CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203085Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	203085
Priority or Standard	Priority
Submit Date(s)	April 27, 2012
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Division / Office	Division of Oncology Products 2 / Office of Hematology Oncology Products
Reviewer Name(s)	Shan Pradhan, MD Kaushik Shastri, MD
Review Completion Date	September 5, 2012
Established Name	Regorafenib
Trade Name	Stivarga
Therapeutic Class	Multikinase inhibitor
Applicant	Bayer Health Care Pharmaceuticals, Inc.
Formulation(s)	40 mg oral tablet
Dosing Regimen	160 mg (four 40 mg tablets) taken orally once daily for 21 days of a 28-day cycle
Indication(s)	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 KRAS wild type, an anti-EGFR therapy
Intended Population(s)	Adults ≥ 18 years of age

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This clinical review team recommends approval of new drug application (NDA) 203085 for regorafenib tablets for 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.

This NDA is primarily supported by a single, multicenter, randomized (2:1), double-blind, placebo-controlled trial, Trial 14387, in a total of 760 patients with previously treated mCRC. All patients received prior treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy and with bevacizumab, and all but one patient with a KRAS wild type tumor received panitumumab or cetuximab. Patients were randomized to receive 160 mg regorafenib orally once daily (n=505) plus best supportive care (BSC) or placebo (n=255) plus best supportive care for the first 21 days of each 28-day cycle. Treatment continued until disease progression, unacceptable toxicity, or death.

The assessment of benefit in this application is based on the primary endpoint of overall survival. This recommendation for approval is based on review of the clinical data, which support the conclusion that regorafenib prolongs overall survival in patients who have failed standard chemotherapy (a population for whom no other therapy is currently approved). A statistically significant, clinically meaningful prolongation in overall survival was observed in patients randomized to receive regorafenib; median survival was 6.4 months in the regorafenib arm (95% CI: 5.8, 7.3) compared to 5.0 months in the placebo arm (95% CI: 4.4, 5.8), with a hazard ratio of 0.77 (95% CI: 0.64, 0.94; p=0.0102).

Supportive efficacy outcome measures in Trial 14387 were progression free survival and overall response rate. The PFS benefit observed was modest, with a median PFS of 2.0 months in the regorafenib arm (95% CI: 1.9, 2.3) compared to 1.7 months in the placebo arm (95% CI: 1.7, 1.8), with a hazard ratio of 0.49 (95% CI: 0.42, 0.58; p<0.0001). The overall response rate was low, consisting of 5 patients (1%) in the regorafenib arm and 1 patient (0.4%) in the placebo arm.

The FDA Guidance for Industry entitled "*Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*" states that for approval, "reliance on only a single study will generally be limited to situations in which a trial has demonstrated a clinically meaningful effect on mortality, irreversible morbidity, or prevention of a disease with a potentially serious outcome, and confirmation of the result in a second trial would be practically or ethically impossible". Trial 14387 was a large randomized trial which demonstrated robust and consistent results across most patient subsets and achieved

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more than one endpoint including a clinically meaningful, statistically significant overall survival benefit in a population for whom no other therapy is approved, providing sufficient basis for approval as set forth in the guidance.

1.2 Risk Benefit Assessment

Trial 14387 included 500 patients who received regorafenib at the proposed dose (160 mg orally once daily for the first 21 days of each 28-day cycle until disease progression, unacceptable toxicity, or death) and 253 patients who received placebo.

The mean duration of therapy was 12 weeks for the regorafenib group and 8 weeks for placebo. Treatment emergent adverse events resulted in dose interruptions in 61% of patients receiving regorafenib and 38% of patients had their dose reduced. In the placebo group, dose interruptions and dose reductions occurred in 22% and 3% of patients, respectively.

The most significant toxicities observed with regorafenib were drug induced liver injury, hemorrhage, dermatologic toxicity (palmar-plantar erythrodysesthesia and rash), hypertension, cardiac ischemic events, and gastrointestinal perforation.

Severe drug induced liver injury with fatal outcome occurred in 0.3% of 1100 regorafenib-treated patients (across all clinical trials). In Trial 14387, fatal hepatic failure occurred in 1.6% of patients in the regorafenib arm and 0.4% of patients in the placebo arm. All patients with hepatic failure had metastatic disease in the liver. Liver biopsy findings in 2 cases showed hepatocyte necrosis and lymphocyte infiltration. This review team recommended inclusion of a boxed warning for hepatotoxicity in the regorafenib product label.

The overall incidence (Grades 1-5) of hemorrhage was 21% among regorafenib-treated patients compared to 8% among placebo-treated patients. Fatal hemorrhage occurred in 4 of 500 (0.8%) regorafenib-treated patients and involved respiratory, gastrointestinal, and genitourinary tracts.

The overall incidence of palmar-plantar erythrodysesthesia (PPE) (45% versus 7%) and the incidence of Grade 3 PPE (17% versus 0) were increased in regorafenib-treated patients compared to placebo. The overall incidence of rash (26% versus 4%) and the incidence of Grade 3 rash (6% versus <1%) were also higher in regorafenib-treated patients. The onset of dermatologic toxicity occurred in the first cycle of treatment in most patients and frequently required dose modification.

Hypertension occurred in 30% of regorafenib-treated patients versus 8% of placebo-treated patients. The onset of hypertension occurred during the first cycle of treatment in most patients.

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The incidence of myocardial ischemia or infarction was higher in regorafenib-treated patients (1.2 % versus 0.4%) compared to placebo. Gastrointestinal perforation or fistula occurred in 0.6% of 1100 patients treated with regorafenib (across all clinical trials). A single case of reversible posterior leukoencephalopathy (RPLS) was observed among the 1100 patients.

The most frequently observed adverse reactions (occurring in ≥ 30% of patients) with regorafenib were asthenia/fatigue, decreased appetite and food intake, palmar-plantar erythrodysesthesia (PPE), diarrhea, mucositis, weight loss, infection, hypertension, and dysphonia.

The safety profile of regorafenib is similar to drugs with similar mechanisms of action including other multikinase inhibitors. This clinical review team concludes, based on the overall survival benefit observed in Trial 14387, that regorafenib has demonstrated an acceptable risk-benefit profile in the proposed population of patients with refractory metastatic colorectal cancer.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None. The proposed USPI contains patient counseling information for prescribing physicians (oncologists) and a patient information leaflet.

The Applicant also included a Risk Management Plan in the submission which referenced the ongoing Expanded Access Study (Treatment Protocol 15967) under IND 75642. In response to an information request from this clinical review team, the Applicant stated that should regorafenib be approved, the Applicant plans to (b) (4)

The Applicant further stated that a minimum of (b) (4) patients will be recruited to the study and that the clinical study report is projected to be complete by October 31, 2014.

1.4 Recommendations for Postmarket Requirements and Commitments

No specific new studies were recommended by the clinical review team.

See Clinical Pharmacology review for recommendations from the clinical pharmacology review team for postmarket requirements and commitments.

The Pediatric Review Committee granted a full waiver of the requirements under the Pediatric Research Equity Act (PREA) because the rarity of colorectal cancer in the pediatric population renders conduct of the necessary studies impossible or highly impractical.

2 Introduction and Regulatory Background (S. Pradhan)

The trade name for regorafenib is Stivarga. Regorafenib is a small molecule inhibitor of multiple kinases (including BRAF, VEGFR 1/2/3, TIE2, PDGFR, FGFR, RET, and KIT) involved in normal cellular functions and in pathologic processes such as oncogenesis and tumor angiogenesis.

2.1 Product Information

Table 1 Regorafenib Product Information

Generic Name:	Regorafenib
Trade Name:	Stivarga
Pharmacologic Category:	Multikinase inhibitor
Drug Class:	Small molecule
Route of Administration:	Oral
Storage:	Store at 25˚C (77˚) in the original container
Drug Product:	Tablets in packages containing 3 bottles, with each bottle containing 28 tablets
Dose and Regimen:	160 mg (four 40-mg tablets) orally once daily for the first 21 days of each 28-day cycle

2.2 Tables of Currently Available Treatments for Proposed Indications

There are no (FDA) approved products for the treatment of patients with mCRC for whom treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF therapy, and, if KRAS wild type, an anti-EGFR therapy, has failed.

2.3 Availability of Proposed Active Ingredient in the United States

Regorafenib is a new molecular entity and is not currently marketed in the United States.

2.4 Important Safety Issues With Consideration to Related Drugs

Regorafenib (BAY 73-4506,   (b) (4)) is a small molecular inhibitor of multiple kinases including BRAF, VEGFR 1/2/3, TIE2, PDGFR, FGFR, RAF-1, KIT and RET. Regorafenib interferes both with tumor-cell proliferation and tumor angiogenesis. Multi-kinase agents that inhibit at least 3 of the main tyrosine kinases targeted by regorafenib (VEGFR, PDGFR and KIT) include sorafenib (Nexavar), sunitinib (Sutent) and pazopanib (Votrient).

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The package insert for Nexavar contains the following potentially serious adverse events in warnings and precautions: cardiac ischemia/infarction, hemorrhage, hypertension, dermatologic toxicity, GI perforation, elevation in INR when taking warfarin, wound healing complications, increased mortality in squamous cell lung cancer when co-administered with carboplatin/paclitaxel and gemcitabine/Cisplatin, QT prolongation, and fetal harm. The most common adverse reactions (≥20%), which were considered to be related to Nexavar are fatigue, weight loss, rash/desquamation, hand-foot skin reaction, alopecia, diarrhea, anorexia, nausea and abdominal pain.

The package insert for Sutent contains the following potentially serious adverse events in warnings and precautions: hepatotoxicity, fetal harm, left ventricular dysfunction, QT prolongation and torsades de pointes, hypertension, hemorrhagic events, osteonecrosis of the jaw, tumor lysis syndrome, thyroid dysfunction, wound healing, adrenal insufficiency (in patients undergoing stress such as surgery, trauma or severe infection). The most common adverse reactions (≥2 0%) are fatigue, asthenia, fever, diarrhea, nausea, mucositis/stomatitis, vomiting, dyspepsia, abdominal pain, constipation, hypertension, peripheral edema, rash, hand-foot syndrome, skin discoloration, dry skin, hair color changes, altered taste, headache, back pain, arthralgia, extremity pain, cough, dyspnea, anorexia, and bleeding.

The package insert for Votrient contains the following potentially serious adverse events in warnings and precautions: hepatotoxicity, QT prolongation and torsades de pointes, cardiac dysfunction, hemorrhagic events, arterial and venous thrombotic events, GI perforation and fistula, RPLS, hypertension, hypothyroidism, wound healing, proteinuria, infection, and increased toxicity with other cancer therapies. The most common adverse reactions in patients with advanced renal cell carcinoma (≥20%) are diarrhea, hypertension, hair color changes (de-pigmentation), nausea, anorexia, and vomiting. The most common adverse reactions in patients with advanced soft tissue sarcoma (≥20%) are fatigue, diarrhea, nausea, decreased weight, hypertension, decreased appetite, vomiting, tumor pain, hair color changes, musculoskeletal pain, headache, dysgeusia, dyspnea, and skin hypo-pigmentation.

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2.5 Summary of Presubmission Regulatory Activity Related to Submission

The following table summarizes key regulatory background for this application.

Table 2 NDA 203085 Key Regulatory Background

September 2009	End-of-Phase 2 meeting
January 2010	SPA No Agreement letter issued
April 2010	Response to Type A meeting questions issued
June 2011	Fast Track designation granted
August 2011	Pre-NDA meeting

September 2009 End of Phase 2 Meeting
- FDA recommended overall survival as the primary efficacy endpoint for Trial 14387.
- FDA stated that placebo plus best supportive care would be acceptable as the control arm treatment, provided patients experienced disease progression after all approved therapies for mCRC.
- Bayer proposed a new study design with OS as the primary endpoint and two formal interim analyses for efficacy; FDA stated that this proposal was acceptable.
- FDA agreed to the use of RECIST (b) (4) for tumor response assessments.
- FDA stated that the stratification factors proposed (ECOG performance status, prior targeted therapy, and geographic region) were acceptable.

January 2010 SPA No Agreement Letter Issued
- FDA stated that whether a 1.5-month increment in median OS would be clinically relevant would be a review issue.
- FDA stated that any subgroup analyses would be considered exploratory and may not be included in labeling.
- FDA stated that Bayer would need to ensure enrollment of a population that is representative of the US population.
- Bayer proposed testing PFS, ORR, and DCR (b) (4)

April 2010 Response to Type A Meeting Questions
- FDA stated that whether the population ultimately enrolled in Trial 14387 is representative of the US population would be a review issue.

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Reference ID: 3185412

August 2011 Pre-NDA Meeting

- Bayer proposed including the text portion of the ISS and ISE in Module 2 and agreed to include tables, figures, appendices, and datasets in Module 5. FDA stated that this plan was acceptable.
- FDA stated that CRFs for SAEs should be submitted.
- FDA requested that narratives for all SAEs except those related to disease progression be submitted.
- FDA stated that the differential between the data cutoff date for the 120 day safety update and submission of the 120-day safety update should not be greater than 6 months.

2.6 Other Relevant Background Information

None.

3 Ethics and Good Clinical Practices (S. Pradhan)

3.1 Submission Quality and Integrity

Electronic datasets were submitted in CDISC format as requested by the Division. Adverse events (AE) from a subset of case report forms for Trial 14387 were reviewed and compared to the datasets in order to confirm accuracy of the data transfer. Verbatim terms for all Grade 3, 4, or 5 (NCI CTCAE v3.0) AEs in Trial 14387 were compared to the corresponding MedDRA lower level terms and AE coding was deemed adequate.

The submission was of adequate quality and integrity to allow for review of the clinical trial pertaining to the proposed indication.

3.2 Compliance with Good Clinical Practices

The submission [module 2, section 2.5 (Clinical Overview), page 39)] contained a statement that Trial 14387 was conducted in accordance with the Declaration of Helsinki and the ICH Good Clinical Practice (GCP) Guideline.

Because Stivarga is an NME, an OSI consult was requested for the clinical inspection of 4 trial sites. Sites were selected based upon analyses of site-specific efficacy data, numbers and types of protocol violations, patient enrollment per site, and investigator financial conflict of interest disclosures.

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Table 3 DSI Clinical Inspections

Site Number	PI / Site	Number of Patients
22004	Dr. Alfredo Falcone A.O.U. Pisana, Oncologia Medica 2 ITALY	29
28001	Dr. Eric Van Cutsem UZ Leuven Gasthuisberg BELGIUM	34
14001	Dr. Axel Grothey Mayo Clinic - Rochester USA	22
22005	Dr. Salvatore Siena A.O. Osp Niguarda Ca. Granda, Oncologia Medica Falck ITALY	36

Clinical inspection results were not available at the time of completion of this review.

3.3 Financial Disclosures

The submission included a Form 3454 (Certification: Financial Interests and Arrangements of Clinical Investigators) completed by the Applicant. All financial disclosure materials in section 1.3.4 (Financial Disclosure) were reviewed.

