CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203085Orig1s000

SUMMARY REVIEW

Division Director Summary Review

Date	September 20, 2012
From	Patricia Keegan
Subject	Division Director Summary Review
NDA #	NDA 203085
Applicant Name	Bayer Healthcare Pharmaceuticals, Inc.
Date of Submission	April 27, 2012
PDUFA Goal Date	October 27, 2012
Proprietary Name / Established (USAN) Name	Stivarga Tablets / regorafenib
Dosage Forms / Strength	Tablets for oral administration/ 40 mg
Proposed Indication(s)	For the treatment of patients with metastatic colorectal cancer (mCRC) who have been previously treated with, (b) (4) fluoropyrimidine-based chemotherapy, an anti-VEGFR therapy, and, if KRAS wild type, an anti-EGFR therapy
Recommended Action for NME:	*Approval*

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Regulatory Project Manager Review	Monica Hughes
Medical Officer Reviews	Shan Pradhan & Kaushikkumar Shastri
Statistical Review	Huanyu (Jade) Chen
Pharmacology Toxicology Review	M. Anwar Goheer & Andrew McDougal
ONDQA Reviews	Donghao R Lu & Elsbeth Chikhale
Clinical Pharmacology Review	Stacy Shord
OPDP/DPP	Carole Broadnax & Karen Munoz-Nerez
OSI	Janice Pohlman
CDTL Review	Steven Lemery
OSE/DMEPA	James Schlick
OSE/DRISK	Amarylis Vega
Maternal Health Team Consult Review	Carrie Ceresa
Predictive Safety Consult Review	Keith Burkhart & Naomi Kruhlak

OND=Office of New Drugs
ONDQA=Office of New Drugs Quality Assessment
OPDP=Office of Prescription Drug Promotion
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
OSI=Office of Scientific Investigations
DRISK=Division of Risk Management
CDTL=Cross-Discipline Team Leader

Division Director Summary Review

1. Introduction

Regorafenib (Stivarga Tablets, Bayer) is a small molecule inhibitor of multiple membrane-bound and intracellular kinases (multi-kinase inhibitor) involved in a wide range of normal cellular functions and in pathologic processes, such as oncogenesis, tumor angiogenesis, and maintenance of the tumor microenvironment. The kinase inhibition profile of regorafenib affect the angiogenic (VEGFR 2/3, TIE2), stromal (PDGFR-ß, FGFR) and oncogenic (KIT, RET and B-RAF) cellular processes and pathways.

The clinical efficacy and safety of regorafenib were primarily supported by a single clinical trial (Protocol 14387; "CORRECT") enrolled 670 patients with metastatic colorectal cancer with disease progression following all FDA-approved therapy. The results of this single trial were considered sufficient to serve as the sole trial in support of this NDA since it was a large multicenter study with consistency of the treatment effects across study subsets; met both the primary endpoint of overall survival as well as one of the key secondary efficacy endpoints, progression-free survival, which involves different events; and the effects on survival and progression-free survival were statistically very persuasive.

CORRECT was an international, multicenter, randomized (2:1), double-blind, placebo-controlled, trial comparing the effect of regorafenib at a dose of 160 mg once daily for 3 weeks (days 1-21) of a 28-day cycle plus best supportive care (BSC) (n=505) to matching placebo plus BSC (n=255) on overall survival (primary endpoint). Key secondary endpoints were progression-free survival, objective response rate, and response duration.

The CORRECT trial demonstrated statistically significant improvements in both overall survival and in progression-free survival for regorafenib treatment patients over those receiving best supportive care alone, however there was inadequate tumor shrinkage among regorafenib-treated patients, as determined by RECIST criteria, to consider this a part of the clinical benefit of this drug.

Efficacy Outcomes	Stivarga + BSC (N=505)	Placebo + BSC (N=255)
Overall Survival		
Number of deaths, n (%)	275 (55%)	157 (62%)
Median Overall Survival (months)	6.4	5.0
95% CI	(5.8, 7.3)	(4.4, 5.8)
HR (95% CI)	0.77 (0.64, 0.94)	
Stratified Log-Rank Test P-value [a,b]	0.01	
Progression-free Survival		
Number of Death or Progression, n (%)	417 (83%)	231 (91%)
Median Progression-free Survival (months)	2.0	1.7
95% CI	(1.9, 2.3)	(1.7, 1.8)
HR (95% CI)	0.49 (0.42, 0.58)	
Stratified Log-Rank Test P-value [a]	<0.0001	
Overall Response Rate		
Overall response, n (%)	5 (1%)	1 (0.4%)
95% CI	0.3%, 2.3%	0%, 2.2%

The most frequently observed adverse drug reactions (≥30%) in regorafenib-treated patients are asthenia/fatigue, decreased appetite and food intake, palmar-plantar erythrodysesthesia (hand-foot syndrome), diarrhea, mucositis, weight loss, infection, hypertension and dysphonia. The most frequent laboratory abnormalities are cytopenias (anemia, thrombocytopenia, and lymphopenia), liver dysfunction (hyperbilirubinemia, transaminitis), and metabolic derangements (hypocalcemia, hypophosphatemia, and hypokalemia). The most serious adverse drug reactions of regorafenib in the CORRECT trial, occurring at an increased incidence in regorafenib-treated patients and placebo-treated patients, respectively, were Grade 3 palmar-plantar erythrodysesthesia (17% vs. 0), fatal hepatotoxicity (1.6% vs. 0.4%), myocardial ischemia and infarction (1.2% vs. 0.4%), and fatal hemorrhage (0.8% vs. 0).

Across the clinical trials safety database of 1100 patients, serious adverse drug reactions with regorafenib were identified at the following rates: gastrointestinal perforation (0.6%), fatal drug-induced liver injury (0.3%), hypertensive crisis (0.18%), and reversible posterior leukoencephalopathy (0.09%). These adverse drug reaction profile for regorafenib appear to be arise primarily from its inhibition of the VEGF pathway (i.e., hypertension, RPLS, cardiac ischemia/infarction, hemorrhage, viscus perforation, fistula formation, dysphonia) and of the EGFR pathway (rash), although some of the common and serious adverse drug reactions of regorafenib are seen in drugs both with and without known kinase inhibition (e.g., hepatotoxicity, asthenia/fatigue, decreased appetite and food intake, palmar-plantar erythrodysesthesia, diarrhea, and mucositis) and cannot be attributed to a specific mechanism.

