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf)

FDA eCTD web page
(http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm)

For general help with eCTD submissions: ESUB@fda.hhs.gov

NEW PROTOCOLS AND CHANGES TO PROTOCOLS

To ensure that the Division is aware of your continued drug development plans and to facilitate successful interactions with the Division, including provision of advice and timely responses to your questions, we request that the cover letter for all new phase 2 or phase 3 protocol submissions to your IND or changes to these protocols include the following information:

1. Study phase
2. Statement of whether the study is intended to support marketing and/or labeling changes
3. Study objectives (e.g., dose finding)
4. Population
5. A brief description of the study design (e.g., placebo or active controlled)
6. Specific concerns for which you anticipate the Division will have comments
7. For changes to protocols only, also include the following information:
    - A brief summary of the substantive change(s) to the protocol (e.g., changes to endpoint measures, dose, and/or population)
    - Other significant changes
    - Proposed implementation date

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

ISSUES REQUIRING FURTHER DISCUSSION

No issues requiring further discussion.

ACTION ITEMS

No action items.

ATTACHMENTS AND HANDOUTS

"Stivarga (regorafenib) Study 15982 (RESORCE) Key Results"

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

IDARA UDOH
07/27/2016