One sub-investigator for Trial 14387,   (b) (6)   , was listed as holding disclosable financial interest. A Form 3455 (Disclosure: Financial Interests and Arrangements of Clinical Investigators) completed by the Applicant and naming Dr.
     (b) (6)   was included in the application.   (b) (6)

A Statement of Actions to Minimize Bias was submitted for   (b) (6)   and the steps taken by the Applicant were acceptable. Additionally, the primary endpoint of Trial 14387 (and the basis for the assessment of benefit in this application) was overall survival, not a subjective endpoint open to investigator bias.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines (S. Pradhan)

This section summarizes issues relating to the safety and efficacy of regorafenib identified by other review disciplines as of September 3, 2012. Some portions were

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excerpted all or in part directly from the respective discipline reviews. This summary should be considered partial and preliminary; please refer to the respective discipline reviews for a full description of issues identified during the NDA review.

4.1 Chemistry Manufacturing and Controls

The CMC drug substance (DS) review encompassed CMC information provided in the original NDA and amendments received through August 28, 2012. The structure was adequately defined, the   (b) (4) were adequate, information for all impurities was adequately presented. The DS was physically and chemically stable based on evaluation of stability testing data. The CMC DS reviewer concluded that Bayer submitted adequate information to support the DS section of the NDA.

The CMC drug product (DP) reviewer recommended approval of the NDA. Inspection results for the Bayer Pharma AG, Leverkausen, Germany facility are pending. The CMC DP reviewer recommended changes to the carton and container labeling; refer to the CMC DP review.

4.2 Clinical Microbiology

Not applicable (not required for a solid oral dosage form).

4.3 Preclinical Pharmacology/Toxicology

Target organs for regorafenib-mediated toxicity identified in toxicology studies conducted using rats and dogs included the liver, kidney, adrenal gland, thyroid, pancreas, gastrointestinal tract, hematopoietic/lymphoid system, reproductive system, and skeletal system.

Findings of changes in dentin and epiphyseal growth plates were present in both species. These changes have been associated with many VEGF inhibitors and may be relevant to the pediatric population. The pharmacology/toxicology review team recommended inclusion of these findings in product labeling.A single dose study in rats also demonstrated decreases in gastric motility following administration of regorafenib.

In the hematopoietic system, there were findings of bone marrow hypocellularity, atrophy of the spleen, lymph nodes, and thymus in rats at doses resulting in exposures similar to the exposure in humans at the recommended daily dose. In dogs, thymic atrophy was observed at the high dose levels in all studies; atrophy was also observed in lymph nodes.

Both rats and dogs had histopathological findings in the liver along with elevations in liver enzymes in short and long term repeat dose toxicology studies. Skin toxicity was observed in dogs at all dose levels of regorafenib administration in a 13-week study.

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Administration of regorafenib to both rats and dogs also resulted in increases in thyroid stimulating hormone (TSH). Renal toxicity was observed in all repeat-dose toxicology studies conducted with regorafenib.

Renal findings in rats and dogs included glomerulopathy, tubular degeneration / regeneration, tubular dilation, and interstitial fibrosis. No renal toxicity was noted in 1-month studies with either the M-2 or the M-5 metabolite. Thus differences in metabolism between humans, rats, and dogs leading to significantly higher human exposures to M-2 and M-5 compared to the species used for toxicological assessment may account for higher levels of renal toxicity seen in animals compared to humans.

Cardiovascular safety was examined in both single and repeat-dose toxicology studies in dogs. None of the studies revealed significant changes in ECG parameters. In *in vitro* experiments, regorafenib showed low potential for QTc prolongation; however, the M-2 and M-5 metabolites had IC_{50}s of 1.1 and 1.8 µM, respectively in the hERG assay, suggesting a higher potential for QTc prolongation. The M-2 and M-5 metabolites were not present in dogs at significant levels, thus the animal studies may have underpredicted the potential for regorafenib-induced QTc prolongation in humans. To address this issue, single dose cardiovascular safety studies in dogs were conducted using each of the metabolites. There were no clearly adverse effects noted for either metabolite in these studies and in 1-month repeat-dose toxicology studies conducted in mice using each of the metabolites, no unique toxicities compared to those observed in animals administered regorafenib were identified.

Dedicated studies examining fertility and pre- and post-natal development were not conducted to support the treatment of patients with advanced cancer. However, findings in the toxicology studies described above suggest that regorafenib could affect fertility in humans.

Embryofetal studies were conducted in Wistar rats and Himalyan rabbits. In both species, at doses resulting in exposures significantly lower than the human exposure at the recommended daily dose, there were increases in post-implantation loss and teratogenic effects including skeletal and cardiovascular malformations and renal findings of dilation of the renal pelvis or hydronephrosis. Pregnancy category D was recommended.

In a distribution study in pregnant rats administered radiolabeled regorafenib, there was clear exposure to the fetus. Findings suggested a high risk for neonatal exposure to regorafenib in breast milk from women taking regorafenib.

Regorafenib was not mutagenic in *in vitro* or *in vivo* assessments of genotoxicity; however, the M-2 metabolite was clastogenic in an *in vitro* assay suggesting that the

drug may have mutagenic potential in humans. No carcinogenicity studies were conducted to support the marketing application.

The pharmacology/toxicology review team concluded that there were no pharmacology/toxicology issues precluding approval of regorafenib for the proposed indication.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Regorafenib is a small molecule inhibitor of multiple tyrosine kinases involved in normal cellular functions and in pathologic processes such as oncogenesis, tumor angiogenesis, and maintenance of tumor microenvironment.

4.4.2 Pharmacodynamics

In *in vitro* assays, regorafenib or its major human active metabolites M-2 and M-5 inhibited the activity of RET, PTK5, FGFR-1 and -2, VEGFR-1, -2, and -3, SAPK2, Tie2, Abl, TrkA, EphA2, PDGFR-α and –β, KIT, RAF-1, BRAF, and $BRAF_{V600E}$ at clinically relevant concentrations of regorafenib. In *in vivo* models regorafenib demonstrated inhibitory activity in a tumor-bearing rat angiogenesis model and in multiple mouse xenograft models. The M-2 and M-5 metabolites of regorafenib inhibited some of the same protein kinases as regorafenib and with IC_{50} values similar to regorafenib.

The applicant included an interim analysis of QT/QTc intervals recorded from 25 patients with advanced solid tumors enrolled in a dedicated cardiovascular safety study. Because Trial 14387 was completed earlier than anticipated (and demonstrated a benefit in overall survival), several clinical pharmacology studies, including the QT/QTc study, remain ongoing. Prior to the NDA submission, FDA agreed to the Applicant's proposal to submit the reports of these ongoing studies in November 2012 under postmarketing requirements and postmarketing commitments. The cardiovascular safety study report and an analysis of cardiac data will be a PMR.

FDA agreed with the Applicant's proposal to submit an exposure-response (E-R) analysis for Trial 14387 postmarketing (PMC). Based on an analysis conducted in Study 11650 (a dose-finding study), no clear E-R relationship was observed for regorafenib, M-2, or M-5 between exposure and selected indices of safety or clinical activity.

4.4.3 Pharmacokinetics

M-2 and M-5 were measured in the PK studies along with regorafenib. Following a single 160 mg dose, regorafenib reached mean C_{max} of 2.5 µg/mL at a median time (T_{max}) of 3 hrs and the mean AUC of 70.4 µg*h/mL. At steady-state, regorafenib reached mean C_{max} of 3.9 µg/mL and the mean AUC of 58.3 µg*h/mL. The mean elimination half-life ($t_{1/2}$) was 28 hrs. The metabolites M-2 and M-5 reached steady-state concentrations that were similar to regorafenib. The mean $t_{1/2}$ for M-2 was 25 hrs and for M-5 was 51 hrs.

Regorafenib is recommended to be administered with a low-fat meal. As compared to the fasted state, a low-fat breakfast increased the mean AUC of regorafenib, M-2 and M-5 by 36%, 40% and 23%, respectively, whereas a high-fat meal increased the mean AUC of regorafenib by 48%, but decreased the mean AUC of M-2 and M-5 by 20% and 51%, respectively.

No differences in the mean exposure of regorafenib and the metabolites M-2 and M-5 were observed in 10 patients with mild renal impairment (CLcr 60 to 89 mL/min) as compared to 18 patients with normal renal function. The applicant will be required to conduct a repeat dose study to determine an appropriate dose for patients with severe renal impairment as a PMR.

No differences in the exposure of regorafenib and the metabolites M-2 and M-5 were observed in 14 patients with hepatocellular cancer (HCC) and mild hepatic impairment (Child-Pugh A) and 4 patients with HCC and moderate hepatic impairment (Child-Pugh B) relative to 10 patients with solid tumors and normal hepatic function. Regorafenib has not been administered to patients with severe hepatic impairment (Child-Pugh C).

The administration of ketoconazole 400 mg daily for 18 days with a single 160 mg dose of regorafenib increased the mean AUC of regorafenib by 33% and decreased the mean AUC of M-2 and M-5 each by 93%. The administration of rifampin 600 mg daily for 9 days with a single 160 mg dose of regorafenib decreased the mean AUC of regorafenib by 50% and increased the mean AUC of M-5 by 264%; the mean AUC of M-2 was similar with and without rifampin. Regorafenib or the active metabolites M-2 or M-5 inhibited CY2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4 *in vitro.* Regorafenib did not induce cytochrome P450 activity *in vitro*; however, it is not known if regorafenib, M-2 or M-5 induce CYP1A2, CYP2B6, and/or CYP3A4 mRNA expression levels*.*

Regorafenib inhibited UGT1A9 and the three active moieties (regorafenib, M-2 and M-5) inhibited UGT1A1 *in vitro*. When irinotecan was administered five days after the last dose of seven daily doses of regorafenib, the mean AUC of SN-38 increased by 44% and the mean AUC of irinotecan increased by 28%.

Population PK (PopPK) analyses are ongoing. The Applicant will submit an integrative population PK (PopPK) report as a PMC.

5 Sources of Clinical Data (S. Pradhan)

5.1 Tables of Studies/Clinical Trials

Biopharmaceutic Studies	Comparative Bioequivalence and Bioavailability	PH-36595 (Study 12437)
	Bioavailability	PH-36525 (Study 14656)
Human PK Studies	Healthy Subject PK and Initial Tolerability	PH-36734 (Study 12436)
	Patient PK and Initial Tolerability	PH-36733 (Study 11650)
		PH-36742 (Study 11651)
		PH-36741 (Study 11651)
		A51164 (Study 13172)
		A51600 (Study 14996)
		PH-36735 (Study 11656)
	Extrinsic Factor PK	PH-36717 (Study 12435)
		PH-36716 (Study 15524)
		PH-36721 (Study 12434)
Human PD Studies	Patient PD and PK/PD	PH-36720 (Study 14814)
Efficacy and Safety Studies	Proposed mCRC Indication	A53306 (Study 14387)
	Hepatocellular Carcinoma	A51601 (Study 14596)
	Metastatic or Unresectable Renal Cell Cancer	A46572 (Study 11726)
		A55873 (Study 11726)

5.2 Review Strategy

The safety and efficacy data including the clinical study report, CRFs, and electronic datasets for Trial 14387 were reviewed. Trial 14387 was a single, multicenter, randomized (2:1), double-blind, placebo-controlled trial that enrolled patients with previously treated mCRC and formed the basis of this NDA. Other studies submitted to the NDA included relatively few patients, populations outside that proposed in this application, or varied regorafenib dosing regimens.

Trial 14387 enrolled 760 patients, utilized the regorafenib dosing regimen proposed in the application, and consisted of the application's intended population (this review team recommended modification of the Indication statement in the product labeling, see section 6.1 Indication).

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Section 5.3 contains a description of the design of Trial 14387. Refer to section 6.1.8 for brief descriptions of Studies 11650 and 11651 (dose-finding studies). Also refer to sections 6.1.1 and 7.1, the Methods sections of the Efficacy and Safety portions of this clinical review, respectively, for efficacy-specific or safety-specific review methodologies.

5.3 Discussion of Individual Studies/Clinical Trials

<u>Trial 14387</u>

Trial 14387 was a single, multicenter, randomized (2:1), double-blind, placebo-controlled trial that enrolled patients with previously treated mCRC who received prior treatment with fluoropyrimidine-, oxaliplatin-, or irinotecan-based chemotherapy, bevacizumab, and, if KRAS wild type, an anti-EGFR therapy.

The trial compared regorafenib with placebo with respect to the following endpoints:

- <u>Primary</u>: overall survival (time from randomization to death due to any cause)

- <u>Secondary</u>: progression free survival, tumor response rate, and disease control rate

- <u>Other</u>: included health-related quality of life measures, regorafenib PK, and biomarker evaluations

Patients were randomized to receive 160 mg regorafenib orally once daily (n=505) plus best supportive care (BSC) or placebo (n=255) plus best supportive care for the first 21 days of each 28-day cycle. Treatment continued until disease progression, unacceptable toxicity, or death.

The three randomization factors were as follows:

- Prior treatment with VEGF-targeting drugs
  - o Yes
  - o No

- Time from diagnosis of metastatic disease
  - o ≥ 18 months
  - o < 18 months

- Geographic region
  - o Region 1
    - North America
    - Western Europe

- Israel
- Australia

  o Region 2
     - Asia

  o Region 3
     - South America
     - Turkey
     - Eastern Europe

Figure 1 Trial 14387 Design

760 patients randomized; 753 received ≥ 1 dose
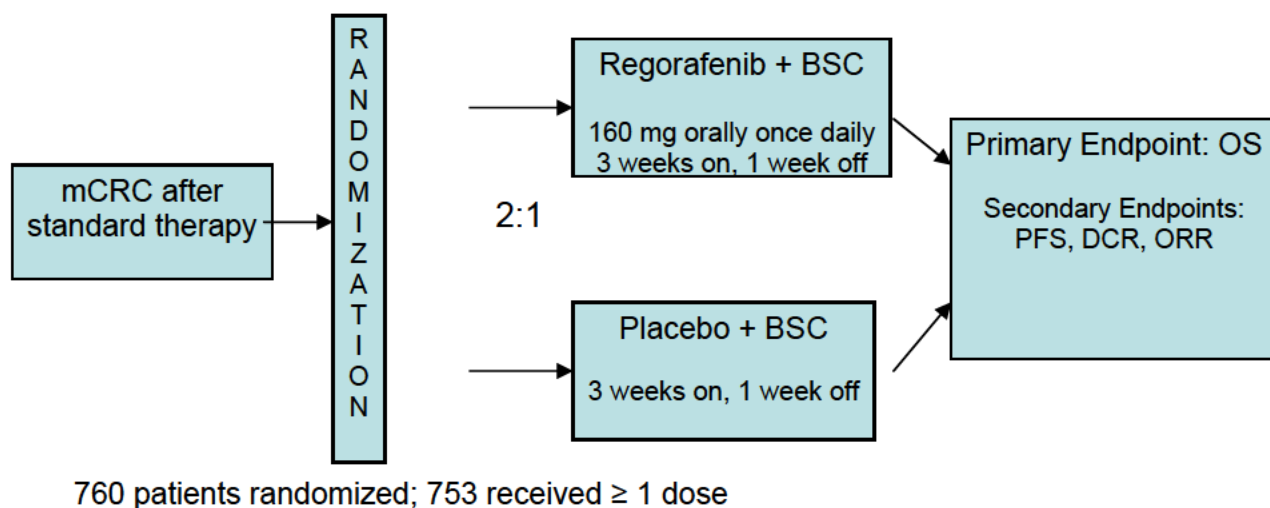
Upon discontinuation of regorafenib or placebo treatment, all patients entered the follow-up period. All patients were followed-up for survival (approximately each month) until documented death except for those patients who withdrew consent for follow-up. Patients who withdrew consent from study drug treatment only were allowed to enter the follow-up period.

