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APPLICATION NUMBER:

203085Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	10 Sep 2012
From	Steven Lemery, M.D., M.H.S.
Subject	Cross-Discipline Team Leader Review
NDA #	203085
Applicant	Bayer HealthCare Pharmaceuticals, Inc.
Date of Submission	27 Apr 2012
PDUFA Goal Date	27 Oct 2012
Proprietary Name / Established Name	Stivarga / regorafenib
Dosing Regimen	160 mg regorafenib (four 40 mg tablets) taken orally once daily for the first 21 days of each 28-day cycle.
Proposed Indication(s)	Regorafenib 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
Recommended:	<i>Approval pending final agreement on labeling and Post-Marketing Requirements</i>

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1. Introduction

FDA received NDA 203085 from Bayer on 27 Apr 2012 requesting marketing authorization (regular approval) for regorafenib (proposed trade-name Stivarga) 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.

Disclaimer: Any data or information described below that Bayer does not own (for example, summary data from other drugs used to treat patients with mCRC or other cancers) is included for descriptive purposes only. This information was not relied upon or necessary to make a decision regarding this application.

The following section describes the primary issues identified during the review of this application:

1.1 One versus two trials

The primary issue considered during the review of this application was whether the results of a single adequate and well-controlled trial were sufficient to support approval. FDA Guidance (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidance/ucm078749.pdf>) identified characteristics that can contribute to the conclusion that results from a single study can support an efficacy claim. The characteristics identified were (a) large multicenter study; (b) consistency across study subsets; (c) multiple studies in a single study; (d) multiple endpoints involving different events; and (e) statistically very persuasive findings. Results of the Bay73-4506/11650 trial submitted in support of this NDA satisfied all of these characteristics except (c).

Bay 73-4506/11650 was a large, randomized (2:1), multi-national trial that randomized 760 patients with previously treated mCRC. Patients in Bay 73-4506/11650 received regorafenib plus best supportive care or placebo plus best supportive care. Table 1 (data obtained from the statistical review) summarizes the efficacy results from Bay 73-4506/11650. The results (demonstrating that regorafenib prolonged overall survival in patients with previously treated mCRC) were statistically robust and supported by consistent results in subgroup analyses.

Table 1 Summary of efficacy results

	Regorafenib N = 505	Placebo N = 255
Overall survival		
# of events	275	157
Median (in mos.)	6.4	5.0
Stratified HR (95% CI)	0.77 (0.64, 0.94)	
p-value (two-sided)	0.01	
Progression free survival (FDA analysis)		
# of events	417	231
Median (in mos.)	2	1.7

	Regorafenib N = 505	Placebo N = 255
Stratified HR (95% CI)	0.49 (0.42, 0.58)	

The May 1998 FDA Guidance document also states that reliance on 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 results in a second trial would be practically or ethically impossible.

Bay 73-4506/11650 established that patients receiving regorafenib experienced a modest improvement in overall survival compared to placebo. Although one can reasonably argue whether a second trial could ethically be conducted in the third-line setting based on a median 1.4 month improvement in OS, modest survival benefits have resulted in approval of cancer drugs in other settings (especially for patients who have terminal cancer and no adequate alternative therapies). Physicians and patients will need to individually consider whether the modest improvement in OS is of sufficient magnitude to offset the increased toxicity conferred by regorafenib.

Unfortunately, biomarkers have not been identified that will allow for the selection of certain groups of patients who will benefit from treatment (or perhaps more importantly, who will not benefit from treatment). Given the modest effect size observed in Bay 73-4506/11650, this reviewer encourages Bayer to conduct additional research into identifying potential biomarkers that will allow for better selection of patients for treatment with regorafenib (i.e., to maximize benefit or to minimize harms in patients who will not benefit). At this time, however, based on the lack of a suitable candidate biomarker, a specific PMC cannot be recommended to conduct a pivotal clinical trial using a biomarker.

1.2 Clinical-pharmacology submission

This application did not contain exposure-response analyses from pivotal trial Bay 73-4506/14387, population pharmacokinetic analyses from Bay 73-4506/14387, final results from all drug-interaction studies, or final results from the dedicated cardiovascular safety study to assess effects on QT/QTc.

OCP and DOP2 agreed to exercise regulatory discretion regarding the lack of complete pharmacology information in this NDA based on the following: completion of pivotal trial Bay 73-4506/14387 earlier than anticipated based on the pre-planned stopping rule; overall-survival effect in patients with late-stage metastatic colorectal cancer (without available treatment options); no QTc interval effects were observed in the analysis of preliminary data; and agreement by Bayer to submit this information (from ongoing and nearly complete studies) as PMRs and PMCs. Although not optimal, DOP2 and OCP were able to make a determination of the safety and effectiveness of regorafenib for this late-stage population (with an overall survival effect) based on the information submitted in the NDA.

1.3 Food effects

The label proposed by Bayer instructs patients to take regorafenib with a low-fat meal. FDA initially acknowledged the uncertainty regarding food effects on the pharmacokinetics of regorafenib in a 22 Jan 2010 letter to Bayer.

During the review of this application, OCP analyzed the results of a food effects study conducted in 24 healthy men. The study was a randomized, open-label, three-way crossover study to determine the effect of a high-fat breakfast, a low-fat breakfast, and fasting state on the PKs of a single 160 mg dose of regorafenib. Each study period was separated by a 14-day washout period and PK samples were collected up to 336 hours.

OCP found that after a high-fat meal, the mean AUC of regorafenib was increased by 48% and the mean AUC of two active metabolites, M2 and M5, were decreased by 20% and 51%, respectively, resulting in an overall exposure approximately 8% lower as compared to the fasted state. OCP found that the low-fat breakfast increased the mean AUC of regorafenib by 36% and the mean AUC of M2 and M5 by 40% and 23%, respectively, resulting in overall exposure approximately 33% higher as compared to the fasted state.

Based on the available data, this reviewer agrees that the label should instruct patients to take regorafenib with a low-fat meal because patients enrolled in Bay 73-4506/14387 (pivotal trial) took regorafenib with a low-fat meal. Review staff recommended inclusion of examples of low-fat meals (that were contained within the Bay 73-4506/14387 protocol) in product labeling so that patients will be able to understand what types of foods constitute a low-fat meal.

Due to the wide variability of diets in the U.S., these low-fat dosing instructions may introduce the possibility of increased variability in the exposure to regorafenib. Nevertheless, substantial evidence for effectiveness only exists for treatment with a low-fat meal. Additionally, in regards to regorafenib, substantial inter-patient variability in exposure also occurs in the fasting state (part of the reasoning to administer drugs with a narrow therapeutic index in the fasting state is to reduce variability).

2. Background

2.1 Disease and therapy related issues

Bayer requested marketing authorization for regorafenib for the treatment of patients with metastatic colorectal cancer (mCRC) who have been previously treated with, (b) (4) fluoropyrimidine-based chemotherapy, an anti-VEGF therapy, and, if *K-Ras* wild type, an anti-EGFR therapy. In general, because mCRC is an incurable disease [with the notable exception of patients who have oligometastatic disease (usually hepatic)], the goal of treatment for these patients is to prolong life and/or improve quality of life (refer to the clinical review for details regarding the epidemiology of mCRC).

Table 2 shows FDA approved drugs (in alphabetical order) for the treatment of patients with colorectal cancer. The table shows that FDA granted regular approval for most drugs intended to treat patients with mCRC based on demonstrated effects on overall survival (OS). For

brevity, drugs no longer marketed in the U.S. (e.g., levamisole); no longer (or rarely) used in practice for mCRC [e.g., vincristine (component of MOF with fluorouracil and methyl-CCNU)]; indicated as a palliative regional intra-arterial treatment (e.g., floxuridine); approved more than 20 years ago (e.g., fluorouracil and leucovorin); or approved under the 505(b)(2) pathway (e.g., levoleucovorin) were not included in the table.

Table 2 FDA approved drugs for the treatment of patients with CRC

Drug	Date Indication Approved	Indication	Primary Basis for Approval*
Ziv-Aflibercept	03 Aug 12	mCRC with FOLFIRI 2 nd line	Improved OS [HR 0.816, p=0.0032 (ziv-aflib + FOLFIRI vs. placebo + FOLFIRI)]
Bevacizumab	26 Feb 04	mCRC with 5-FU based ctx 1 st line	Improved OS [HR 0.66, p< 0.001 (bev + IFL vs. placebo + IFL)]
Bevacizumab	20 Jun 06	mCRC with 5-FU based ctx 2 nd line	Improved OS [HR 0.77, p=0.001 (bev + FOLFOX4 vs. FOLFOX4 alone)]
Capecitabine	30 Apr 01	1 st line treatment of mCRC when FP therapy alone preferred	NI for OS to 5FU/LV
Capecitabine	15 Jun 05	Single-agent adjuvant treatment for Dukes' C colon cancer when FP therapy alone preferred	NI for DFS to 5FU/LV
Cetuximab	12 Feb 04*	Single agent, EGFR-expressing mCRC: intolerant to irinotecan ctx	Durable objective responses: ORR 25.8% (irinotecan-refractory group) when administered with irinotecan and 11.4% as monotherapy
Cetuximab	12 Feb 04*	EGFR-expressing mCRC in combination with irinotecan in pts refractory to irinotecan ctx	Durable objective responses: ORR 25.8% (irinotecan-refractory group) when administered with irinotecan and 11.4% as monotherapy
Cetuximab	02 Oct 07	Single agent, EGFR-expressing mCRC after failure of both irinotecan and oxaliplatin ctx	<i>Converted to full approval for single-agent indication: Improved OS [HR 0.77, p=0.0046 (cetuximab + BSC vs. BSC)]</i>
Cetuximab	06 Jul 12	<i>K-Ras</i> mutation-negative, EGFR-expressing, mCRC with FOLFIRI 1 st line	<i>Converted to full approval for cetuximab + irinotecan indication: Improved OS (<i>K-Ras</i> wild-type group) [HR 0.80, 95% CI 0.67, 0.94 (cetuximab + FOLFIRI vs. FOLFIRI)] plus supportive evidence from external trials</i>
Irinotecan	22 Oct 98	mCRC, recurred or progressed following 5-FU based therapy	<i>Converted to full approval: Improved OS: irinotecan (every three weeks) vs. BSC 2nd line in two trials</i>
Irinotecan	14 Jun 96*	mCRC, recurred or progressed following 5-FU based therapy	Durable objective responses
Irinotecan	20 Apr 00	mCRC 1 st line therapy with 5FU + LV	Improved OS in 2 studies of irinotecan + 5FU/LV vs. 5FU/LV
Oxaliplatin	09 Aug 02*	mCRC with 5-FU/LV recurred or progressed after first-line 5-FU/LV and irinotecan	Improved ORR compared to 5FU/LV

Drug	Date Indication Approved	Indication	Primary Basis for Approval*
Oxaliplatin	09 Jan 04	mCRC with infusional 5-FU + LV	<i>Converted to full approval:</i> Improved OS compared to bolus-IFL regimen (previously untreated patients)
Oxaliplatin	04 Nov 04	Adjuvant treatment of stage III colon cancer with infusional 5-FU/LV	Improvement in DFS compared to infusional 5-FU/LV
Panitumumab	27 Sep 06*	EGFR-expressing, mCRC: progression on or following FP, oxaliplatin, and irinotecan ctx	Improved PFS and ORR versus best supportive care (p < 0.0001, non-proportional KM hazard curves)

*Accelerated approval

Abbreviations: ctx = chemotherapy; 5-FU = fluorouracil; OS = overall survival; bev = bevacizumab; IFL = bolus irinotecan plus fluorouracil regimen; BSC = best supportive care; LV = leucovorin

Table 1 showed that most drugs approved for the treatment of patients with mCRC are labeled in combination with other drugs. Table 3 lists regimens described by the NCCN (http://www.nccn.org/professionals/physician_gls/pdf/colon.pdf, accessed 12 Jul 2012) for the first- and second-line treatment of patients with mCRC (note this reviewer modified the table to include ziv-aflibercept following the 03 Aug 2012 approval). Inclusion of these regimens in this review does not necessarily indicate endorsement by this reviewer or the Agency; however, the table lists regimens offered to patients in the United States.