All review disciplines recommended approval. The approval was based on a single, adequate and well-controlled trial that showed a highly robust effect on 23% relative reduction in the immediate risk of death and 51% relative reduction in the immediate risk of disease progression or death. While the absolute magnitude of the treatment effects on survival (difference of 1.4 months in median survival times) and progression-free survival (difference of 1.2 weeks in median progression-free survival times) are small, the ability of any single

agent to demonstrate efficacy in this heavily pre-treated population represents clinical benefit, when considered in the context of serious adverse drug reactions occurring in fewer than 1% of patients and common toxicities already considered acceptable with other approved agents for the treatment of metastatic colorectal cancer (e.g., palmar-plantar erythrodysesthesia, nausea/vomiting, mucositis, diarrhea, and hypertension) and which are generally manageable with dose modification and symptomatic treatment.

2. Background

Proposed indication

In 2012, there will be an estimated 103, 170 new cases of colon cancer, 40, 290 new cases of rectal cancer,, and an estimated 51, 690 deaths from colon or rectal cancers[1] While the mortality from colorectal cancer has decreased in the past 50 years, approximately half the decline in mortality rates (from 28 deaths per 100,000 to 17 deaths per 100,000) is attributed to screening and early diagnosis[2]. The identification of new systemic treatments for patients with metastatic disease has improved short-term outcomes but not long-term cure rates. The standard of care in the United States for the treatment of metastatic colorectal cancer includes first-line and second-line treatment with fluoropyrimidine-based combination chemotherapy (FOLFOX or FOLFIRI) administered with bevacizumab for the majority of patients. Cetuximab and panitumumab are indicated for the treatment of patients with metastatic colorectal cancer in which the tumor does not contain mutations in the *c* oncogene (*K-Ras* wild-type), either as an addition to combination chemotherapy for initial treatment (cetuximab) or as monotherapy in patients with recurrent, chemotherapy-refractory disease (cetuximab, panitumumab). . The very elderly or those with co-morbid conditions which may render intensive treatment intolerable, are generally treated either with combinations of approved drugs (5-flurouracil and leucovorin, capecitabine, oxaliplatin, irinotecan, with or without anti-EGFR directed antibodies) or with single agent therap.

Bayer has requested approval for the proposed indication:

> "For the treatment of patients with metastatic colorectal cancer (mCRC) who have been previously treated with, (b) (4), fluoropyrimidine-based chemotherapy, an anti-VEGFR therapy, and, if KRAS wild type, an anti-EGFR therapy."

There are no FDA-approved therapies for the proposed indication, which was adequately reflected by the patient population enrolled in the primary efficacy trial. Thus this patient population represents a disease with a clear, unmet medical need.

Regulatory History of NDA

July 19, 2006: Submission for IND 75642

[1] http://www.cancer.gov/cancertopics/types/colon-and-rectal
[2] http://www.cancer.gov/cancertopics/factsheet/cancer-advances-in-focus/colorectal

September 3, 2009: End-of-Phase 2 meeting
Key agreements regarding the proposed registration trial

- The primary objective should be overall survival; an earlier assessment of the treatment effect may be obtained in Phase 2 trial or through an interim analysis for futility in the planned Phase 3 trial
- A single trial could support an NDA if well-conducted & designed, with statistically persuasive results so that a second trial is unethical or infeasible
- Control arm of best supportive care plus placebo was acceptable in patients no longer responding to approved therapies or standard combination regimens
- Sample size is adequate based on assumptions regarding treatment effects
- The proposed Phase 3 trial, supported by Phase 2 studies in mCRC, would not support claims for (b) (4), given the number of approved drugs for mCRC and trial design
- Pharmacokinetic studies, including food effect studies, supporting the NDA should evaluate regorafenib and the metabolites M2 and M5
- Hepatic impairment studies and studies to assess possible drug interactions should also be conducted

January 22, 2010: Special Protocol Assessment (SPA) No Agreement letter issued for Protocol 14387; "CORRECT" trial. Areas of outstanding disagreement or requiring further clarification:

- Inclusion of a futility interim analysis earlier than (b) (4) of the planned final analysis and inclusion in the protocol of a single interim analysis for overall survival for efficacy.
- Whether a 1.5 month difference in median overall survival times would be considered "clinically significant" is a review issue.
- Clarify the proportion of patients to be enrolled in the United States

April 13, 2010: Based on FDA's draft responses to the Type A meeting to discuss FDA's January 22, 2010 SPA No Agreement letter, Bayer cancelled the Type A meeting and will submit the revised protocol

April 13, 2010: Submission of the revised Protocol 14387 under a request for Special Protocol Assessment. The request for review under SPA was withdrawn on May 3, 2010.

June 10, 2011: Fast Track designation granted for regorafenib for the treatment of patients with metastatic colorectal cancer (mCRC) after failure of standard therapies

August 23, 2011: Pre-NDA meeting
Key agreements regarding the proposed NDA content and format:

- Proposed nonclinical program acceptable to support NDA
- Proposed content/format for ISE and ISS acceptable
- Pooled analysis of efficacy not required (based on one major efficacy trial)
- ISS should include serious adverse event information from all regorafenib trials (monotherapy and combination therapy in patients with cancer, healthy volunteer trials). ISS would contain all data from regorafenib monotherapy studies and used pooled data to

assess for risks in subgroups (e.g., by age, gender, organ dysfunction). Case report forms required for all serious adverse events, unless event is a manifestation of disease progression.

- Datasets to be provided in CDISC, SDTM
- Data cut-off between clinical data an in 120-day safety update should not exceed 6 months from date of 120-day safety update submission.
- Bayer will make "best efforts" to include QTc study report in the initial NDA submission
- Bayer encouraged to include "biomarker report" in the initial NDA submission.
- [redacted] (b) (4)
- Proposed rolling submission scheduled for NDA is acceptable.

April 27, 2012: NDA 203085 submitted.