An independent Data Monitoring Committee (DMC) evaluated the safety and efficacy data during the conduct of the study.

Eligibility criteria included mCRC with disease progression within 3 months after the last administration of approved standard therapies (or intolerance, and approved therapies had to include a fluoropyrimidine, oxaliplatin, irinotecan, bevacizumab, and, if KRAS

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wild type, cetuximab or panitumumab), ECOG performance status 0-1, and age ≥ 18 years.

Tumor response and disease progression were evaluated using RECIST v1.1. Radiologic measurements were performed at baseline and then every 8 weeks during the treatment period until progressive disease was documented. In cases when radiographic imaging was not possible, clinical progression was used. Clinical progression was based on the judgment of the investigator.

Regorafenib was orally administered. The protocol stated that regorafenib should be taken in the morning with 8 ounces of water and "after a low-fat (<30% fat) breakfast." Two examples of "a low-fat breakfast" were included in an appendix to the protocol. Refer to the Clinical Pharmacology review for analysis of food effects.

The protocol allowed for dose delays or reductions in case of specified toxicities. Three dose levels (160 mg QD, 120 mg QD, and 80 mg QD) were predefined. The protocol included dose modification instructions for hand-foot skin reaction, hypertension, and transaminitis or elevated bilirubin.

Permitted Concomitant Therapies (modified from the CSR for brevity):
- Standard therapies for concurrent medical conditions, including prophylactic anti-emetics
- Nonconventional therapies (e.g., herbs or acupuncture) and vitamin/mineral supplements provided they do not interfere with the study endpoints in the opinion of the investigator
- Bisphosphonates
- Warfarin or heparin provided the dose and INR/PTT are stable.

Prohibited Therapies (modified from the CSR for brevity):
- Systemic anticancer therapy
- TKIs
- BMT or stem cell rescue
- Concomitant palliative radiotherapy was allowed only if the target lesions were not included within the radiation field and no more than 10% of the bone marrow was irradiated
- Biologic response modifiers such as granulocyte colony stimulating factor (GCSF) within 3 weeks of study entry. GCSF and other hematopoietic growth factors were permitted during the study in the management of acute toxicity such as febrile neutropenia when clinically indicated or at the discretion of the investigator (though not as a substitute for protocol-specified dose reduction)
- Traditional medicines with an anticancer indication, including Traditional Chinese Medicine
- St. John's Wort

-

Figure 2 Schedule of Assessments (copied from CSR)

Procedures[56]	Screening (Assessments can be completed in one or more visits, as long as they are completed within the time frames.)			Cycle 1 (4 weeks)		Cycle 2+ (4 weeks)		End of Treatment	Safety Follow-up	Follow-up
	Within 28 days	Within 14 days	Within 7 days	Day 1	Day 15	Day 1	Day 15 [k]	Within 14 days	Within 30 days	Every month
Informed consent	X									
Inclusion/exclusion Criteria Checked		X		X						
Demographics	X									
Diagnosis Confirmation	X									
Tumor assessment (CT or MRI) [a]	X					X[a]		X		X[a]
Head CT/MRI (if brain metastases are suspected)	X									
Past cancer chemotherapy, radiotherapy and surgery	X									
12-lead ECG [b]	X			X		X[b]		X		
Echocardiography or MUGA (LVEF assessment) [c]	X				X[c]					
Adverse Events & Toxicities [d]					X[d]					
Concomitant Medications					X					

Procedures[56]	Screening (Assessments can be completed in one or more visits, as long as they are completed within the time frames.)			Cycle 1 (4 weeks)		Cycle 2+ (4 weeks)		End of Treatment	Safety Follow-up	Follow-up
	Within 28 days	Within 14 days	Within 7 days	Day 1	Day 15	Day 1	Day 15 [k]	Within 14 days	Within 30 days	Every month
Complete medical history	X									
Archived Biopsy - Biomarker Sampling	X[e]									
Blood - Biomarker Sampling [e]			X[e]							
Plasma - Biomarker Sampling [e]			X[e]	X[e,f,57]	X[e]	X[e]		X[e]		
ECOG Performance Status		X		X		X		X		
Physical examination		X		X		X		X		
CBC with differential [f]			X	X[f]	X	X	X[k]	X		
Chemistry & Electrolyte Panel [f]			X	X[f]	X	X	X[g]	X		
Urinalysis [f]			X	X[f]	X	X	X[k]	X		
Thyroid function test (TSH, T3, T4) [f]			X	X[f]		X				
Coagulation Panel (PT/PT-INR, PTT) [g,f]			X	X[g,f]		X		X		
Pregnancy Test (if applicable)			X							
Pharmacokinetic Sampling [h]					X[h]		X[h]			
Randomization				X						
Blood pressure monitoring [i]					X[i]					
Patient-reported Quality of Life Questionnaires [j]				X		X[j]		X		
Drug dispensing				X		X				
Drug accountability						X	X[k]			
Anti-cancer medications									X	X

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Procedures[56]	Screening (Assessments can be completed in one or more visits, as long as they are completed within the time frames.)			Cycle 1 (4 weeks)		Cycle 2+ (4 weeks)		End of Treatment	Safety Follow-up	Follow-up
	Within 28 days	Within 14 days	Within 7 days	Day 1	Day 15	Day 1	Day 15 [k]	Within 14 days	Within 30 days	Every month
Survival assessment										X[106]

[a] Tumor assessment (CT or MRI)	Tumor measurements (CT/MRI scans) will be conducted every 8 weeks until PD. 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.
[b] 12 lead ECG	After 6 cycles, ECG can be performed based on the investigator's discretion.[58] ECG is not required at Day 1 of Cycle 1 if done within 7 days of starting study drug treatment. [59]
[c] Echocardiography or MUGA (LVEF assessment)	Echocardiogram or MUGA should be performed if clinically indicated.
[d] Adverse Events & Toxicities	AE assessment to be started after signing of IC until 30 days after last study treatment (excluding survival assessment)
[e] Biomarker Sampling	A biopsy sample obtained from an archived diagnostic biopsy, to be requested during Screening. Genetic tests will only be performed on tissue samples from patients who have signed a genetic consent form. A whole blood sample will be obtained during screening from (within 7 days prior to start of study drugs) only from subjects who provide genetic consent. Blood for plasma preparation will be obtained at the following timepoints: (1) Screening (within 7 days prior to start of study drugs); (2) Cycle 1/Day 1 (prior to start of study drugs); (3) Cycle 1/Day 15; (4) Cycle 2/Day 1, (5) Cycle 3/Day 1 and (6) End of Treatment. Genetic tests will only be performed on plasma samples from patients who have signed a genetic consent form.
[f] Laboratory Evaluations	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.[107]
[g] Coagulation Panel (PT/PT-INR, PTT)	If a subject is on warfarin with stable PT/INR at baseline, the PT/INR should be assessed on Day 5 (+/- 3 days). [60] If value is above the therapeutic[61] 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] Pharmacokinetic Sampling	In all subjects from selected sites, a pre-dose blood sample will be collected on Day 15 of Cycles 1 and 2. In approximately 150 subjects three blood samples will be collected (see separate Lab Manual for sample collection and processing procedure) at Cycle 1 Day 15 at

Important Protocol Amendments:

September 28, 2010
- The inclusion criteria were modified to include the following:
  - Formally require that patients have metastatic colorectal adenocarcinoma (Stage IV)
  - Patients who progress more than 6 months after completion of oxaliplatin-containing adjuvant therapy must be retreated with oxaliplatin-based therapy to be eligible
  - Patients with unknown KRAS status at screening must have received prior anti-EGFR treatment
  - Transfusion of patients in order to meet required hematology laboratory parameters will not be allowed
- The exclusion criteria were modified to include the following:
  - Extended field radiotherapy within 4 weeks or limited field radiotherapy within 2 weeks prior to randomization. Patients must have recovered from all therapy-related toxicities. The site of previous radiotherapy should have evidence of progressive disease if this is the only site of disease.
  - History of or currently known brain metastases
  - Pleural effusion or ascites that causes respiratory compromise (≥ CTC Grade 2 dyspnea)
  - Active hepatitis B or C or chronic hepatitis B or C if requiring treatment with antiviral therapy

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- - o Systemic anticancer therapy including cytotoxic therapy, signal transduction inhibitors, immunotherapy and hormonal therapy during this trial or within 4 weeks before starting to receive study medication
- New Zealand and South Africa were removed from the geographic region stratification factor
- The protocol was modified to state that missed or vomited tablets cannot be made up
- Potentially severe skin reactions (Stevens Johnsons Syndrome, Erythema multiforme and Toxic Epidermal Necrolysis) and acute liver failure were identified as adverse events of special interest

August 3, 2011
- Dose modification rules for liver function test abnormalities were added
- The schedule of assessments was modified to include weekly checks of ALT, AST, and bilirubin during the first two cycles of study treatment

November 1, 2011
- The protocol was modified to state that after the primary endpoint of the study is reached and the study results support a positive benefit/risk assessment for regorafenib in the trial by judgment of Bayer and the DMC, those patients currently on placebo at that time will be offered the opportunity to receive open-label regorafenib (cross over from placebo to regorafenib)

Statistical Considerations:

Trial 14387 was designed to have 90% power to detect a hazard ratio (HR) of 0.75 with a two-sided alpha of 0.05 and a 2:1 randomization ratio, assuming a median overall survival of 4.5 months for the placebo arm and 6 months for the regorafenib arm. It was estimated that 582 events were needed for the final OS analysis, which could be expected from a total of 690 patients. Overall survival was compared using a stratified log-rank test, stratified by the factors applied at randomization.

Two interim analyses were planned. The first interim analysis for futility was planned at approximately 174 deaths (30%) at 15.5 months. The second OS interim OS analysis for efficacy and futility was planned at approximately 408 deaths (70%) at 23.5 months. The Lan-DeMets alpha spending function with an O-Brien type boundary was used to adjust the alpha for the second efficacy interim and final analyses.

The trial proved positive for OS at the second interim analysis therefore was stopped at that point.

6 Review of Efficacy (S. Pradhan)

Efficacy Summary

This NDA was supported by a single, multicenter, randomized (2:1), double-blind, placebo-controlled trial, Trial 14387, that enrolled a total of 760 patients with previously treated mCRC. All patients received prior treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy and with bevacizumab, and all but one patient with a KRAS wild type tumor received panitumumab or cetuximab. Patients were randomized to receive 160 mg regorafenib orally once daily (n=505) plus best supportive care (BSC) or placebo (n=255) plus best supportive care for the first 21 days of each 28-day cycle. Treatment continued until disease progression, unacceptable toxicity, or death. The primary endpoint was overall survival and secondary endpoints were PFS, objective tumor response rate, and disease control rate. Other endpoints included health-related quality of life measures, regorafenib pharmacokinetics, and biomarker evaluations.

The assessment of benefit in this application is based on the primary endpoint of overall survival. This reviewer's recommendation for approval is based on review of the clinical data, which support the conclusion that regorafenib prolongs overall survival in patients who have failed standard chemotherapy (a population for whom no other therapy is approved). A statistically significant, clinically meaningful prolongation in overall survival was observed in patients randomized to receive regorafenib; median survival was 6.4 months in the regorafenib arm (95% CI: 5.8, 7.3) compared to 5.0 months in the placebo arm (95% CI: 4.4, 5.8), with a hazard ratio of 0.77 (95% CI: 0.64, 0.94; p=0.0102).

Supportive efficacy outcome measures in Trial 14387 were progression free survival and overall response rate. The PFS benefit observed was modest, with a median PFS of 2.0 months in the regorafenib arm (95% CI: 1.9, 2.3) compared to 1.7 months in the placebo arm (95% CI: 1.7, 1.8), with a hazard ratio of 0.49 (95% CI: 0.42, 0.58; p<0.0001). The overall response rate was low, consisting of 5 patients (1%) in the regorafenib arm and 1 patient (0.4%) in the placebo arm.

Trial 14387 was a large randomized trial that demonstrated a statistically significant overall survival benefit in a population for whom no other therapy is approved. Trial 14387 also demonstrated consistent results across most patient subsets and demonstrated a statistically significant improvement in the secondary endpoint of progression free survival. This reviewer concludes that Trial 14387 demonstrated adequate evidence of clinical benefit to support the proposed indication, modified as below (refer to section 6.1 Indication).

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6.1 Indication

The proposed indication is "Stivarga is indicated for the treatment of patients with metastatic colorectal cancer (CRC) who have been previously treated with,   (b) (4)
                                   fluoropyrimidine-based chemotherapy, an anti-VEGF therapy, and, if KRAS wild type, an anti-EGFR therapy."

Reviewer's Comment: This reviewer recommended expanding "fluoropyrimidine-based chemotherapy" to "fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy" to clarify the indicated population. This reviewer also recommended removal of " (b) (4)
                                   as this descriptor is unclear and, in addition, no such patients were studied.

6.1.1 Methods

This efficacy review focuses on results from the single randomized controlled trial, Trial 14387; refer to section 5.3 Discussion of Individual Studies/Clinical Trials for a description of the Trial 14387 design. The trial enrolled 760 patients, utilized the regorafenib dosing regimen proposed in the application, and consisted of the application's intended population (this review team recommended modification of the Indication statement in the product labeling as above, see section 6.1 Indication). The efficacy results presented in the application were from the planned second interim analysis for efficacy, defined in the protocol, with a data cutoff date of July 21, 2011. As of this date, the prespecified efficacy boundary was crossed and on December 23, 2011, the DMC recommended that the Applicant stop Trial 14387 based on the second interim analysis results.

Efficacy data including the clinical study report, CRFs, and electronic datasets for Trial 14387 were reviewed. Refer to section 5.3 Discussion of Individual Studies/Clinical Trials and the statistical review of this application by Dr. Huanyu (Jade) Chen (under separate cover) for a description of the statistical methodologies.

6.1.2 Demographics

Patient demographics and baseline characteristics for the intent to treat (ITT) population are shown in the tables below and were derived from the ADBCC dataset. Overall, demographics and baseline characteristics were balanced between treatment arms. The median age was 61 years. There were more men than women enrolled. Most patients were White. All patients in both treatment arms received prior treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, and bevacizumab.

Of the patients with a KRAS wild type tumor, all but one patient in the regorafenib arm and all patients in the placebo arm were previously treated with cetuximab and/or panitumumab. There were fewer patients with a KRAS mutation in the regorafenib arm

(54%) than in the placebo arm (62%). All patients with unknown KRAS mutation status at baseline were previously treated with cetuximab and/or panitumumab.

Fewer patients in the regorafenib arm received systemic anti-cancer therapy during follow-up than patients in the placebo arm (30% versus 26%). Of patients with KRAS mutations, more patients in the placebo arm received anti-cancer therapy during follow-up than in the regorafenib arm (33% versus 25%). Of patients with KRAS wild type tumors, more patients in the regorafenib arm received anti-cancer therapy during follow-up than in the placebo arm (29% versus 25%).