Table 3 Regimens used to treat mCRC

Initial therapy	Therapy after progression
FOLFOX or CapeOX ± bevacizumab <i>or</i> FOLFOX ± panitumumab (only if KRAS WT)	FOLFIRI; <i>or</i> irinotecan; <i>or</i> FOLFIRI + cetuximab or panitumumab (only if KRAS WT); <i>or</i> irinotecan + cetuximab or panitumumab (only if KRAS WT); <i>or</i> FOLFIRI + bevacizumab or ziv-aflibercept
FOLFIRI + bevacizumab <i>or</i> FOLFIRI ± cetuximab or panitumumab (only if KRAS WT)	FOLFOX or CapeOX <i>or</i> irinotecan + cetuximab or panitumumab (only if KRAS WT) If not able to tolerate combination, single agent cetuximab or panitumumab (only if KRAS WT)
5FU/LA ± bevacizumab <i>or</i> capecitabine ± bevacizumab	FOLFOX <i>or</i> CapeOX <i>or</i> FOLFIRI <i>or</i> irinotecan ± oxaliplatin
FOLFOXIRI	Single agent cetuximab or panitumumab (only if KRAS WT) ± irinotecan.

Patients with mCRC who have progressed following a second-line of treatment (in the metastatic setting) have few beneficial treatment options. Best supportive care or participation in clinical trials are two options described for these patients in treatment guidelines.

Currently, two anti-VEGF therapies are approved for the treatment of patients with mCRC: bevacizumab and ziv-aflibercept. However, multiple small molecule tyrosine kinase inhibitors approved for the treatment of patients with other cancers exhibit anti-VEGF properties. Drugs that target the VEGF pathway cause a characteristic pattern of adverse events that include hypertension, proteinuria, thromboembolic events, hemorrhage, and reversible posterior leukoencephalopathy (RPLS).

2.2 U.S. regulatory history

The following summarizes the pertinent regulatory history and meetings held in relation to this NDA. Meetings held to discuss (b) (4) were not summarized in this review.

03 Sep 2009 (Type B meeting): FDA and Bayer held this meeting to discuss a proposed clinical trial in patients with mCRC. FDA recommended that Bayer revise the primary endpoint for the proposed trial (b) (4) to overall survival.

FDA agreed that Bayer can randomize patients in the control arm to placebo as long as the patients “failed” all approved drugs or drug combinations for the proposed indications. FDA stated that for a single randomized trial to support an NDA, the trial should be well designed, well conducted, internally consistent, and provide statistically persuasive efficacy findings so that a second trial would be ethically or practically impossible to perform.

FDA recommended that Bayer do the following in regards to the clinical pharmacology program: (1) evaluate the PKs of active metabolites (e.g., M2 and M5) in addition to regorafenib; (2) use a ketoconazole dose of 400 mg daily in the evaluation of CYP 3A4-related effects; (3) evaluate the PKs of active metabolites (e.g., M2 and M5) in the drug-drug interaction (DDI) studies; (4) extend sampling times beyond 12 hours for midazolam and beyond 96 hours for warfarin when conducting the appropriate DDI studies; and (5) conduct a DDI study using repaglinide or rosiglitazone as a probe substrate of CYP 2C8. FDA recommended that Bayer evaluate the effects of hepatic impairment on regorafenib PKs using the proposed 160 mg dosing regimen (three out of four weeks). FDA also provided recommendations regarding hepatic impairment study designs.

22 Jan 2010 (SPA no agreement letter): FDA sent this SPA no agreement letter based upon a 08 Dec 2009 SPA request submitted by Bayer for the following clinical protocol: “A Randomized, Double-blind, Placebo-controlled Phase III Study of Regorafenib Plus BSC versus Placebo Plus BSC in Patients with Metastatic Colorectal Cancer (CRC) Who Have Progressed after Standard Therapy.” The primary endpoint of the trial was overall survival (OS).

In the letter, FDA recommended that Bayer conduct a futility analysis earlier than the planned (b) (4) information fraction and conduct a single interim analysis for efficacy at a later time-point [FDA discussed the rationale for this recommendation during the 03 Sep 2009 meeting: specifically, Bayer intended to initiate this phase 3 trial after enrolling a limited number of patients (with mCRC) with few responses in earlier studies]. FDA also expressed uncertainty regarding how any potential modifications in the administration of regorafenib with respect to

food would influence exposure response. FDA agreed to the proposed patient population in that patients must have progressed during or within 3 months following the last administration of approved standard therapies (depending on the approval status in each of the participating countries, the therapies must include a fluoropyrimidine drug, oxaliplatin, irinotecan, bevacizumab, and cetuximab or panitumumab (if *K-Ras* wild-type)).

09 Apr 2010 FDA responses to Bayer questions: FDA agreed with Bayer's revised plan to conduct (for the proposed phase 3 trial) a futility analysis at 30% of the planned events with a second analysis for futility and efficacy at 70% of the planned events (with stopping rules based on O'Brien-Fleming boundaries).

24 Jan 2011 FDA email to Bayer regarding QTc protocol: FDA provided comments regarding a proposal to evaluate the effects of regorafenib on QTc intervals. FDA stated that the proposed dose (not specified in the email) and the proposed size of the study were acceptable (specifically, the size of the study was acceptable to exclude large QTc effects). FDA recommended that Bayer collect additional ECG/PK samples of both the parent compound and the major metabolites at the time of C_{max} .

10 Jun 2011 Fast Track letter: FDA granted Fast Track designation for the "investigation of regorafenib for the treatment of patient with metastatic colorectal cancer (CRC) after failure of standard therapies."

23 Aug 2011 (Type B pre-NDA meeting): FDA and Bayer met to discuss the contents of a planned NDA submission. FDA stated that the non-clinical program appeared acceptable to support the NDA. FDA agreed to Bayer's proposals regarding which information to include in Modules 2 and 5 of the NDA. Bayer agreed to include tables, figures, appendices, and datasets in Module 5. *FDA agreed to this proposal following FDA guidance (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidance/UCM136174.pdf>) regarding exceptions to the normally required NDA format (this NDA was primarily based on the results of a single study).*

Bayer agreed to an FDA request to include data from combination or healthy volunteer studies in the ISS if patients enrolled in the studies experienced regorafenib-related serious adverse events. FDA agreed to accept datasets in STDM and analysis formats.

Bayer stated that enrollment into the pivotal trial occurred faster than expected and that patient recruitment into studies 12434 and 14814 (DDI and QTc studies) was not completed. Bayer proposed to provide interim reports from these studies. FDA stated that this approach was generally acceptable, but recommended that Bayer try to submit final study reports in the NDA submission. FDA strongly recommended submission of the QT study results in the NDA.

03 Mar 2012 FDA letter to Bayer: FDA provided comments regarding the final version of the statistical analysis plan submitted to the Agency on 07 Feb 2012. FDA did not agree with the proposed methods for imputation for death based on partial information. FDA also recommended limiting PFS events to those defined by objective pathologic or radiologic findings.

16 Mar 2012 FDA letter to Bayer: FDA informed Bayer that the Agency did not agree with the proposed trade name (b) (4)

03 Apr 2012 Informal teleconference between FDA and Bayer:

FDA requested this meeting with Bayer to discuss the content of a complete application. FDA did not agree with a plan proposed by Bayer to submit complete reports of clinical pharmacology studies at the time of the 120 day safety update. This plan would not allow FDA review staff sufficient time to review the information and determine whether labeling changes were required. FDA stated that Bayer needed to justify why an application should be considered complete without a full assessment of clinical pharmacology data generally expected at the time of an NDA submission. FDA further stated that Bayer will need to propose PMRs in the original submission that will require Bayer to submit the clinical pharmacology data after approval. FDA also requested that Bayer submit all safety data regarding effects on the QT interval from the completed phase 3 trial. Bayer agreed to submit interim reports from other clinical pharmacology studies in the NDA.

2.3 Application history

The following table summarizes the purpose(s) of amendments submitted to this NDA.

Table 4 Amendments to NDA 203085 (as of the date of the completion of this review)

Date of Submission	Purpose of Submission
04 Apr 2012	Original submission
30 Apr 2012	Request for proprietary name review for the proposed name "Stivarga"
03 May 2012	Submission of information requested by the Office of Scientific Investigations (OSI) in order to facilitate clinical inspections
16 May 2012	Provided (1) ad hoc analyses of OS and PFS at U.S. and non-U.S. sites; (2) analyses of PFS excluding "clinical progression" events; (3) additional documentation regarding information requested by OSI
24 May 2012	Provided a response to 10 May and 15 May 2012 information requests sent by the statistical reviewer
04 Jun 2012	(1) Provided efficacy datasets in a revised format as requested by FDA; (2) amended the Request for Waiver of Pediatric Studies Section of the NDA to clarify that Bayer did request a waiver (and not a deferral) for the requirement to conduct studies in children; and (3) provided an update on the risk of gastrointestinal perforation and fistula (with updated labeling)
07 Jun 2012	Provided clinical observation, body weight, and other exposure/toxicity data as requested by the Agency from non-clinical micronucleus study T3074309
03 Jul 2012	Submission of updated information relating to container-closure and stability (CMC information amendment)
13 Jul 2012	Provided revised labeling based on preliminary comments from CDER/SEALD
24 Jul 2012	Submission of NDA safety update
30 Jul 2012	Submission of datasets, programs, and documentation in reference to an 18 Jul 2012 FDA memorandum (with 19 Jul 2012 email clarification). These assisted the statistical reviewer to complete the analysis of efficacy results.

Date of Submission	Purpose of Submission
13 Aug 2012	Provided information requested by CMC review staff including a specification for the (b) (4). Bayer also provided information regarding the manufacture of the drug product.
24 Aug 2012	Provided updated drug product specifications with revised dissolution acceptance criteria following a 15 Aug 2012 teleconference between Bayer and the Agency.
28 Aug 2012	Provided information regarding the ongoing expanded access study (treatment protocol) and provided chemistry information regarding an FDA information request letter sent to Bayer on 20 August 2012.

