

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**203085Orig1s000**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

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## Clinical Pharmacology Review

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<b>NDA</b>	NDA 203-085  \\CDSESUB1\EVSPROD\NDA203085\0000\
<b>Type/Category</b>	NME; Priority
<b>Brand Name</b>	Stivarga
<b>Generic name</b>	Regorafenib
<b>Proposed Indication</b>	Treatment of patients with metastatic colorectal cancer (mCRC) who have been previously treated with, (b) (4) (b) (4), fluoropyrimidine-based chemotherapy, an anti-VEGF therapy, or an anti-EGFR therapy (if KRAS wild type).
<b>Dosage Form</b>	Film-coated tablet, 40 mg
<b>Route of Administration</b>	Oral
<b>Dosing Regimen and Strength</b>	160 mg oral once daily for the first 21 days of each 28-day treatment cycle
<b>Applicant</b>	Bayer HealthCare Pharmaceuticals, Inc.
<b>OCP Division</b>	DCP 5
<b>OND Division</b>	DOP 2
<b>Submission Date</b>	April 27, 2012
<b>PDUFA</b>	October 27, 2012; Internal action goal, September 27, 2012
<b>Primary Reviewer</b>	Stacy S. Shord, Pharm.D.
<b>Team Leader</b>	Hong Zhao, Ph.D.

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## 1 EXECUTIVE SUMMARY

Regorafenib is a new molecular entity (NME) that inhibits multiple kinases. The proposed indication is 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, or if KRAS wild type, an anti-EGFR therapy. (b) (4)

The proposed dose regimen is 160 mg as four 40 mg film-coated tablets administered orally once daily for the first 21 days of each 28-day treatment cycle. The bioequivalence (BE) of regorafenib between the 'to-be-marketed' formulation and clinical trial formulation was demonstrated after a single oral dose, but the exposure of the active metabolites M2 and M5 was clinically insignificantly higher for the 'to-be-marketed' formulation.

A single clinical safety and efficacy trial was conducted in 760 patients with mCRC who were randomized 2:1 to receive oral regorafenib or placebo with best supportive care (BSC) until disease progression or unacceptable toxicity. Regorafenib resulted in a longer overall survival (OS) of 1.4 months compared to placebo [regorafenib: 6.4 mo. vs. placebo: 5.0 mo.; HR = 0.77; 95% CI 0.64, 0.94; p=0.0102]. The OS benefit was independent of age, KRAS mutation status, and the number of previous therapies. Most patients received three or fewer previous therapies for metastatic disease. Regorafenib is associated with several adverse events (AE) commonly seen with drugs that interact with the same kinases: hepatotoxicity, hemorrhage, palmar-plantar erythrodysesthesias, rash, hypertension, cardiac ischemia or infarction, gut perforation, diarrhea, mucositis, and hypophosphatemia.

The clinical pharmacology studies included in this NDA are two dose escalation studies, three drug interaction studies, one food effect study and one BE study. The clinical safety and efficacy trial was completed earlier than anticipated with demonstrated OS benefit, while several clinical pharmacology studies including exposure-response (E-R) analyses, population pharmacokinetic (PopPK) analyses, an assessment of the risk of QT/QTc interval prolongation and an assessment of a pharmacokinetic (PK) drug interaction with cytochrome P450 probe substrates are still ongoing. Prior to the NDA submission, FDA agreed to the sponsor's proposal to submit the reports of these ongoing studies in November 2012 under post marketing requirements (PMRs) and post marketing commitments (PMCs) if the applicant believes that there are no safety signals or evidence of important but incompletely characterized clinical pharmacologic effects that will preclude an adequate risk-benefit assessment.

## **1.1 RECOMMENDATIONS**

This NDA is acceptable from a clinical pharmacology perspective provided that the applicant and the FDA come to an agreement regarding the labeling language and the identified clinical studies to be conducted as PMRs or PMCs.

## **1.2 PHASE 4 REQUIREMENTS AND COMMITMENTS**

### **1.2.1 Post Marketing Requirements (PMRs)**

The Office of Clinical Pharmacology requires the applicant to conduct the following PMRs. These studies are included in the action letter with milestones agreed upon after negotiation with the applicant.

1. Complete a clinical trial evaluating the potential for regorafenib to prolong the QT/QTc interval in an adequate number of patients administered repeated doses of 160 mg of regorafenib and submit the final study report, along with a thorough review of cardiac safety data.
2. Complete a clinical trial and submit the final study report to evaluate the effect of repeated doses of 160 mg of regorafenib on the pharmacokinetics of a probe substrate of CYP2C8, CYP2C9, CYP3A4 and CYP2C19.
3. Conduct a multiple dose study to determine the appropriate dose of regorafenib in patients with severe renal impairment. Submit the final protocol for FDA review before conducting the trial.

### **1.2.2 Post Marketing Commitments (PMCs)**

The Office of Clinical Pharmacology requires the applicant to conduct the following PMCs. These studies are included in the action letter with milestones agreed upon after negotiation with the applicant.

1. 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 M-2 and M-5.
2. Submit an exposure-response analysis for regorafenib and the active metabolites M-2 and M-5 for measures of both effectiveness and toxicity using data collected from the CORRECT trial (Study 14387).

### **1.2.3 Additional Comments for the Applicant's Consideration**

The following clinical pharmacology pertinent comments will be sent to the sponsor under the IND for the applicant to address during future development of this drug.

1. Conduct a pharmacokinetic drug interaction study in subjects administered an oral P-glycoprotein probe substrate with and without regorafenib in accordance with the FDA draft Guidance for Industry: *“Drug Interaction Studies — Study Design, Data Analysis, and Implications for Dosing and Labeling.”* Submit the final protocol for FDA review before conducting the trial.

2. Conduct a pharmacokinetic drug interaction study in subjects administered a cytochrome P450 (CYP) 2D6 probe substrate with and without regorafenib in accordance with the FDA draft Guidance for Industry: “*Drug Interaction Studies — Study Design, Data Analysis, and Implications for Dosing and Labeling*” if a drug interaction is demonstrated between regorafenib and a CYP2C8, CYP2C9, CYP3A4 or CYP2C19 probe substrate following the completion of the ongoing Study 12434. Submit the protocol for FDA review before conducting the trial.
3. Conduct *in vitro* studies to determine if regorafenib and the active metabolites M-2 or M-5 induce CYP1A2, CYP2B6 or CYP3A4 mRNA expression levels in accordance with the FDA draft Guidance for Industry “*Drug Interaction Studies — Study Design, Data Analysis, and Implications for Dosing and Labeling.*”
4. Conduct a pharmacokinetic drug interaction study to determine the pharmacokinetics of a sensitive substrate or a substrate with a narrow therapeutic index of the cytochrome P450 enzymes likely to be induced in humans if the calculated  $R_3$  value is less than 0.9 following the completion of the *in vitro* studies to assess the ability of regorafenib, M-2 or M-5 to induce cytochrome P450 enzymes. Submit the final protocol for FDA review before conducting the trial(s).
5. Conduct a pharmacokinetic drug interaction study in subjects administered regorafenib with and without rifaximin in accordance with the FDA Guidance for Industry: “*Drug Interaction Studies — Study Design, Data Analysis, and Implications for Dosing and Labeling.*” Submit the final protocol for FDA review before conducting the trial.
6. Submit a summary report and data files of the exploratory biomarker analyses completed during the clinical development of regorafenib, including genetic and nongenetic markers in various matrices (e.g., blood, plasma and tumor).

**Signatures:**

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Cc: DOP2: RPM-**M Hughes**; MO- **S Pradhan, S Kaushik**; MTL- **S Lemery**  
 DCP-5: DDD - **B Booth**

A Required OCP Office Level Briefing occurred on Wednesday, August 15, 2012. The attendees included Drs. Zineh, Abernethy, Rahman, Booth, Reynolds, Pacanowski and others.

### 1.3 SUMMARY OF IMPORTANT CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS

*Pharmacokinetics:* Following a single 160 mg dose, regorafenib reached mean  $C_{max}$  of 2.5  $\mu\text{g/mL}$  at a median time ( $T_{max}$ ) of 4 hrs and mean AUC of 70.4  $\mu\text{g}\cdot\text{h/mL}$ . At steady-state, regorafenib reached mean  $C_{max}$  of 3.9  $\mu\text{g/mL}$  and the mean AUC of 58.3  $\mu\text{g}\cdot\text{h/mL}$ . The coefficient of variation of  $C_{max}$  and AUC is between 35% to 44%. Regorafenib underwent enterohepatic circulation with multiple peak plasma concentrations observed within 24 hrs after the oral administration. Regorafenib was highly protein bound (99.5%). It was primarily metabolized by CYP3A4 and UGT1A9 and about 71% of a single radiolabeled dose (24% as metabolites) was excreted in feces. The mean (range) elimination half-life ( $t_{1/2}$ ) was 28 (14 to 58) hrs. 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 (range)  $t_{1/2}$  for M2 was 25 (14 to 32) hrs and for M5 was 51 (32 to 70) hrs.

*Food Effect:* Regorafenib is recommended to be administered with a low-fat meal. As compared to the fasted state, a low-fat breakfast increased the mean AUC of regorafenib, M2 and M5 by 36%, 40% and 23%, respectively, whereas a high-fat meal increased the mean AUC of regorafenib by 48%, but decreased the mean AUC of M2 and M5 by 20% and 51%, respectively.

*Product Comparability:* No clinically important differences in exposure were observed between the 'to-be-marketed' formulation and clinical trial formulation after administration of a single dose of 160 mg of regorafenib.

*Organ Impairment:* No differences in the mean exposure of regorafenib and the metabolites M2 and M5 were observed in 10 patients with mild renal impairment ( $CL_{cr}$  60 to 89 mL/min) as compared to 18 patients with normal renal function. The applicant is requested to conduct a multiple dose study to determine an appropriate dose for patients with severe renal impairment as a PMR.

No differences in the exposure of regorafenib and the metabolites M2 and M5 were observed in 14 patients with hepatocellular cancer (HCC) and mild hepatic impairment (Child-Pugh A) and 4 patients with HCC and moderate hepatic impairment (Child-Pugh B) relative to 10 patients with solid tumors and normal hepatic function. Regorafenib has not been administered to patients with severe hepatic impairment (Child-Pugh C).

*Drug Interactions:* 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 CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4 *in vitro*. The effect of regorafenib on the PK of CYP2C8, CYP2C9, CYP2C19 and CYP3A4 probe substrates are being evaluated in an ongoing study. Regorafenib did not induce cytochrome P450 activity *in vitro*; however, it is not known if regorafenib, M2 or M5 induce CYP1A2, CYP2B6, and/or CYP3A4 mRNA expression levels.

Regorafenib M2 and M5 inhibited UGT1A1 and UGT1A9 *in vitro*. When irinotecan was

administered five days after the last dose of seven daily doses of regorafenib, the mean AUC of SN-38 increased by 44% and the mean AUC of irinotecan increased by 28%.

Regorafenib is not a substrate for P-gp, BCRP, OATP1B1, and OATP1B3 *in vitro*. It inhibits P-gp and BCRP *in vitro*. Regorafenib did not inhibit OATP1B1, OATP1B3, OAT1, OAT3 and OCT2 *in vitro*.

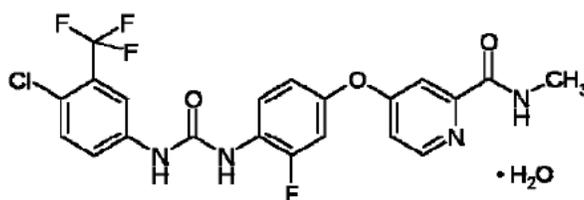
*Exposure-Response and Population Pharmacokinetic Analyses:* The applicant plans to submit these analyses post marketing.

## 2 QUESTION BASED REVIEW

### 2.1 GENERAL ATTRIBUTES

#### 2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they related to clinical pharmacology and biopharmaceutics review?

The proposed drug product is available as 40 mg film-coated tablets. Each tablet contains 40 mg of regorafenib which corresponds to 41.49 mg of regorafenib monohydrate. The structural formula for the drug substance regorafenib monohydrate is:



Regorafenib monohydrate has a molecular weight of 501 g/mol. (b) (4)

Regorafenib monohydrate is practically insoluble in water (b) (4)

Regorafenib showed a high permeability across Caco-2 cells. The applicant claims that regorafenib is a BCS class 2 compound with high permeability and low solubility.