Table 4 Demographics - Age

Age (years)	Regorafenib N=505	Placebo N=255
Min	22	25
Median	61	61
Max	82	85
Mean	61	60

Table 5 Demographics

	Regorafenib N=505 n (%)	Placebo N=255 n (%)
Age		
≥ 65 years	196 (39)	89 (35)
Female		
Yes	194 (38)	102 (40)
Race		
White	392 (78)	201 (79)
Asian	76 (15)	35 (14)
Other	37 (7)	19 (7)
US		
Yes	47 (9)	36 (14)

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Table 6 Baseline Characeristics

	Regorafenib N=505 n (%)	Placebo N=255 n (%)
Stage IV		
Yes	505 (100)	255 (100)
ECOG PS		
0	265 (52)	146 (57)
1	240 (48)	109 (43)
KRAS mutation		
Yes	273 (54)	157 (62)
No	205 (41)	94 (39)
Primary site of disease		
Colon	323 (64)	172 (68)
Rectum	151 (30)	69 (27)
Colon and rectum	30 (6)	14 (5)
Prior surgical treatment procedure		
Yes	505 (100)	255 (100)
Prior radiotherapy		
Yes	135 (27)	78 (31)
Prior systemic anti-cancer therapy		
0-1	0	0
2	82 (16)	39 (15)
3	121 (24)	59 (23)
≥ 4	302 (60)	157 (62)

The stratification factors are shown in the table below.

Table 7 Stratification Factors

	Regorafenib N=505 n (%)	Placebo N=255 n (%)
Time from first diagnosis of metastatic disease to randomization		
< 18 months	91 (18)	49 (19)
≥ 18 months	414 (82)	206 (81)
Prior anti-VEGF therapy		
Yes	505 (100)	255 (100)
Geographic region*		
1	420 (83)	212 (83)
2	69 (14)	35 (14)

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	Regorafenib N=505 n (%)	Placebo N=255 n (%)
3	16 (3)	8 (3)

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

6.1.3 Subject Disposition

Patient disposition and protocol violations were similar between arms and are summarized in the tables below. Patient disposition was derived from the ADDS dataset and protocol deviations were derived from the ADDV dataset.

The numbers of patients in the ADDS dataset who permanently discontinued IP or study due to an adverse event were lower than the numbers in the ADAE dataset (refer to subsection 7.3.3 of the Review of Safety). The ADAE and ADDS datasets were each derived from different pages of the CRFs.

The most common enrollment criterion that was not met and thus constituted a protocol violation was "patient has uncontrolled hypertension." The most common procedure deviation and time schedule protocol violations were "procedures, tests, or measurements for this patient were not performed when scheduled".

Table 8 Patient Disposition

	Regorafenib N=505 n (%)	Placebo N=255 n (%)
Adverse Event	7 (1)	5 (2)
Completed	505 (100)	255 (100)
Death	373 (74)	195 (76)
Lost to Followup	26 (5)	23 (9)
Noncompliance	0 (0)	1 (0)
Other	12 (2)	3 (1)
Physician Decision	3 (1)	0 (0)
Progressive Disease	341 (67)	207 (81)
Protocol Violation	2 (0)	0 (0)
Withdrawal by Subject	22 (4)	12 (5)

Table 9 Protocol Violations by Category

	Regorafenib N=505 n (%)	Placebo N=255 n (%)
Exclusionary medication taken on study	3 (1)	3 (1)
Enrollment criteria not met	67 (13)	34 (13)
Missing	81 (16)	30 (12)
Treatment deviations	85 (17)	30 (12)
Time schedule deviations	157 (31)	63 (25)
Procedure deviations	308 (61)	140 (55)
Other protocol deviations	54 (11)	18 (7)
Withdrawal criteria met	21 (4)	10 (4)

6.1.4 Analysis of Primary Endpoint(s)

The analyses presented in this section were performed by Dr. Huanyu (Jade) Chen, the statistical reviewer for this application; refer to Dr. Chen's review (under separate cover).

The primary endpoint in Trial 14387 was overall survival (OS), defined as the time from randomization to death from any cause. Thirty percent of CRFs submitted by the Applicant were audited during the clinical review to verify that the survival data contained in the datasets were an accurate reflection of the patient information documented in the CRFs. No discrepancies between the CRFs and datasets were observed.

The OS results presented in the application were from the planned second interim analysis for efficacy, defined in the Trial 14387 protocol, with a data cutoff date of July 21, 2011. By this date, 432 (57%) death events had occurred. Results for overall survival and the K-M curves are shown below.

A statistically significant, clinically meaningful prolongation in overall survival was observed with regorafenib; median survival was 6.4 months in the regorafenib arm (95% CI: 5.8, 7.3) compared to 5.0 months in the placebo arm (95% CI: 4.4, 5.8), with a hazard ratio of 0.77 (95% CI: 0.64, 0.94; p=0.0102). The 23% risk reduction is clinically meaningful in the proposed indicated population, for whom no other therapy is approved. Results for OS were robust and consistent across subgroups; refer to section 6.1.7 Subpopulations.

Table 10 Overall Survival

	Regorafenib N=505	Placebo N=255
Number of Events (%)	275 (55)	157 (62)
Median OS in months (95% CI)	6.4 (5.8, 7.3)	5.0 (4.4, 5.8)
HR (95% CI)	0.77 (0.64, 0.94)	
Stratified Log-Rank Test p-value	0.0102	

Figure 3 K-M Curves of Overall Survival
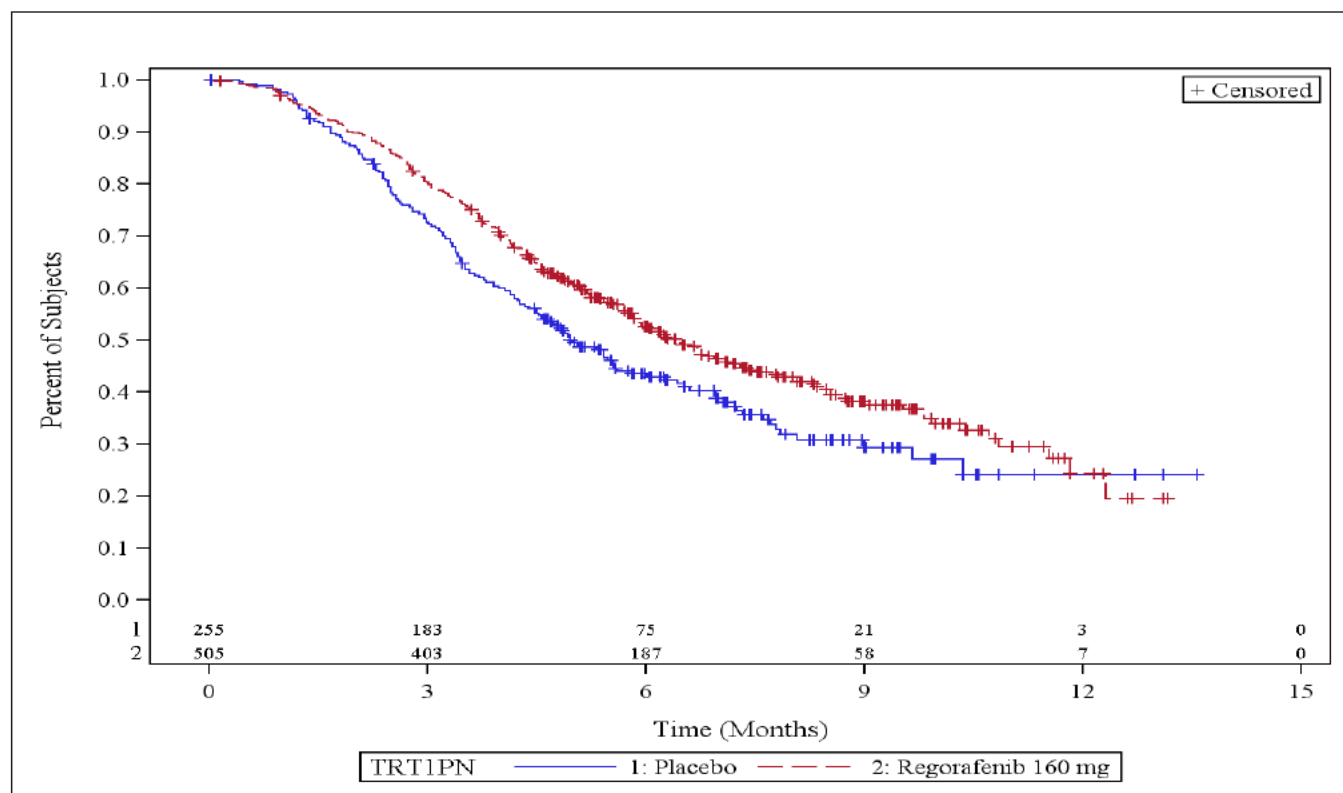
6.1.5 Analysis of Secondary Endpoints(s)

The analyses presented in this section were performed by Dr. Huanyu (Jade) Chen, the statistical reviewer for this application; refer to Dr. Chen's review (under separate cover).

One key secondary endpoint was PFS per investigator assessment. When patients were unable to obtain radiologic examinations due to deterioration of medical condition, clinical progression was reported by investigators and the date of clinical progression was used by the Applicant as the date of progression in determining PFS. FDA's analysis of PFS, however, excluded clinical progression events, such that PFS was defined by pathologic or radiologic findings only. The Applicant's analysis and FDA's analysis and K-M curves are shown below.

Another key secondary endpoint was ORR per investigator assessment, defined as the percentage of patients with complete or partial response.

The PFS benefit observed with regorafenib was modest, with a median PFS of 2.0 months in the regorafenib arm (95% CI: 1.9, 2.3) compared to 1.7 months in the placebo arm (95% CI: 1.7, 1.8), with a hazard ratio of 0.49 (95% CI: 0.42, 0.58; p<0.0001). The overall response rate was low, consisting of 5 patients (1%) in the regorafenib arm and 1 patient (0.4%) in the placebo arm.

Table 11 Progression Free Survival - FDA's Analysis

	Regorafenib N=505	Placebo N=255
Number of Events (%)	417 (83)	231 (91)
Median PFS in months (95% CI)	2.0 (1.9, 2.3)	1.7 (1.7, 1.8)
HR (95% CI)	0.49 (0.42, 0.58)	
Stratified Log-Rank Test p-value	< 0.0001	

Table 12 Progression Free Survival - Applicant's Analysis

	Regorafenib N=505	Placebo N=255
Number of Events (%)	430 (85)	241 (95)
Median PFS in months (95% CI)	1.9 (1.9, 2.1)	1.7 (1.7, 1.7)
HR (95% CI)	0.49 (0.42, 0.58)	
Stratified Log-Rank Test p-value	< 0.0001	

Figure 4 K-M Curves of PFS
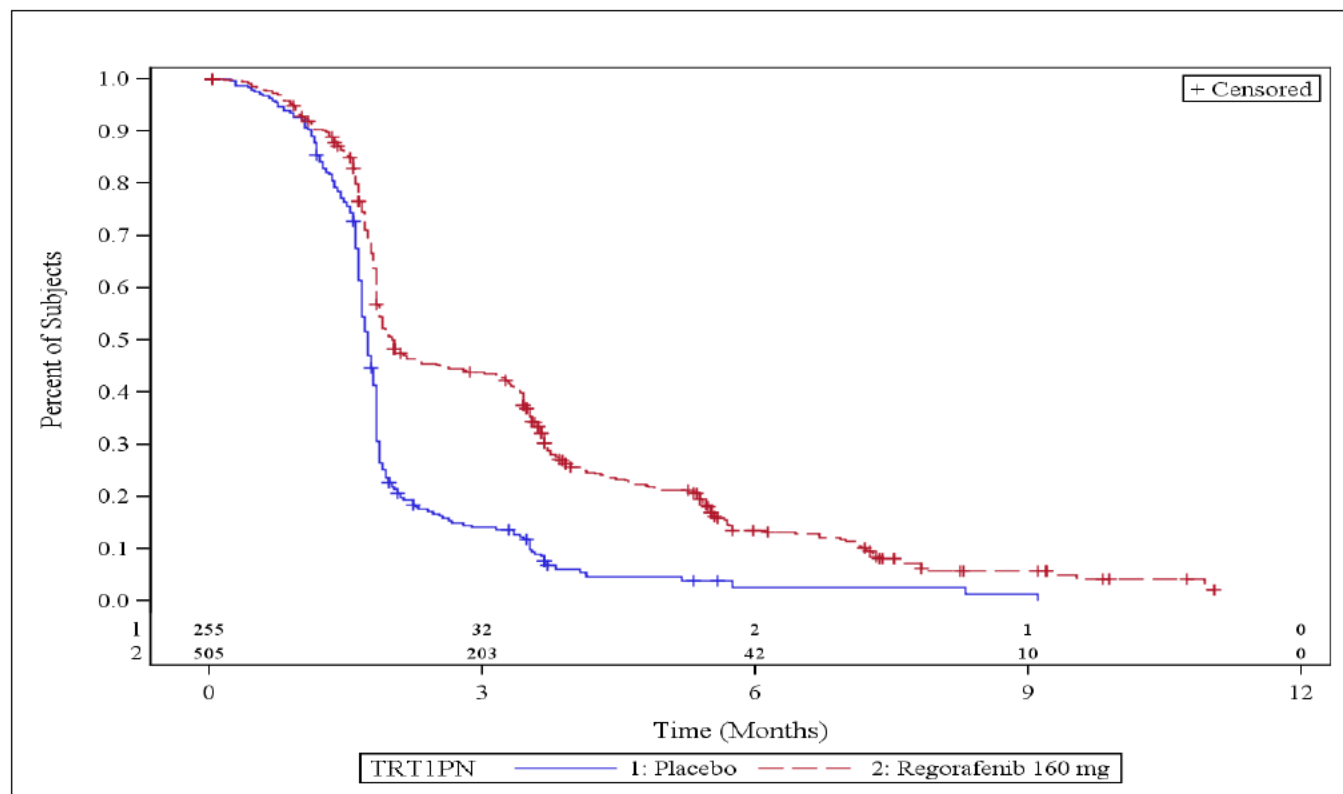
Table 13 Objective Response Rate

	Regorafenib N=505	Placebo N=255
Overall Response (%)	5 (1)	1 (0.4)
95% CI	0.3%, 2.3%	0%, 2.2%
Difference (95% CI)	0.6% (-0.5%, 1.7%)	
Stratified CMH Test p-value	0.38	

6.1.6 Other Endpoints

There were no additional efficacy endpoints considered for regulatory decision making from Trial 14387.

6.1.7 Subpopulations

Exploratory subgroup analyses of overall survival were performed by Dr. Huanyu (Jade) Chen, the statistical reviewer for this application; refer to Dr. Chen's review under separate cover. Summary results of these analyses are shown in the following table

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and overall were consistent with results of the primary analysis for Trial 14387 (refer to section 6.1.4 Analysis of the Primary Endpoint).

In the exploratory analyses shown below, the hazard ratios for the KRAS subgroups show a trend toward a smaller survival benefit with regorafenib in the KRAS mutant subgroup compared to wild type.