3. CMC

Bayer manufactures Stivarga in a formulation containing light pink, oval-shaped, film-coated tablets debossed with “Bayer” on one side and “40” on the other. The ONDQA Division Director stated that all CMC review issues were resolved and that ONDQA recommended approval of this application (pending agreement on labeling).

3.1 Drug substance review

Dr. Lu from ONDQA evaluated the CMC information pertaining to the regorafenib monohydrate drug substance (see CMC review for exact chemical nomenclature information) and recommended approval of the application. Dr. Lu found that the applicant adequately defined the regorafenib drug structure and that the manufacturing process (b) (4) was adequate. Adequate stability testing was conducted according to ICH recommendations and a retest period of (b) (4) was acceptable for the regorafenib monohydrate drug substance.

3.2 Drug product review

Dr. Jee from ONDQA evaluated the CMC information pertaining to the regorafenib drug product to be marketed under the trade-name Stivarga. Dr. Jee recommended approval of the application from a DP perspective; however, the review acknowledged that final agreement on labeling is pending at this time. Refer to the CMC review for details regarding the inactive ingredients and the tablet formulation. ONDQA granted a (b) (4) expiry for this product when stored in commercial packaging at 25 degrees Celsius.

During the review cycle, the applicant proposed (b) (4) as an alternate test to evaluate the (b) (4) of regorafenib throughout the shelf-life of the regorafenib DP. Currently, the applicant evaluates the (b) (4) using a dissolution test that the CMC reviewer considered as an acceptable surrogate for the (b) (4) (see CMC review for details regarding the specification limits).

At this time, (b) (4) is not a test included as a drug product specification; however, FDA will assess the acceptability of an additional proposed testing method (b) (4) if the information is submitted post-approval.

3.3 Biopharmaceutics review

Dr. Chikhale from ONDQA found that the proposed dissolution methodology and dissolution acceptance criteria to be acceptable and that this application can be approved from a Biopharmaceutics perspective.

3.4 Manufacturing inspections

DOP2 received notification by email on 5 Sep 2012 that OC determined that this application is acceptable.

4. Nonclinical Pharmacology/Toxicology

Dr. McDougal and Dr. Goheer stated in their review of nonclinical data that there were no non-clinical findings or outstanding issues that would preclude the approval of regorafenib.

As described in the non-clinical review, regorafenib (and the metabolites M2 and M5) inhibits multiple kinases including RET and several RET variants, PTK5, VEGFR-1,-2, and -3, FGFR-1 and -2, DDR2, SAPK2, Lyn, Tie2, Abl, TrkA, EphA2, KIT and several Kit variants, c-RAF, BRAF, and BRAF^{V600E}. Regorafenib demonstrated anti-angiogenic/anti-VEGF effects and anti-tumor activity (including mCRC models) in *in vivo* studies performed in mice or rats.

Target organ toxicities found in animal studies (rats or dogs or both) included findings in the liver (increases in liver enzymes, histopathological findings); kidney (including glomerulopathy and tubular findings; however differences in metabolism may have accounted for differences in renal toxicity in animals compared to humans); heart (including valvulopathy after long term dosing), adrenal gland; thyroid; pancreas; gastrointestinal tract (liquid feces, blood in feces, vomiting, decreased motility); hematopoietic/lymphoid system (thymic and lymph node atrophy, neutropenia, thrombocytopenia); reproductive system; and skeletal system. Findings observed in animals potentially relevant to children (if Bayer later intends to study regorafenib in this population) included changes in dentin and changes in epiphyseal growth plates. Skin findings occurred in 13- and 52-week studies in dogs; findings included dyskeratosis, hyperkeratosis, acanthosis, dermatitis, and hair growth arrest.

Dedicated fertility and pre- and post-natal development studies were not required or conducted to support this application for a drug intended to treat patients with advanced cancer. However, the non-clinical reviewer noted histopathological findings of increased necrotic corpus lutea and atrophy in the ovaries and uterus in female rats administered regorafenib at dose levels resulting in exposures similar to those observed in humans at the clinically recommended dose. Male rats receiving regorafenib at the same dose had histopathological findings of mononuclear infiltration and cellular debris as well as decreased weight of the testes, prostate, and seminal vesicles compared to control animals. Dogs also experienced findings that may predict effects on fertility in humans (see non-clinical review).

Embryofetal studies conducted in Wistar rats and Himalayan rabbits demonstrated increases in post-implantation loss and teratogenic effects including skeletal and cardiovascular malformations and renal findings of dilation of the renal pelvis or hydronephrosis. Thus, non-clinical review staff recommended Pregnancy Category D for regorafenib.

The M-2 metabolite demonstrated clastogenicity in an *in vitro* assay suggesting that regorafenib may have mutagenic potential in humans. A dedicated carcinogenicity study was not required or conducted to support this application for a drug intended to treat patients with advanced cancer.

5. Clinical Pharmacology

5.1 General clinical pharmacology considerations

Major pharmacology considerations regarding this application included the following:

- Lack of exposure-response data from pivotal trial Bay 73-4506/14387,
- Lack of population pharmacokinetic analyses from Bay 73-4506/14387,
- Lack of final results from all drug-interaction studies, and
- Lack of final results from the dedicated cardiovascular safety study to assess effects on QT/QTc,
- Food effects.

For this application, OCP and DOP2 agreed to exercise regulatory discretion regarding the submission of this NDA without complete pharmacology information based on the following: completion of pivotal trial Bay 73-4506/14387 earlier than anticipated based on the pre-defined stopping rule; overall-survival effect in patients with late-stage metastatic colorectal cancer; lack QTc interval effects observed in preliminary data; and agreement by Bayer to submit this information (from ongoing nearly complete studies) as PMRs and PMCs. Although not optimal, FDA can make a determination of safety and effectiveness for this late-stage population with an overall survival effect based on the information submitted in the NDA.

The clinical pharmacology review team (Dr. Shord as primary reviewer) concluded that this NDA is acceptable from a clinical pharmacology perspective. OCP recommended several PMCs and PMRs (all but one of which are to submit a Final Study Report from ongoing or completed studies; see Section 13, below) and also provided several additional comments sent to Bayer under the IND (to address future development of regorafenib).

5.1.1 Dose selection

In order to select the dose for the pivotal trial, Bayer conducted two dose escalation trials with either intermittent or continuous daily dosing. Different dosing formulations were also investigated.

In Bay 73-4506/11650 (dose-escalation trial: 21 days of treatment followed by 7 days off), Bayer enrolled 85 patients with advanced, histologically or cytologically confirmed solid tumors; however, 9 patients were considered screening failures and were not included in the safety analysis. In this study, a total of 3 out of 6 patients at the 120 mg dose level (solution formulation) experienced dose limiting toxicity (DLT) during cycle 1. DLTs included Grade 3 palmar plantar erythrodysesthesia and infection. None of 6 patients who received regorafenib

tablets at 120 mg experienced a DLT during cycle 1. Mean AUC was similar with the two formulations; however, Bayer found moderate-to-high inter-subject variability in AUC and C_{max} at steady state. Based on the findings from all patients at the 120 mg dose level (tablet plus solution), the sponsor studied an additional 160 mg daily dose cohort (tablets) where 3 out of 12 subjects experienced DLT. Because one of the adverse events was not considered dose dependent (allergic reaction), the applicant studied a subsequent 220 mg daily dose cohort where 4 out of 12 subjects experienced DLT during cycle 1.

Ultimately, Bayer selected the 160 mg dose level for the pivotal trial (Bay 73-4506/14387) based upon the dose-escalation results as well as the frequency of dose reductions, interruptions, or permanent discontinuations through 2 cycles of therapy. In the 160 mg cohort, 3 out of 12 subjects experienced adverse events during the first two cycles leading to dose reduction, dose interruption, or permanent discontinuation. In the 220 mg cohort, 8 out of 12 subjects experienced adverse events during the first two cycles leading to dose reduction, dose interruption, or permanent discontinuation.

Although the results of the continuous dosing, dose-escalation trial are not presented here, the applicant selected the intermittent schedule because the intermittent schedule led to a higher total dose per cycle, higher steady-state concentrations, and a better estimated disease control rate. Additionally, the intermittent dose allowed patients a chance to recover from adverse events.

Reviewer comment: The applicant developed regorafenib in similar accordance with multiple other cancer drugs on the market. Nevertheless, the lack of formal comparisons of dosing schedules or doses precluded any formal conclusions regarding whether the optimal dose of regorafenib was selected.

5.1.2 Pharmacokinetics

The M2 and M5 metabolites, both of which are active, must be considered in order to describe the pharmacokinetic (PK) profile of regorafenib. It was difficult to parse out the effects of extrinsic PK modifiers because the PK modifiers (e.g., food, drugs, etc.) can differentially change the levels of all three moieties (regorafenib, M2, and M5).

Dr. Shord summarized the following PK characteristics of regorafenib in her review:

Following a single 160 mg dose, regorafenib reached mean C_{max} of 2.5 $\mu\text{g}/\text{mL}$ at a median time (T_{max}) of 3 hrs and a mean AUC of 70.4 $\mu\text{g}\cdot\text{h}/\text{mL}$. At steady-state, regorafenib reached mean C_{max} of 3.9 $\mu\text{g}/\text{mL}$ and a mean AUC of 58.3 $\mu\text{g}\cdot\text{h}/\text{mL}$. Solubility in the GI tract did not appear dependent on pH.

Regorafenib underwent enterohepatic circulation with two additional peak plasma concentrations observed at 8 hours and 24 hours after the dose. Regorafenib, M2, and M5 were highly protein bound (99.5%) and regorafenib was primarily metabolized by CYP3A4 and UGT1A9. Approximately 71% of a single radiolabeled dose (24% as metabolites) was excreted in feces. The mean elimination half-life ($t_{1/2}$) was 28 hours. The metabolites M2 and M5 reached steady-state concentrations that were similar to regorafenib and demonstrated similar activity and degree of protein binding as regorafenib in the nonclinical and the *in vitro*

studies. The mean half-lives ($t_{1/2}$) for the M2 and M5 metabolites were 25 and 51 hours, respectively.

Cross-study comparisons suggested similar mean AUC and C_{max} following a single dose of regorafenib when administered to healthy men versus patients with cancer (noting the high variability).

5.1.3 Food effects

OCP analyzed the results of a food effects study conducted in 24 healthy men. The study was a randomized, open-label, three-way crossover study to determine the effects of a high-fat breakfast, a low-fat breakfast, and fasting state on the PKs of a single 160 mg dose of regorafenib. Each study period was separated by a 14-day washout period and PK samples were collected for up to 336 hours.

The applicant defined a high-fat breakfast as two eggs fried in butter, two slices of white toast with two pats of butter, two strips of bacon, four ounces of hash brown potatoes, and eight ounces of whole milk (approximately 945 calories and 54.6 grams of fat). After a high-fat meal, the mean AUC of regorafenib was increased by 48% and the mean AUCs of M2 and M5 were decreased by 20% and 51%, respectively, resulting in an overall exposure approximately 8% lower as compared to the fasted state.