- Approval requested under 505 (b)(1) of the Federal Food, Drug and Cosmetic Act for "the treatment of patients with metastatic colorectal cancer (CRC) who have been previously treated with [redacted] (b) (4), fluoropyrimidine-based chemotherapy, an anti-VEGF therapy, and, if KRAS wild type, an anti-EGFR therapy.
- Priority review requested based on results of study 14387 which demonstrate that Regorafenib is the first agent to demonstrate a statistically significant improvement in overall survival (OS) for patients that have previously been treated with all approved therapies for metastatic colorectal cancer (including fluoropyrimidine-based chemotherapy, an anti-VEGF therapy, and, if KRAS wild type, an anti-EGFR therapy) while presenting a manageable adverse event profile. The survival advantage is clinically meaningful and establishes Regorafenib as the only treatment for these patients. If approved, Regorafenib has the potential to provide a safe and effective treatment in a disease where no satisfactory alternate therapy exits.
- Request for Waiver of Pediatric Studies submitted to waive the requirement to assess the safety and effectiveness of the drug product in children 16 years of age and below in accordance with 21 CFR 314.55. We request the waiver on the basis that studies are impossible or highly impractical, as the number of pediatric patients is extremely small and the proposed indication, colorectal cancer, qualifies for a disease-specific waiver.

June 25, 2012: Filing letter issued, containing notification of priority review designation and deficiencies identified.

3. CMC

I concur with the conclusions reached by the chemistry reviewers regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable. Stability testing supports an expiry of 36 months. There are no outstanding issues that preclude approval.

Regorafenib monohydrate is the drug substance. [redacted] (b) (4) thus regorafenib is the active drug substance

present in the regorafenib film-coated tablets. The final drug product, Stivarga tablets for oral administration is formulated as light pink oval shaped tablets debossed with "BAYER" on one side and "40" on the other. Each tablet contains 40 mg of regorafenib. Stivarga tablets are supplied in packages containing three bottles, with each bottle containing 28 tablets, for a total of 84 tablets per package. The drug product should be at room temperature in the original bottle containing a desiccant.

4. Nonclinical Pharmacology/Toxicology

I concur with the conclusions reached by the pharmacology/toxicology reviewers that there are no outstanding pharmacology/toxicology issues that preclude approval.

The pharmacology/toxicology reviewers stated that the NDA adequate non-clinical information to support the NDA for the proposed intended use. While the application did not contain carcinogenicity studies or a complete battery of reproductive toxicology studies, these are not required for products to be indicated for the treatment of advanced, incurable cancers. Similarly, the finding of potential mutagenic effects for a major metabolite (M2) did not require a specific Warning based on the indicated population.

The NDA contained the reports for nonclinical primary pharmacology studies confirming the claimed effects of regorafenib and its two major metabolites (M2 and M5) on kinase inhibition, via biochemical assays or cellular assays, examining the phosphorylation of downstream targets, to establish kinase inhibition at clinically achievable exposures in humans at the recommended dose for multiple kinase targets (see product labeling). Both the M-2 and M-5 metabolites showed inhibitory activity equal to or greater than the activity of the regorafenib. In addition, *in vivo* evaluation of anti-angiogenic effects were evaluated in rats and mice,

The application also contained reports of repeat dose toxicology studies in rodents and dogs. Toxicologic findings demonstrated both rats and dogs which were also observed in patients with cancer involved the gastrointestinal tract (vomiting, diarrhea, decreased motility), hematopoietic/lymphoid system (marrow hypocellularity, neutropenia, thrombocytopenia, and lymphopenia), atrophy of lymphoid organs), the reproductive system (atrophy), hepatic enzyme elevation with histopathologic changes in the liver, cutaneous toxicity (dyskeratosis, hyperkeratosis, acanthosis, dermatitis, and alopecia), and skeletal system.

Findings identified in animals that have not been confirmed in clinical trials of adults with cancer include renal toxicity (glomerulopathy, tubular degeneration/regeneration, tubular dilation, and interstitial fibrosis), skeletal changes (changes in dentin and epiphyseal growth plates), reproductive toxicity (increased necrotic corpus lutea and atrophy in the ovaries in females and decreased weight of the testes, prostate, and seminal vesicles and retarded maturation of the testes along with aspermia/oligospermia in the epididymides in males), histopathologic changes in the adrenal glands, and hypothyroidism.

A report of a safety pharmacology study was also submitted to the NDA. This study did not identify significant cardiotoxicity.

Embryofetal studies were conducted in Wistar rats and Himalayan rabbits demonstrated increased post-implantation loss and teratogenic effects including skeletal and cardiovascular malformations and renal findings of dilation of the renal pelvis or hydronephrosis at exposures significantly lower than the human exposure at the recommended daily dose. Based on these findings, and consistent with current practices in the Division of Hematology-Oncology Toxicology, Pregnancy category D was recommended.

A distribution study in pregnant rats documented regorafenib exposure in the fetus, with greater regorafenib concentrations in fetal adrenal glands and brain as compared to the maternal blood and increased concentrations of regorafenib or its active metabolites in maternal mammary fluid as compared to the blood. Based on these studies, labeling directs lactating mothers to discontinue nursing while taking regorafenib.

The pharmacology/toxicology and maternal health team agreed that, based on embryofetal and teratogenic effects observed in general toxicology studies, in which female rats administered regorafenib at dose levels resulting in exposures similar to those observed in humans at the clinically recommended dose, product labeling should indicate the potential risks of impaired fertility in both men and women. Dr. Helms noted that these animals were not followed for a sufficient period to determine reversibility (persistent findings noted at the 4-week recovery period without additional follow-up). Again, given the indicated population, the findings and limitations of the findings (i.e., based on animal data) will be conveyed in product labeling.

5. Clinical Pharmacology

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer that there are no outstanding clinical pharmacology issues that preclude approval.

The NDA contained clinical pharmacology data from two dose-finding trials, evaluating continuous dosing and a three-week on/one-week off dosing schedule, three drug interaction studies, one food effect study and one bioequivalence trial comparing the pharmacokinetic of the tablet form used in the major efficacy trial with that of the "to-be-marketed tablet. FDA accepted the NDA for filing prior to the completion of additional clinical pharmacology trials and expected analyses of exposure-response and population pharmacokinetics because of the findings of improved survival in the efficacy trial for a population with an unmet medical need.

Following oral administration, regorafenib undergoes enterohepatic circulation. It is highly protein bound (99.5%), as are the two major metabolites (M2 and M5) of regorafenib, both of which are clinically active. Regorafenib is primarily metabolized by CYP3A4 and UGT1A9 and about 71% of a single radiolabeled dose (24% as metabolites) was excreted in feces. The mean elimination half-lives of regorafenib, M2, and M5 are 28 hours, 25 hrs and 51 hrs, respectively. Hepatic elimination appears to be the major route of elimination for regorafenib.