#### 2.1.2 What are the proposed mechanism(s) of action and therapeutic indication(s)?

Regorafenib inhibits multiple kinases, including VEGFR1, VEGFR2, VEGFR3, TIE2, KIT, RET, RAF-1, BRAF, BRAFV600E, PDGFR, and FGFR. Regorafenib inhibited VEGFR2, VEGFR3, TIE2, PDGFR $\beta$ , KIT (wild-type and mutant), RET (mutant), BRAF (mutant) and FGFR with IC<sub>50</sub> values ranging from 3 nM to 200 nM. The activation of the MAPK pathway monitored by ERK phosphorylation was inhibited by regorafenib with IC<sub>50</sub> values ranging from 40 nM to 400 nM. These values appear to be at least 20-fold lower than the observed steady-state regorafenib concentrations as measured at the proposed dose in the dose escalation trial.

The M2 and M5 metabolites of regorafenib inhibited some of the same kinases as regorafenib, such as VEGFR2, TIE2, KIT (mutant and wild-type) and BRAF (mutant) at IC<sub>50</sub> values similar to regorafenib. These metabolites exhibited similar anticancer activity compared to regorafenib in tumor models of colorectal cancer.

The proposed indication is for “the treatment of patients with mCRC who have been previously treated with, (b) (4) fluoropyrimidine-based chemotherapy, an anti-VEGF therapy, or if KRAS wild type, an anti-EGFR therapy.” FDA modified the proposed indication to “the treatment of patients with mCRC who have been previously treated with

fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF therapy, and, if KRAS wild type, an anti-EGFR therapy.”

**2.1.3 What are the proposed dosage(s) and route(s) of administration?**

The proposed dose is 160 mg once daily (QD) for the first 21 days of each 28-day treatment cycle. The proposed drug product will be available as 40 mg film-coated tablets.

**2.2 GENERAL CLINICAL PHARMACOLOGY**

**2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?**

Table 1 lists the relevant clinical pharmacology and clinical studies included in the application. The applicant proposes to submit the final study reports and datasets for PopPK analyses, E-R analyses, Study 12434 and Study 14814 in November 2012; these clinical pharmacology studies were not completed before the submission of the application as the clinical safety and efficacy trial was completed earlier than anticipated.

Table 1. Summary of the Clinical Pharmacology and Clinical Studies					
Study Number	Study Design	Dose and Administration	Study Population	Assessment	Status
11650	Dose escalation	10 mg to 220 mg QD x 21 days	Advanced solid tumors (n = 76)	Pharmacokinetics; a post-hoc subgroup analysis was conducted in patients with mild renal impairment Biomarkers	Completed
11651	Dose escalation	20 mg to 140 mg QD daily x 28 days	Advanced solid tumors (n = 84)	Pharmacokinetics; a post-hoc subgroup analysis was conducted in patients with mild and moderate hepatic impairment Biomarkers	Completed
13172	Open label	160 mg QD x 21 days	Advanced refractory tumors (n = 16)	Pharmacokinetics in Asian (Japan) patients	Completed
14996	Open label	160 mg QD x 21 days	Advanced refractory tumors (n = 8)	Pharmacokinetics in Asian (Hong Kong, Singapore) patients	Ongoing
11656	Open label	160 mg QD on days 4-10 and 18-24 with mFOLFOX6 or FOLFIRI	Metastatic colorectal cancer (n = 45)	Drug interaction with irinotecan, fluorouracil and oxaliplatin	Completed
12434	Open label	160 mg QD x 21 days	Advanced solid tumors (n=16)	Drug interaction with substrates of cytochrome P450 enzymes	Ongoing

Study Number	Study Design	Dose and Administration	Study Population	Assessment	Status
14814	Open label	160 mg QD x 21 days	Advanced solid tumors (n=54)	QTc interval prolongation	Ongoing
14656	Open label, randomized, crossover	160 mg x 1 dose in each period	Healthy men (n=24)	Food effect	Completed
12437	Open label, randomized, crossover	160 mg x 1 dose in each period	Healthy men (n=48)	Relative bioavailability	Completed
12436	Open label	120 mg <sup>14</sup> C-radiolabeled regorafenib x 1 dose	Healthy men (n=4)	ADME	Completed
12435	Open label	160 mg x 1 dose	Healthy men (n=24)	Drug interaction with ketoconazole	Completed
15524	Open label	160 mg x 1 dose	Healthy men (n=24)	Drug interaction with rifampin	Completed
14596	Open label (phase 2)	160 mg once daily x 21 days	Hepatocellular carcinoma (n=36)	Pharmacokinetics in White and Korean patients	Completed
11726	Open label (phase 2)	160 mg once daily x 21 days	Renal cell carcinoma (n=48)	Pharmacokinetics	Completed
14387	Randomized, double blind, placebo controlled	160 mg once daily x 21 daily	Metastatic colorectal cancer (n=705)	Overall survival Progression free survival Overall response rate Disease control rate Patient reported outcomes Duration of response Duration of stable disease Safety Pharmacokinetics Biomarkers	Completed

### 2.2.2 What is the basis for selecting the response endpoints or biomarkers and how are they measured in clinical pharmacology and clinical studies?

The primary endpoint of the clinical safety and efficacy trial was OS defined as the time (days) from randomization to death due to any cause. Patients alive at the time of analysis were censored at their last date known to be alive. As stated in the FDA Guidance for Industry “*Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics*”, OS is considered the most reliable cancer endpoint, and when studies can be conducted to adequately assess survival, it is usually the preferred endpoint. The secondary endpoints included progression free survival (PFS), overall response rate (ORR) and disease control rate (DCR).

**2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?**

Yes. Regorafenib and the active metabolites M2 and M5 were appropriately identified and measured in human plasma samples to assess the PK parameters [[see Section 2.6 Analytical Methods](#)].

**2.2.4 Exposure-response**

**2.2.4.1** *What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy?*

The applicant proposes to submit an E-R analysis for Study 14387 post marketing.

Based on the initial analysis conducted in Study 11650, no clear E-R relationship was observed for regorafenib, M2 or M5 between exposure (AUC and  $C_{max}$ ) and selected indices of safety or clinical activity. The absolute and relative changes from baseline for plasma VEGF levels indicate an overall increase in systemic levels and for sVEGFR2 levels indicate an overall decrease in systemic levels. A dose-response relationship was observed for sVEGFR2 levels as sVEGFR levels declined relative to baseline with a greater effect observed for daily doses of  $\geq 60$  mg.

**2.2.4.2** *What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety?*

[See Section 2.2.4.1. Exposure-response.](#)

**2.2.4.3** *Does this drug prolong the QT or QTc interval?*

Regorafenib, M2 and M5 inhibited the hERG  $K^+$  current with an  $IC_{50}$  value of 27  $\mu M$  [PH-33109], 1.4  $\mu M$  [PH-35502] and 1.8  $\mu M$  [PH-35519], respectively. Regorafenib demonstrated no effect on the cardiac action potential in rabbit Purkinje fibers [PH-33827] and no effect on ECG intervals in Beagle dogs after oral or intravenous administration [Reports PH-33963, PH-35619, PH-34580, PH-34182, A45739]. M2 and M5 demonstrated no effect on QT intervals in Beagle dogs after intravenous infusions [PH-35628 and PH-35620].

The applicant included an interim analysis of the QT/QTc intervals recorded from 25 patients with advanced solid tumors enrolled in Study 14814. The final study report for this dedicated cardiovascular safety study will be submitted post marketing. No changes in the QTcF interval were observed throughout treatment in patients with mCRC enrolled into the clinical safety and efficacy trial (Figure 1, Table 2).



- The intermittent dosing provides patients with an opportunity to recover partially from potential adverse events.

## 2.2.5 What are the PK characteristics of the drug and its major metabolite?

### 2.2.5.1 What are the single dose and multiple dose PK parameters?

In Study 11650, the following parameters were calculated for patients administered a dose of 160 mg once daily for 21 days after a light breakfast. PK samples were collected up to 48 hrs following a single dose (day 1; the dose was held on day 2) and up to 72 hrs following repeated doses (day 21). No clinically important differences in the exposure of regorafenib, M2 or M5 were observed between patients with advanced solid tumors and mCRC. See [Table 7](#) located in Section 2.2.5.10 for the inter-patient variability as measured by the % coefficient of variation (%CV).

Table 3. The single and repeat dose (on cycle 1, day 21) mean pharmacokinetic parameters of regorafenib, M2 and M5 in patients administered 160 mg daily x 21 days									
	AUC μg·h/mL	C <sub>max</sub> μg/mL	t <sub>½</sub> h	AUC <sub>0-24h,ss</sub> μg·h/mL	C <sub>max,ss</sub> μg/mL	t <sub>½</sub> h	AUC <sub>0-24h,ss</sub> μg·h/mL	C <sub>max,ss</sub> μg/mL	t <sub>½</sub> h
	Single Dose – Cohort 7 Solid Tumors N=12			Repeat Dose – Cohort 7 Solid Tumors N=10			Repeat Dose – Cohort 9 Colorectal Cancer N=19		
Regorafenib	70.4	2.5	28.4	58.3	3.9	22.2	50.3	3.4	28.4
M2	28.0	0.84	21.5	53.7	3.3	21.0	48.1	3.2	25.0
M5	2.1	0.08	NR	48.7	2.9	NR	64.6	4.0	50.9

NR= not reported

### 2.2.5.2 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

A PopPK analysis was not conducted. A cross study comparison suggests that the mean AUC and the mean C<sub>max</sub> following a single dose are similar between healthy men and patients with cancer.

### 2.2.5.3 What are the characteristics of drug absorption?

The relative bioavailability of the film-coated tablets compared to an oral solution in the fasted state is about 69% for the 20 mg and 83% for the 100 mg film-coated tablets (identified as CP tablets). [Study 11650]

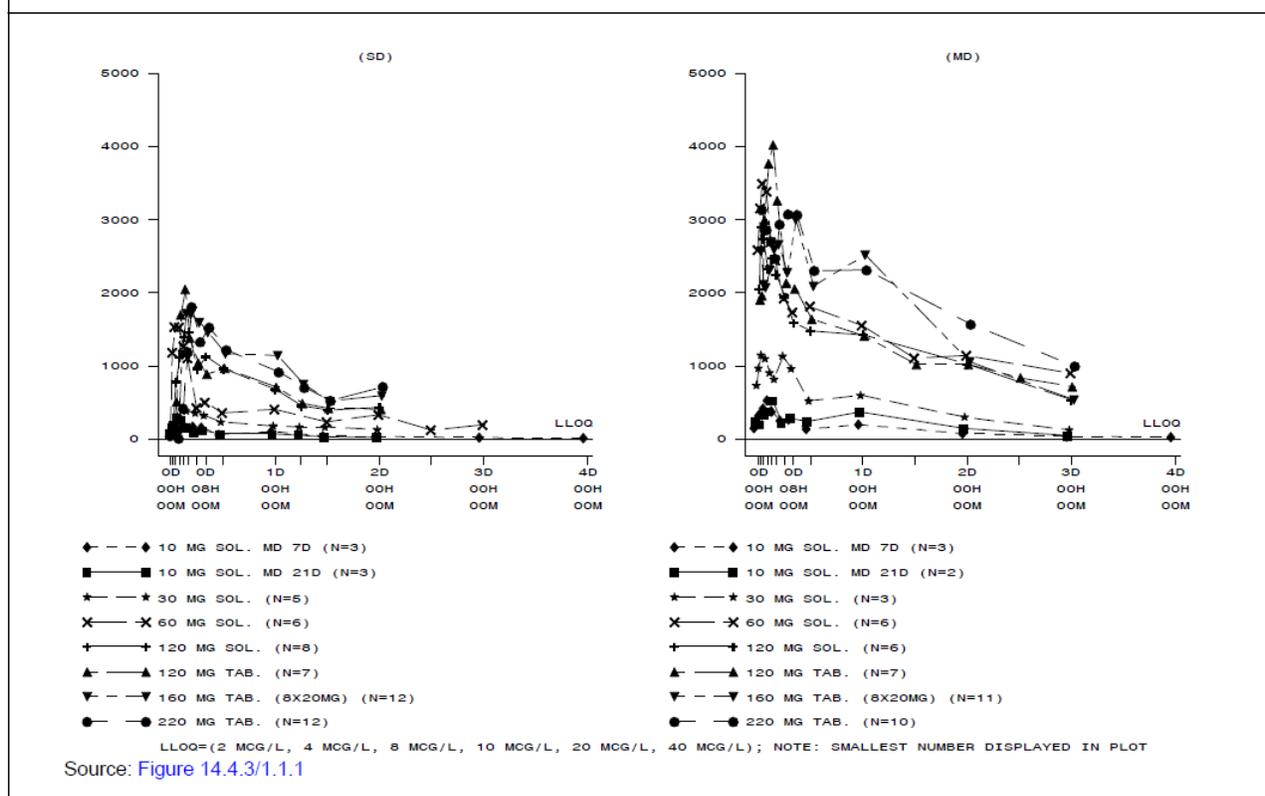
Table 4. The relative bioavailability of the initial tablet formulation relative to oral solution						
Analyte	Ratio	Parameter	n	CV	Estimated ratio (%)	90% confidence interval (%)
Regorafenib	Three 20 mg IR tablets / 60 mg solution	AUC(0-tn)	6	21.56	8.15	[6.52 ; 10.19]
		C <sub>max</sub>	6	34.22	4.75	[3.35 ; 6.73]
	Three 20 mg CP tablets / 60 mg solution	AUC(0-tn)	6	21.56	69.49	[55.60 ; 86.86]
		C <sub>max</sub>	6	34.22	58.97	[41.63 ; 83.54]
BAY 75-7495	Three 20 mg CP tablets / 60 mg solution	AUC(0-tn)	6	19.43	41.94	[33.53 ; 52.47]
		C <sub>max</sub>	6	33.40	39.68	[27.18 ; 57.93]
BAY 81-8752	Three 20 mg CP tablets / 60 mg solution	AUC(0-tn)	6	27.99	20.90	[15.18 ; 28.77]
		C <sub>max</sub>	6	35.84	18.02	[12.03 ; 27.01]