In the food-effects study, the applicant defined a low-fat meal as two slices of white toast with 1 tablespoon of low-fat margarine and 1 tablespoon of jelly and 8 ounces of skim milk (approximately 319 calories and 8.2 grams of fat). A separate example of a low-fat breakfast was described in the protocol for the pivotal clinical trial. OCP found that the low fat breakfast increased the mean AUC of regorafenib by 36% and the mean AUC of M2 and M5 by 40% and 23%, respectively, resulting in an overall exposure approximately 33% higher as compared to the fasted state.

Based on the results of the food effects study, the applicant recommended that patients take regorafenib with a low fat meal.

Comment: The label should instruct patients to take regorafenib with a low-fat meal because patients enrolled in Bay 73-4506/14387 (pivotal trial) took regorafenib with a low-fat meal. Review staff recommended inclusion of examples of low-fat meals (as described in the protocol) in product labeling so that patients can understand what type of foods consist of a low-fat meal. Due to the wide variability of diets in the U.S., these low-fat dosing instructions may introduce the possibility of increased variability in the exposure to regorafenib. Nevertheless, substantial evidence for effectiveness only exists for treatment with a low-fat meal. Additionally, in regards to regorafenib, substantial inter-patient variability in exposure also occurs in the fasting state (part of the reasoning to administer drugs in the fasting state is to reduce variability, especially for drugs with a narrow therapeutic index).

5.2 Drug-drug interactions

OCP evaluated the results of three drug interaction studies and noted that an additional study is ongoing. OCP found that regorafenib is associated with multiple drug-drug interactions.

Dr. Shord summarized the following drug-drug interactions in her review: 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 M2 and M5 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 M5 by 264%; the mean AUC of M2 was similar with and without rifampin.

Regorafenib or the active metabolites M2 or M5 inhibited CY2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4 *in vitro*. The effect of regorafenib on the PKs of CYP2C8, CYP2C9, and CYP3A4 substrates are being evaluated in an ongoing study.

Regorafenib inhibited UGT1A9 and the three active moieties (regorafenib, M2 and M5) inhibited UGT1A1 *in vitro*. When irinotecan was administered five days after the last of seven daily doses of regorafenib, the mean AUC of SN-38 increased by 44% and the mean AUC of irinotecan increased by 28%.

5.3 Demographic interactions/special populations

OCP was not able to formally analyze the effects of intrinsic factors on exposure or response because exposure-response and population PK analyses (from the pivotal trial) were not submitted in the application. OCP could not make recommendations regarding the need for dose modifications based on univariate analyses of intrinsic factors (age, gender, race, or organ function) from the smaller studies submitted in the application.

OCP recommended that Bayer agree to a PMR to complete a repeat-dose PK study in patients with severe renal impairment (see Section 13 below). OCP based this recommendation on *post hoc* pooled analyses of data from patients with mildly impaired renal function.

5.4 Thorough QT study or other QT assessment

The OCP review summarized that regorafenib, M2, and M5 can inhibit the hERG K⁺ current with IC₅₀ values of 27 μM, 1.4 μM, and 1.8 μM. However, regorafenib demonstrated no effect on the cardiac action potential in rabbit Purkinje fibers and no effect on ECG intervals in Beagle dogs after oral and intravenous administration. In the NDA, Bayer provided an interim analysis of QTc findings from 25 patients with advanced solid tumors who were enrolled into Study 14814 (QT assessment study) and general safety findings from Study Bay 73-4506/14387. No large changes in QTc intervals were found during the review of this preliminary data. As described below in Section 13, Bayer will submit the full report of the dedicated cardiovascular safety study after an action has been taken on this application (as a PMR).

5.5 Biomarker assessments

As stated above, at this time, the applicant has not submitted exposure-response or population pharmacokinetics analyses. Bayer documented *K-Ras* status from patients and collected archival tumor tissue and fresh plasma in study Bay 73-4506/14387 in order to perform

preliminary assessments of whether the safety or efficacy of regorafenib is altered by the presence or absence of any biomarkers. OCP asked Bayer to consider submitting a summary report and data files of exploratory biomarker analyses completed during the clinical development of regorafenib, including genetic and nongenetic markers in various matrices (blood, plasma and tumor) post marketing. Reviewer comment: At this time, there is no lead candidate biomarker than can be used to select patients for treatment with regorafenib.

6. Clinical Microbiology

This section is not applicable to this review.

7. Clinical/Statistical-Efficacy

The clinical reviewer of efficacy (Dr. Shan Pradhan) recommended approval of this application based on the improvement in overall survival demonstrated in the Bay 73-4506/14387 clinical trial that was conducted in patients with metastatic colorectal cancer (mCRC). The statistical reviewer [Dr. Huanyu (Jade) Chen] concluded that based on the data and analyses from Bay 73-4506/14387, regorafenib plus best supportive care demonstrated a statistically significant improvement in OS with a marginal improvement in PFS.

7.1 Background of clinical program

The initial protocol for the pivotal trial (Bay 73-4506/14387) was dated 10 Feb 2010. Table 5, below, describes the major revisions described in protocol amendments. The study design described below represents the final protocol version. Bay 73-4506/14387 was the only adequate and well controlled trial conducted in the indicated patient population submitted in support of this NDA.

7.2 Design of Bay 73-4506/14387

7.2.1 Primary endpoint

The primary endpoint of Bay 73-4506/14387 was overall survival (OS), defined as the time from randomization to the date of death due to any cause. *Comment: As stated in the May 2007 FDA Guidance Document regarding endpoints for cancer drugs (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidance/ucm071590.pdf>; accessed on 12 Jul 2012), survival is considered the most reliable cancer endpoint, and when studies can be conducted to adequately assess survival, it is usually the preferred endpoint. An effect on OS is considered regulatory evidence of clinical benefit used by the Agency to substantiate regular approval of a drug.*

7.2.2 Secondary endpoints

The secondary endpoints defined by the protocol included progression free survival (PFS), objective tumor response rate (ORR), and disease control rate (DCR). The protocol contained a hierarchical provision to control the alpha at 0.05 (two-sided) for these secondary endpoints that only allowed testing if the previous specified endpoint was statistically significant.

The protocol defined progression free survival as the time from the date of randomization to the date of the first observed disease progression (radiological or clinical) or death due to any

cause. The protocol included a PFS censoring rule that censored patients without a progression event at the time of the last actual visit date for tumor evaluation. PFS was censored on day 1 for patients who did not undergo a tumor assessment after baseline. The protocol also contained rules for censoring PFS based on missed or non-evaluable tumor assessments or if patients dropped out of the study and died more than 16 days later (see statistical review). *Comment: The definition of PFS included “clinical progression” which can be subjective. The statistical reviewer conducted additional analyses based solely on objective tumor assessments.*

The use of investigator assessments for progression (and response) was acceptable because the primary endpoint was overall survival (i.e., the PFS and ORR endpoints are considered supportive of the overall survival results).

The protocol defined objective tumor response as the proportion of patients experiencing either complete response or partial response using RESCIST criteria, version 1.1. Disease control rate (DCR) was defined as the proportion of patients whose best overall response was not progressive disease. *Comment: The PFS results were more informative than the DCR results (PFS curves represent patients who are responding or continue to experience stable disease); thus DCR will not be included in product labeling or discussed further in this review.*

7.2.3 Eligibility criteria

The protocol specified the following major eligibility criteria: age ≥ 18 years; metastatic adenocarcinoma of the colon or rectum; disease progression during or within 3 months following the last administration of approved therapies which must have included a fluoropyrimidine, oxaliplatin, irinotecan, bevacizumab, and cetuximab or panitumumab (*K-Ras* wild-type); ECOG ≤ 1 ; and adequate organ function/labs (see clinical review).

The protocol excluded patients with New York Heart Association class 2 or greater congestive heart failure; unstable angina or new angina in last three months, myocardial infarction in previous 6 months; cardiac arrhythmias requiring anti-arrhythmic therapy; pleural effusion with Grade 2 dyspnea; arterial or venous thromboembolic events during the previous six months; known HIV infection; active hepatitis B or C or chronic hepatitis requiring antiviral therapy; known history of brain metastases; severe hemorrhage in previous four weeks; non-healing wound, ulcer, or bone fracture; active interstitial lung disease; Grade 3 or greater proteinuria; and inability to swallow oral medications.

7.2.4 General study design/treatment plan

- Bay 73-4506/14387 randomized patients (2:1) to receive either regorafenib 160 mg daily (first 21 days out of each 28 day cycle) plus best supportive care or placebo (first 21 days out of each 28 day cycle) plus best supportive care.
- The protocol specified that patients take regorafenib or placebo with a low-fat breakfast. Bayer included the following examples of low-fat breakfasts in an appendix to the protocol:
 - Two slices of white toast with 1 tablespoon of low-fat margarine and 1 tablespoon of jelly and 8 ounces of skim milk (approximately 319 calories and 8.2 grams of fat).

- One cup of cereal, 8 ounces of skim milk, one piece of toast with jam (no butter or marmalade), apple juice, and one cup of coffee or tea (2 g fat, 17 g protein, 93 g of carbohydrate, 520 calories).
- Patients continued treatment until progressive disease, death, unacceptable toxicity, withdrawal of consent, or substantial non-compliance with the protocol.
- The protocol contained instructions for dose interruption and dose delay for toxicities (refer to clinical review for details).
- The protocol provided additional instructions for the prevention and management of hand-foot skin reactions.
- Patients underwent assessments for tumor progression every 8 weeks with CT or MRI.
- The protocol required weekly evaluations of liver enzymes during the first 8 weeks of treatment. Other labs (CBC, chemistry) to assess safety were obtained at least biweekly for the first six cycles.
- Blood pressure was monitored at least weekly for the first six weeks.
- Patients were followed monthly for survival status.

7.2.5 Statistical design and analysis issues

Randomization/Stratification Factors

Bay 73-4506/14387 randomized patients (2:1) to receive either regorafenib 160 mg daily (first 21 days out of each 28 day cycle) plus best supportive care or placebo (first 21 days out of each 28 day cycle) plus best supportive care. The protocol stated that an Interactive Voice Response System (IVRS) was used to provide a randomization number for each patient.

Bay 73-4506/14387 specified three stratification factors for randomization and analysis: (1) prior treatment with VEGF targeting drugs (yes or no); (2) time from diagnosis of metastatic disease (≥ 18 months versus < 18 months); and (3) geographical region (North America, Western Europe, Israel, and Australia; versus Asia; versus South America, Turkey, and Eastern Europe). The protocol specified that fewer than 250 patients would be enrolled from Asia to maintain a balanced representation in each of the three regions.

Determination of Sample Size

The study was designed with 90% power to detect a 33.3% median improvement in overall survival (HR = 0.75) at a one-sided alpha of 0.025. The protocol specified 528 deaths for the final analysis of OS assuming the above error rates, 2:1 randomization, and two interim analyses with alpha allocated using the O'Brien-Fleming approach. The protocol planned to enroll 690 patients at a rate of 30 subjects per month, a drop out rate of 3%, and assumed a median overall survival time of 4.5 months in the placebo arm and 6 months in the regorafenib arm with exponentially distributed event times for OS.