The bioavailability of regorafenib and its active metabolites are affected by the presence of food (fasted vs. fed) and the fat content (low vs. high-fat meal) when regorafenib is taken with food. Since the major efficacy trial which provides substantial evidence of effectiveness of regorafenib was performed with the direction to take regorafenib following a low-fat meal, and in light of the food-effects, product labeling recommends that regorafenib be administered following a low-fat meal.

Pharmacokinetic data obtained in patients with mild renal impairment (n=10) or mild, Child-Pugh A (n=4) or moderate/ Child-Pugh B (n=10) hepatic impairment do not suggest altered clearance requiring dose adjustments. However, Bayer will be required to conduct trials assessing pharmacokinetics in patients with severe renal impairment and severe hepatic impairment.

Pharmacokinetic studies were conducted to evaluate for interactions between regorafenib and irinotecan, between regorafenib and 5-fluorouracil, and between regorafenib and oxaliplatin. There was no evidence of a pharmacokinetic interaction with fluoropyrimidines. Regorafenib and its metabolites inhibited UGT1A9 and inhibited UGT1A1 *in vitro*; exposure to irinotecan and its major active metabolite, SN-38, were increased by 28% and 44%, respectively when irinotecan was administered following regorafenib. Exposure to oxaliplatin was increased by 39% when oxaliplatin was administered following regorafenib. The mechanism for this apparent interaction is unknown. Because regorafenib is indicated for use as a single agent, these interactions are not included in product labeling.

Additional pharmacokinetic trials demonstrated interactions between regorafenib and ketoconazole and between regorafenib and rifampin. Administration of ketoconazole increased the exposure of regorafenib by 33% and decreased the mean AUC of M2 and M5 each by 93%. Administration of rifampin decreased exposure of regorafenib by 50%, increased exposure of M5 by 264%, and had no apparent effect on exposure of M2. This data is described in product labeling based on the potential for co-administration with regorafenib of drugs that are strong inhibitors or strong inducers the CYP3A4 enzyme.

Regorafenib or its active metabolites M2 or M5 inhibited CY2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4 *in vitro*. The effect of regorafenib on the PK of CYP2C8, CYP2C9, and CYP3A4 substrates are under evaluation in an ongoing study. Regorafenib did not induce cytochrome P450 activity ***in vitro.***

PMRs and PMCs
All post-marketing requirements and commitments were focused on ensuring adequate characterization in the pharmacokinetics of regorafenib to ensure safe dosing recommendations based on food effects, drug interactions, organ dysfunction, and demographics (e.g., age, gender, race).

The required post-marketing trials under 505(o) and the agreed-upon post-marketing commitments requested by the Clinical Pharmacology review staff are summarized in section 13, of this review.

6. Clinical Microbiology

Not applicable for dosage form (oral tablet)

7. Clinical/Statistical-Efficacy

Protocol 14387, titled "A randomized, double-blind, placebo-controlled phase III study of regorafenib plus best supportive care (BSC) versus placebo plus BSC in patients with metastatic colorectal cancer (CRC) who have progressed after standard therapy" provides the data supporting this NDA. Additional clinical trials data included in the application serve to further characterize the adverse drug reaction profile and, for the dose-finding trials, to establish the tolerability of the proposed dose and schedule, 160 mg orally, once daily for 21 days of each 28 day cycle (3-weeks on/1-week off). This schedule was selected over a continuous daily dosing schedule based on higher regorafenib exposure and a perception of higher activity (higher disease control rate).

Protocol 14387 was a randomized (2:1), double-blind, placebo-controlled trial. Randomization was centralized and stratified by prior treatment with vascular endothelial growth factor (VEGF) targeting drugs (yes/no), time from diagnosis of metastatic disease (≥18 months vs. <18 months), or geographical region (region 1: North America, Western Europe, Israel and Australia versus region 2: Asia versus region 3: South America, Turkey and Eastern Europe).

Key inclusion criteria were age 18 years or older, ECOG performance status of 0 or 1, metastatic adenocarcinoma of colon or rectum with disease progression during or within 3 months after the last administration of an FDA-approved drug(s) for colorectal cancer or intolerance to such drugs.

Patients were randomized to regorafenib 160 mg or matching placebo, administered orally, once daily on days 1-21 of each 28-day treatment cycle. Study drug administration continued until objective disease progression (per RECIST), clinical progression, unacceptable toxicity, or death. Treatment could also be terminated for withdrawal of patient consent, physician decision or non-compliance with the protocol.

The planned sample size of 690 patients was designed to detect a hazard ratio (HR) of 0.75 for overall survival after 582 deaths, with a two-sided alpha of 0.05 and 90% power, given the 2:1 randomization ratio. This was based on the assumed median overall survival times of 6 months and 4.5 months for the regorafenib- and placebo-treated arms, respectively. Two formal interim analyses were planned for overall survival; the first interim analysis would be conducted for "futility" after approximately 174 deaths (30% of the planned 582 deaths for the final analysis), while the second interim analysis would be conducted for both futility and to terminate the trial early for efficacy, at approximately 408 deaths (70% of the planned 582 deaths for the final analysis). The type 1 error rate was preserved through adjustment for multiplicity based on the O'Brien-Fleming-type error spending function.

Results

Protocol 14387 enrolled 780 patients at 105 clinical sites across 15 countries; there were 505 patients randomized to regorafenib and 255 patients randomized to placebo, which constitutes the intent-to-treat population for the primary and key secondary efficacy analysis. The first patient was enrolled on April 30, 2010. The data cut-off date for efficacy analyses was July 21, 2011. Baseline demographic and prognostic information (abstracted from the statistical review) are presented in the following table:

Baseline Demographics and Disease Characteristics by Treatment Arm CORRECT Trial		
Demographic or Disease Characteristic	Regorafenib (n=505)	Placebo (n=255)
Age (years)		
Median	61	60
≥ 65 years	196 (39%)	89 (35%)
Gender		
Female	194 (38%)	102 (40%)
Race		
White	392 (78%)	201 (79%)
Asian	76 (15%)	35 (14%)
Other	47 (9%)	19 (7%)
Region		
1	420 (83%)	212 (83%)
US	**47 (9%)**	**36 (14%)**
2	69 (14%)	35 (14%)
3	16 (3%)	8 (3%)
Time from 1st diagnosis of metastatic disease to randomization		
< 18 months	91 (18%)	49 (19%)
≥ 18 months	414 (82%)	206 (81%)
Prior bevacizumab		
Yes	505 (100%)	255 (100%)
ECOG PS		
0	265 (52%)	146 (57%)
1	240 (48%)	109 (43%)
K-Ras tumor status		
wild-type	273 (54%)	157 (62%)
mutant	205 (41%)	94 (39%)
Primary site		
Colon	323 (64%)	172 (68%)
Rectum	151 (30%)	69 (27%)
Colon and Rectum	30 (6%)	14 (5%)
Prior surgical resection		
Yes	505 (100%)	255 (100%)
Prior Radiotherapy		
Yes	135 (27%)	78 (31%)
Prior Lines of Systemic Anti-Cancer Therapy for Metastatic Disease		
0-1	16 (3%)	5 (2%)
2	119 (24%)	58 (23%)
3	125 (25%)	72 (28%)
4	113 (22%)	49 (19%)
5	60 (12%)	32 (13%)
≥6	72 (14%)	39 (15%)
Prior Treatment with		
Fluoropyrimidine	505 (100%)	255 (100%)
Oxaliplatin	505 (100%)	255 (100%)
Irinotecan	505 (100%)	255 (100%)
Panitumumab or cetuximab		
K-Ras wild-type	204/205 (99.5%)	94/94 (100%)
K-Ras status - unknown	27/27 (100%)	4/4 (100%)
K-Ras mutant	33/273 (12%)	23/157 (15%)

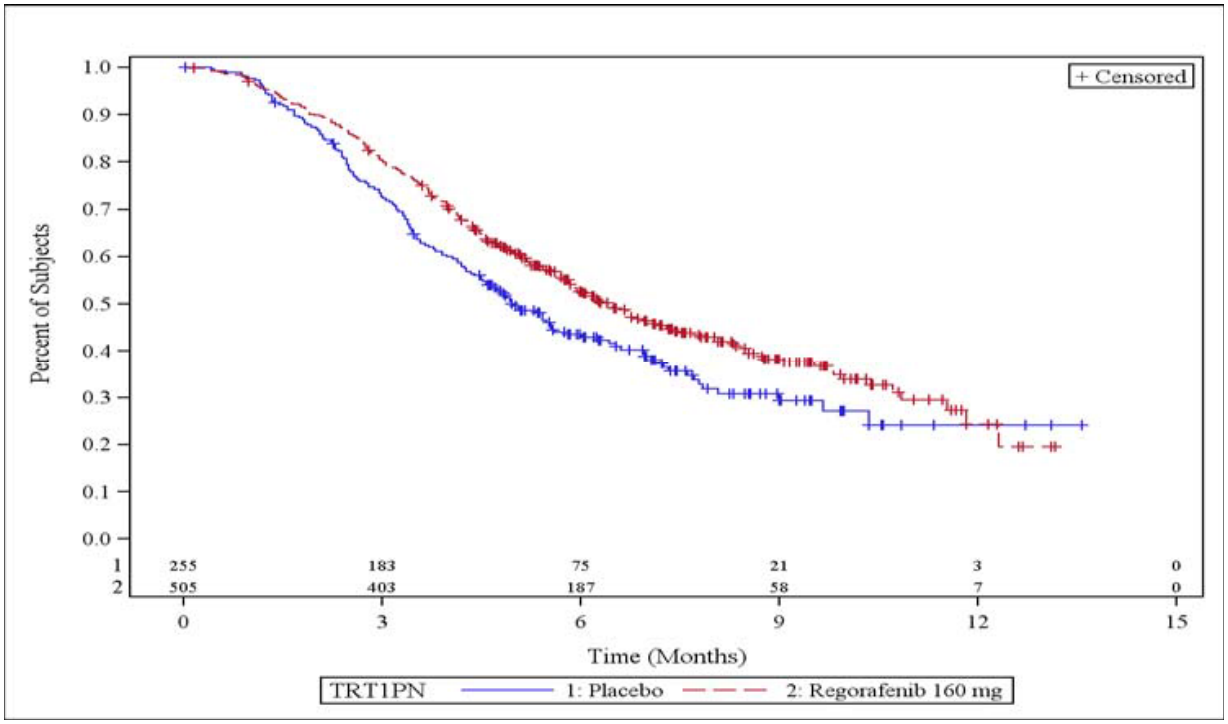
The trial was terminated at the first interim analysis of overall survival for efficacy, after 432 deaths (74% of the planned 582 deaths for the final analysis). Based on the O'Brien-Fleming-type error spending function, the boundary was considered to have been crossed (< p=0.018) at the interim analysis which yielded a hazard ratio of 0.77, p=0.0102 stratified log-rank test. Efficacy was tested for the secondary endpoints of progression-free survival, which was also statistically significant, and for overall response rate, which was not significantly different between arms. The results of the key efficacy analyses are summarized in the following table, abstracted from the statistical review.

Efficacy Results from the CORRECT Trial		
Efficacy Endpoint	**Regorafenib (n=505)**	**Placebo (n=255)**
Overall Survival		
Number of deaths, n (% of all ITT)	275 (55%)	157 (62%)
# of deaths - Region 1 (% of all deaths)	238 (86.5%)	135 (86%)
# of deaths - Region 2 (% of all deaths)	29 (10.5%)	16 (10%)
# of deaths - Region 3 (% of all deaths)	8 (3%)	6 (4%)
Median Overall Survival (months)	6.4	5.0
95% CI	(5.8, 7.3)	(4.4, 5.8)
HR (95% CI)	0.77 (0.64, 0.94)	
Stratified Log-Rank Test p-value	0.01	
Progression-free Survival		
Number of Death or Progression, n (%)	417 (83%)	231 (91%)
Median Progression-free Survival (months)	2.0	1.7
95% CI	(1.9, 2.3)	(1.7, 1.8)
HR (95% CI)	0.49 (0.42, 0.58)	
Stratified Log-Rank Test p-value [a]	<0.0001	
Overall Response Rate		
Overall response, n (%)	5 (1%)	1 (0.4%)
95% CI	0.3%, 2.3%	0%, 2.2%