Analyte	Ratio	Parameter	n	CV	Estimated ratio (%)	90% confidence interval (%)
Regorafenib	100 mg CP tablets / 100 mg solution	AUC(0-tn)	7	11.15	83.20	[74.13 ; 93.38]
		C <sub>max</sub>	7	28.72	54.87	[40.96 ; 73.51]
BAY 75-7495	100 mg CP tablets / 100 mg solution	AUC(0-tn)	7	37.05	39.61	[27.29 ; 57.49]
		C <sub>max</sub>	7	54.06	32.02	[18.92 ; 54.17]
BAY 81-8752	100 mg CP tablets / 100 mg solution	AUC(0-tn)	7	68.87	16.69	[8.74 ; 31.88]
		C <sub>max</sub>	7	48.19	21.10	[13.12 ; 33.91]

The applicant claims that regorafenib is BCS Class 2, since it demonstrated high permeability in Caco-2 cells [Study PH-36645] and poor solubility independent of medium or pH. [See Section 2.5 General Biopharmaceutics]

Regorafenib likely undergoes enterohepatic cycling [Study 11650]. At least three peak plasma concentrations are observed around 4 hrs, 8 hrs and 24 hrs after the dose (Figure 2). Enterohepatic circulation likely contributes to the relatively long elimination half-life. Antibiotics could decrease the exposure of regorafenib, M2 and M5 by reducing the amount of drug that undergoes enterohepatic circulation. The applicant is asked to address this concern by conducting a clinical study to determine the effects of rifamixin on the PK of regorafenib.

Figure 2. The plasma concentration-time profiles of regorafenib following a single (left) and repeat dose (right) demonstrating multiple peak concentrations at ~ 3 hrs, 8 hrs and 24 hrs



#### 2.2.5.4 What are the characteristics of drug distribution?

Regorafenib is highly bound (> 99.5%) to human plasma proteins at the concentrations range of 0.5 µg/mL to 18 µg/mL; the main binding protein is albumin. Regorafenib was not displaced from protein binding sites by other highly protein bound drugs *in vitro*. M2 and M5 are similarly highly protein bound (99.8% and 99.95%, respectively) [Study Reports A44224, A47928, PH-34096 and PH-34277].

The partition coefficient between human erythrocytes and plasma ranges from 0.16 to 0.26 and the plasma to blood concentration ratio is 1.6 in human blood *in vitro* [Study Report PH-34096].

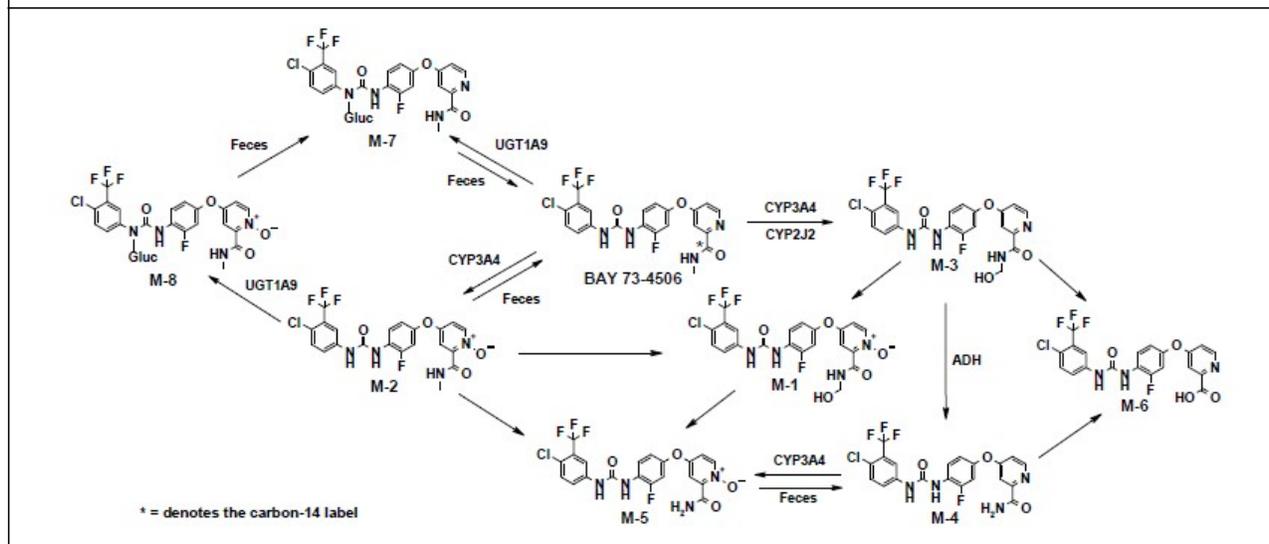
#### 2.2.5.5 Does the mass balance study suggest renal or hepatic as the major route of elimination?

Hepatic elimination appears to be the major route of elimination. Four healthy men received a single oral dose of 120 mg [<sup>14</sup>C] regorafenib as an oral solution in the fasted state in an open-label, non-randomized, uncontrolled study [Study 12436]. Blood, urine and feces samples were collected up to 288 hrs (12 days).

#### 2.2.5.6 What are the characteristics of drug metabolism?

Regorafenib undergoes metabolism to several metabolites by CYP3A4, UGT1A9 and other enzymes as illustrated in Figure 3. The enzyme responsible for the biotransformation of M2 to M5 is unknown.

Figure 3. The metabolism of regorafenib after a single radiolabeled dose in four healthy men



#### 2.2.5.7 What are the characteristics of drug excretion?

Biliary-fecal elimination accounted for 71.2% ± 3.8% of the radiolabeled dose and urinary elimination accounted for 19.3 ± 3.7% of the dose [Study 12436]. About 47% of a total radiolabeled dose is excreted in the feces as regorafenib representing either unabsorbed drug or absorbed drug that was secreted into bile and eliminated in the feces (without metabolism). Two glucuronides accounted for at least 17% of the radiolabeled dose excreted in the urine and four

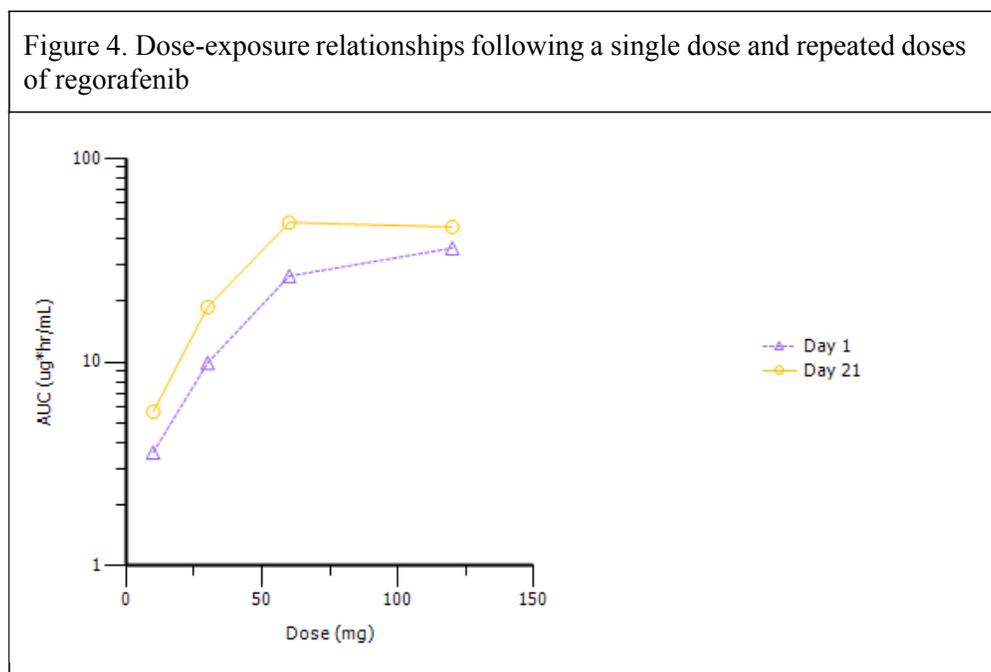
metabolites accounted for about 24% of the radiolabeled dose excreted in the feces [Report A59022].

Table 5. The percentage of a 120 mg radiolabeled oral dose of regorafenib identified in plasma and excreta			
Compound	Plasma 0-144 h	Urine 0-288 h	Feces 0-288 h
Regorafenib	57.4%	Not Found	47.1%
M1	Trace		
M2	28.7%	Not Found	
M3	Trace		1.8%
M4	Trace		2.2%
M5	6.3%		
M6			
M7	3.1%	4.7%	14.7%
M8	Trace	13.0%	5.0%
<b>Total</b>	<b>95.5%</b>	<b>17.7%</b>	<b>70.8%</b>

The amount of the individual metabolites found in excreta is likely to vary following repeated daily doses. Whereas M2 is the only major circulating metabolite after a single dose, both M2 and M5 are major metabolites at steady-state.

**2.2.5.8** *Based on PK parameters, what is the degree of linearity or non-linearity based in the dose-concentration relationship?*

The PK of regorafenib were generally linear up to a dose of 160 mg following a single dose and up to a dose of 60 mg following repeat doses [Study 11650]. At higher doses, the mean AUC at steady-state increased less than dose-proportionally and the mean  $C_{max}$  at steady-state remained relatively constant as shown in Figure 4.



### 2.2.5.9 *How do the PK parameters change with time following chronic dosing?*

No clinically important differences in the mean exposure of regorafenib, M2 and M5 measured following cycles one and two were observed in patients with mCRC enrolled into an expansion cohort (Cohort 9) of Study 11650 (Table 6).