Analyses

The primary endpoint overall survival was analyzed using the log-rank test, stratified by the three factors specified at randomization. A data monitoring committee (DMC) reviewed the results of the protocol-specified interim analyses.

Protocol Amendments

Table 5, below, describes the major revisions described in the protocol amendments. The amendments did not appear to affect the overall integrity of the protocol.

Table 5 Amendments to Bay 73-4506/14387

Amendment Date	Revisions Described in the Amendments
28 Sep 2010	<ul style="list-style-type: none"> - Formally excluded all histology types except for adenocarcinoma of the colon. - Clarified that patients must have been retreated with an oxaliplatin-containing regimen if they progressed more than 6 months after receiving oxaliplatin in the adjuvant setting. - Clarified that patients with unknown <i>K-Ras</i> status at screening must have received prior anti-EGFR therapy. - Clarified that transfusion was not permitted in order to make a patient eligible for the protocol. - Excluded patients who received extended-field radiotherapy within 4 weeks or limited-field within 2 weeks; pleural effusion with Grade 2 dyspnea; active hepatitis B or C requiring anti-hepatitis therapy (rather than any known hepatitis B or C); any history of brain metastases; any history of bleeding diathesis; and systemic anti-cancer therapy within 4 weeks. - New Zealand and South Africa were removed from strata regions. - Clarified that missed or vomited tablets were not to be made up. - Removed bone scan from screening procedures. - Specified allowable timing of screening and treatment labs, ECGs, and imaging.
03 Aug 2011	<ul style="list-style-type: none"> - Included specific dose adjustment information regarding liver function abnormalities. - Required weekly monitoring of AST, ALT, and bilirubin during the first two cycles (previously were required on day 1 of each cycle). - Provided a provision for a study drug diary to monitor treatment compliance. - Required additional phone contacts for “sweeps” of overall survival at the time of the interim and primary analyses.
01 Nov 2011	<ul style="list-style-type: none"> - The protocol was revised to allow patients assigned to the placebo arm to receive regorafenib if the primary endpoint was reached and the study results supported a positive risk/benefit assessment as determined by both the Data Monitoring Committee and the sponsor.

7.3 Summary results

7.3.1 Demographics

Median age of patients randomized to both arms was 61 years. Table 6 (data from Dr. Pradhan's review) shows that the gender and ethnic background of patients enrolled into Bay 73-4506/14387 were similar between arms. More patients were enrolled in the U.S. in the placebo arm; however the proportion of patients in the North America, Western Europe, Israel, and Australia stratum were similar between arms.

Table 6 Demographics, Bay 73-4506/14387

	Regorafenib N=505 (%)	Placebo N=255 (%)
Age		
≥ 65 years	39	35
Female		
Yes	38	40
Race		
White	78	79
Asian	15	14
Other	7	7
US		
Yes	9	14

All enrolled patients had metastatic colorectal cancer (stage IV) and all received at least two prior lines of anti-systemic therapy. Table 7 (data from Dr. Pradhan's review) shows the distribution of other baseline disease characteristics in the two treatment arms. Time to first diagnosis of metastatic disease to randomization, prior anti-VEGF therapy, and geographic region constituted the protocol-specified strata. Similar numbers of patients were enrolled in each stratum with 100% of patients receiving prior anti-VEGF therapy in both arms.

Modest imbalances in two potential prognostic variables were found between arms. The randomization procedure allocated a higher proportion of patients with ECOG PS 0 to the placebo arm (potentially favoring this arm); however, a higher proportion of patients with known *K-Ras* mutant tumors were allocated to placebo (potentially favoring the regorafenib arm). There was also a slight difference in *K-Ras* unknown status between arms; so overall, the known differences between arms in patients with *K-Ras* wild type tumors were smaller than the differences between arms in patients with *K-Ras* mutant tumors.

Table 7 Disease characteristics at baseline, Bay 73-4506/14387

	Regorafenib N=505 (%)	Placebo N=255 (%)
ECOG PS		
0	52	57
1	48	43
KRAS mutation		
Yes	54	62

	Regorafenib N=505 (%)	Placebo N=255 (%)
No	41	37
Unknown	5	2
Primary site of disease		
Colon	64	68
Rectum	30	27
Colon and rectum	6	5
Prior systemic anti-cancer therapy		
2	16	15
3	24	23
≥ 4	60	62
Time from first diagnosis of metastatic disease to randomization		
< 18 months	18	19
≥ 18 months	82	81
Prior anti-VEGF therapy		
Yes	100	100
Geographic region*		
1	83	83
2	14	14
3	3	3

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

7.3.2 Disposition

Table 8 (data from Dr. Pradhan's review) shows that most patients were followed until death in both arms. More patients had progressive events on the placebo arm.

Table 8 Patient disposition, Bay 73-4506/14387

	Regorafenib N=505 (%)	Placebo N=255 (%)
Adverse Event	1	2
Completed	100	100
Death	74	76
Lost to Follow-up	5	9
Other	2	1
Physician Decision	1	0
Progressive Disease	67	81
Protocol Violation	0	0
Withdrawal by Subject	4	5

7.3.3 OS analyses

Table 9, copied from the statistical review, shows the OS results determined at the time of the planned second interim analysis (data cut-off of 21 Jul 2011). Based on the study-stopping rules, this analysis constituted the final analysis of OS. The p-value of 0.01 crossed the

protocol specified nominal alpha boundary of 0.018 (two-sided). The protocol set the boundary using the Lan-DeMets alpha spending function with an O’Brien-Fleming boundary.

Bay 73-4506/14387 demonstrated a statistically significant improvement in OS. The magnitude of the effect was clinically modest: median difference of 1.4 months with a hazard ratio of 0.77 (23% risk reduction).

Table 9 OS analyses (ITT), Bay 73-4506/14387

	Regorafenib	Placebo
N	505	255
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) ^b	0.77 (0.64, 0.94)	
Stratified Log-Rank Test P-value ^{a,b}	0.01	

a Stratified by planned stratification factors: geographic region and time from diagnosis of metastatic disease (TFDM)

b Crossed the O’Brien-Fleming boundary (p value < 0.018) at second interim analysis.

Figure 1 shows that the separation in the KM curves remained constant throughout the duration of the curves until the tails of the curves were reached. Because few patients were assessable after 9 months, no conclusions can be made regarding the tails of these curves. The statistical reviewer performed different sensitivity analyses for OS, confirming the overall robustness of the results.

Figure 1 K-M curves for OS, Bay 73-4506/14387

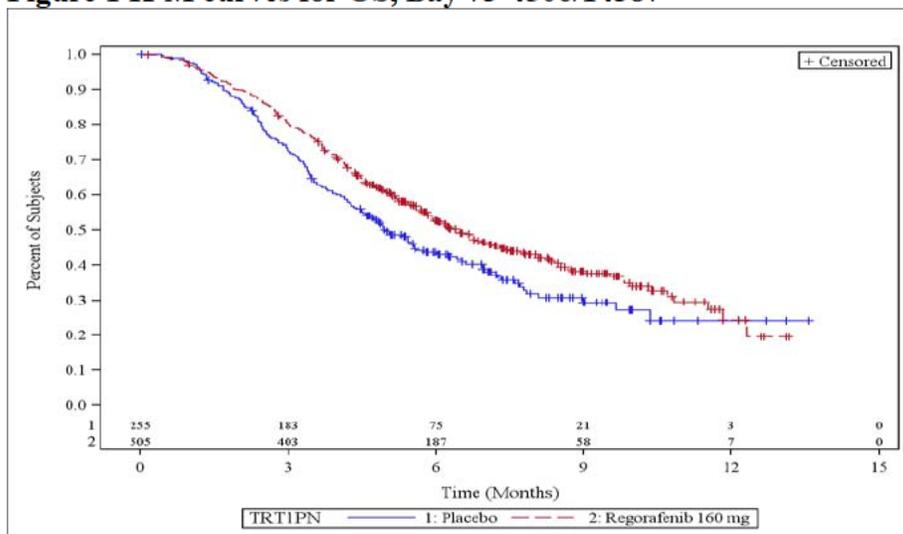


Table 10 (data copied from the statistical review) shows that for almost all subgroups tested, that the HR (point estimate) was less than one. These results provided additional evidence for the consistency of effects on OS and the overall robustness of the results. The 95% CIs crossed one for many of the analyses; however, the sample size in these subgroups was smaller (than the overall patient population) and thus these subgroups were not adequately powered to demonstrate a statistically significant (nominally) effect on OS.

The only OS point estimate that was greater than one was for the subgroup of patients classified as having primary disease in both the colon and the rectum. This result (as should the other subgroup analyses) should be considered exploratory. The number of patients in this group was small and (at this time) there is not a biologically plausible reason that patients in this category should fare worse than other patients with mCRC following regorafenib treatment.

Patients with no *K-Ras* mutation appeared to do better than patients with *K-Ras* mutations; however, the point-estimate favored regorafenib in both groups. The difference between arms in patients without a confirmed mutation was less than that compared to patients with confirmed mutations.

Table 10 Subgroup analyses for OS, Bay 73-4506/14387

Subgroup	Number	HR (95% CI)
Race		
White	593	0.76 (0.61, 0.94)
Asian	111	0.79 (0.44, 1.45)
Gender		
Men	464	0.77 (0.60, 1.00)
Women	296	0.75 (0.55, 1.02)
Age in years		
<65	475	0.72 (0.56, 0.91)
≥ 65	285	0.86 (0.61, 1.19)
Region		
North America, Western Europe, Israel, Australia	632	0.77 (0.62, 0.95)
Asia	104	0.79 (0.43, 1.46)
South America, Turkey, Eastern Europe	24	0.69 (0.20, 2.47)
Time metastatic disease to randomization in months		
< 18	140	0.82 (0.53, 1.25)
≥ 18	620	0.76 (0.61, 0.95)
Number of prior treatment lines		
≤3	301	0.71 (0.52, 0.97)
>3	459	0.80 (0.62, 1.04)
Number of prior lines after diagnostics of metastatic disease		
≤3	395	0.79 (0.60, 1.04)
>3	365	0.75 (0.56, 0.99)
KRAS Mutation		
No	299	0.65 (0.48, 0.89)
Yes	430	0.87 (0.67, 1.12)
ECOG PS		
0	411	0.70 (0.53, 0.93)
1	349	0.77 (0.59, 1.02)

Subgroup	Number	HR (95% CI)
Primary Site of Disease		
Colon	495	0.70 (0.56, 0.89)
Rectum	220	0.95 (0.63, 1.44)
Both	44	1.1 (0.44, 2.70)
US		
No	677	0.82 (0.66, 1.01)
Yes	83	0.46 (0.25, 0.84)

7.3.4 Secondary endpoints

Table 11 (data copied from the statistical review) shows that the PFS results were similar irrespective of the analysis conducted (applicant versus FDA). The FDA analysis only considered objectively confirmed progression events. The table shows that regorafenib treatment improved PFS by about 50%. Sensitivity analyses of PFS conducted by the statistical reviewer confirmed the robustness of the primary PFS results.