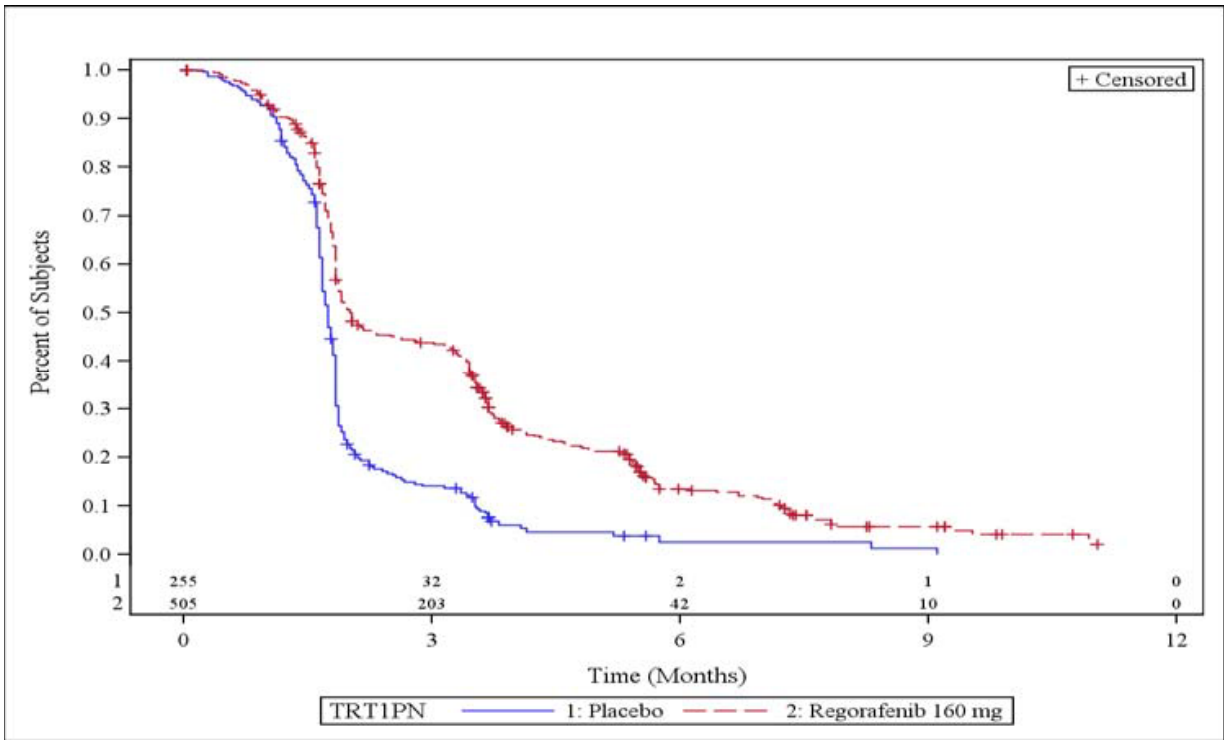
In exploratory subset analyses based on demographic parameters (age, gender, race) and on prognostic factors (ECOG performance status, *K-Ras* mutation status, time from metastatic cancer diagnosis of less than 18 months or 18 months or longer, number of prior lines of chemotherapy), there was consistent evidence of a treatment effect favoring the regorafenib arm for overall survival.

Kaplan-Meier curves for the two treatment arms for overall survival and for progression-free survival, respectively, abstracted from the statistical review, are presented below.

Kaplan-Meier Curves for Overall Survival, by Treatment Arm, for the CORRECT trial



Kaplan-Meier Curves for Progression-Free Survival, by Treatment Arm, for the CORRECT trial



The results described above, demonstrate a statistically persuasive and clinically meaningful increase in overall survival in patients for whom there is no FDA-approved treatment. The effects were supported by consistent trends in improved overall survival in relevant patient subgroups and evidence of a significant improvement in progression-free survival.

8. Safety

Safety evaluation across multiple trials

There was adequate data in the application to assess the risks of regorafenib treatment. The evaluation of safety in this application was supported primarily by data from the CORRECT trial in which 500 patients with mCRC received regorafenib and safety was compared with the 253 patients with mCRC who received placebo.

Evaluation of serious adverse reactions was evaluated across the 1,145 patients with cancer, which included 621 regorafenib-treated patients with mCRC in Phase 1-2 and Phase 3 trials, a Phase 3 study (Protocol 11726) in patients with renal cell carcinoma, a Phase 2 study (Protocol 14596) in patients with hepatocellular carcinoma, and 12 Phase 1 studies (7 studies in patients with advanced solid tumors and 5 studies enrolling 124 healthy volunteers).

Across the pooled safety database, there were 138 deaths occurring during or within 30 days of drug treatment; the majority of these deaths (n=111) were attributed to disease progression by the medical reviewer after evaluation of the case narratives. The most common causes of death after disease progression in regorafenib-treated patients were hemorrhage (4 patients: upper GI hemorrhage; rectal and vaginal hemorrhage, pulmonary hemorrhage; and intracranial hemorrhage), cardiac arrest (3 patients), and pneumonia (3 patients).

There were 13 patients (1 in the placebo group and 12 treated with regorafenib) in the safety database with evidence of hepatotoxicity [AST/ALT > 3 times the upper limit of normal (ULN), alkaline phosphatase < 2 times the ULN, and total bilirubin 2 times ULN]. Of the 12 regorafenib-treated patients, only 2 of the 13 met all of the Hy's law criteria as the other eleven had underlying liver disease (hepatocellular carcinoma or liver metastases).

Other serious adverse events identified in regorafenib-treated patients in the integrated safety database were impaired wound healing (6 cases), gastrointestinal perforation (7 cases), and Reversible Posterior Leukoencephalopathy Syndrome (RPLS, 1 case).

Safety evaluation in the CORRECT trial

In Protocol 14387, the evaluation of adverse reaction profile was based on 500 patients with mCRC received at least one dose of regorafenib and 253 patients with mCRC who received at least one dose of matching placebo. The demographic and baseline characteristics for this safety population were similar to that for the efficacy population. The mean duration of therapy was 12 weeks for patients receiving regorafenib and 8 weeks for patients receiving placebo; 16% of the regorafenib-treated patients (n=80) in the safety population received 6 or

more cycles of protocol-specified treatment. 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 common adverse reactions leading to drug discontinuation were general health deterioration (4%) and palmar-plantar erythrodysesthesia, hepatic failure, decreased appetite, pneumonia and rash (1% for each). The most common adverse reactions leading to dose reduction were palmar-plantar erythrodysesthesia (18%), diarrhea (3.8%), hypertension (3.2%), fatigue (2%), rash (2%), mucositis (1.2%), abdominal pain (1%) and asthenia (1%).