Table 6. The accumulation of regorafenib, M2 (BAY 75-7495) and M5 (BAY 81-8752)

Analyte	Ratio	Parameter	n	CV	Estimated ratio (%)	90% confidence interval (%)
Regorafenib	160 mg (8 x 20 mg CP tablets) Cycle 2 / 160 mg Cycle 1	AUC(0-24) <sub>ss</sub>	14	34.22	91.61	[73.32 ; 114.47]
		C <sub>max,ss</sub>	14	32.41	94.11	[76.17 ; 116.29]
BAY 75-7495	160 mg (8 x 20 mg CP tablets) Cycle 2 / 160 mg Cycle 1	AUC(0-24) <sub>ss</sub>	14	45.94	102.84	[76.72 ; 137.83]
		C <sub>max,ss</sub>	14	37.19	105.21	[82.68 ; 133.86]
BAY 81-8752	160 mg (8 x 20 mg CP tablets) Cycle 2 / 160 mg Cycle 1	AUC(0-24) <sub>ss</sub>	14	63.48	124.66	[84.45 ; 184.03]
		C <sub>max,ss</sub>	14	51.56	132.33	[95.61 ; 183.14]

Source: Table 14.4.4/4

### 2.2.5.10 *What is the inter- and intra-subject variability of the PK parameters in volunteers and patients and what are the major causes of variability?*

The inter-patient variability was measured (defined as %CV) in patients administered regorafenib 160 mg (Table 7) in Study 11650. The variability appears similar following a single or repeat dose, but higher in patients with CRC compared to patients with solid tumors.

Table 7. The inter-patient variability (%CV) observed for regorafenib, M2 and M5 following a single dose and repeat doses (cycle 1, day 21)

Compound / Parameter	Single Dose – Cohort 7 Solid Tumors N=12		Repeat Dose – Cohort 7 Solid Tumors N=10		Repeat Dose – Cohort 9 Colorectal Cancer N=19	
	C <sub>max</sub>	AUC	C <sub>max,ss</sub>	AUC <sub>0-24 hr,ss</sub>	C <sub>max,ss</sub>	AUC <sub>0-24 hr,ss</sub>
Regorafenib	44%	35%	44%	43%	63%	86%
M2	64%	48%	69%	78%	72%	89%
M5	88%	96%	83%	89%	174%	182%

The intra-patient variability was measured in 14 patients with mCRC enrolled into Cohort 9 of Study 11650 using the PK samples collected on day 21 of cycles 1 and 2. The intra-patient variability appears low for regorafenib, but moderate for the active metabolites M2 and M5 (Table 8).

Table 8. The intra-patient variability (%CV) observed for regorafenib, M2 and M5

Compound / Parameter	C <sub>max,ss</sub>	AUC <sub>0-24hrs,ss</sub>
Regorafenib	32%	34%
M2	37%	46%
M5	52%	64%

A PopPK analysis has not been completed. Therefore, it is not known which covariates are likely contributing to the observed inter-patient and intra-patient variability.

## 2.3 INTRINSIC FACTORS

### 2.3.1 What intrinsic factors influence exposure and/or response and what is the impact of any differences in exposure on effectiveness or safety responses?

It is not known which intrinsic factors influence exposure and/or response, since the applicant has not completed E-R or PopPK analyses. The applicant proposes to submit these analyses post marketing. The applicant did complete a univariate analysis for age, gender, race and organ function using pooled data from five clinical studies [Study 11650, 14595 (hepatocellular carcinoma), 11726 (renal cell carcinoma), 13172 (Japanese) and 14996 (Chinese)]. A total of 79 patients who received regorafenib at a dose of 160 mg were included in these analyses. The findings from these univariate analyses should be viewed with caution, since other covariates which could influence the exposure of regorafenib, M2 and M5 were not considered. No recommendations regarding the need for dose modifications for these covariates can be made in the absence of the final PopPK analyses with a covariate model.

The applicant did not conduct a dedicated PK study in patients with hepatic or renal impairment. Post-hoc analyses were conducted for patients with mildly impaired renal function enrolled in Study 11650 and for patients with mildly and moderately impaired hepatic function enrolled into an expansion cohort of patients with HCC in Study 11651. The applicant is requested to complete a repeat-dose PK study in patients with severe renal impairment as a PMR.

### 2.3.2 Based upon what is known about exposure-response relationships and their variability and the groups, healthy volunteers vs. patients vs. specific populations, what dosage regimen adjustments, if any, are recommended for each of these groups?

#### 2.3.2.1 *Elderly*

Table 9 lists the mean (%CV) exposure of regorafenib, M2 and M5 in patients < 65 years and ≥ 65 years using the data from the pooled analysis. It appears the mean exposure of M2 and more profoundly of M5 is higher in older patients.

Table 9. Pooled mean (%CV) exposure of patients < 65 years and ≥ 65 years.

Units	Regorafenib		M-2		M-5	
	< 65 yr (n=44)	≥65 yr (n=16)	< 65 yr (n=25)	≥65 yr (n=13)	< 65 yr (n=25)	≥65 yr (n=13)
AUC(0-24) <sub>ss</sub> mg·h/L	46.2 (62.9)	43.0 (83.2)	22.2 (148)	29.2 (247)	14.5 (458)	30.6 (1043)
C <sub>max</sub> mg/L <sub>ss</sub>	3.54 (50.2)	3.03 (85.1)	1.66 (105)	1.96 (255)	1.12 (297)	1.92 (917)

Source: Module 5.3.5.3.3, Integrated analysis of PK parameters, Table 2.4/1 ff.

#### 2.3.2.2 *Pediatric patients*

The FDA Pediatric Review Committee (PeRC) granted a full waiver for regorafenib for studies required under PREA (Pediatric Research Equity Act), because the disease or condition does not exist in children.

### 2.3.2.3 Gender

Table 10 summarizes the mean (%CV) exposure of regorafenib, M2 and M5 in men and women using the data from the pooled analysis. The mean exposure of regorafenib appears similar in men and women, but the mean exposure of the metabolites appears to be higher in women, especially the mean exposure of M5.

Table 10. Pooled mean (%CV) exposure in men and women

	Units	Regorafenib		M-2		M-5	
		Male (n=40)	Female (n=20)	Male (n=28)	Female (n=10)	Male (n=28)	Female (n=10)
AUC(0-24) <sub>ss</sub>	mg-h/L	45.3 (72.3)	45.5 (60.3)	22.2 (176)	31.5 (181)	13.0 (424)	52.6 (996)
C <sub>max</sub>	mg/L	3.33 (67.4)	3.54 (44.7)	1.58 (152)	2.36 (128)	0.913 (327)	4.04 (459)
mg/L <sub>ss</sub>							

Source: Module 5.3.5.3, Integrated analysis of PK parameters, Table 2.4/13 ff.

### 2.3.2.4 Race, in particular differences in exposure and/or response in Caucasians, African-Americans and/or Asians.

The PK of regorafenib, M2 and M5 were measured in three Asian populations as part of two dedicated studies and a substudy.

- In Study 14596, PK samples were collected up to 96 hrs after repeat doses (day 21) in 8 Korean subjects with HCC and mild hepatic impairment (Child-Pugh A) after regorafenib was administered with a light breakfast. Since only trough concentrations were collected in 20 Whites on cycle 1, day 15, a within study comparison between Whites and Koreans could not be made.
- In Study 14996, PK samples were collected up to 96 hrs after a single dose (cycle 0) and repeated doses (cycle 1, day 21) of regorafenib with a low-fat breakfast in Chinese patients. Only an interim study report was provided that included PK data from two patients.
- In Study 13172, PK samples were collected up to 96 hrs after a single dose (cycle 0) and repeat doses (cycle 1, day 21) of regorafenib in the fasted state or after a low-fat breakfast in Japanese patients.

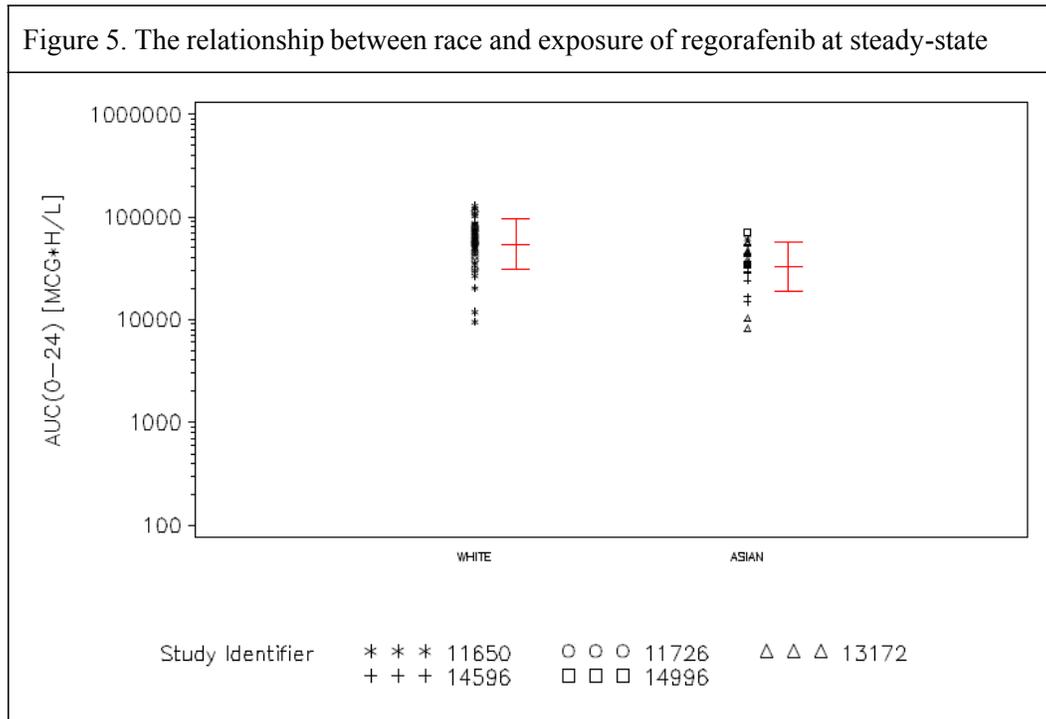
A cross study comparison suggests that the mean exposure of regorafenib, M2 and M5 appears lower in Asian populations compared to the White population enrolled into Study 11650 (Table 11).

Table 11. The mean (%CV) exposure of regorafenib, M2 and M5 in Asian populations after repeat doses

Study	14596 – Korean (N=8) Hepatocellular		13172 – Japanese (N=12) Solid Tumors		11650 – White (N=10) Colorectal Cancer	
	C <sub>max, ss</sub> (µg/mL)	AUC <sub>0-24 hr,ss</sub> (µg*h/mL)	C <sub>max, ss</sub> (µg/mL)	AUC <sub>0-24 hr,ss</sub> (µg*h/mL)	C <sub>max, ss</sub> (µg/mL)	AUC <sub>0-24 hr,ss</sub> (µg*h/mL)
Regorafenib	2.5 (41%)	27.0 (38%)	2.5 (77%)	33.0 (68%)	3.4 (63%)	50.3 (86%)
M2	0.9 (76%)	8.6 (106%)	1.0 (214%)	15.6 (213%)	3.2 (72%)	48.1 (88%)
M5	0.3 (150%)	3.1 (193%)	0.5 (414%)	7.1 (459%)	4.0 (174%)	64.6 (182%)

## Pooled Analysis

Figure 5 summarizes the exposure of regorafenib, M2 and M5 in Asians and Whites using the data from the pooled analysis. As suggested by the cross study comparison, the mean exposure of regorafenib appears lower in Asians compared to Whites, but the individual exposures appear largely overlapping due to high inter-subject variability.



### 2.3.2.5 Renal impairment

A dose modification is not needed in patients with mild renal impairment, since no clinically important difference in exposure was observed between patients with mild (CrCL 60 to 89 ml/min) renal impairment and patients with normal renal function. However, a pooled univariate analysis suggests that mean exposure increases with worsening renal function. The applicant is requested to conduct a multiple dose PK study in patients with severe renal impairment as a PMR. A multiple dose study is being requested, because the M2 and M5 metabolites demonstrate activity in nonclinical and *in vitro* studies and demonstrate similar plasma concentrations at steady-state but not after a single dose in clinical trials.

#### Study 11650

The applicant conducted a post-hoc analysis in 18 patients with normal renal function, 10 patients with mild renal impairment and one patient with moderate renal impairment who were enrolled into Study 11650. PK samples were collected up to 72 hrs following the dose administered on cycle 1, day 21 with a light breakfast. Renal function was estimated using the Cockcroft Gault (CG) and the Modified Diet in Renal Disease (MDRD) equations and categorized as recommended in the draft FDA Guidance for Industry for renal impairment.