Table 14 Subgroup Analyses of Overall Survival

	N	HR (95% CI)	Median OS
Age			
≥ 65 years	285	0.86 (0.61, 1.19)	5.6/5.9
< 65 years	475	0.72 (0.56, 0.91)	4.9/6.7
Sex			
Male	464	0.77 (0.60, 1.00)	5.5/6.7
Female	296	0.75 (0.55, 1.02)	4.8/6.0
Race			
White	593	0.76 (0.61, 0.94)	4.9/6.2
Asian	111	0.79 (0.44, 1.45)	7.0/6.6
Geographic Region			
1	632	0.77 (0.62, 0.95)	4.9/6/0
2	104	0.79 (0.43, 1.46)	7.0/6.6
3	24	0.69 (0.20, 2.47)	NA
KRAS Mutation			
No	299	0.65 (0.48, 0.89)	4.9/7.2
Yes	430	0.87 (0.67, 1.12)	5.1/6.1

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

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Two phase 1 studies (Studies 11650 and 11651) were conducted in cancer patients to define the regorafenib dose and dose regimen to be carried into phase 2 and 3 development.

In first-in-human study 11650, in adult patients with advanced solid tumors refractory to standard therapy, regorafenib was administered orally on a 21 days on / 7 days off schedule in repeated cycles, until tumor progression or discontinuation due to toxicity. A total of 76 patients were enrolled and received regorafenib at dose levels from 10 mg to 220 mg daily. The MTD was determined to be 160 mg daily, on the 21 days on / 7 days off dosing schedule. Dose levels between 160 mg and 220 mg daily resulted in increased toxicity (8 of 12 patients experienced ≥ Grade 3 toxicity; 5 cases were PPE) and permanent discontinuation of the study medication (in 7 of 12 patients).

Study 11651 was a phase 1 study in a population comparable to that in Study 11650 (patients with advanced solid tumors refractory to standard therapy). However, regorafenib was administered daily in a continuous treatment regimen. Eighty-four patients were included and dose levels from 20 mg to 140 mg daily were evaluated. The MTD on this continuous dosing schedule was 100 mg daily.

The Applicant reported that the safety and tolerability at the MTD were similar between the 21 days on / 7 days off and continuous dosing regimens, and that the 160 mg daily dose on the 21 days on / 7 days off schedule was selected based on the following (copied with modifications from the CSR):

- A 20% higher total dose of regorafenib could be delivered in a 28-day cycle on the 21 days on / 7 days off schedule.
- The 7 day "off" period in the intermittent schedule may allow for partial recovery from toxicities.
- Because the 100 mg and 160 mg dose levels on the respective continuous versus intermittent schedules were not administered within the same study, the PK of 120 mg and 160 mg (administered within the same study) doses were compared; based on exposure to all three pharmacologically active moieties (regorafenib and its two pharmacologically active metabolites M-2 and M-5), steady-state exposure was higher at the 160 mg dose level than the 120 mg level.
- The intermittent dosing schedule may allow greater flexibility with regard to combined dosing with other cytotoxic agents also dosed intermittently.

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 (K. Shastri)

Safety Summary

Regorafenib is a small molecular inhibitor of multiple kinases including BRAF, VEGFR 1/2/3, TIE2, PDGFR, FGFR, RAF-1, KIT and RET. Regorafenib interferes both with tumor cell proliferation and tumor angiogenesis. Multi-kinase agents that inhibit at least 3 of the main tyrosine kinases targeted by regorafenib (VEGFR, PDGFR and KIT) include sorafenib (Nexavar), sunitinib (Sutent) and pazopanib (Votrient). The safety profile of this new molecular entity reflects its mechanism of action.

The safety data for regorafenib was primarily derived from study 14387, a large multi-center randomized, double-blind, placebo controlled trial in which 500 patients with previously treated metastatic colorectal cancer (mCRC) received regorafenib at an oral dose of 160 mg for the first 3 weeks of each 4 week cycle until toxicity, disease progression, or death. Two hundred and fifty-three patients in the study received a corresponding placebo. The placebo-control provided an adequate assessment of the safety of regorafenib against background adverse events that occur in this population with a terminal illness. The safety assessment was supplemented with data from an additional 318 patients with cancer in phase I and II studies, and pharmacovigilence information (deaths and serious adverse events) from the applicant's ongoing studies, providing overall safety assessment from over 1100 patients with cancer exposed to regorafenib. The available information was thus adequate for the safety assessment.

In study 14387, the mean duration of therapy was 12 weeks for patients receiving regorafenib and 8 weeks for patients receiving placebo. Treatment-emergent adverse events resulted in dose interruptions in 61% of the patients receiving regorafenib and 38% of the patients had their dose reduced. In placebo group, the incidences of dose interruption and dose reduction were 22% and 3%, respectively. Drug-related adverse reactions that resulted in treatment discontinuation were reported in 8.2% of regorafenib-treated patients compared to 1.2% of patients who received placebo.

The most significant toxicities caused by regorafenib included drug induced liver injury, hemorrhage, dermatologic toxicity (palmar-planter erythrodysesthesia and rash), hypertension, cardiac ischemic events and gastro-intestinal perforation.

Severe drug induced liver injury with fatal outcome occurred in 0.3% of 1100 regorafenib-treated patients across all clinical trials. Liver biopsy results, when available, confirmed that hepatocyte necrosis with lymphocyte infiltration occured. In Study 14387, fatal hepatic failure occurred in 1.6% of patients in the regorafenib arm and 0.4% of patients in the placebo arm; all the patients with hepatic failure had metastatic disease in the liver. Since most patients with colorectal cancer have or develop liver metastasis, hepatotoxicity is difficult to evaluate in this population. However, based on comparison with placebo and the fact that liver biopsy findings when available (2 patients) showed hepatocyte necrosis and lymphocyte infiltration, severe drug induced liver injury is a valid safety signal for regorafenib. Additional information from ongoing studies   (b) (4) will provide further clarity on this toxicity.

The overall incidence (Grades 1-5) of hemorrhage was 21% in regorafenib-treated patients compared to 8% in patients who received placebo in Study 14387. Fatal hemorrhage occurred in 4 of 500 (0.8%) of patients who received regorafenib and involved the respiratory, gastrointestinal, or genitourinary tracts.

The overall incidence of palmar-plantar erythrodysesthesia (PPE) (45% versus 7%) and the incidence of Grade 3 PPE (17% versus 0) were increased in regorafenib-treated patients in Study 14387. The overall incidence of rash (26% versus 4%) and the

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incidence of Grade 3 rash (6% versus <1%) were higher in regorafenib-treated patients in Study 14387. The onset of dermatologic toxicity occurred during the first cycle of treatment in most patients and frequently required dose modification.

Hypertension occurred in 30% of regorafenib-treated patients vs. 8% of patients who received placebo in Study 14387. The onset of hypertension occurred during the first cycle of treatment in most patients.

The incidence of myocardial ischemia and infarction was higher in regorafenib-treated patients (1.2 % vs.0.4%) compared to patients who received placebo.

Gastrointestinal perforation or fistula occurred in 0.6% of 1100 patients treated with regorafenib across clinical trials and there was a single case of reversible posterior leukoencephalopathy among the database of 1100 patients.

The most frequently observed adverse drug reactions (≥30%) in patients receiving regorafenib are asthenia/fatigue, decreased appetite and food intake, palmar-plantar erythrodysethesia (PPE), diarrhea, mucositis, weight loss, infection, hypertension and dysphonia.

There was no evidence of QTc prolongation in the clinical study 14387. The applicant provided an interim report from the completely enrolled but ongoing dedicated cardiac safety study (study 14814), which also did not show evidence of QTc prolongation. Although the final results of this safety study are pending, based on the available evidence, there does not appear to be an increased risk of QTc prolongation with regorafenib.

In summary, the safety profile of regorafenib is consistent with other multi-kinase inhibitors. The overall survival advantage seen with regorafenib in the proposed patient population of previously treated metastatic colorectal cancer patients provides a favorable benefit risk assessment for regorafenib.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The primary focus of this safety review involved analyzing the data from study 14387, since this study was a large placebo-controlled study where regorafenib was administered at the recommended dose in the indicated patient population with late-stage metastatic colorectal carcinoma. This placebo-controlled study provided an adequate assessment of the safety of regorafenib against the background of adverse events that occur in this population with terminal cancer. In this study, the adverse events experience of 500 patients treated with regorafenib was compared to 253 patients who received placebo.

Other studies that contributed to the overall evaluation of adverse events included the following Phase I or II studies:

Table 15 Supportive Phase I and II studies

Study	Type/ regorafenib dose	Population	Total Patients	Patients with CRC
A46572 (11726)	Uncontrolled phase II; 160 mg 3 wks every 4 weeks	Renal cancer	49	0
A51601 (14596)	Uncontrolled phase II; 160 mg 3 wks every 4 weeks	Hepatocellular cancer	36	0
PH-36733 (11650)	Phase I dose escalation 10-220 mg 3 wks every 4 weeks	Advanced solid tumors	76	39
A51164 (13172)	Uncontrolled phase II; 160 mg 3 wks every 4 weeks	Advanced solid tumors	16	0
A51600 (14996)	Uncontrolled phase II; 160 mg 3 wks every 4 weeks	Advanced solid tumors	12	8
PH36742 (11651)	Phase I dose escalation 20-140 mg continuous	Advanced solid tumors	84	6
PH-36735 (11656)	Open label with FOLFOX or FOIFIRI 160 mg on days 4-10 and 18-24 every cycle	Metastatic CRC	45	45

In the completed studies described above, 818 cancer patients were exposed to regorafenib; this number included the 500 patients treated in Study 14387.

The applicant also provided information and analyses of available pharmacovigilence safety regarding specific adverse events of interest including liver toxicity, GI perforation/fistula, and RPLS from ongoing studies ((b) (4)
                                                       . The overall exposure to regorafenib including the ongoing studies (applicant sponsored as well as investigator initiated study) is estimated to be 1145. In deriving incidences of rare adverse events for labeling purposes using this data, the applicant proposed incidences based on a conservative denominator of 1100. This denominator is acceptable to this reviewer since information from ongoing studies is being used to provide best available estimates of toxicities.

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7.1.2 Categorization of Adverse Events

Adverse events during the studies were recorded and evaluated using NCICTC version 3.0. The applicant also provided adverse event listings based on MedDRA version 14.1. This reviewer performed analyses using MedDRA hierarchical terminology as well as grouping of terms by standardized MedDRA queries (SMQs).

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

Pooling of data across clinical trials to estimate and compare the incidence rates of common adverse events was not considered useful by this reviewer since, as shown in the table above, compared to the main study 14387, the number of patients in the other supportive studies was small, had different patient populations, different dose/dosing schemes, or lacked the placebo control to assess the background incidence of adverse events. The applicant provided a safety data set with MedDRA terms for the first 6 studies noted in the table in section 7.1.1 (in addition to the datasets from the placebo-controlled study 14387). The information from the uncontrolled Phase I and II studies was used in additional assessments of select adverse events of interest during this review.

7.2 Adequacy of Safety Assessments

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

In the regorafenib arm, the mean treatment duration (±SD) was 12.08 (±9.74) weeks (median 7.27 weeks) and the mean daily dose was 147.15 mg (median 160 mg). The mean number of treatment cycles completed (±SD) was 3.3 (±2.3) (median 2 cycles). In comparison, in the placebo group, the mean treatment duration (±SD) was 7.78 (±5.19) weeks (median of 6.98 weeks). The mean daily dose of placebo was 159.25 mg (median 160 mg).

The following table shows the duration of treatment as measured by overall time under treatment cycles for patients in both groups.

Table 16 Duration of treatment

Cycle	Regorafenib N=500	Placebo N=253
1	87 (17%)	48 (19%)
2	188 (37%)	147 (58%)
3	33 (7%)	26 (10%)
4	78 (16%)	16 (6%)
5	34 (7%)	9 (4%)
6	30 (6%)	4 (2%)
7	11 (2%)	1 (0.4%)
8	18 (4%)	1 (0.4%)
9	8 (2%)	0
10	5 (1%)	1 (0.4%)
11	6 (1%)	0
12	2 (0.4%)	0

A total of 16% of patients (80 patients) received treatment for 6 cycles or more in the regorafenib arm providing somewhat longer-term safety information in this disease with an otherwise poor prognosis.

The following table shows the demographics of the safety population in study 14387.

Table 17 Demographics: Safety Population of Study 14387

		Regorafenib N=500	Placebo N=253
Age	Median (range)	61 (22 to 82)	61 (25 to 85)
	< 65 years	307 (61%)	164 (65%)
	≥ 65 years	193 (39%)	89 (35%)
Sex	Female	193 (39%)	101 (40%)
	Male	307 (61%)	152 (60%)
Race	White	389 (78%)	200 (79%)
	Black	6 (1%)	8 (3%)
	Asian	74 (15%)	34 (13%)
	Others	31 (6%)	11 (4%)
Baseline ECOG score	0	263 (53%)	144 (57%)
	1	237 (47%)	109 (43%)

7.2.2 Explorations for Dose Response

The placebo-controlled, international multicenter study (study 14387), that forms the basis of this application for the treatment of patients with metastatic colorectal cancer

was conducted with a fixed dose of 160 mg regorafenib daily for 3 weeks of each 4 week treatment cycle.

The placebo-controlled, international multicenter study (study 14387), that forms the basis of this application for the treatment of patients with metastatic colorectal cancer was conducted with a fixed dose of 160 mg regorafenib daily for 3 weeks of each 4 week treatment cycle.

The dose and the dosing schedule used in study 14387 was based on the Phase I dose escalation trial (study 11650) in which adult patients with advanced solid tumors refractory to standard treatment were given oral regorafenib in a 21 days on / 7 days off schedule in repeated cycles, until discontinuation due to toxicity or tumor progression. Adverse events (AEs) were assessed using NCI CTCAE v3.0. A total of 76 patients (53 in dose escalation; 23 in mCRC extension cohort) were enrolled and received regorafenib at dose levels from 10 mg to 220 mg daily. The MTD dose was determined to be 160 mg. Doses beyond 160 mg daily to 220 mg daily resulted in increased toxicities (8 of 12 patients with ≥ Grade 3 toxicities; 5 of these were PPE) and permanent discontinuation of the study medication (in 7 of 12 patients).

Refer to the clinical pharmacology review for explorations of plasma drug levels and toxicity from the phase I clinical studies. The application did not contain pharmacologic drug level data (pop PK) or analyses for such exploration from study 14387.

7.2.3 Special Animal and/or In Vitro Testing

Please see toxicology review. This reviewer is not aware of any outstanding issues from a toxicology standpoint that would preclude recommendation of approval of this drug

7.2.4 Routine Clinical Testing

The routine clinical testing of patients was appropriate including efforts to elicit adverse event data and monitoring of laboratory parameters, vital signs and ECGs.

7.2.5 Metabolic, Clearance, and Interaction Workup

Please refer to the clinical pharmacology review for details.

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 of them having similar pharmacological activity and steady-state concentrations as regorafenib. M-2 and M-5 are highly protein bound (99.8% and 99.9%, respectively). Following oral administration, the mean elimination

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half-lives for regorafenib and the M-2 metabolite in plasma are 28 hours and 25 hours, respectively. M-5 has a longer mean elimination half-life of 50 hours.

Effect of CYP3A4 strong inducers on regorafenib: Twenty-two healthy men received a single 160 mg dose of regorafenib 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 M-5 AUC increased by 264%. No change in the mean M-2 AUC was observed [see Drug Interactions (7.1)].

Effect of CYP3A4 strong inhibitors on regorafenib: Eighteen healthy men received a single 160 mg dose of regorafenib 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%.

Effect of regorafenib on a substrate of UGT1A1 substrates: Eleven patients received irinotecan - containing combination chemotherapy with regorafenib at a dose of 160 mg. The mean AUC of irinotecan increased 28% and the mean AUC of SN-38 increased by 44% when irinotecan was administered 5 days after 7 daily doses of regorafenib.