Table 11 PFS analyses (ITT), Bay 73-4506/14387

	FDA		Applicant	
	Regorafenib N=505	Placebo N=255	Regorafenib N=505	Placebo N=255
No. of Events (%)	417 (83%)	231 (91%)	430 (85%)	241 (95%)
No. of Deaths, (%)	66 (13%)	34 (13%)	37 (7%)	13 (5%)
Median PFS (months), 95%CI	2.0 (1.9, 2.3)	1.7 (1.7, 1.8)	1.9 (1.9, 2.1)	1.7 (1.7, 1.7)
Stratified HR (95% CI) [P value] ^a	0.49 (0.42, 0.58) [<.0001]		0.49 (0.42, 0.58) [<.0001]	

^a Stratified by geographic region, prior treatment with vascular endothelial growth factor targeting drugs, and time from diagnosis of metastatic disease

Overall, the magnitude of effect on median PFS was not clinically important; however, the KM curves shown in Figure 2 show that the medians do not capture the treatment effect demonstrated throughout the curves as the curves split after the median. Nevertheless, even after the curves split, the overall magnitude of effect (in months) appeared modest (except perhaps at the tails of the curves which may have too few subjects to make any conclusions).

Figure 2 K-M curves for PFS, Bay 73-4506/14387

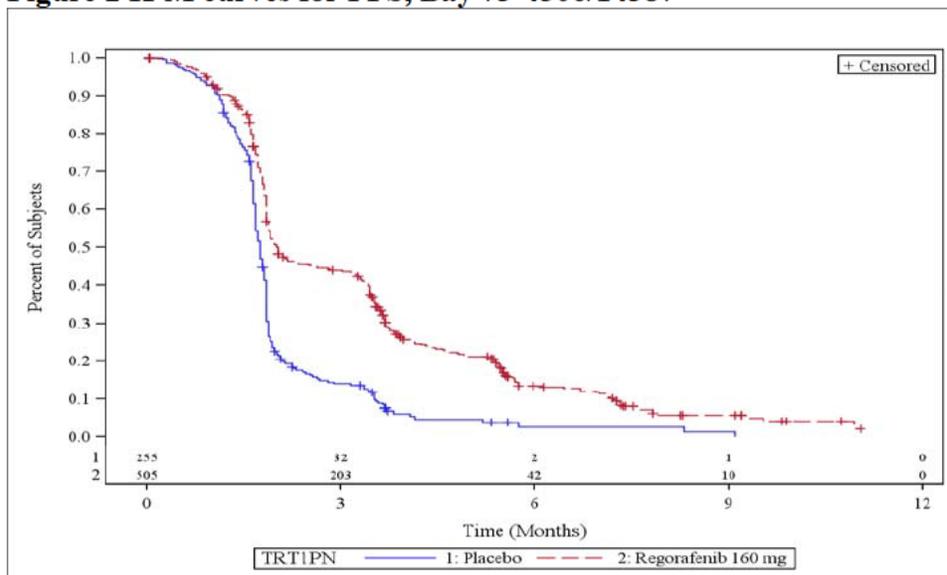


Table 12 shows that few patients responded to regorafenib.

Table 12 Response rate (ITT), Bay 73-4506/14387

	Regorafenib N=505	Placebo N=255
Overall response, n (%)	5 (1%)	1 (0.4%)
Complete response, n (%)	0 (0%)	0 (0%)
Partial response, n (%)	5 (1%)	1 (0.4%)
95% CI	0.3%, 2.3%	0%, 2.2%

Stratified by geographic region, prior treatment with vascular endothelial growth factor targeting drugs, and time from diagnosis of metastatic disease

8. Safety

8.1 Adequacy of database

The clinical review (Dr. Kaushikkumar Shastri) primarily focused on data from Trial Bay 73-4506/14387 as this was the large controlled trial intended to support approval of regorafenib for the indicated patient population. The placebo control allowed for the safety reviewer to conduct an analysis of safety against background adverse events that commonly occur in patients with advanced cancer. The safety population of Bay 73-4506/14387 included 500 patients with advanced mCRC who received regorafenib and 253 who received placebo plus best supportive care. The clinical review also considered data from other trials, primarily in the assessment of adverse events of interest, from a total of approximately 1,145 patients. The clinical reviewer found the safety database adequate to take an action on this application. This reviewer agrees with this assessment based on the demonstrated improvement in OS in a patient population with terminal cancer.

In Bay 73-4506/14387, patients received regorafenib for a median treatment duration of 7.3 weeks compared to a median duration of 7 weeks in the placebo arm. Mean treatment duration was slightly longer in both arms: 12.1 weeks for regorafenib versus 7.7 weeks for placebo.

8.2 Deaths, SAEs, discontinuations due to AEs, general AEs, and results of laboratory tests

8.2.1 Deaths

The clinical reviewer found that the majority of deaths (from Bay 73-4506/14387) occurring during treatment and up to 30 days post permanent treatment discontinuation were related to disease progression [58 of 69 deaths in the regorafenib arm (n=500) versus 35 of 41 deaths in the placebo arm (n=253)]. The table in Section 7.3.1 of the clinical review shows that 1.6% of patients in the regorafenib arm and 1.2% of patients in the placebo arm died due to an adverse event not associated with progressive disease during treatment or within 30 days post-treatment. Deaths found to not be associated with disease progression in the regorafenib arm included hemorrhage (n=3); pneumonia (n=2); cardiac arrest (n=1); general physical health deterioration (n=1); intestinal obstruction (n=1); cerebrovascular accident (n=1); sudden death (n=1); and unknown (n=1). Fatal pneumonia events occurred in two patients in the regorafenib arm; however, two patients randomized to placebo also died of pneumonia.

The primary concerning event in the analysis of deaths was hemorrhage. One of the two fatal events occurred in a patient on warfarin with an elevated INR. A second patient appeared coagulopathic. Bayer proposed a warning to describe hemorrhagic events in the product label.

Overall, the analysis of overall survival performed in Bay 73-4506/14387 provided some assurance of the relative safety of regorafenib.

8.2.2 SAEs

In general, the clinical reviewer found the incidence rate of most nonfatal serious adverse events occurring in Trial Bay 73-4506/14387 to be similar between the two arms. Table 13, with data copied from the clinical review, shows that SAEs due to pyrexia and diarrhea were modestly more frequent among regorafenib-treated patients. Overall, the condition studied (late stage mCRC) likely caused the majority of SAEs in Bay 73-4506/14387 as evidenced by the high incidence rate of SAEs in the placebo arm.

Table 13 SAEs, Bay 73-4506/14387

	Regorafenib N=500 (%)	Placebo N=253 (%)
Any SAE	44	40
General health deterioration	7	10
Pyrexia	3	0.4
Abdominal pain	2	1
Pneumonia	2	2
Dyspnea	2	1
Diarrhea	2	0
Intestinal Obstruction	1	1

	Regorafenib N=500 (%)	Placebo N=253 (%)
Hepatic Failure	1	1
Multi-organ failure	1	2

8.2.3 Drop-outs and discontinuations due to adverse events

Permanent discontinuation due to adverse events occurred more frequently among regorafenib-treated patients compared to patients who received placebo. Table 14, with data copied from the clinical review, shows that no single drug-related adverse reaction was responsible for the majority of permanent drug discontinuation events (general health deterioration occurred at a similar incidence rate across arms).

Table 14 AEs leading to permanent discontinuation ($\geq 1\%$), Bay 73-4506/14387

	Regorafenib N=500 (%)	Placebo N=253 (%)
Any Event	18	13
General health deterioration	4	3
Palmar-Plantar erythrodysesthesia	1	0
Hepatic Failure	1	1
Decreased Appetite	1	0.4
Pneumonia	1	0
Rash	1	0

Dose reductions due to adverse events frequently occurred among regorafenib-treated patients (37.6% compared to 3.2% in the placebo arm). Palmar plantar erythrodysesthesia was the most common event requiring dose reduction (in 18.2% of patients). The other adverse events causing dose reductions in more than two percent of regorafenib-treated patients were diarrhea (3.8%), hypertension (3.2%), fatigue (2%), and rash (2%).

Dose interruptions due to adverse events occurred more frequently than dose reductions with 60.8% of regorafenib-treated patients undergoing a dose-interruption versus 21.7% of patients who received placebo. Palmar plantar erythrodysesthesia was the most frequent reason for dose interruption (refer to Section 7.3.2 of the clinical review for details regarding specific events leading to interruption of treatment).

8.2.4 Common adverse events

Table 15, with data copied from the clinical review, shows the most common adverse events that occurred during Bay 73-4506-14387. Other tyrosine kinase inhibitor drugs also cause many of the same toxicities (e.g., PPE) and some toxicities including hypertension and hemorrhage likely are related to anti-VEGF effects of regorafenib.

Severe toxicities (i.e., \geq Grade 3) occurred more frequently among regorafenib-treated patients. Grade 3 or greater PPE occurred in 17% of patients treated with regorafenib. As stated above, this adverse event frequently caused dose interruptions and resulted in dose reduction of regorafenib. Other more common severe toxicities (i.e., $\geq 5\%$) included asthenia/fatigue, decreased appetite, diarrhea, infection, hypertension, and rash. These toxicities are generally

understood by licensed oncologists and can usually be managed (with the possible exception of infection) with close monitoring, dose interruption, and dose reduction.

Table 15 Common AEs, Bay 73-4506/14387

	Regorafenib (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 described in the clinical review (but more common among regorafenib-treated patients 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).

8.2.5 Laboratory tests

Table 16, with data copied from the clinical review, shows that hematologic abnormalities frequently occurred (as expected) in patients with late-stage mCRC. Changes in hematological parameters occurred more frequently in patients receiving regorafenib; however, overall few patients developed severe treatment-emergent anemia, thrombocytopenia, or neutropenia.

Table 16 Hematologic findings, Bay 73-4506/14387

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	-

A more formal discussion of liver toxicity is contained in the subsequent section. Table 17, shows that overall, LFT abnormalities were more common among regorafenib-treated patients, although most events were Grade 1 or 2 in severity. LFT abnormalities were common in patients who received placebo, likely related to the frequent occurrence of liver metastases in patients with mCRC.

Table 17 Liver function tests, Bay 73-4506/14387

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

In the analysis of chemistry findings, the clinical reviewer found the most frequent \geq Grade 3 abnormality to be hypophosphatemia. This occurred in 32% (1% was Grade 4) of regorafenib-treated patients compared to 4% of patients who received placebo. The clinical reviewer found Grade 3 hypokalemia to occur in 4% of patients and Grade 3 increased lipase to occur in 9% of patients. The incidence rate of \geq Grade 3 amylase elevations occurred at the same rate between arms and pancreatitis occurred at a similar incidence rate in the two arms (1 patient in each arm).