Table 12. The point estimate and 90% CI for regorafenib, M2 and M5 measured in patients with mild renal impairment relative to normal renal function

Analyte	Ratio	Parameter	N	CV	Estimated ratio (%)	90% confidence interval (%)
Regorafenib (BAY 73-4506)	CG: mild / normal	AUC(0-24) <sub>ss</sub>	10/18	66.96	65.98	[43.81 ; 99.35]
		C <sub>max,ss</sub>	10/18	51.74	67.37	[48.55 ; 93.48]
	MDRD: mild / normal	AUC(0-24) <sub>ss</sub>	10/18	71.28	90.77	[58.98 ; 139.70]
		C <sub>max,ss</sub>	10/18	55.48	84.09	[59.35 ; 119.15]
BAY 75-7495	CG: mild / normal	AUC(0-24) <sub>ss</sub>	10/18	78.43	61.42	[38.55 ; 97.85]
		C <sub>max,ss</sub>	10/18	70.43	63.05	[41.14 ; 96.63]
	MDRD: mild / normal	AUC(0-24) <sub>ss</sub>	10/18	84.37	104.90	[64.06 ; 171.78]
		C <sub>max,ss</sub>	10/18	75.94	102.22	[64.93 ; 160.95]
BAY 81-8752	CG: mild / normal	AUC(0-24) <sub>ss</sub>	10/18	143.92	71.56	[35.09 ; 145.92]
		C <sub>max,ss</sub>	10/18	141.87	78.01	[38.49 ; 158.11]
	MDRD: mild / normal	AUC(0-24) <sub>ss</sub>	10/18	145.10	129.68	[63.37 ; 265.39]
		C <sub>max,ss</sub>	10/18	141.87	128.20	[63.26 ; 259.84]

Source: Table 14.4.5 / 3

Using the MDRD formula to estimate eGFR, no differences in the steady-state exposure of regorafenib and M2 were observed between patients with mild renal impairment and patients with normal renal function. The steady-state exposure of the M5 metabolite appears elevated in patients with mild renal impairment. The wide 90% CI reflects the large inter-patient variability commonly observed in regard to exposure of regorafenib, M2 and M5 after administration of a dose of 160 mg.

The exposure of regorafenib, M2 and M5 appears lower in patients with mild renal impairment compared to patients with normal renal function as estimated by the CG equation. If renal impairment limits the elimination of regorafenib, M2 or M5, the exposure would increase. The differences are not likely clinically important.

### Pooled Analysis

The pooled analysis suggests that the exposure of regorafenib, M2 and M5 appear to be increased with worsening renal function as estimated by the MDRD formula. However, the mean AUC<sub>0-24h,ss</sub> of regorafenib, M2 and M5 in patients with normal renal function in this analysis appears lower than that observed in the dose escalation Study 11650. The mean steady-state exposure of M2 and M5 also appears lower in patients with mild renal impairment compared to observed data in Study 11650. The lower exposure of regorafenib, M2 and M5 seen in this analysis relative to the dose escalation study could reflect racial differences, as the mean exposure appears lower in Asians compared to Whites and about 42% of patients included in this pooled analysis were Asian. The observed substantial overlap in exposure between each category and the wide 90% CI suggest large inter-patient variability that exceeds the variability observed in a single study.

Table 13. The mean (% CV) exposure as measured by AUC <sub>0-24h,ss</sub> of regorafenib, M2 and M5 in patients with solid tumors across five clinical studies following administration of 160 mg once daily for 21 days			
Compound / Category AUC <sub>0-24h,ss</sub> (µg*h/mL)	Normal Renal Function N=26-32	Mild Renal Impairment N=10-20	Moderate Renal Impairment N=2-8
Regorafenib	38.2 (76%)	51.7 (55%)	64.8 (36%)
M2	21.9 (239%)	28.1 (62%)	48.1 (17%)
M5	17.4 (102%)	20.6 (242%)	30.2 (107%)

### Renal Cell Carcinoma

Fourteen patients with renal cell carcinoma (RCC) provided PK samples up to 24 hrs after administration of a dose of 160 mg daily for 15 days in Study 11726. A cross study comparison suggests that the mean exposure of regorafenib and the metabolite M2 in this population is similar to that observed in patients with other solid tumors enrolled in Study 11650. However, it appears that the metabolite M5 was not reached steady-state yet.

Table 14. The median (range) for regorafenib, M2 and M5 measured in patients with renal cell carcinoma (n=14)			
Analyte	AUC(0-24) <sub>ss</sub> [mg·h/L]	C <sub>max,ss</sub> [mg/L]	t <sub>max,ss</sub> <sup>1</sup> [h]
Regorafenib	58.3 (34)	4.49 (33)	3 (0.5–12)
M-2	41.3 (47)	2.83 (53)	3 (0.5–8)
M-5	24.7 (109) <sup>2</sup>	1.57 (122)	3 (0.5–24)

### **2.3.2.6** *Hepatic impairment*

No dose modification is recommended for patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment. No dedicated PK studies in patients with hepatic impairment appear necessary, since mild and moderate hepatic impairment do not appear to affect the PK of regorafenib, M2 and M5 in patients with HCC.

#### Study 11651

The applicant included an expansion cohort in the dose escalation trial Study 11651 in patients with HCC. The PK samples were collected up to 48 hrs after a single 100 mg dose of regorafenib in the fasted state (the dose was held on day 2) and the point estimate and two-sided 90% CI for the AUC<sub>0-t<sub>n</sub></sub> were calculated. No clinically important differences in the mean exposure of regorafenib, M2 and M5 were observed in the 14 patients with mild hepatic impairment (Child-Pugh A) and the 4 patients with moderate hepatic impairment (Child-Pugh B) as compared to the 10 patients with normal hepatic function. The PK of regorafenib were not studied in patients with severe hepatic impairment (Child-Pugh C).

Table 15. The point estimate and 90% CI for regorafenib, M2 and M5 in patients with mild (n=14) and moderate (n=4) hepatic impairment as compared to patients with normal (n=10) hepatic function

Analyte	Parameter	Child-Pugh A/Cohort 3	Child-Pugh B/Cohort 3
Regorafenib	AUC <sub>0-tn</sub>	0.82 (0.54-1.24)	1.01 (0.56-1.82)
Regorafenib	C <sub>max</sub>	1.11 (0.69-1.77)	1.14 (0.59-2.23)
M-2	AUC <sub>0-tn</sub>	0.78 (0.43-1.43)	1.18 (0.50-2.81)
M-2	C <sub>max</sub>	1.04 (0.55-1.99)	1.36 (0.54-3.41)
M-5	AUC <sub>0-tn</sub>	1.04 (0.47-2.30)	0.84 (0.28-2.55)
M-5	C <sub>max</sub>	1.19 (0.57-2.49)	1.18 (0.42-3.32)

### Study 14596

Twenty White patients with HCC and mild hepatic impairment were enrolled in a phase 2 study. Trough concentrations (C<sub>trough</sub>) were measured on two occasions. Table 16 compares the mean (%CV) C<sub>trough</sub> estimated from this study and Study 11650. It appears that the mean C<sub>trough</sub> of regorafenib is similar, but the mean C<sub>trough</sub> of M2 appears higher. The M5 plasma concentrations did not reach steady-state by day 15. The mean C<sub>trough</sub> of M5 would be expected to be higher at steady-state and therefore, the higher mean C<sub>trough</sub> observed in the control patients at day 21 as compared to mean C<sub>trough</sub> in patients with mild hepatic impairment at day 15 might be due to the difference in sampling times.

Table 16. The mean trough concentrations (%CV) measured in patients with hepatocellular carcinoma and mild hepatic impairment and in patients with advanced solid tumors and normal hepatic function

	Units	Child-Pugh A (Study 14596) Cycle 1, Day 15 N = 20	Control Patients (Study 11650) Cycle 1, Day 21
Regorafenib	mg/L	1.77(95)	1.40(57)
M-2	mg/L	1.11(156)	1.31(76)
M-5	mg/L	0.859(145)	1.99(51)

Source: Module 5.3.5.2.1, A51601, Table 9-6; Module 5.3.3.2.1, PH-36733

### 2.3.2.7 What pregnancy and lactation use information is there in the application?

There are no data on the use of regorafenib in pregnant women. Animal studies have shown reproductive toxicity. The proposed labeling lists regorafenib under pregnancy category D.

It is unknown whether regorafenib or the active metabolites are excreted in human milk. In rats, regorafenib, M2 and M5 are excreted in milk. The proposed labeling states that a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

## 2.4 EXTRINSIC FACTORS

### 2.4.1 What extrinsic factors influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?

The applicant did not conduct PopPK or E-R analyses. Three drug interaction studies were completed and a fourth study is ongoing. The *in vitro study* data and the results of the ongoing study will determine the need for additional studies to assess the potential for regorafenib to affect the PK of sensitive substrates of CYP2D6 and P-gp.

### 2.4.2 Drug-drug interactions

#### 2.4.2.1 *Is there an in vitro basis to suspect in vivo drug-drug interactions?*

Yes. See below.

#### 2.4.2.2 *Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?*

Yes. Regorafenib underwent metabolism by CYP3A4 (to M2) and UGT1A9 (to M7) [Study Report A59099, A580506]. M2 underwent metabolism by UGT1A9 to M8. The enzyme responsible for the biotransformation of M2 to M5 is not known. Metabolites M2 and M5 were found in the plasma and metabolites M7 and M8 were found in the urine of patients enrolled in Study 11650 after administration of repeated daily doses. [See Figure 3]

#### Study 12435 – a Strong CYP3A4 Inhibitor

The applicant evaluated the effect of a strong CYP3A4 inhibitor, ketoconazole, on the PK of regorafenib, M2 and M5. During period 1, healthy men received a single dose of 80 mg (N= 6) or 160 mg of regorafenib (N=18) with a low-fat meal (<30% fat). During period 2, they received the same single dose of regorafenib as in period 1 on day 1 and ketoconazole at a dose of 400 mg daily starting day -4 and continuing for 7 days (80 mg dose cohort) or 18 days (160 mg dose cohort). PK samples were collected up to 336 hrs. The mean exposure of regorafenib increased by 33%, but the mean exposure of the M2 and M5 metabolites decreased each by 93%. The overall mean exposure of regorafenib, M2 and M5 appears to be decreased by approximately 50%. Given this magnitude of change in mean exposure, the coadministration of strong CYP3A4 inhibitors with regorafenib should be avoided.

Table 17. The point estimate and 90% CI for regorafenib, M2 and M5 measured in patients administered a single dose of regorafenib with and without a strong CYP3A4 inhibitor

Analyte	Comparison	Parameter	N	Point estimate [%] (Ratio)	2-sided 90% confidence interval [%]
Regorafenib	80 mg regorafenib + ketoconazole 400 mg/d / 80 mg regorafenib alone	AUC	6	127	[103 ; 156]
		C <sub>max</sub>	6	132	[105 ; 166]
	160 mg regorafenib + ketoconazole 400 mg/d / 160 mg regorafenib alone	AUC	18	133	[121 ; 146]
		C <sub>max</sub>	18	140	[125 ; 158]
M-2	80 mg regorafenib + ketoconazole 400 mg/d / 80 mg regorafenib alone	AUC	6	6.79	[5.33 ; 8.66]
		C <sub>max</sub>	6	3.27	[2.41 ; 4.44]
	160 mg regorafenib + ketoconazole 400 mg/d / 160 mg regorafenib alone	AUC	18	5.61	[4.88 ; 6.46]
		C <sub>max</sub>	18	2.73	[2.28 ; 3.27]
M-5	80 mg regorafenib + ketoconazole 400 mg/d / 80 mg regorafenib alone	AUC	4	15.0	[6.02 ; 37.5]
		C <sub>max</sub>	5	9.24	[4.27 ; 20.0]
	160 mg regorafenib + ketoconazole 400 mg/d / 160 mg regorafenib alone	AUC	17	6.84	[5.05 ; 9.26]
		C <sub>max</sub>	18	6.39	[5.28 ; 7.72]

Source: Module 5.3.3.4.1, PH-36717, Table 9-4 f.