Most frequent treatment-emergent adverse drug reactions, i.e., occurring at a higher rate among regorafenib patients as compared to those receiving placebo, reported in CORRECT trial were: decreased appetite, palmar-plantar erythrodysesthesia (PPE), diarrhea, fatigue, decreased weight, hypertension, dysphonia, pyrexia, asthenia, constipation, and rash.

Per-Patient Incidence of Selected Adverse Reactions al Occurring in ≥ 5% of Regorafenib-Treated Patients in the CORRECT Trial				
Adverse Reactions MedDRA SOC and Preferred Term	**regorafenib (n=500)**		**Placebo (n=253)**	
	Grade		**Grade**	
	1-5	**≥3**	**1-5**	**≥3**
Infections and infestations				
Infection	31%	9%	17%	6%
Metabolism and nutrition disorders				
Decreased appetite and food intake	47%	5%	28%	4%
Vascular disorders				
Hemorrhage*	21%	2%	8%	<1%
Hypertension	30%	8%	8%	<1%
Respiratory, thoracic and mediastinal disorders				
Dysphonia	30%	0	6%	0
Gastrointestinal disorders				
Diarrhea	43%	8%	17%	2%
Mucositis	33%	4%	5%	0
Skin and subcutaneous tissue disorders				
PPE	45%	17%	7%	0
Rash	26%	6%	4%	<1%
General disorders and administration site conditions				
Asthenia/fatigue	64%	15%	46%	9%
Pain	29%	3%	21%	2%
Fever	28%	2%	15%	0
Investigations				
Weight loss	32%	<1%	10%	0

Per-Patient Incidence of Selected Laboratory Abnormalities Occurring in ≥ 5% of Regorafenib-Treated Patients in the CORRECT Trial						
Laboratory Parameter	**Regorafenib (n=500)****			**Placebo (n=253)****		
	Grade*			**Grade**		
	1-4	**3**	**4**	**1-4**	**3%**	**4**
Hematology						
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
Metabolic						
Hypocalcemia	59%	1%	<1%	18%	1%	0
Hypokalemia	26%	4%	0	8%	<1%	0
Hypophosphatemia	57%	31%	1%	11%	4%	0
Increased INR ***	24%	4%	N/A	17%	2%	N/A
Increased Lipase	46%	9%	2%	19%	3%	2%
Increased Amylase	26%	2%	<1%	17%	2%	<1%
Hepatobiliary disorders						
Hyperbilirubinemia	45%	10%	3%	17%	5%	3%
Increased AST	65%	5%	1%	46%	4%	1%
Increased ALT	45%	5%	1%	30%	3%	<1%
Renal						
Proteinuria	60%	<1%	0	34%	<1%	0

* National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), Version 3.0
** Proportion corrected for number of patients with data available where < 500 (regorafenib) or < 253 (placebo) patients had samples obtained
*** International normalized ratio
N/A: No Grade 4 identified for this laboratory value in Common Terminology Criteria for Adverse Events (CTCAE), Version 3.0

The incidence of both Grade 3 (56% vs. 26.5%) and Grade 4 (8.6% vs. 7.9%) toxicities were higher among regorafenib-treated patients as compared to those receiving placebo in the CORRECT trial. The most common of grades 3 and 4 adverse drug reactions of regorafenib observed in the CORRECT trial were palmar-plantar erythrodysesthesia, fatigue, diarrhea, hypertension, asthenia, rash, and hyperbilirubinemia.

Other adverse drug reactions of special interest, based on the toxicity spectrum of other agents with similar mechanism of action, which occurred at higher rate in regorafenib-treated patients in the CORRECT trial were: hemorrhage (regorafenib 13% vs. 4.3% placebo), cardiac

ischemia (regorafenib 1.2% vs. 0.4% placebo), and hypertension (regorafenib 30% vs. 8% placebo).

Based on evaluation of EKG findings obtained serially in the CORRECT trial, there was no evidence of QTc prolongation in regorafenib-treated patients. The final results of an ongoing dedicated cardiac safety study (study 14814), are pending.

- *REMS*
  The DRISK reviewer concurred with the clinical review team's recommendation that a Risk Evaluation and Mitigation Strategy is not required to ensure that safe use of regorafenib for US marketing and that the risks of regorafenib can be managed through product labeling. The DRISK reviewer noted that the risks of regorafenib are qualitatively similar to those identified for currently marketed tyrosine kinase inhibitors affecting the VEGF, c-KIT, PDGF, and B-RAF signaling pathways. Other approved products affecting these pathways do not require REMS for qualitatively similar adverse drug reactions but which mitigate risks through product labeling include pazopanib, sorafenib, and sunitinib, in which product labeling contains Warnings for teratogenicity, hypertension, and hemorrhagic events, and pazopanib and sunitinib, in which product labeling contains Warnings for hepatotoxicity.

- *PMRs and PMCs*
  All post-marketing requirements and commitments were focused on ensuring adequate characterization in the pharmacokinetics of regorafenib to ensure safe dosing recommendations based on food effects, drug interactions, organ dysfunction, and demographics (e.g., age, gender, race).

  The required post-marketing trials under 505(o) and the agreed-upon post-marketing commitments requested by the Clinical Pharmacology review staff are summarized in section 13, of this review.

The adverse drug reaction profile of regorafenib is qualitatively similar to that observed with drugs previously approved for the treatment of metastatic solid tumors and which have been deemed acceptable by the patient and medical community in light of the potential benefits.

9. Advisory Committee Meeting

The NDA for this new molecular entity was not presented to the Oncologic Drugs Advisory Committee for all of the following reasons: the safety profile is similar to that of other drugs approved for this indication; the clinical study design was acceptable; the application did not raise significant safety or efficacy issues that were unexpected for a drug indicated for the treatment of metastatic colorectal cancer; the application did not raise significant public health questions on the role of regorafenib in the treatment of metastatic colorectal cancer; and there were no controversial issues that would benefit from advisory committee discussion.

10. Pediatrics

Bayer requested a full waiver from the requirements under PREA because the disease/condition (metastatic colorectal cancer) does not exist in children. This waiver was presented to the PeRC on July 25, 2012. Both the clinical reviewers and the PeRC concurred that a full waiver should be granted.

11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.