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

Regorafenib (BAY 73-4506,   (b) (4) is a small molecular inhibitor of multiple kinases including BRAF, VEGFR 1/2/3, TIE2, PDGFR, FGFR, RAF-1, KIT and RET. Multi-kinase drugs that inhibit at least 3 of the main tyrosine kinases targeted by regorafenib (VEGFR, PDGFR and KIT) include sorafenib (Nexavar), Sunitinib (Sutent) and pazopanib (Votrient).

The following potentially serious adverse events have been described with the multi-kinase inhibitors noted above: hepatotoxicity, cardiac ischemia/infarction, left ventricular dysfunction, QT prolongation, hemorrhage, hypertension, dermatologic toxicity, GI perforation, elevation in INR when taking warfarin, wound healing complications, arterial and venous thrombotic events, RPLS, hypothyroidism, proteinuria, infection and fetal harm.

The applicant performed an adequate assessment of the above noted adverse events.

7.3 Major Safety Results

7.3.1 Deaths

In study 14387, there were 110 total deaths reported during treatment and up to 30 days post permanent treatment discontinuation as shown in the table below. The majority of deaths were associated with clinical disease progression. Deaths not

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associated with disease progression in the regorafenib group included 3 patients with hemorrhage (1 patient with upper GI hemorrhage, 1 patient with rectal and vaginal hemorrhage, and 1 patient with pulmonary hemorrhage); 2 patients who died of pneumonia; 1 patient with cardiac arrest; 1 patient with general physical health deterioration; 1 intestinal obstruction; 1 cerebrovascular accident; 1 with sudden death and in one other patient the cause of death was unknown. Deaths not associated with disease progression in the placebo group included 2 patients who died suddenly, 2 patients who died of pneumonia, one patient who died of cardiac arrest, and one other death. The tabular summary of these deaths is shown below:

Table 18 Overview of deaths during treatment and within 30 days post-treatment

	Regorafenib N=500	Placebo N=253
Total Deaths	69 (13.8 %)	41 (16.2%)
Adverse event not associated with progressive disease	8 (1.6 %)	3 (1.2%)
Other[a]	1 (0.2%)	2 (0.8%)
Progressive disease	58 (11.6%)	35 (13.8%)
Unknown	2 (0.4%)	1 (0.4%)

a: include worsening of general condition for 1 patient in the regorafenib arm and cardiac arrest in 1 patient in the placebo arm

Deaths due to hemorrhage are further discussed in section 7.3.4.

7.3.2 Nonfatal Serious Adverse Events

The incidence of nonfatal serious events was 44% in the regorafenib arm and 40% in the placebo arm. The following table depicts the incidence of SAE's (>1%) in the regorafenib arm as described by MedDRA (14.1) preferred terms.

Table 19 Serious Adverse Events

	Regorafenib N=500	Placebo N=253
Any SAE	219 (44%)	100 (40%)
General health deterioration	36 (7%)	24 (10%)
Pyrexia	14 (3%)	1 (0.4%)
Abdominal pain	12 (2.4%)	2 (1%)
Pneumonia	10 (2%)	4 (2%)
Dyspnea	10 (2%)	3 (1%)
Diarrhea	8 (2%)	0
Intestinal Obstruction	7 (1%)	2 (1%)
Hepatic Failure	7 (1%)	2 (1%)
Multi-organ failure	6 (1%)	4 (2%)

The incidence of SAE's was similar in both treatment arms, reflecting the disease condition being treated.

7.3.3 Dropouts and/or Discontinuations

Permanent Discontinuation of the study drug due to adverse events occurred in 17.6% of patients compared to 12.6% of patients in the placebo arm. The following table lists the commonly reported adverse events by MedDRA preferred term that lead to permanent discontinuation in ≥1% of patients.

Table 20 AEs leading to permanent discontinuations (≥ 1%)

	Regorafenib N=500	Placebo N=253
Any Event	88 (17.6%)	32 (12.6%)
General health deterioration	18 (4%)	8 (3%)
Palmar-Plantar erythrodysaesthesia	7 (1%)	0
Hepatic Failure	4 (1%)	2 (1%)
Decreased Appetite	4 (1%)	1 (0.4%)
Pneumonia	4(1%)	0
Rash	4 (1%)	0

As shown in the table above, the most frequent treatment-emergent AEs causing discontinuation were general physical health deterioration and palmar-plantar erythrodysaesthesia syndrome. When only adverse events that were considered to be drug-related were considered, the incidence of adverse events leading to permanent discontinuation was 8.2% in the regorafenib arm and 1.2% in the placebo group. Skin

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toxicity (PPE or rash) was the most common drug-related cause of permanent drug discontinuation in patients treated with regorafenib.

Dose reductions due to adverse events occurred in 37.6% of regorafenib-treated patients compared to 3.2% in the placebo group.. The most frequent AE's (≥ 1%) are shown in the table below.

Table 21 AEs leading to dose reductions (≥ 1%)

	Regorafenib N=500	Placebo N=253
Any Event	188 (37.6%)	8 (3.2 %)
Palmar-Plantar erythrodysaesthesia	91 (18.2%)	1 (0.4 %)
Diarrhea	19 (3.8%)	0
Hypertension	16 (3.2%)	1 (0.4 %)
Fatigue	10 (2%)	5 (2 %)
Rash	10 (2%)	0
Mucositis	6 (1.2%)	0
Abdominal pain	5 (1%)	0
Asthenia	5 (1%)	0

Dose interruptions due to adverse events occurred in 60.8% of regorafenib-treated patients compared to 21.7% in the placebo group. . The most frequent AE's (≥ 1%) are shown in the table below.

Table 22 AEs leading to dose interruptions (≥ 1%)

	Regorafenib N=500	Placebo N=253
Any Event	304 (60.8%)	55 (21.7 %)
Palmar-Plantar erythrodysaesthesia	94 (18.8%)	0
Diarrhea	31 (6.2)	2 (0.8%)
Pyrexia	23 (4.6%)	3 (1.2 %)
Fatigue	20 (4.0%)	4 (1.6%)
Rash	18 (3.6%)	0
Hyperbilirubinemia	18 (3.6%)	5 (2 %)
Decreased appetite	15 (3%)	5 (2 %)
Asthenia	14 (2.8%)	0
Hypertension	13 (2.6%)	1 (0.4%)
Abdominal pain	12 (2.4%)	0
Stomatitis	11 (2.2%)	0
Dyspnea	10 (2%)	3 (1.2 %)
AST increased	9 (1.8%)	1 (0.4%)
Vomiting	9 (1.8%)	1 (0.4%)
Thrombocytopenia	8 (1.6%)	0
ALT increased	7 (1.4%)	1 (0.4%)
Proteinuria	6 (1.2%)	2 (0.8%)

7.3.4 Significant Adverse Events

Hepatotoxicity:

Adverse events as reported under the SOC Hepatobiliary disorders in study 14387 occurred at a frequency of 19.8% in the regorafenib arm and 12.3% in the placebo group. This difference was largely accounted for by the difference in grades 1 through 3 events which occurred in 3.8%, 5.6%, and 8% of patients, respectively in the regorafenib group compared to 1.6%, 2.8%, and 4.7%, respectively in the placebo group.

Hepatic adverse events were also evaluated by the SMQ of Hepatic failure, fibrosis, and cirrhosis and other liver damage related conditions according to whether the patient had liver metastasis at baseline. The results are shown in the table below.

Table 23 Hepatic Failure, Fibrosis, cirrhosis and other liver damage (SMQ)

	Regarofanib		Placebo	
	Patients with Liver metastasis (N=387)	Patients without Liver Metastasis (N=113)	Patients with Liver metastasis (N=181)	Patients without Liver Metastasis (N=72)
Any Event	36 (9.3%)	1 (0.9%)	12 (6.6%)	1 (1.4%)
Grade 3	4 (1%)	0	5 (2.8%)	0
Grade 4	1 (0.3%)	0	0	0
Grade 5	8 (2.1 %)	0	1 (0.6%)	0

The grade 5 (fatal) events in the regarofenib arm included hepatic encephalopathy (1), hepatic failure (6), and hepatic coma (1). In the placebo group, the one grade 5 event was hepatic failure. Review of case narratives showed that these cases were associated with disease progression; however, a contribution of regorafenib could not be excluded due to the imbalance in the two arms of these events.

Clinical laboratory abnormalities of liver enzymes and serum bilirubin were analyzed for those patients meeting Hy's law laboratory criteria. The results are shown in the table below:

Table 24 Hepatotoxicity: Laboratory Evaluation

	Regorafenib		Placebo	
	Patients with Liver metastasis (N=387)	Patients without Liver Metastasis (N=113)	Patients with Liver metastasis (N=181)	Patients without Liver Metastasis (N=72)
AST or ALT >3x ULN[*]	64 (17%)	6 (6%)	28 (16%)	1 (1%)
Total Bili. > 2 x ULN	81 (22%)	7 (6%)	25 (14%)	1 (1%)
AST or ALT >3x and Bili. > 2x ULN	34 (9%)	1 (1%)	17 (10%)	0
Hy's Law lab. Criteria[**]	2 (1%)	2 (2%)	1 (1%)	0

* ULN = upper limit of normal
** AST/ALT > 3x ULN, Total bilirubin > 2X ULN and alkaline phosphatase < 2X ULN

A brief narrative summary of the 4 cases in the regorafenib arm that met the laboratory criteria for Hy's law is as follows:

Patients without liver metastasis:
- A 69 yr. old patient with metastatic CRC developed ALT 14 x ULN, LDH 2 x ULN with normal alkaline phosphatase and bilirubin on day 43. Regorafenib was discontinued for progressive disease. On day 57, the patient developed more severe liver function test abnormalities with ALT 27 x normal, AST 19 x normal, bilirubin 2.8 x normal and alkaline phosphatase 1.4 x normal. The event improved to grade 1 after 1 week. The patient died 3 months later from progressive disease (PD). This event was unlikely to be severe drug induced liver injury.
- A 34 yr. old woman with metastatic colorectal cancer developed AST 3.3 x ULN, bilirubin 2 x ULN, ALT 1.2 x ULN 2 weeks after starting treatment with regorafenib and had associated fever, dyspnea, diarrhea, and vomiting. The patient was able to restart treatment in 2 weeks and received treatment for 8 more cycles. This event was unlikely to be severe drug induced liver injury, because of the successful re-challenge

Patients with liver metastasis:

- A 62 yr. old patient with liver, lung, and lymph node metastases from colorectal carcinoma developed ALT 31 x normal, Alt 31 x normal and bilirubin 8 x normal 43 days into treatment, progressively deteriorated and died. Post-mortem liver biopsy showed hepatic cell necrosis, fibrosis, and lymphocyte infiltration. This case represents severe drug induced liver injury in this study based on the microscopic findings in the liver.
- 52 yr old woman with liver metastases developed isolated hyperbilirubinemia, transient transaminitis resumed therapy at a reduced dose without recurrence of hepatic findings; hence not likely to be severe drug induced liver injury.

In the Phase I and II studies, 6 patients met the laboratory criteria for Hy's law; all had either hepatocellular carcinoma (HCC) or liver metastasis from their underlying disease. There was no conclusive evidence of drug induced liver injury based on the patient narratives.

Additionally, the applicant provided an analysis of the available pharmacovigilance information from other ongoing studies and identified two additional cases of severe drug induced liver injury using the criteria proposed by the international DILI Working Group. The criteria included the liver enzyme and bilirubin elevation but additionally required INR elevation or ascites and/or encephalopathy, or other organ failure considered to be due to DILI (Aithal GP, Watkins PB, Andrade RJ, Larrey D, Molokia M, et al. Case definition and phenotype standardization in drug-induced liver injury.

Clin Pharmacol Ther 2011; 89 (6):806-815). A brief description of these cases is given below:

- A 49 year old man ((b) (4) with advanced GIST (no liver mets) and normal LFTs at study start died of hepatic failure during cycle 2 of treatment. Pre-mortem liver biopsy showed acute necrotic changes with lymphocyte and neutrophil infiltration. Hepatitis serologies (for hepatitis) were negative.

- A 68 year old woman with a history of alcohol abuse and bronchitis was treated with FOLFOX and regorafenib in a phase I study (Study 11656). On day 1 of the second cycle, she was noted to have grade 3 elevation of liver enzymes and grade 1 elevation of bilirubin. Treatment was delayed at that time; patient subsequently developed grade 4 liver enzyme elevation and grade 3 hyperbilirubinemia in the ensuing week although the patient was asymptomatic. The patient was then admitted with hepatic coma on the following week and died one day later.

Reviewer Comment: Hepatotoxicity is difficult to evaluate in patients with metastatic colorectal cancer due to the frequency of liver metastases with resultant complications from the metastases. However, based on comparisons with placebo and the fact that liver biopsy findings, when available (2 patients), showed hepatocyte necrosis and lymphocyte infiltration, severe drug induced liver injury is a valid safety signal for regorafenib. This information will be appropriately conveyed in the label. The applicant proposed package insert included a monitoring plan and proposed dose modifications based on liver function tests.

Hemorrhage:

Since hemorrhage events can occur in any organ system, the overall incidence of the risk of hemorrhage with regorafenib compared to placebo was evaluated using the MedDRA SMQ Hemorrhage terms (excluding laboratory terms). The results of this analysis are shown below:

Table 25 Incidence of Hemorrhage (SMQ)

	Regorafenib N=500	Placebo N=253
All Grades	107 (21.4%)	19 (7.5%)
Grade 1	87 (17.4%)	13 (5.1%)
Grade 2	9 (1.8%)	4 (1.6%)
Grade 3	7 (1.4%)	0
Grade 4	0	0
Grade 5	4 (0.8%)	0

As seen in the table above, the majority of cases of hemorrhage were grades 1 or 2 in the regorafenib arm. However, there was 1.4% incidence of grade 3 hemorrhagic events and 0.8% fatal hemorrhagic events. Epistaxis, hematuria, anal or rectal hemorrhage accounted for approximately 70% of all instances of hemorrhage in patients treated with regorafenib.

The following are the case narratives from the four fatal hemorrhagic events:

- A 62-year-old woman, with metastatic colorectal cancer, multiple prior chemotherapies, pelvic radiation, hysterectomy, recto-vaginal fistula, mild thrombocytopenia, and anemia, developed rectal and vaginal bleeding 58 days after starting regorafenib treatment. PT and PTT were moderately elevated. Regorafenib was permanently discontinued due to these events, and the patient received a transfusion with blood products, however she died the next day.

- A 64-year-old man, with known lung metastases, developed hemoptysis and pulmonary alveolar hemorrhage 28 days after starting regorafenib treatment. He also developed superior vena cava thrombosis for which an angioplasty was performed. The patient died on day 31. An autopsy showed diffuse pulmonary hemorrhage. The Investigator considered the event to be related to regorafenib and not progression of disease.

- A 76 yr old woman with metastatic colorectal cancer, history of portal vein thrombosis and ascites, on oral anticoagulants, had an elevated INR on 14 days of study medication, which was treated with vitamin K. The study medication was stopped and not resumed since the patient withdrew her consent one week later. She developed upper GI bleeding for which she received red cell transfusions. She subsequently died on day 32 from 'upper GI bleeding'. An autopsy was not performed.