8.3 Special safety concerns

8.3.1 Drug-demographic interactions

The clinical reviewer for safety conducted analyses of adverse events by age range (\geq 65 years versus less than 65 years), gender, and ethnic background. In general, adverse events occurred at similar rates in the various treatment groups. Meaningful conclusions of differences in

adverse events were difficult to make because these were non-randomized subgroups, and in some cases, the numbers of patients in certain groups was small. Refer to Section 7.5.3 of the clinical review for adverse events that differed in proportion between subgroups. The clinical reviewer did not recommend labeling changes based on these differences for the reasons described above.

8.3.2 Additional in-depth analyses of specific events

Based on prior knowledge of adverse reactions related to other TKIs and adverse events occurring in regorafenib clinical trials, the clinical reviewer performed additional in-depth analyses of the following adverse events: hepatotoxicity; hemorrhage; dermatological toxicity including palmar plantar erythrodysesthesia; gastrointestinal perforation and fistula; hypertension; cardiac toxicity; diarrhea and mucositis; renal events; thromboembolic events; infections; wound healing impairment; and posterior reversible leukoencephalopathy syndrome (reversible posterior encephalopathy syndrome). In general, many of these events are briefly described above (i.e., incidence rates in tables) and are described in product labeling (renal events were mainly related to proteinuria). Refer to the clinical review for the more in-depth discussion of these events.

This reviewer agrees with the primary review teams' recommendation to include a boxed warning for hepatotoxicity. Analyses of hepatic events in this population were difficult because patients with mCRC frequently have underlying liver dysfunction related to metastatic disease (or prior therapies). Nevertheless, two patients who died of liver failure had liver biopsy findings showing hepatocyte necrosis and lymphocyte infiltration. Additionally, the incidence of LFT abnormalities of all Grades was higher among regorafenib-treated patients. According to the applicant's analysis, treatment emergent serious adverse events in the regorafenib-treated group occurred in 3.2% of patients versus 1.6% in the placebo arm. Finally, other TKIs cause hepatotoxicity and fatal cases have been reported.

Although the incidence of severe liver dysfunction was modestly higher than placebo, an important reason to include this event as a boxed warning is that this is an adverse reaction that physicians can potentially monitor (acknowledging that the data cannot provide certainty that the monitoring plan will prevent fatal events).

8.4 Discussion of primary reviewer's findings and conclusions

The primary safety reviewer summarized that the addition of regorafenib to best supportive care in the Bay 73-4506/14387 trial resulted in adverse events that have been observed following the use of other multi-kinase inhibitors (including typical anti-VEGF toxicities).

The safety reviewer determined the safety database to be adequate for the intended indication; a total of 500 patients received regorafenib in Bay 73-4506/14387, and over 1,100 patients were exposed to regorafenib in all clinical trials. Based on the poor prognosis of patients with mCRC treated with third (or greater) lines of therapy and the modest effect of regorafenib, treatment duration was limited in Bay 73-4506/14387; patients received regorafenib for median treatment duration of 7.3 weeks compared to a median duration of 7 weeks in the placebo arm.

The most important adverse reactions caused by regorafenib included drug induced liver injury (DILI), hemorrhage, dermatologic toxicity (palmar-planter erythrodysesthesia and rash), hypertension, cardiac ischemic events, and gastro-intestinal perforation. The clinical review team recommended inclusion of DILI in a boxed warning based on the increased incidence of LFT abnormalities and the occurrence of fatal hepatic failure in regorafenib-treated patients (with evidence of DILI on liver biopsy).

The most common toxicity resulting in dose reduction was palmar-planter erythrodysesthesia. A total of 17% of patients experienced Grade 3 PPE. This toxicity is familiar to trained oncologists, and this toxicity usually occurred during the first cycle of treatment. Overall, treatment-emergent adverse events resulted in dose interruptions in 61% of the patients receiving regorafenib and 38% of the patients had their dose reduced.

Other common anti-VEGF toxicities occurred following the administration of regorafenib including hypertension (including a case of PRES), myocardial ischemia and infarction, gastrointestinal perforation, hemorrhage (including fatal cases), proteinuria, and dysphonia.

Although regorafenib can cause serious (including fatal toxicities), the overall risk benefit profile was considered favorable based on the demonstrated improvement in overall survival in a patient population with terminal cancer. Most of the toxicities are familiar to trained oncologists, and it is standard practice to monitor for these adverse reactions, institute treatment as necessary, and to dose modify therapy or discontinue therapy if necessary.

Comment: This reviewer agreed with the major conclusions in the clinical review. The incidence of adverse events in the clinical review was, in general, similar to those of the applicant. Small differences in the incidence rates of certain adverse events were not clinically significant.

9. Advisory Committee Meeting

The review team determined that an ODAC meeting was not necessary for review of this NDA. The effect on OS was statistically robust, and trained oncologists are familiar with the types of toxicities caused by regorafenib.

Nevertheless, DOP2 attempted to contact potential Special Government Employees (SGE) for advice regarding the Action on this indication and advice regarding labeling. DOP2 received notification (from the Advisors and Consultants staff) that one SGE received clearance. Consultation with the SGE is pending at this time.

10. Pediatrics

In the NDA, as amended on 04 Jun 2012, Bayer requested a full waiver of the Pediatric Research and Equity Act requirement to assess the safety and effectiveness of regorafenib for the claimed indication in pediatric age groups 0-16 years. In the application, Bayer stated that regorafenib qualifies for a disease-specific waiver as outlined in the September 2005 draft FDA Guidance, How to Comply with the Pediatric Research Equity Act.

This reviewer agrees that a full waiver is appropriate as described in 21 CFR 314.55(c)(2)(ii) and Section 505B(a)(4)(A)(i) of the Act. Specifically, 21 CFR 314.55(c)(2)(ii) states that an applicant can request a waiver if the “necessary studies are impossible or highly impractical because, e.g., the number of such patients is so small or geographically dispersed.” FDA guidance (draft FDA Guidance for Industry: How to Comply with the Pediatric Research and Equity Act dated September 2005) describes colorectal cancer as one of the diseases that qualifies for a waiver based on the limited number of children diagnosed with the disease.

The PeRC met on 25 Jul 2012 and agreed to grant a full waiver because studies are impossible or highly impractical because the disease/condition does not exist in children.

11. Other Relevant Regulatory Issues

11.1 Application Integrity Policy (AIP)

The Application contained a statement signed by Dr. John Talian of Bayer HealthCare Pharmaceuticals that certified that Bayer did not use and will not use, in any capacity, the services of any person debarred under Section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application.

11.2 Financial disclosures

The majority of investigators reported that they did not enter into any financial arrangements whereby the value of compensation to the investigator would be expected to affect the outcome of the study as defined in 21 CFR 54.2(a). The applicant also certified that the listed investigators referenced on Form 3454 did not disclose financial interests as defined in 21 CFR 54.2(b) or significant payments as described in 21 CFR 54.2(f).

Bayer appeared to obtain initial financial disclosure forms (FCD) from all investigators and sub-investigators. Reasons for failure to obtain follow-up FCD forms were provided in the application. Common reasons included investigators leaving the study (or site) or closure of sites. One ex-U.S. sub-investigator reported a conflict and Bayer provided this information on Form 3455. The investigator's (b) (6) was employed by Bayer and she received approximately \$442,000 in compensation in 2010. A total of (b) (4) were randomized at this site and the sub-investigator who reported the potential conflict treated (b) (4) of the (b) (4). Based on this information, it is unlikely that this conflict would invalidate the study results (with a primary endpoint of OS, large multi-center study, and robust results).

11.3 GCP issues

Bayer provided an audit certificate that stated that 10 investigational sites (from Study Bay 73-4506/14387) were audited for compliance with GCP. Additionally, Bayer also audited (b) (4) (monitoring and study management), (b) (4) (central laboratory), (b) (4) monitoring), and (b) (4) (statistics). Bayer included a statement in the Bay734506/14387 final study report that the protocol and protocol amendments were reviewed and approved by each site's IEC/IRB and that the conduct of the study met all local legal and regulatory requirements. Bayer provided a list of IRBs or IECs that provided oversight for Study Bay 73-4506/14387. Bayer also included a statement that Bay 73-4506/14387 was conducted in accordance with the ethical principles that have their origin in the Declaration of

Helsinki and the International Conference on Harmonization guideline E6: Good Clinical Practice (GCP).

In general, the numbers of protocol violations were similar between arms. The most important deviations related to efficacy (enrollment criteria and withdrawal criteria) occurred at the same rate in both arms. Hypertension constituted the most common reason for classifying protocol violations related to eligibility criteria.

11.4 OSI audits

Because regorafenib is an NME, DOP2 requested OSI inspections of clinical sites. DOP2 and OSI selected sites based on site-specific efficacy results, protocol violations, or patient enrollment at each site. OSI inspected four clinical sites (one U.S., two in Italy, and one in Belgium). OSI also inspected (b) (4) because (b) (4) held the trial master file for Bay 73-4506/14387. (b) (4) and all ex-U.S. sites received preliminary inspection classifications of NAI (no action indicated). The single U.S. site inspected (Mayo Clinic) received an inspection classification of VAI (voluntary action indicated). The VAI classification at this site was primarily related to issues regarding investigational drug disposition records; the study otherwise was found to be conducted in accordance with GCPs. The OSI review stated that based on the preliminary inspections findings, the study data appear reliable in support of NDA 203085.

11.5 Other discipline consults

11.5.1 DRISK

Dr. Vega from DRISK completed a review of the applicant's proposed Risk Management Plan (RMP) and concurred that a Risk Evaluation and Mitigation Strategy (REMS) is not required for regorafenib and that the risks can be managed through labeling based on the data available and the OS benefit to patients with late-stage metastatic colorectal cancer.

11.5.2 DMEPA

James Schlick from DMEPA completed a review of the carton and container on July 25, 2012. DMEPA provided recommendations for both the container labeling and carton labeling (see DMEPA consult). Final negotiations regarding contents of the carton and container are pending at this time.

11.5.3 Pediatric and Maternal Health Staff review

Based on internal discussion with PMHS-MMT, the Division added a warning to the label to describe embryofetal toxicity. FDA determined that this drug will be considered Pregnancy Category D and information was included in labeling to describe embryofetal toxicities observed in rats and rabbits.

11.5.4 Predictive Safety consult

Keith Burkhart from OCP (Predictive Safety Team) conducted an analysis using the MASE tool (Molecular Analysis of Side Effects). The consult stated that "the results of the analysis support the potential addition of a number of adverse events (AEs) to the label and recommend modifications to a number of the regorafenib warnings." However, the review later states that

MASE should be considered a hypothesis generating or signal strengthening tool and that MASE reflects uncontrolled experience from use outside of a clinical trial. The consult also states that the frequency and severity of adverse events can vary within a product class.

The January 2009 FDA Labeling Guidance limits inclusion of adverse events to those events for which there is some basis to believe there is a causal relationship between the occurrence of an adverse event and use of the drug. Ultimately the PST provided recommendations based on the inclusion of certain adverse reactions in labels of other TKIs. Inclusion of an adverse reaction in a different TKI label does not meet this standard.