12. Labeling

- Proprietary name:
  The Office of Prescription Drug Promotion (OPDP), the Division of Medication Error and Prevention Analysis (DMEP), and the Division of Oncology Products 2 determined the proposed proprietary name (Stivarga Tablets, 40 mg) is acceptable from a promotional perspective. DMEPA also determined that the proposed proprietary name was acceptable from the perspective of the low potential for medication errors. Bayer was notified that the proposed proprietary name was conditionally acceptable in correspondence dated June 29, 2012.

- Physician labeling
  Labeling negotiations are not completed. Major issues which have been resolved include
  - Addition of Boxed Warning for severe and fatal hepatotoxicity
  - (b) (4) to include a listing of the prior treatments in the indication statement.
  - Dosage and Administration
    - Extensively revised sections 2.1 and 2.2 for brevity; deleted information on monitoring for specific adverse reactions and moved to Warnings and Precautions.
    - Added instruction to take following a low fat (30%) meal
  - Dosage Forms and Strengths: editorial changes
  - Warnings and Precautions
    - Revised to include information on incidence of serious adverse reactions and included information on monitoring to mitigate risk, as per FDA Guidance for this section of product labeling.
    - Deleted (b) (4) and placed data with specific adverse reaction for which monitoring is indicated, e.g., hepatotoxicity, hypertension.

- Removed redundant information (e.g., information also described in sections 7, 8, and/or 12)
- Re-ordered Warnings and Precautions subsections to list most common and most serious first (e.g., moved up Dermatologic Toxicity)
- Added subsection on "Embryofetal Toxicity" for Category D drug

- Adverse Reactions
  - Added bulleted list of serious adverse reactions described in Section 5
  - Deleted (b) (4)
  - Limited adverse drug reactions to those occurring in ≥ 10% of regorafenib-treatment patients and at a higher incidence than in patients receiving placebo (≥ 5% higher incidence for Grades 1-5 or ≥ 2% for Grades 3-5)
  - Removed (b) (4)
- Drug Interactions
  - Removed (b) (4)
  - Added directions on avoidance of concomitant use of Strong CYP3A4 inhibitors and Strong CYP3A4 inducers
- Use in Specific Populations
  - Subsection on Pregnancy Category D (8.1) extensively revised to include new subsections on risk summary, additional details on animal data
  - Strengthened dosing recommendations in section 8.6 and 8.7 to state that dosing adjustments are not recommended for mild/moderate renal or hepatic impairment.
  - Added new subsection on Females and Males of Reproductive potential to provide recommendations regarding contraceptive use during regorafenib treatment and to identify possible risk of impairment of fertility based on animal data.
  - Moved information on gender and race to section 12
- Overdosage
  - Edited for brevity and command language
- Description
  - Modified drug substance name (b) (4) to regorafenib monohydrate and modified chemical name and structure accordingly.
- Clinical Pharmacology
  - Edited for brevity
  - Added information on pharmacokinetics in patients with organ impairment and on potential drug interactions based on P450 metabolism, P-glycoprotein, uridine disphosphate glucuronyltransferases
  - Deleted (b) (4)
- Nonclinical Pharmacology/Toxicology
  - Deleted (b) (4)

- Clinical Studies
  - Added information on study endpoints, described dosing regimen in greater detail, including direction to take with low fat meal
  - Provided additional detail on patient population characteristics
  - Removed (b) (4)
  - Revised KM curve for overall survival to include number of patients at risk at various time points, as recommended in FDA Guidance on labeling for Clinical Studies section
  - Deleted (b) (4)
  - Added information on overall response rate and details regarding number of events on which results are based
- How Supplied: edited for brevity
- Patient Counseling
  - Replaced numbered subsections with bullets
  - Added information on importance of storage to ensure product stability (protection from moisture)

- Carton and immediate container labels
  - Final labeling pending, no major unresolved issues

- Patient labeling
  - Edited for readability at 6th grade level and for compliance with applicable labeling regulations and guidance
  - Edited for brevity (to remove redundant information contained in more than one place in the PPI

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action

- Risk Benefit Assessment
  The CORRECT trial demonstrated a statistically persuasive and clinically meaningful increase in overall survival in patients for whom there is no FDA-approved treatment. The effects were supported by consistent trends in improved overall survival in relevant patient subgroups and evidence of a significant improvement in progression-free survival. Specifically, the benefits of regorafenib are longer overall survival and longer progression-free survival. While both effects are modest, judged in the context of the very short survival and progression-free survival expected these improvements are clinically meaningful in this population for which there are currently no FDA-approved treatments. Furthermore, the clinical benefits are meaningful in light of the adverse drug reaction profile. The adverse drug reaction profile of regorafenib is qualitatively similar to that observed with drugs previously approved for the treatment

of metastatic solid tumors and which have been deemed acceptable by the patient and medical community in light of the potential benefits.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies
  As noted above, the adverse drug reaction profile of regorafenib is qualitatively similar to that observed with drugs previously approved for the treatment of metastatic solid tumors and which have been deemed acceptable by the patient and medical community in light of the potential benefits. The clinical review team and the DRISK consultant agreed that a REMS is not needed to ensure safe and effective use of regorafenib.

- Recommendation for other Postmarketing Requirements and Commitments

  Post-marketing Requirements under 505(o)

  - Complete a clinical trial evaluating the potential for a regorafenib to prolong the QT/QTc interval in an adequate number of patients administered repeated doses of 160 mg of regorafenib and submit the final study report, along with a thorough review of cardiac safety data.

  - Complete a clinical trial and submit the final study report to evaluate the effect of repeated doses of 160 mg of regorafenib on the pharmacokinetics of a substrate of CYP2C8, CYP2C9, CYP3A4 and CYP2C19.

  - Conduct a multiple dose trial to determine the appropriate regorafenib dose in patients with severe renal impairment. Submit the final protocol for FDA review before conducting the trial.

  Post Marketing Commitments (PMCs)

  - Submit an integrative population pharmacokinetic analysis report to evaluate the effect of intrinsic and extrinsic factors on the pharmacokinetics of regorafenib and its active metabolites M2 and M5.

  - Submit an exposure-response analysis for regorafenib and its active metabolites M2 and M5 for measures of both effectiveness and toxicity using data collected from the CORRECT trial (Study 14387) in patients with metastatic colorectal cancer (mCRC) who have progressed after standard therapy.

Rationale whether required under FDAAA or voluntary, post vs. preapproval, significant negotiations or discussions, and questions to be addressed

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/s/

PATRICIA KEEGAN
09/20/2012