- A 78 year old man with metastatic CRC, developed grade 2 anorexia, which lead to suspension of the drug on day 22 of treatment. The study drug was not restarted when on day 41 of the study the patient died of GI hemorrhage,

presumed to be from the site of tumor in the transverse colon from disease progression.

As seen from the narratives, all the above events occurred in the setting of other confounding factors and malignancies at the site of hemorrhage. However, the contribution of regorafenib can not be excluded, especially when hemorrhage of all grades occurred at a higher frequency among regorafenib-treated patients.

Dermatological toxicity:

Adverse events under the system organ class of skin and subcutaneous disorders occurred frequently in the regorafenib arm (72%) compared to placebo (24%).

Table 26 Skin and subcutaneous tissue disorders (incidence >5%):

Adverse Event	Regorafenib (n=500)			Placebo (n=253)		
	Grade			Grade		
	All %	3 %	4 %	All %	3 %	4 %
Any Event	72	22	0.2	24	0.8	0
Palmer-planter erythrodysaesthesia Syndrome	45	17	0	7	0	0
Rash	22	5	0	3	0.4	0
Dry Skin	9	0	0	3	0	0
Alopecia	8	0	0	2	0	0

By combining various MedDRA terms for rash, the overall incidence of rash was 26% in the regorafenib arm (6% grade 3 and none of grade 4 severity) and 4% in placebo arm (0.4% grade 3 and none of grade 4).

Gastrointestinal Perforation and Fistula:

There were no cases of GI perforation in the regorafenib arm compared to 1 in the placebo arm. The incidence of GI fistula was 0.8% in the regorafenib arm versus 0.4% in the placebo arm.

The applicant conducted a search of the pharmacovigilence data and identified 21 cases (however3 were not exposed to regorafenib) illustrating the existence of a background risk (of castrophic abdominal events) related to underlying disease in patients with intra-abdominal malignancies. In 2 cases the cause was iatrogenic, and in

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4 cases there were no actual perforation or fistula but rather disease-related abscesses. In 5 cases, fistula events were reported, all of which occurred in the context of complications of underlying disease and/or progressive disease, and for which the investigators considered the underlying disease contributory. In the 7 remaining cases, GI perforation at various sites was reported. Extensive intra-abdominal malignant lesions, other confounding medical history (diverticulitis, constipation, gastro-esophageal reflux disease, auto-immune inflammatory conditions), and concomitant medications (e.g. NSAIDs, opiates) were reported in these cases. All 7 cases were considered by the investigators as possibly related to regorafenib. The outcome was fatal in 4 cases, and improved in 3 cases.

Since GI perforation and GI fistula are known class-effects of VEGF-antagonists, the applicant proposed that this adverse reaction be included in the product label. The estimated frequency of GI perforation, based on the overall safety database is 0.6%.

Hypertension:

Hypertension occurred in 30% of patients on regorafenib compared to the 8% incidence rate of hypertension recorded in patients who received placebo. Most of the events in either arm were grades 1 or 2 with grade 3 events noted in 8% of regorafenib patients and 1% in the placebo arm. None of the patients had grade 4 hypertension. Analysis of the onset of hypertension events in regorafenib-treated patients showed that 72% of the events were observed in the first cycle and 92% events occurred in the first 2 cycles of therapy.

From other pharmacovigilence information provided by the sponsor, there was one patient with hypertensive crisis in the GIST study (ongoing study) in the setting of reversible posterior leukoencephalopathy syndrome, who recovered with standard medical management.

Cardiac Toxicity:

Ischemia/infarction: Under the SMQ (broad) of ischemic heart disease, 6 subjects (1.2%) had an ischemic heart disease event in the regorafenib arm compared to 1 (0.4%) in the placebo group. The events in the regorafenib arm included 3 ischemic events and 3 infarctions (subject 14387-1401-7001 is considered MI because of non-specific ST-T changes associated with an increase in CK with MB fraction, based on the patient narrative). These included 3 patients with infarction and 3 with ischemia but without infarction. All three patients with infarction had one or more risk factors (history of diabetes, hypertension, or hyperlipidemia).

Arrhythmias: Under the SMQ of arrhythmias there were more events reported in the regorafenib arm (3% vs. 0.8%) compared to placebo. However most of these events were not clinically significant and included sinus bradycardia, Only 0.6% events in

regorafenib arm were grade 3 which included 2 cases of atrial fibrillation and 1 patient with PVCs. The prolonged QT interval reported in 3 patients was not more than 500 ms and had no clinical consequence. The overall incidence of atrial fibrillation was 1.2% in the regorafenib arm versus none in the placebo. Five of the six events were assessed by the investigator as not related to the study drug.

Congestive heart failure: Using the SMQ term of cardiac failure, the incidence of any cardiac failure related term was slightly higher in the regorafenib arm than in the placebo arm (9.8% versus 7.1%). However the major difference was due to the inclusion of the term peripheral edema (9.2 % versus 6.7%) which could be due to a myriad of causes in this population. Analyses of the data from Phase I and II studies were not indicative of an increased risk of cardiac failure. The applicant carried out a systemic evaluation of cases of cardiac failure. In 13 cases identified by the MedDRA SMQ Cardiac failure, only 7 of were confirmed as having a cardiac event. Well-established risk factors for ischemic heart disease and cardiac failure were present in these cases, including age, weight, hypertension, diabetes mellitus, hyperlipidemia, or already established ischemic heart disease and chronic renal impairment. All patients had received multiple prior lines of anti-cancer therapies, including cytotoxic drugs. Additional acute serious conditions such as sepsis and disease progression were reported in some cases and probably triggered heart failure. Thus, from the data available thus far, there dose not appear to be a signal sufficient to conclude that regorafenib increases the risk of CHF.

Diarrhea and Mucositis: The incidence of diarrhea was 43% in the regorafenib arm and 17% in the placebo arm. Most of the diarrhea events in either arm were grades grade 1 or 2 with grade 3 events noted in 8% of regorafenib patients and 2% in the placebo arm. One patient treated with regorafenib experienced grade 4 diarrhea (0.2%). Mucositis (including the terms stomatitis, mucosal inflammation, esophagitis, pharyngeal inflammation and glossitis) occurred in 33% of patients on regorafenib (4% grade 3, no grade 4) and 5% of patients in the placebo arm (no grade 3 or 4 events).

Renal Events: The incidence of renal events when analyzed by SOC renal and urinary disorders was 16.4% in the regorafenib arm (4% grade 3, no grade 4 events) versus 8.7% in the placebo arm (4% grade 3, 0.4% grade 4). This difference was mainly driven by the difference in the adverse event of proteinuria (7.4% in regorafenib arm versus 2.4% in placebo arm). The incidence of proteinuria was better determined assessed by using laboratory urinary findings (see section 7.4.2). The incidence of renal failure as evaluated by SMQ for acute renal failure (narrow scope) yielded similar incidences in both arms (2.4%).

The applicant also conducted and provided a cumulative review of pharmacovigilance database using SMQ acute renal failure and did not identify an increased risk of renal failure in regorafenib-treated patients.

Thromboembolic events:

The incidence and type of thromboembolic events are shown below:

Table 27 Thromboembolic events

	Regorafenib (N= 500)		Placebo (N=253)	
	All grades (%)	≥ grade 3 (%)	All grades (%)	≥ grade 3 (%)
Pulmonary embolism	4 (0.8)	4 (0.8%)	3 (1.2%)	2 (0.8%)
Other venous thromboembolism	6 (1.2%)	3 (0.6%)	2 (0.8%)	2 (0.8%)
Arterial thromboembolism	9 (1.8%)	5 (1%)	2 (0.8%)	2 (0.8%)

The 'other venous thromboembolism' included MedDRA terms of deep venous thrombosis, pelvic venous thrombosis, venous thrombosis, and vena cava thrombosis. The nine events of arterial thromboembolic events in the regorafenib arm included 6 cardiac ischemic events noted in the review under cardiac toxicity, 2 cerebrovascular events and 1 event of an arterial thrombosis of limb. Except for the slight increased in cardiac ischemic events, there was not an increased risk of other thrombotic events.

In the uncontrolled phase I and 2 studies, the overall incidence of pulmonary embolism was 1.5% (4 of 272 patients), other venous thrombosis was 1.1%, ischemic heart disease was 2.9% and cerebrovascaular events was 0.7%.

Infections:
Under the SOC of infections, there was a 30.8% overall infection rate in the regorafenib arm and 17% in the placebo arm. This difference was primarily due to a difference in the rate of grades 1-2 infections, which occurred in 22% of patients in regorafenib arm versus 10.6% in the patients who received placebo. Infections ≥ grade 3 occurred in 8.8% of patients in regorafenib arm compared to 6.3% in the placebo arm. Grade 5 infections occurred in 0.6% in the regorafenib arm compared to 0.8% in the placebo arm.

The most frequent preferred terms with an increased incidence in the regorafenib group compared to the placebo group were urinary tract infections (7.2% vs. 2.8%), nasopharyngitis (3.4% vs. 1.2%), and cystitis (2.4% vs. 0.4%). The incidence of pneumonia was 2.8% in the regorafenib arm and 2.4% in the placebo patients.

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Wound healing impairment:

Wound healing complications are a class adverse effect of VEGF pathway inhibitors. The applicant conducted a search for wound healing complications using the following MedDRA terms: Abdominal wound dehiscence, Anastomotic complication, Anastomotic fistula, Anastomotic leak, Debridement, Eschar, Failure to anastomose, Gastrointestinal anastomotic leak, Impaired healing, Incision site complication, Incision site oedema, Incisional hernia, Incisional hernia gangrenous, Incisional hernia repair, Incisional hernia, obstructive, Inflammation of wound, Intestinal anastomosis complication, Open wound, Pharyngeal anastomotic leak, Post procedural fistula, Postoperative hernia, Postoperative wound complication, Procedural hemorrhage, Promotion of wound healing, Reproductive tract anastomotic leak, Suture related complication, Suture rupture, Urinary anastomotic leak, Wound closure, Wound complication, Wound contamination, Wound decomposition, Wound dehiscence, Wound drainage, Wound evisceration, and Wound hematoma. This reviewer finds the selection of the terms appropriate.

In study 14287, there were no events with the above terms in the regorafenib arm and 2 events in the placebo group. Both of the events in the placebo group were under the term 'wound complication'. In the pooled phase I/II studies, there were 3 cases identified (1 case of abdominal wound dehiscence (grade 4) and 2 cases of 'impaired healing' (both grade 1).

The applicant conducted and provided results of a search of their pharmacovigilance database and identified 6 cases, of which 1 had occurred in a patient who received placebo. Two of these patients had concurrent infections and had also received concurrent chemotherapy. In two patients, the events (one of which was 'incisional hernia') occurred in the context of disease progression several weeks after the last dose of regorafenib. Thus, the cumulative review of the pharmacovigilance data also did not provide conclusive evidence of an increased risk of wound healing complications. However, based on the VEGF antagonism class effect, guidance on regorafenib treatment interruption for major surgical interventions and timing of subsequent restart is proposed by the applicant for inclusion in the label.

Reversible Posterior Leukoencephalopathy (RPLS):

There were no events of RPLS in study 14387 or in the pooled Phase I/II studies. From the pharmacovigilance information, there was only one case of RPLS reported (in a patient with GIST), which developed in the context of hypertensive crisis, and resolved with standard medical management. The applicant proposed that this information be included in the warnings and precautions of the label.

7.3.5 Submission Specific Primary Safety Concerns

None.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The following table shows the common adverse events that occurred in more than 10% of patients in the regorafenib arm at an incidence that was greater than that in placebo.

Table 28 Common Adverse Events (≥10% incidence in regorafenib arm)

	Regarofanib (N= 500)		Placebo (N=253)	
	All grades (%)	≥ grade 3 (%)	All grades (%)	≥ grade 3 (%)
Asthenia/fatigue	64	15	46	9
Decreased Appetite	47	5	28	4
PPE	45	17	7	0
Diarrhea	43	8	17	2
Mucositis	33	4	5	0
Weight loss	32	<1	10	0
Infection	31	9	17	6
Hypertension	30	8	8	<1
Dysphonia	30	0	6	0
Pain	29	3	21	2
Fever	28	2	15	0
Rash	26	6	4	<1
Hemorrhage	21	2	8	<1
Headache	10	<1	7	0

Other less common adverse events that occurred more frequently in the regorafenib arm compared to placebo included alopecia (7.6 vs. 1.6), taste disorder (7.6 vs. 2.4), musculoskeletal stiffness (6.0 vs. 2.0), dry mouth (4.8 vs. 2.0), hypothyroidism (4.2 vs. 0.4), tremor (2.0 vs. 0.0), and gastroesophageal reflux (1.4 vs. 0.0).

7.4.2 Laboratory Findings

Hematologic Laboratory Evaluation: Changes in the hematological parameters based on routine blood counts are shown below as the worst toxicity grade (CTC AE version 3.0) observed in the study:

Table 29 Hematology Laboratory Evaluation

Parameter	Regorafenib (n=500)			Placebo (n=253)		
	Grade*			Grade		
	All %**	3 %	4 %	All %	3 %	4 %
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	34	3	0
Increased INR	24	4	-	17	2	-

It should be noted that there is no grade 4 INR in the CTC version 3.

Liver Function Tests: Changes in the liver function test parameters based on routine blood counts are shown below as the worst toxicity grade (CTC AE version 3.0) observed in the study. Liver function tests that met the Hy's law criteria are discussed in section 7.3.4

Table 30 Liver Function Tests

Laboratory Parameter	Regorafenib (n=500)			Placebo (n=253)		
	Grade*			Grade		
	All %**	3 %	4 %	All %	3 %	4 %
Bilirubin increased	45	10	3	17	5	3
AST increased	65	5	1	46	4	1
ALT increased	45	5	1	30	3	<1
Alkaline phosphatase increased	77	11	0	67	13	0
Hypoalbuminemia	25	1	0	16	0.4	0

Changes in other routine laboratory metabolic tests are shown below as the worst toxicity grade (CTC AE version 3.0) observed in the study:

Table 31 Laboratory tests: Chemistries and urinalysis

Laboratory Parameter	Regorafenib plus BSC (n=500)			Placebo plus BSC (n=253)		
	Grade*			Grade		
	All %**	3 %	4 %	All %	3 %	4 %
Hypocalcemia	59	1	<1	18	1	0
Hypokalemia	26	4	0	8	<1	0
Hypophosphatemia	57	31	1	11	4	0
Increased Lipase	46	9	2	19	3	2
Increased Amylase	26	2	<1	17	2	<1
Proteinuria	60	0.4	0	34	0.4	0

Although there was increased incidence of elevated serum lipase and amylase, clinical pancreatitis was only reported in one patient in each arm.

Thyroid Function Tests: Among the thyroid function tests, elevated TSH at any time during the study or at the end of treatment was found in 21% of patients treated with regorafenib compared to 12% of placebo patients. However elevation of TSH combined with reduction of Free T4 occurred in 3% of patients in both arms. The incidence of hypothyroidism was reported as an adverse event in 4.2% of regorafenib-treated patients compared to 0.4% in the placebo patients as noted in section 7.4.1.