Both internal and external factors related to a drug can result in different adverse event profiles for different TKIs or VEGF inhibiting drugs. For example, the duration of use of regorafenib is expected to be of shorter duration compared to other TKIs because regorafenib will be administered to patients with late stage mCRC. For example, patients in the pazopanib trial (RCC) received pazopanib for a median duration of 7.4 months (data from product labeling) whereas patients received regorafenib for a median treatment duration of less than 2 months. This difference in exposure may result in differences in toxicities (especially for toxicities that require long-term drug exposure).

Also, patients receiving TKIs or VEGF inhibitors receive these drugs for different indications. The incidence of certain toxicities may be influenced by both the disease under study as well as concomitant or prior therapies. For example, anti-VEGF antibody therapies appeared to increase the incidence rate of adverse events caused by typical cytotoxic chemotherapy (when used in combination). Also, patients with underlying pathology in the kidney, lung, or liver due to their cancers may be at higher risk for drug-related toxicities based on limited reserve of that organ. Patients also may be at higher risk for certain adverse events based upon prior chemotherapy (for example, patients who received prior anthracyclines may be at higher risk for CHF). Finally, the consult did not describe relative affinities for receptors and pharmacokinetics of the different drugs.

In summary, the analysis using MASE should be considered exploratory for labeling purposes. Nevertheless, the analyses may be useful for pharmacovigilance purposes in the post-marketing setting (b) (4)

11.6 Drug name review

During the review of this application, DMEPA sent a letter on 29 Jun 2012 informing Bayer that the proposed trade name of Stivarga was (conditionally) acceptable. The formal DMEPA review considered the name from a promotional perspective in consultation with DOP2 and OPDP. DMEPA also considered the name Stivarga from a safety perspective (i.e., performed assessments for look-alike and sound-alike drugs) and found the name acceptable.

12. Labeling

FDA sent draft labeling recommendations to Bayer prior to the date stipulated by the 21st Century Review Process on 29 Aug 2012. Labeling recommendations described below should not be considered final as labeling negotiations are ongoing.

In general, DOP2 revised all sections of the label for brevity and clarity. Command language was preferred as directed by the PLR. The remainder of this section of the review will only focus on high-level issues regarding the label submitted by Bayer. Numbering below is consistent with the applicable sections in product labeling. This review will not comment on all sections (for example, if only minor edits were made to a section). This CDTL agreed with the recommendations made by the review teams that are described below.

(b) (4)

2. Dosage and Administration: FDA review staff recommended including examples of a low-fat meal in order to reduce variability in drug exposure following regorafenib. FDA also revised the dose modification section to include instructions for dose modifications for non-liver or PPE toxicities.

5. Warnings and Precautions: In general, FDA staff recommended revising specific Warnings and Precautions to provide data where available regarding the specific events (for example, incidence rates). Statements not pertinent to describing the Warnings in the section were removed (e.g., (b) (4)

FDA recommended inclusion of a boxed warning to highlight the risk of hepatotoxicity (see Section 8.3.2 of this review). The Division removed (b) (4)

(b) (4)

(thus the Division determined that this does not meet the standard for inclusion in the Warnings section—however, FDA stated that Bayer can provide additional justification to the Division if they feel this Warning should remain in the label). FDA recommended inclusion of an additional Warning to describe the risk of embryo-fetal toxicity.

6. Adverse Reactions: FDA recommended inclusion of data to describe the patient population in the pivotal clinical trial. FDA included skin toxicity as the most adverse reaction leading to permanent drug discontinuation. FDA recommended combining the data from both stomatitis and mucosal inflammation events under the mucositis term. FDA recommended inclusion of the case of kearatoacanthoma/squamous cell carcinoma.

7. Drug Interactions: OCP recommended adding a section to the label to describe the effects of strong CP3A4 inhibitors on regorafenib.

8.1. Pregnancy: FDA staff recommended inclusion of animal data justifying the designation of Pregnancy Category D.

8.2. Females and Males of Reproductive Potential: FDA moved this information to (a new) Section 8.8 as Section 8.2 (if it exists in a label) pertains to Labor and Delivery.

8.4. Pediatric Use: FDA review staff recommended inclusion of animal data pertaining to pediatric use (specifically effects on dentin alteration and thickening of the femoral epiphyseal growth plate).

8.5. Geriatric use: FDA recommended removal of the following proposed statement: (b) (4) This statement was considered non-informative.

8.6. Hepatic Impairment: OCP and DOP2 recommended including a statement that Stivarga is not recommended for use in patients with baseline severe hepatic impairment (Child-Pugh Class C).

11. Description: ONDQA recommended inclusion of a water molecule as part of the molecular structure of regorafenib.

12.3 Pharmacokinetics: OCP recommended inclusion of additional data regarding the food effects study and deletion of information regarding (b) (4) OCP recommended deletion of this information (b) (4) Bay 73-4506/14387 were not submitted in the application.

14. Clinical Studies: FDA recommended inclusion of the following in this section: administration information concerning the low-fat breakfast; *K-Ras* baseline status; information regarding the median number of prior therapies that patients received; and revised PFS information describing the effect observed when evaluating only objective progression events (the difference in PFS estimates between Bayer and the FDA were minimal).

For brevity, FDA recommended deletion of (b) (4)

(b) (4) DA recommended removal of the following statement: (b) (4)

(b) (4) The study was not adequately powered to determine effects in these specific subgroups.

13. Recommendations/Risk Benefit Assessment

13.1 Recommended regulatory action

This reviewer recommends regular approval of NDA 203085 based on substantial evidence from one adequate and well controlled trial demonstrating a modest effect on OS (clinical benefit) observed in Bay 73-4506/14387. This approval recommendation is contingent upon reaching agreement on labeling and PMCs.

13.2 Risk-benefit assessment

The recommendation for approval of this application is based on a modest effect on OS observed in Bay 73-4506/14387. According to the May 2007 FDA Guidance Document regarding endpoints for cancer drugs (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidance/ucm071590.pdf>; accessed on 12 Jul 2012), survival is considered the most reliable cancer endpoint, and when studies can be conducted to adequately assess survival, it is usually the preferred endpoint. An effect on OS is considered regulatory evidence of clinical benefit used by the Agency to substantiate regular approval of a drug.

In general, because mCRC is an incurable disease [with the notable exception of patients who have oligometastatic disease (usually hepatic)] the goal of treatment is to prolong life and/or improve quality of life. The Bay 73-4506/14387 trial established that patients who received regorafenib in combination with best supportive care lived a median 1.4 months longer than patients who received placebo in combination with best supportive care (HR 0.77; 95% CI: 0.64, 0.94). The effect on OS was supported by a statistically significant effect on progression free survival and consistent results across subsets for these endpoints. The modest effects on PFS should be considered supportive of the robustness of the Bay 73-4506/14387 results rather than as evidence of direct benefit.

Adverse events observed in the Bay 73-4506/14387 trial were generally considered in-line with toxicities observed following the administration of other multi-TKI drugs. Although regorafenib causes multiple, including serious, toxicities, the overall toxicity profile was considered acceptable because regorafenib improves overall survival in patients with terminal mCRC (and there are no other adequate treatment options). The most frequently observed adverse reactions (occurring in $\geq 30\%$ of patients) with regorafenib were asthenia/fatigue, decreased appetite and food intake, palmar-plantar erythrodysesthesia (PPE), diarrhea, mucositis, weight loss, infection, hypertension, and dysphonia.

In general, treatment duration of regorafenib was brief (median duration of therapy less than 2 months) and many of the common toxicities including hypertension and palmar-plantar erythrodysesthesia can be managed with careful monitoring and dose interruption when appropriate.

The most serious adverse reactions caused by regorafenib included hepatotoxicity and hemorrhage. Although serious cases were infrequent, fatal cases were reported in clinical trials. Fatal cases of hemorrhage occurred in the setting of anticoagulation and coagulopathy. Both hemorrhage and hepatotoxicity will carry a warning in the label and hepatotoxicity will carry a boxed warning. Additionally, similar to other drugs with anti-VEGF effects, the incidence of myocardial ischemia or infarction was higher in regorafenib-treated patients compared to placebo (1.2 % versus 0.4%).

In summary, the risk-benefit assessment is considered favorable in light of the overall survival effect observed in a patient population with incurable metastatic cancer. Nevertheless, physicians and patients will need to consider whether the modest improvement in OS is of sufficient magnitude to offset the toxicities caused by regorafenib.

13.3 Recommendation for postmarketing Risk Evaluation and Management Strategies

The review teams did not identify any REMS as necessary prior to a marketing authorization for regorafenib. Regorafenib will be prescribed by oncologists who are trained in how to monitor, diagnose, and manage serious toxicities caused by anti-neoplastic drugs. Standard practice in oncology dictates informed consent prior to prescribing or administering anti-neoplastic drugs.

13.4 Recommendation for other postmarketing requirements and commitments

All PMCs and PMRs were recommended by the Office of Clinical Pharmacology (OCP). All but one PMR involves completion or submission of results from ongoing or completed studies. Bayer and FDA discussed these potential PMCs/PMRs (except for the PMR for the new renal impairment study) during a 03 Apr 2012 pre-submission telephone conference. Agreement on final language and completion dates regarding the PMCs and PMRs are pending; however, Bayer indicated near completion of two of the PMCs and two of the PMRs with a tentative Final Report Submission date of 30 Nov 2012.

OCP recommended the following two post-marketing *requirements* to further ensure the safe use of regorafenib.

- Complete Study 14814 and submit the final study report, along with a thorough review of cardiac safety data, to address any potential impact of regorafenib on QTc interval prolongation in patients.

The goal of this PMR is to assess the risk of regorafenib on prolonging the QT/QTc interval. This has been a serious risk observed following the use of some drugs including multiple TKI inhibitors. Study 14814 is a thorough QT study and the study is ongoing and near completion.

- Complete Study 12434 to evaluate the effect of regorafenib on the pharmacokinetics of rosiglitazone (a substrate of CYP2C8), warfarin (a substrate of CYP2C9) and midazolam (a substrate of CYP3A4) in patients and submit the final study report.

OCP recommended the following two post-marketing *commitments* to further characterize the exposure profile of regorafenib. These analyses will be conducted to determine whether they can support recommendations for dose modifications in specific populations/settings.

- Submit an integrative population pharmacokinetic analysis report to evaluate the effect of intrinsic and extrinsic factors on the pharmacokinetics of regorafenib and the active metabolites M2 and M5.
- Submit an exposure-response analysis for regorafenib and the active metabolites M2 and M5 for measures of both effectiveness and toxicity using data collected from the CORRECT trial (Study 14387).

Finally, OCP recommended one new post-marketing *requirement* following an analysis that suggested that exposure to regorafenib increased with worsening renal function. OCP recommended that Bayer conduct a multiple-dose pharmacokinetic trial in patients with severe renal impairment. Such a trial appears necessary to determine whether regorafenib can be safely administered to this population or whether a different dose is necessary for this population of patients. Bayer will need to submit a protocol for FDA review prior to conducting the trial.

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/s/

STEVEN J LEMERY
09/10/2012