#### Study 15524 – a Strong CYP3A4 Inducer

Twenty-four healthy men received a single 160 mg dose of regorafenib in a fasted state. Following a washout of three weeks, they received rifampin at a dose of 600 mg daily starting on day -6 for 9 days and a single 160 mg dose of regorafenib on day 1. The mean exposure of regorafenib was decreased by 50% and the mean exposure of the M5 metabolite was increased by 264%. The mean AUC of the M2 metabolite appeared to be unchanged, but the mean C<sub>max</sub> was substantially increased. Overall, it appears that the mean exposure of regorafenib, M2 and M5 increased by 68%. Given this magnitude of change in the mean exposure, the coadministration of strong CYP3A4 inducers with regorafenib should be avoided.

Table 18. The point estimate and two-sided 90% CI for regorafenib, M2 and M5 measured in patients administered regorafenib with and without a strong CYP3A4 inhibitor

Analyte	Comparison	Parameter	N	Point estimate [%] (Ratio)	2-sided 90% confidence interval [%]
Regorafenib	160 mg regorafenib + rifampin 600 mg/d / 160 mg regorafenib alone	AUC	22	50.4	[45.2 ; 56.2]
		C <sub>max</sub>	22	80.3	[67.6 ; 95.5]
M-2	160 mg regorafenib + rifampin 600 mg/d / 160 mg regorafenib alone	AUC	22	90.9	[78.2 ; 106]
		C <sub>max</sub>	22	158	[132 ; 188]
M-5	160 mg regorafenib + rifampin 600 mg/d / 160 mg regorafenib alone	AUC	22	364	[290 ; 456]
		C <sub>max</sub>	22	418	[328 ; 533]

Source: Module 5.3.3.4.2, PH-36716, Table 9-2

Without E-R analyses, it is difficult to predict the effect of these interactions on the tolerability or effectiveness of regorafenib, especially since regorafenib, M2 and M5 likely contribute to the effectiveness and toxicities. Furthermore, the magnitude of effects will likely be different at steady-state. The potential to recommend a dose modification in which the mean exposure with a strong CYP3A4 inhibitor or inducer is matched to the mean exposure without a strong CYP3A4 inducer or inhibitor will be revisited once the E-R and PopPK analyses are completed.

#### Genetic Variation

It is not known if genetic variants impact exposure and/or response of regorafenib. Regorafenib undergoes metabolism by polymorphic enzymes and interacts with multiple kinases with known variants. The applicant has not completed E-R or PopPK analyses. The applicant isolated DNA from plasma collected from patients enrolled in Study 11650 to determine KRAS mutational status and collected archival tumor tissue and fresh plasma from patients enrolled in Study 14387 to evaluate mutations in KRAS, BRAF and PIK3CA. The applicant does not appear to be assessing the relationship between genetic variants of drug metabolizing enzymes and exposure or response. The applicant is asked to consider submitting a summary report and data files of the exploratory biomarker analyses completed during the clinical development of regorafenib, including genetic and nongenetic markers in various matrices (e.g., blood, plasma and tumor) post marketing.

#### **2.4.2.3** *Is the drug an inhibitor and/or an inducer of CYP enzymes?*

##### Induction

Regorafenib did not induce the enzyme activity of CYP1A2, CYP2B6, CYP2C19 and CYP3A4 *in vitro* [Study Report PH-34703]. Human hepatocytes were treated with regorafenib at concentrations of 5 ng/mL to 10,000 ng/mL starting 48 hr post-plating and continuing for 5 days until the determination of enzyme activity on day 8. However, these results might not accurately reflect the inductive potential of regorafenib, since regorafenib, M2 and M5 can inhibit these enzymes. No studies were conducted to determine the ability of the active metabolites M2 and M5 to induce these enzymes. The applicant should assess the ability of regorafenib, M2 and M5 to induce mRNA expression levels of CYP1A2, CYP2B6 and CYP3A4 in accordance with the 2012 draft FDA Guidance for Industry regarding drug interaction studies. The need for a clinical study to assess the effect of regorafenib on the PK of sensitive substrates of these enzymes will be determined based on the results of the *in vitro* study.

##### Inhibition

Regorafenib, M2 or M5 inhibited CYP2B6, CYP2C9, CYP2C8, CYP2C19, CYP2D6 or CYP3A4 *in vitro* [Study Report PH-34364, A57533]. Table 19 lists the R values calculated assuming a maximal steady-concentration of 8.1  $\mu\text{M}$  (3.9  $\mu\text{g/mL}$ ), 6.6  $\mu\text{M}$  (3.3  $\mu\text{g/mL}$ ), and 6.0  $\mu\text{M}$  (2.9  $\mu\text{g/mL}$ ) for regorafenib, M2 and M5, respectively. These R values suggest that a study to assess the effects of regorafenib on the PK of sensitive substrates of CYP2B6, CYP2C19, CYP2C8, CYP2C9, CYP2D6, and CYP3A4 is likely warranted. A study to assess the effects of regorafenib on the PK of a probe substrate of CYP2C8, CYP2C9, CYP2C19 and CYP3A4 is ongoing. The final study report will be submitted by November, 2012. The applicant will also be asked to assess the effect of regorafenib on the PK of a probe substrate of CYP2D6 post marketing if regorafenib affects the PK of a CYP2C8, CYP2C9, CYP2C19, or CYP3A4 probe substrate based on the ongoing clinical study.

Table 19. The  $K_i$  value determined by the applicant and the calculated R value based on observed steady-state concentrations of regorafenib, M2 and M5

Compound	Regorafenib		M2		M5	
	$K_i$	R	$K_i$	R	$K_i$	R
CYP1A2	n.d.		n.d.		n.d.	
CYP2B6	5.2	2.6	n.d.		n.d.	
CYP2C8	0.6	14.5	1.0	7.6	1.3	5.6
CYP2C9	4.7	2.7	0.8	9.2	n.d.	
CYP2C19	16.4	1.5	n.d.		n.d.	
CYP2D6	n.d.		7.8	1.8	n.d.	
CYP3A4	11.1	1.7	4.0	2.6	n.d.	

$R = 1 + ([I]/K_i)$ ; n d = not determined

#### 2.4.2.4 *Is the drug a substrate and/or inhibitor of P-glycoprotein transport processes?*

Regorafenib is not a substrate of human P-gp *in vitro* [Study Report A58796].

Regorafenib inhibited P-gp *in vitro*. The R values calculated to assess the potential for regorafenib to inhibit P-gp transport in the blood and the gut suggest that a drug interaction study is warranted with a sensitive P-gp substrate (Table 20) [Study Report PH-36201]. The applicant should consider assessing the potential for regorafenib to inhibit the transport of oral sensitive P-gp substrates post marketing.

Table 20. The  $IC_{50}$  values determined by the applicant and the calculated R values based on observed steady-state concentrations of regorafenib and predicted gastrointestinal concentrations

	$IC_{50}$ $\mu$ M	[I] $\mu$ M	R
Blood	Dipyridamole: 2 - 3 Digoxin: 0.8 - 3.4	8.1	3.3 to 4.5 3.1 to 9.8
Gut	Dipyridamole: 2 - 3 Digoxin: 0.8 - 3.4	1330	443 to 665 392 to 1660

#### 2.4.2.5 *Are there other metabolic/transporter pathways that may be important?*

##### Transporters

Regorafenib is not a substrate for human BCRP, OATP1B1, and OATP1B3 *in vitro* [Study Report PH-36646, A58678].

Regorafenib also strongly inhibited transport by BCRP with mean  $IC_{50}$  values of 44.7 nM (topotecan) and 67.7 nM (PhIP). The fold differences in the  $IC_{50}$  values to the steady-state concentrations in the blood and gut suggest that regorafenib can competitively inhibit BCRP in humans [Study Report PH-36293]. Regorafenib did not inhibit OATP1B1, OATP1B3, OAT1, OAT3 and OCT2 *in vitro* [Study Report R-6684, PH-36646].

##### Uridine Diphosphate Glucuronosyltransferase (UGT) *In Vitro*

Regorafenib, M2 and M5 inhibited UGT1A1 and UGT1A9 *in vitro*. It does not appear that these compounds inhibit other UGT enzymes, including UGT1A4, UGT1A6, and UGT2B7. The fold difference in the  $K_i$  values and the steady-state concentrations suggest that regorafenib, M2 and M5 has the potential to inhibit UGT1A1 and regorafenib has the potential to inhibit UGT1A9 in

humans [Study Report PH-35818, PH-34036].

Table 21. The $K_i$ values determined by the applicant relative to the observed steady-state concentrations of regorafenib						
Compound	Regorafenib		M2		M5	
	$K_i$ ( $\mu\text{M}$ )	Fold Difference	$K_i$ ( $\mu\text{M}$ )	Fold Difference	$K_i$ ( $\mu\text{M}$ )	Fold Difference
UGT1A1	3.0	2.7	0.6	11.0	1.1	4.6
UGT1A9	2.1	3.9	4.3	1.5	7.9 <sup>a</sup>	0.6

<sup>a</sup>The  $K_i$  value was estimated by dividing the  $\text{IC}_{50}$  value by two.

#### Dihydropyrimidine Dehydrogenase (DPD) *In Vitro*

Regorafenib, M2 and M5 do not appear to inhibit human DPD in human hepatic cytosol following the application of radiolabeled fluorouracil. The  $\text{IC}_{50}$  values are  $> 20 \mu\text{M}$  [Study Report A50624].

#### Study 11656 – Interaction with Fluorouracil, Irinotecan and Oxaliplatin

The applicant conducted a dedicated study to assess the potential for PK interactions between regorafenib and two commonly administered chemotherapy regimens in patients with mCRC. Twenty-five patients received FOLFIRI and 20 patients received mFOLOX6 on days 1 and 15 in combination with regorafenib at a dose of 160 mg on days 4-10 and days 18-24. PK samples for irinotecan, SN-38, total platinum, bound platinum, and fluorouracil were collected on days 1 – 3 during cycle 1 (without regorafenib) and cycle 2 (five days after last dose of regorafenib). Trough concentrations for regorafenib, M2 and M5 were measured on day 15 of cycle 1, days 1-3 of cycle 2 and on days 1 and 15 of cycles 2 - 6.

The mean AUC of irinotecan and SN-38 increased by 28% and 44%, respectively, when irinotecan was administered five days after the last of seven daily doses of regorafenib (Table 22). Since irinotecan is metabolized by carboxylesterases to SN-38 and then SN-38 is metabolized by UGT1A1, it appears that regorafenib inhibits UGT1A1 in humans. CYP3A4 also contributes to the metabolism of irinotecan to inactive metabolites and BCRP likely contributes to the transport of irinotecan. Neutropenia and diarrhea associated with irinotecan might be dose- or concentration-dependent. The clinical significance of this interaction is not known.

No clinically important differences in the mean AUC of fluorouracil were observed when fluorouracil was administered five days after the last of seven daily doses of regorafenib.

The mean AUC of total platinum was increased by 39% when oxaliplatin was administered five days after the last of seven daily doses of regorafenib. The potential mechanism and clinical significance are not known.

Table 22. The point estimate and two-sided 90% CI for irinotecan and SN-38 measured in patients
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administered FOLFIRI with and without regorafenib					
Analyte	Comparison	Parameter	N	Point estimate [%] (Ratio)	2-sided 90% CI [%]
Irinotecan	FOLFIRI after regorafenib / FOLFIRI alone	AUC	11	128	[107 ; 154]
		C <sub>max</sub>	11	122	[80 ; 185]
SN-38	FOLFIRI after regorafenib / FOLFIRI alone	AUC	9	144	[112 ; 184]
		C <sub>max</sub>	11	91	[55 ; 150]
Source: Module 5.3.3.2.6, PH-36735, Table 9-11					
Analyte	Comparison	Parameter	N	Point estimate [%] (Ratio)	2-sided 90% confidence interval [%]
Total platinum	mFOLFOX6 after regorafenib / mFOLFOX6 alone	AUC	12	139	[123 ; 158]
		C <sub>max</sub>	12	109	[98 ; 122]
Unbound platinum	mFOLFOX6 after regorafenib / mFOLFOX6 alone	AUC	10	117	[96 ; 143]
		C <sub>max</sub>	10	119	[96 ; 147]
Source: Module 5.3.3.2.6, PH-36735, Table 9-12					
Analyte	Comparison	Parameter	N	Point estimate [%] (Ratio)	2-sided 90% CI [%]
5-FU	mFOLFOX6 with regorafenib / mFOLFOX6 alone	AUC	8	106	[69 ; 164]
		C <sub>max</sub>	11	89	[50 ; 161]
	FOLFIRI with regorafenib / FOLFIRI alone	AUC	-	-	-
		C <sub>max</sub>	4	92	[6 ; 139]
Source: Module 5.3.3.2.6, PH-36735, Table 9-13					

**2.4.2.6** *Does the label specify co-administration of another drug and, if so, has the interaction potential between these drugs been evaluated?*

No. Regorafenib is recommended as monotherapy.