7.4.3 Vital Signs

No notable changes were seen in the mean heart rate from baseline to the end of treatment visit or in the mean body temperature in either treatment group. The mean blood pressure measurements for both systolic and diastolic blood pressures were similar across the two arms. The mean change in diastolic BP from baseline to the end of treatment visit was 1.6 (± 11.3; 1 SD) mmHg in the regorafenib + BSC group and -0.9 (± 11.0; 1 SD) mmHg in the placebo+ BSC group. The mean change in systolic BP for the same period was -2.9 (±17.1; 1 SD) mmHg in the regorafenib + BSC group and -1.2 (±15.3; 1 SD) mmHg in the placebo + BSC groups, respectively.

Very few patients in either treatment group had severe abnormally high blood pressure values during the study at their scheduled visits. Diastolic blood pressure defined as > 105 mm of Hg and an increase of over 20 mm of Hg over baseline occurred in approximately 1% of subjects during the first 4 cycles and none in the subsequent cycles in the regorafenib arms; high systolic blood pressure defined as >190 mm of Hg and an increase of over 20 mm of Hg over baseline occurred in ≤ 0.5% of patients in the regorafenib arm during the first 3 cycles and in none of the patients in the subsequent cycles. It should be noted that clinically significant changes in blood pressure

measurements would have been reported as adverse events. There were no adverse events of hypertensive crises in study 14387.

7.4.4 Electrocardiograms (ECGs)

In study 14387, a 12-lead ECG was performed on Day 1 of each cycle for the first 6 cycles. No clinically relevant changes were observed for any of the ECG parameters.

7.4.5 Special Safety Studies/Clinical Trials

Please see clinical pharmacology review. The applicant has completed enrollment in cardiac safety study (Study 14814) to evaluate QTc prolongation, if any, and left ventricular ejection fraction. The study is performed in approximately 50 patients with advanced solid tumors who are refractory to standard treatment. The current application contained an interim analysis on QTc assessment in 25 patients in the form of a preliminary report. As per this report, the analysis showed that at the maximum concentrations of regorafenib (t_{max}), the mean changes from baseline in QTcB and QTcF were -1 and 2 msec, respectively. Results for the QTcB and QTcF maximal median change from baseline were 7 and 9 msec, respectively. No subject had a QTcB or QTcF value > 500 msec during the post-treatment Holter monitoring visits (at Cycle 1 or 2, Day 21). Overall, the effect of regorafenib at t_{max} on the QTc intervals of the ECG, observed in the study were minimal, and even the most conservative evaluation, the maximal median change, was modest and unlikely to be of clinical significance in the setting of cancer treatment.

7.4.6 Immunogenicity

Immunogenicity information was not provided and not considered necessary for this orally available small molecule drug.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

The placebo controlled, international multicenter study (study 14387), that forms the basis of this application for the treatment of patients with metastatic colorectal cancer was conducted with a fixed dose of 160 mg regorafenib daily for 3 weeks of each 4 week treatment cycle.

Please see clinical pharmacology review for exploration of plasma drug levels and toxicity from phase I clinical studies. The applicant did not provide pharmacologic drug level data or analyses of such analyses from study 14387.

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7.5.2 Time Dependency for Adverse Events

Most of the treatment-emergent common adverse events occurred during the first two cycles of the treatment in either arm, considering that the mean duration of treatment with regorafenib was 12 weeks and for placebo was 8 weeks.

A similar pattern was seen with adverse events of special interest. The incidence of PPE was highest during the first cycle in regorafenib-treated patients accounting for 32% of the total 45% incidence. The incidence in the second cycle accounted for 11% of these cases. The incidence of rash was highest during the first cycle in regorafenib-treated patients accounting for 21% of the total 26% incidence. The incidence in the second cycle accounted for an additional 3% of these cases. Of the six cardiac ischemic events in the regorafenib arm, 3 occurred during the first 2 cycles with one event occurring as late as the sixth cycle. Twenty three of the 37 events included in the SMQ of hepatic injury/failure occurred during the first 2 cycles. However the last event occurred as late as during the tenth cycle.

7.5.3 Drug-Demographic Interactions

Analysis of adverse events occurring in age groups < 65 years of age and ≥ 65 years of age showed that the incidences of adverse events were similar in the two groups. In the regorafenib plus BSC group, there was a lower incidence of decreased appetite (43 % vs. 53%), hypertension (28% vs 34 %), and headache (8.5% vs 13%) in the <65 years group, and a higher incidence of palmar plantar erythrodysaesthesia syndrome (49% vs. 39%), hyperbilirubinemia (15 % vs. 10%) and back pain (15% vs. 10%) when compared to the ≥ 65 years group. With the exception of decreased appetite and headache, similar trends were seen in the placebo group. These minor differences were not clinically significant.

Analyses of adverse events according to gender showed that the incidences of most of the adverse events were similar in the male and female patients. In the regorafenib + BSC group, there was a higher incidence of weight loss (35% vs 28%) and dysphonia (36% vs. 20%) in the male group; however, similar trends were seen in the placebo group for these two events (11% vs. 9% for weight loss and 7% vs. 5%). Rash (29% vs 18%), stomatitis (22% vs 14%), and vomiting (21% vs. 13%) were higher in women.

Meaningful conclusions of the differences in adverse events based on race were difficult to make because the majority of patients were White and there were very few Black patients. Palmar-planter erythrodysaesthesia occurred more frequently in Asian patients (78%) compared to the other populations (White- 38%, Black 50%).

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7.5.4 Drug-Disease Interactions

Please see clinical pharmacology review.

No clinically important differences in the mean exposure of regorafenib or the active metabolites M-2 and M-5 were observed in patients with hepatocellular carcinoma and mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment compared to patients with normal hepatic function. No dose adjustment is recommended in patients with mild or moderate hepatic impairment. Regorafenib was not studied in patients with severe hepatic impairment (Child-Pugh Class C); hence use in this population is not recommended.

No clinically relevant differences in the mean exposure of regorafenib and the active metabolites M-2 and M-5 were observed in patients with mild renal impairment (CLcr 60-89 mL/min/1.73m^2) compared to patients with normal renal function following regorafenib 160 mg daily for 21 days. No dose adjustment is recommended for patients with mild renal impairment. Limited pharmacokinetic data are available from patients with moderate renal impairment (CLcr 30-59 mL/min/1.73m^2). Regorafenib has not been studied in patients with severe renal impairment or end-stage renal disease.

7.5.5 Drug-Drug Interactions

Please see clinical pharmacology review for details.

In vitro screening on cytochrome P450 enzymes: In vitro studies with human hepatic microsomes or recombinant enzymes showed that regorafenib competitively inhibits CYP2C8, CYP2B6, CYP2C9, CYP2C19 and CYP3A4 with R1 values > 1.1; M-2 inhibits CYP2C9, CYP2C8, CYP2D6 and CYP3A4 with R1 values > 1.1 and M-5 inhibits CYP2C8 with a R1 value > 1.1. In vitro studies with primary human hepatocytes showed that regorafenib is not expected to induce CYP1A2, CYP2B6, CYP2C19 and CYP3A4 enzyme activity.

In vitro screening on uridine diphosphate glucuronosyltransferases: In vitro studies with human hepatic microsomes showed that regorafenib competitively inhibits UGT1A9 and UGT1A1 and M-2 and M-5 competitively inhibit UGT1A1 at therapeutically relevant concentrations.

In vitro screening on transporters: In vitro data showed that regorafenib is an inhibitor of ABCG2 (Breast Cancer Resistance Protein) and ABCB1 (P-glycoprotein).
Effect of CYP3A4 Strong Inducers on Regorafenib: Twenty-two healthy men received a single 160 mg dose of Regorafenib 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 M-5 AUC increased by 264%. No change in the mean M-2 AUC was observed.

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Effect of CYP3A4 Strong Inhibitors on Regorafenib: Eighteen healthy men received a single 160 mg dose of Regorafenib 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%.

Effect of regorafenib on a substrate of UGT1A1 substrates: Eleven patients received irinotecan - containing combination chemotherapy with Regorafenib at a dose of 160 mg. The mean AUC of irinotecan increased 28% and the mean AUC of SN-38 increased by 44% when irinotecan was administered 5 days after 7 daily doses of Regorafenib.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

The applicant has not performed studies on carcinogenic potential of regorafenib. Regorafenib itself was negative in *in vitro* and *in vivo* assays for genotoxicity; however, a major human active metabolite of regorafenib, (M-2), was positive for clastogenicity, causing chromosome aberration in Chinese hamster V79 cells. Please see toxicology review for details

7.6.2 Human Reproduction and Pregnancy Data

The applicant has not provided human reproduction or pregnancy data since regorafenib was not studied in pregnant women. In animal studies, 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 humans at the clinical recommended dose based on AUC. In female rats, there were increased findings of the 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.

Please see toxicology review for additional details.

7.6.3 Pediatrics and Assessment of Effects on Growth

Not applicable. Regorafenib has not been studied in the pediatric population.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

The highest dose of regorafenib studied clinically was 220 mg per day. The most frequently observed adverse drug reactions at this dose were dermatological events, dysphonia, diarrhea, mucositis, dry mouth, decreased appetite, hypertension, and fatigue.

As per the applicant, in the regorafenib clinical trial program, only one case of inadvertent self-administration of a higher than planned dose was reported (160 mg twice daily for 6 days, instead of 160 mg once daily in study 11650). The patient (11650-3009) experienced fatigue from day 7 as well as hand-foot skin syndrome and rash from day 14 of this treatment cycle. These events are expected within the normal dose range of regorafenib, and were not severe in this patient.

The applicant did not report any evidence of drug abuse potential, withdrawal or rebound.

7.7 Additional Submissions / Safety Issues

None.

8 Postmarket Experience (S. Pradhan)

There is no postmarketing experience with regorafenib because regorafenib has not been approved.

9 Appendices

9.1 Literature Review/References

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Van Cutsem E, Peeters M, Siena S, Humblet Y, Hendlisz A, Neyns B, et al. Open-label Phase III trial of panitumumab plus best supportive care compared with best supportive care alone in patients with chemotherapy-refractory metastatic colorectal cancer. J Clin Oncol. 2007; 25:1658-1664.

9.2 Labeling Recommendations

This clinical team recommended the following key labeling changes. In addition, inclusion of a boxed warning regarding hepatotoxicity was recommended.

Indications and Usage
- Change the indication from   (b) (4)

  to "treatment of patients with 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"   (b) (4)

Dosage and Administration
- Inclusion of examples of a low-fat breakfast
- Removal of   (b) (4)

  (instructions regarding monitoring for pertinent toxicities and management are included in Warnings and Precautions)
- Replacement of the term 'hand-foot-skin reaction (HFSR)' with the term 'palmar-plantar dysesthesia (PPE)'

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- Revision of dose modification instructions for clarity and to include dose modification rules for events other than PPE and liver toxicity.

Warnings and Precautions
- Revision of the Hepatotoxicity warning to include the incidence of severe drug-induced liver injury with fatal outcome in regorafenib-treated patients, information regarding cases of hepatic failure in Trial 14387, and instructions regarding monitoring for hepatotoxicity and management
- Revision of the Hemorrhage warning to include additional information regarding Trial 14387 including incidence and types of hemorrhage events, and revision of instructions regarding patient monitoring and management (for clarity)
- Revision of the Dermatologic Toxicity warning for clarity
- Replacement of _____ (b) (4) with a warning regarding hypertension, and revision of the instructions regarding monitoring for hypertension and management (for clarity)
- Revision of the Cardiac Ischemia and Infarction warning for clarity
- Revision of the RPLS warning to include instructions regarding confirmation of RPLS diagnosis with MRI and to discontinue regorafenib in patients who develop RPLS
- Inclusion of information in the Wound Healing Complications warning regarding the VEGFR inhibitor class effect.

Adverse Reactions
- Replacement of the term 'hand-foot-skin reaction (HFSR)' with the term 'palmar-plantar dysesthesia (PPE)'
- Inclusion of mucositis in the list of most frequently observed adverse drug reactions in patients receiving Stivarga
- To reduce redundancy; the following recommendations were made
  - Removal of information already described in section 5 (Warnings and Precautions)
  - Removal from the text of information also included in the adverse reactions and laboratory abnormalities tables
  - Removal from the adverse reactions table of information also included in the laboratory abnormalities table (i.e., regarding anemia, thrombocytopenia, and hyperbilirubinemia)
- In the adverse reactions table, replacement of the terms _____ (b) (4) _____ with the single term 'mucositis'

Use in Specific Populations
- Removal of the statement that _____ (b) (4) _____

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- Inclusion of the statement that "Stivarga is not recommended for use in patients with baseline severe hepatic impairment"

Clinical Studies

- Replacement of the list of   (b) (4), for Trial 14387 with the list of supportive efficacy outcome measures (and removal of   (b) (4)   from the list)
- Inclusion of demographic information for the study populations
- Removal from the text of information included in the efficacy results table (i.e., OS and PFS results)
- Inclusion of overall response rate results in the efficacy results table
- Removal   (b) (4)

Patient Counseling Information

- Revision of information regarding hepatotoxicity, hemorrhage, PPE, and cardiac ischemia or infarction (for clarity)
- Inclusion of a list of symptoms associated with hypertension

9.3 Advisory Committee Meeting

Patients in the regorafenib arm of Trial 14387 experienced a clinically meaningful, statistically significant improvement in overall survival. Therefore, the Office of Hematology and Oncology Products did not require advice from the Oncologic Drugs Advisory Committee (ODAC) in order to render a regulatory decision.

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CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 203085   **Applicant: Bayer**   **Stamp Date:**

Drug Name: Regorafenib   **NDA/BLA Type: NME**   **4/27/12**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
	FORMAT/ORGANIZATION/LEGIBILITY				
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			eCTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
	LABELING				
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			On initial review, the label appears to be in acceptable PLR format.
	SUMMARIES				
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			As agreed upon by FDA (8/2011 Pre-NDA meeting minutes), the ISE submission in Module 5.3.5.3 references Module 2.7.3 for the text portion.
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?			X	
	DOSE				
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e*., appropriately designed dose-ranging studies)? Study Number: 11650 and 11651 Sample Size: 76, 84 Arms: Dose levels ranging from 10-220 mg and continuous and intermittent dosing was evaluated. Location in submission: Module 2, Summary of Clinical	X			

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Efficacy				
EFFICACY					

14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application?
	
	Pivotal Study #1 Study 14387 (CORRECT Study)
	        Indication: "treatment of patients with metastatic colorectal cancer who have been previously treated with, [redacted] (b) (4) [redacted] fluoropyrimidine-based chemotherapy, and anti-VEGF therapy, and, if KRAS wild-type, an anti-EGFR therapy"
	
	Pivotal Study #2
	        Indication:
		X			

15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?	X			
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?	X			Contains Interim study report of QT study as agreed upon by FDA
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?			X	
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	X			

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[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	X			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			X	
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			A request for pediatric deferral was submitted with the BLA.
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?	X			
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?				
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial	X			

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[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

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CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Disclosure information?				
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			A statement that "all clinical studies performed in the framework of the submission were or are being conducted in accordance with ICH GCP" is included in the Summary of Clinical Efficacy in Module 2.

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ___Yes_

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Shan Pradhan (efficacy review)
Kaushik Shastri (safety review)
_____
Reviewing Medical Officer   Date

Steven Lemery
_____
Clinical Team Leader   Date

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

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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/

SHAN PRADHAN
05/30/2012

KAUSHIKKUM A SHASTRI
05/31/2012

STEVEN J LEMERY
06/06/2012