**2.4.2.7** *What other co-medications are likely to be administered to the target population?*

The target population is likely to be taking medications to manage comorbid diseases commonly identified in an older patient population (e.g. hypertension, hypercholesteremia, etc.) and adverse events associated with past and current treatment for colorectal cancer.

**2.4.2.8** *Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?*

No data is available.

**2.4.2.9** *Is there a known mechanistic basis for pharmacodynamic drug-drug interactions, if any?*

No data is available.

**2.4.2.10** *Are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions or protein binding?*

Yes. Please refer to the recommendations for a PMR and additional comments for drug interaction studies.

**2.4.3 What issues related to dose, dosing regimens or administration are unresolved and represent significant omissions?**

The applicant completed the clinical safety and efficacy trial earlier than anticipated and requested a meeting with the FDA prior to submitting the NDA to discuss the possibility of submitting the NDA without completing the clinical pharmacology studies. During the teleconference on April 3, 2012, FDA stated that the applicant’s application should be complete upon submission. If the applicant believes that an adequate risk-assessment can be made without a complete assessment of regorafenib’s clinical pharmacology generally expected at the time of the NDA submission, then the applicant should submit the justification as to why these trials are not required for review of the NDA and include proposed PMRs for the ongoing clinical pharmacology studies with milestone timelines. If the applicant believes that there are safety signals or evidence of important but incompletely characterized clinical pharmacologic effects that will preclude an adequate risk-benefit assessment, then the applicant should delay the NDA submission until the results of these clinical pharmacology trials are available.

**2.5 GENERAL BIOPHARMACEUTICS**

**2.5.1 Based on Biopharmaceutics classification system (BCS) principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?**

The applicant classifies regorafenib as BCS class 2 based on data that showed regorafenib has low solubility and high permeability across Caco-2 cells with a relative bioavailability of 69% to 83%. [Study Report PH-36645]

Direction	Papp value (nm/s)	Dose Recovered (%)	Efflux Ratio
A to B	124 ± 26.2	73.8 ± 21.2	0.835 ± 0.344
B to A	104 ± 29.0	21.0 ± 1.50	

**2.5.2 What is the relative bioavailability of the proposed ‘to-be-marketed’ formulation to the pivotal clinical trial?**

The ‘to-be-marketed’ formulation contains an (b) (4) coating (40 mg tablets), whereas clinical trial formulation contains an (b) (4) film coating (20 mg and 100 mg tablets). A dedicated BE trial was conducted in 48 healthy men to compare the PK of regorafenib administered at a dose of 160 mg as the clinical trial formulation (1 x 100 mg + 3 x 20 mg tablets) to the ‘to-be-marketed’ formulation (4 x 40 mg tablets) [Study 12437]. Each volunteer was randomized to receive regorafenib on two separate occasions with a washout period of seven days. PK samples were collected up to 168 hrs (7 days). The mean AUC (based on the point estimate and 90% CI) of regorafenib suggests that there were no clinically important differences between these two tablet formulations.

Table 24. The bioequivalence assessment between the ‘to-be-marketed’ tablet and the clinical trial tablet

Analyte	Parameter	Comparison	N	CV [%]	Point estimate [%] (Ratio)	2-sided 90% confidence interval [%]
Parent	AUC	Test/Reference	46	20.2	99.7	[93.0 ; 107]
	C <sub>max</sub>	Test/Reference	46	28.3	111	[101 ; 122]
M-2	AUC	Test/Reference	46	30.3	116	[105 ; 129]
	C <sub>max</sub>	Test/Reference	46	35.2	124	[110 ; 140]
M-5	AUC	Test/Reference	45	36.4	124	[110 ; 141]
	C <sub>max</sub>	Test/Reference	46	33.3	117	[104 ; 131]

Source: Module 5.3.1.2.1, PH-36595, Table 9-2  
 Test: 160 mg regorafenib as 40 mg solid solution tablets (#142)  
 Reference: 160 mg regorafenib as 100 mg (#101) + 20 mg solid solution tablets (#021)

**2.5.2.1** *What data support or do not support a waiver of in vivo BE data?*

Not applicable.

**2.5.2.2** *What are the safety or efficacy issues, if any, for BE studies that fail to meet the 90% CI using equivalence limits of 80-125%?*

Not applicable.

**2.5.2.3** *If the formulations do not meet the standard criteria for bioequivalence, what clinical pharmacology and/or clinical safety and efficacy data support the approval of the ‘to-be-marketed’ product?*

Not applicable.

**2.5.3** **What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?**

Regorafenib is recommended to be administered with a low-fat meal, since regorafenib was administered with a low-fat meal (< 30% fat) in the clinical safety and efficacy trial. The clinical safety and efficacy trial included the following examples of a low-fat breakfast:

- 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 (i.e., Special K), 8 ounces of skimmed 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).

Twenty-four healthy men were enrolled into a randomized, open label, three-way crossover study to determine the PK after the administration of a single 160 mg dose of regorafenib on three separate occasions: high-fat breakfast, low-fat breakfast and fasting state. Each period was separated by a 14-day washout period. PK samples were collected up to 336 hrs [Study 14656].

A high-fat breakfast was defined 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 AUC of M2 and M5 was decreased by

20% and 51%, respectively, resulting in an overall exposure approximately 8% lower as compared to the fasted state.

A low-fat breakfast, defined as the first example above, 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.

The inter-patient variability appears moderate to high in healthy volunteers regardless of fasted or fed state and similar to patients with solid tumors enrolled into Study 11650.

Table 25. The mean pharmacokinetic parameters (%CV) of regorafenib, M2 and M5 after a high-fat and low-fat meal compared to fasted state in healthy volunteers

Parameter	Unit	Fasted (n=24)	Low Fat (n=24)	High Fat (n=24)
<b>BAY 73-4506</b>				
AUC	mg*h/L	45.39 (36.9)	61.75 (31.4)	67.27 (35.6)
C <sub>max</sub>	mg/L	1.25 (36.9)	1.93 (28.0)	2.16 (31.8)
t <sub>max</sub> <sup>a</sup>	h	4.0(2.0-24.0)	4.0(2.0-16.0)	6.0(3.0-6.0)
t <sub>1/2</sub>	h	37.94 (28.7)	34.95 (20.9)	35.0 (21.7)
<b>BAY 75-7495 (M-2)</b>				
AUC	mg*h/L	27.43 (52.8)	38.28 (37.2)	21.94 (70.2)
C <sub>max</sub>	mg/L	0.89 (45.7)	1.17 (34.6)	0.65(66.3)
t <sub>max</sub> <sup>a</sup>	h	4.0(2.0-24.0)	6.0(3.0-16.0)	6.0(3.0-12.0)
t <sub>1/2</sub>	h	28.05 (21.6)	26.22 (21.5)	27.51 (23.0)
<b>BAY 81-8752 (M-5)</b>				
AUC	mg*h/L	12.77 (68.6)	15.67 (41.5)	6.22 (71.6)
C <sub>max</sub>	mg/L	0.12 (64.0)	0.14 (41.0)	.05 (78.2)
t <sub>max</sub> <sup>a</sup>	h	24.0(4.0-48.0)	48.0(12.0-96.0)	48.0(12.0-96.0)
t <sub>1/2</sub>	h	64.08 (28.0)	56.75 (17.3)	65.46 (36.6)

a Median(Range)  
Source: Table 14.4 / 2 to 14.4 / 4

Table 26. The relative exposure of regorafenib, M2 and M5 after a high-fat or a low-fat meal compared to fasted state in healthy volunteers

Analyte	Comparison	Parameter	N	Point estimate [%] (Ratio)	2-sided 90% CI [%]
Regorafenib	Low-fat / fasted	AUC	24	136	[123 ; 150]
		C <sub>max</sub>	24	154	[138 ; 173]
	High-fat / fasted	AUC	24	148	[134 ; 164]
		C <sub>max</sub>	24	173	[154 ; 193]
	High-fat / low-fat	AUC	24	109	[98.6 ; 120]
		C <sub>max</sub>	24	112	[100 ; 125]
M-2	Low-fat / fasted	AUC	24	140	[115 ; 169]
		C <sub>max</sub>	24	130	[106 ; 159]
	High-fat / fasted	AUC	24	80.0	[66.1 ; 96.8]
		C <sub>max</sub>	24	72.3	[59.1 ; 88.4]
	High-fat / low-fat	AUC	24	57.3	[47.3 ; 69.4]
		C <sub>max</sub>	24	55.5	[45.4 ; 67.9]
M-5	Low-fat / fasted	AUC	24	123	[101 ; 149]
		C <sub>max</sub>	24	112	[89.1 ; 140]
	High-fat / fasted	AUC	24	48.7	[40.0 ; 59.3]
		C <sub>max</sub>	24	40.7	[32.5 ; 51.1]
	High-fat / low-fat	AUC	24	39.7	[32.6 ; 48.3]
		C <sub>max</sub>	24	36.5	[29.1 ; 45.7]

Source: Module 5.3.1.1.1, PH-36525, Table 9-2

Fasted: 4 x 40 mg regorafenib solid solution tablets administered after overnight fasting

Low-fat: 4 x 40 mg regorafenib solid solution tablets administered immediately after a low-fat breakfast

High-fat: 4 x 40 mg regorafenib solid solution tablets administered immediately after a high-fat breakfast

**2.5.4 When would a fed BE study be appropriate and was one conducted?**

[See response to section 2.5.3.](#)

**2.5.5 How do dissolution conditions and specifications ensure in vivo performance and quality of the product?**

Yes. Please refer to biopharmaceutical review for more information.

**2.5.6 If different strength formulations are not bioequivalent based on standard criteria, what clinical safety and efficacy data support the approval of various strengths of the ‘to-be-marketed’ product?**

Not applicable. Only one tablet strength will be marketed upon approval.

**2.5.7 If the NDA is for a modified release formulation of an approved immediate product without supportive safety and efficacy studies, what dosing regimen changes are necessary, if any, in the presence or absence of PK-PD relationship?**

Not applicable.

**2.5.8 If unapproved products or altered approved products were used as active controls, how is BE to the ‘to-be-marketed’ product? What is the basis for using either in vitro or in vivo data to evaluate BE?**

Not applicable.

**2.5.9 What other significant, unresolved issues relation to in vitro dissolution of in vivo BA and BE need to be addressed?**

None.

**2.6 ANALYTICAL SECTION**

**2.6.1 How are the active moieties identified and measured in the plasma and the other matrices?**

Regorafenib, M2, M3, M4 and M5 were identified in human plasma and regorafenib, M2, M7 (regorafenib glucuronide) and M8 (M2 glucuronide) were identified in human urine using LC/MS/MS [Study report A59117].

**2.6.2 Which metabolites have been selected for analysis and why?**

M2 and M5 were measured in the PK studies along with regorafenib. These metabolites were major circulating metabolites at steady-state and exhibited similar anticancer activity compared to regorafenib in tumor models of colorectal cancer. M2 and M5 inhibited the same protein kinases as regorafenib with IC<sub>50</sub> values.

**2.6.3 For all moieties measured is free, bound or total measured?**

Given that regorafenib and the two active metabolites M2 and M5 are greater than 99.5% protein bound, total plasma concentrations and urinary excretion were measured.

**2.6.4 What bioanalytical methods are used to assess concentrations?**

LC/MS/MS was used to measure the concentrations of regorafenib, M2 and M5 in human plasma and urine.

**2.6.4.1** *What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used?*

Ten calibration samples were prepared by spiking human plasma and urine with appropriate volumes of working standard solutions of regorafenib or a metabolite to produce a range from 2 µg/L (LLOQ) to 10,000 µg/L for plasma and a range from 10 µg/L (LLOQ) to 5,080 µg/L for urine. The LLOQ in human plasma was increased to 4 µg/L for some runs. Calibration functions were validated for relative peak areas which were obtained by weighted (1/x<sup>2</sup>) linear regression of the nominal concentration or by fitting to an exponential function. The calibration range reasonably represents the concentrations of regorafenib, M2 and M5 in humans.

**2.6.4.2** *What are the lower and upper limits of quantification?*

[See Section 2.6.4.1.](#)

**2.6.4.3** *What are the accuracy, precision and selectivity at these limits?*

The accuracy and precision of the QC samples for regorafenib, M2 and M5 in human plasma and urine as listed in the report for Study 11650 appear adequate based on the current FDA Guidance

for Industry *Bioanalytical Method Validation*. The accuracy and precision calculated for other runs appear similar based on the summary included in the report of the bioanalytical methods and validation for clinical studies.

Table 27. The accuracy and precision estimated for the quality control samples in the concentration range of 5 µg/L to 1600 µg/L in human plasma and urine		
Compound	Accuracy	Precision
	Human Plasma	
Regorafenib	101 % to 104 %	2.8 % to 9.6 %
M2	101 % to 103 %	7.1 % to 13.1 %
M5	97.8 % to 102 %	3.6 % to 11.8 %
Human Urine		
Regorafenib	95.6 % to 102 %	4.1 % to 6.8 %
M2	95.2 % to 99.4 %	3.9 % to 5.9 %

**2.6.4.4** *What is the sample stability under the conditions used in the study (long-term, freeze-thaw, sample-handling, sample transport, autosampler)?*

Regorafenib, M2 and M5 were stable following

- Three freeze-thaw cycles at concentrations of 5 µg/L and 1600 µg/L in human plasma (regorafenib, M2, M5)
- Three free-thaw cycles at approximate concentrations of 24 µg/L, 190 µg/L and 4000 µg/L in human urine (regorafenib, M2)
- Protein extraction at concentrations of 5 µg/L and 1600 µg/L (M2, M5) human plasma in the autosampler up to 4 days
- Protein extraction at concentrations of 9 µg/L, 90 µg/L and 1600 µg/L (regorafenib, M2, M5) in human urine in the autosampler up to 7 days.
- Preparation of stock solutions at concentrations of 1000 µg/L (regorafenib, M2, M5) for 412 days at ≥8°C.
- Preparation of stock solutions at concentrations of 1000 µg/L for 24 hr (regorafenib) or 1 hr (M2, M5) at ambient temperature with day light. Yellow light extended stability to 7 hr for M2 and 24 hr for M5 under these conditions.

**2.6.4.5** *What is the QC sample plan?*

Five to seven QC samples were prepared at a concentrations range of 2 µg/L to 20,000 µg/L by spiking human plasma with an appropriate volume of working solutions of regorafenib, M2 and M5. The QC samples were included in duplicate in each run.

**3 DETAILED LABELING RECOMMENDATIONS**

Only relevant clinical pharmacology sections are included. An underline indicates the content that was added to the proposed draft label by the agency and ~~strikethroughs~~ indicate content taken out by the agency from the proposed draft label.

**2 DOSAGE AND ADMINISTRATION**

8 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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STACY S SHORD  
09/25/2012

HONG ZHAO  
09/25/2012  
I concur.

NAM ATIQUR RAHMAN  
09/25/2012

<b>BIOPHARMACEUTICS REVIEW</b> <b>Office of New Drug Quality Assessment</b>			
<b>Application No.:</b>	NDA 203-085	<b>Reviewer:</b> Elsbeth Chikhale, Ph.D	
<b>Submission Date:</b>	April 27, 2012	<b>Secondary Signature:</b> Sandra Suarez-Sharp, Ph.D	
<b>Division:</b>	Division of Oncology Products	<b>Acting Supervisor:</b> Richard Lostritto, Ph.D	
<b>Applicant:</b>	Bayer Healthcare Pharmaceuticals, Inc.	<b>Date Assigned:</b>	April 30, 2012
<b>Trade Name:</b>	Stivarga	<b>Date of Review:</b>	August 28, 2012
<b>Generic Name:</b>	Regorafenib	<b>Type of Submission:</b> 505(b)(1) Original New Drug Application	
<b>Indication:</b>	Treatment of patients with metastatic colorectal cancer (CRC)		
<b>Formulation/ strengths</b>	Film coated IR tablet/ 40 mg		
<b>Route of Administration</b>	Oral		

**SUBMISSION:**

This 505(b)(1) New Drug Application is for a (b)(4) film coated immediate release tablet, containing 40 mg of regorafenib as the active ingredient. The proposed indication is for the treatment of patients with metastatic colorectal cancer (CRC) who have been previously treated with, (b)(4) 1) fluoropyrimidine-based chemotherapy, 2) an anti-VEGF therapy, and 3) if KRAS wild type, an anti-EGFR therapy. Regorafenib is an orally active, multikinase inhibitor that has been shown to target the following receptor tyrosine kinases: VEGFR1-3, TIE2, PDGFR-β, FGFR, KIT, RET, RAF-1, BRAF, BRAFV600E.

**BIOPHARMACEUTICS INFORMATION:**

The Biopharmaceutics review for this NDA is focused on the evaluation and acceptability of 1) the proposed dissolution methodology and 2) the proposed dissolution acceptance criteria.

The applicant states that (b)(4) A comparative BA study demonstrated that the relative bioavailability of regorafenib from conventional 20 mg tablets (b)(4) had a relative bioavailability of < 10% when compared to the oral solution, whereas the 20 mg and 100 mg (b)(4) tablets (b)(4) had a relative bioavailability of 70% and 83% respectively, when compared to the oral solution. Therefore, a (b)(4) (b)(4) tablet formulation was developed.

The Applicant has proposed to test the drug product for absence of (b) (4) using the proposed dissolution test. This approach was discussed in a teleconference with the Applicant on August 15, 2012, as described below on page 7-9 of this review. The Applicant states that regorafenib is a BCS Class 2 compound (low solubility and high permeability). During drug product development, 20 mg and 100 mg tablets were used in some phase 1 and phase 2 clinical studies. (b) (4)

The tablet strength was changed from 20 mg and 100 mg tablets to 40 mg tablets prior to the Phase 3 studies. The final, to be marketed (b) (4) (b) (4) tablet formulation (40 mg/tablet) was used in the pivotal Phase 3 study. A comparative bioavailability study was conducted to demonstrate that at a dose of 160 mg, the exposure to regorafenib was the same after administration of the final to-be marketed (b) (4) 40 mg tablets (4x40 mg) and the "old" 100 mg and 20 mg tablets (1x100 mg + 3x20 mg) with (b) (4) (90% CI for AUC ratio: 93-107%).

#### **DISSOLUTION INFORMATION:**

The proposed dissolution method is as follows:

USP Apparatus II (paddle)

Volume: 900 mL

Dissolution medium: acetate buffer pH 4.5 containing 0.1% sodium dodecyl sulfate

Temperature: 37 °C

Rotation speed: 75 rpm

Analysis: UV at 265 nm

The dissolution method development report (P.5.3.21-01) included the following information:

(b) (4)

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**Reviewer's assessment of the proposed dissolution method:**

Based on the dissolution method development report data (discussed above), the proposed dissolution method is found acceptable.

**PROPOSED DISSOLUTION ACCEPTANCE CRITERION:**

Proposed dissolution acceptance criterion:

Test	Release specification (P.5.1.01)	Shelf life specification (P.5.1.02)
Dissolution after 30 minutes	Q = (b) (4)	Q = (b) (4)
Stage testing according to Ph. Eur., USP, Ph. Jap.		

As justification for the proposed acceptance criterion, the Applicant claims that the proposed acceptance criterion is in line with common compendial acceptance criteria for immediate release solid oral dosage forms.

Dissolution data at release and during stability studies:

The dissolution data for the following clinical batches were provide in the NDA and copied below:

**Table 1: Clinical batches of Regorafenib coated tablet 40 mg**

Batch no.	Batch size [tablets]	Date of manufacture
AM128	(b) (4)	2009-04-02
AM129	(b) (4)	2009-04-01
BX035F7	(b) (4)	2009-03-03
AN074	(b) (4)	2010-05-26
AN077	(b) (4)	2010-05-21
AN078	(b) (4)	2010-05-21

**Table 2: Dissolution rates [%], batch no. AM128**

Time [minutes]	V1	V2	V3	V4	V5	V6	Mean ± confidence interval (95 %)	Coefficient of variation
15	(b) (4)	67 ± 2.6	3.7					
30	(b) (4)	95 ± 1.9	1.9					
45	(b) (4)	96 ± 2.0	2.0					
60	(b) (4)	96 ± 2.0	2.0					

**Table 3: Dissolution rates [%], batch no. AM129**

Time [minutes]	V1	V2	V3	V4	V5	V6	Mean ± confidence interval (95 %)	Coefficient of variation
15	(b) (4)	63 ± 5.4	8.1					
30	(b) (4)	96 ± 3.7	3.6					
45	(b) (4)	98 ± 1.4	1.4					
60	(b) (4)	98 ± 1.6	1.5					

**Table 4: Dissolution rates [%], batch no. BX035F7**

Time [minutes]	V1	V2	V3	V4	V5	V6	Mean ± confidence interval (95 %)	Coefficient of variation
15	(b) (4)	62 ± 6.4	10.1					
30	(b) (4)	92 ± 2.2	2.4					
45	(b) (4)	93 ± 0.5	0.6					
60	(b) (4)	93 ± 0.5	0.5					

**Table 5: Dissolution rates [%], batch no. AN074**

Time [minutes]	V1	V2	V3	V4	V5	V6	Mean ± confidence interval (95 %)	Coefficient of variation
15	(b) (4)	60 ± 8.4	13.4					
30	(b) (4)	92 ± 4.2	4.3					
45	(b) (4)	94 ± 1.2	1.2					
60	(b) (4)	93 ± 1.1	1.2					

Table 6: Dissolution rates [%], batch no. AN077

Time [minutes]	V1	V2	V3	V4	V5	V6	Mean ± confidence interval (95 %)	Coefficient of variation
15	(b) (4)						61 ± 4.3	6.8
30	(b) (4)						92 ± 6.0	6.2
45	(b) (4)						97 ± 2.5	2.5
60	(b) (4)						98 ± 1.0	0.9

Table 7: Dissolution rates [%], batch no. AN078

Time [minutes]	V1	V2	V3	V4	V5	V6	Mean ± confidence interval (95 %)	Coefficient of variation
15	(b) (4)						62 ± 4.8	7.4
30	(b) (4)						96 ± 2.7	2.6
45	(b) (4)						98 ± 1.2	1.2
60	(b) (4)						98 ± 1.3	1.2



The Applicant states that the dissolution test results remain unchanged after storage at room temperature (25 °C/60% RH) for up to 24 months or after storage at accelerated conditions (40 °C/75% RH) for up to 6 months.

**Reviewer’s assessment of the proposed dissolution acceptance criteria:**

Based on the provided dissolution data, and with the goal to set the acceptance criterion in a way to ensure consistent drug product performance from lot to lot and to prevent release of any drug product lot with dissolution profiles outside those that were clinically tested, it is recommended that the proposed acceptance criterion be tightened to:  $Q = (b) (4)$  at 30 minutes. The recommended acceptance criterion of  $Q = (b) (4)$  at 30 minutes was communicated to the Applicant in the filing communication letter dated June 25, 2012. In addition, the CMC reviewer had requested information from the Applicant regarding the control of  $(b) (4)$  in the drug product in an information request letter dated August 7, 2012. The Applicant responded in an amendment dated August 13, 2012, indicating and confirming that they intend to use dissolution to test the drug product for  $(b) (4)$  using  $Q = (b) (4)$  at 30 minutes. However, this proposed acceptance criterion will allow for drug product batches containing  $(b) (4)$  in the drug product to be released. Since there are no clinical data included in the application to support the release of such drug product batches with  $(b) (4)$ , this is unacceptable. A teleconference was held between the FDA and the Applicant on August 15, 2012 to resolve this issue and to set appropriate drug product dissolution acceptance criteria. The teleconference meeting discussion can be summarized as follows:

The Agency informed the applicant that they lacked adequate/direct control over  $(b) (4)$  during manufacture, at release, and on stability. Instead the Applicant

proposed to use dissolution testing as a surrogate for (b) (4). While potentially allowable, their proposed specification of  $Q = (b) (4)$  at 30 minutes would not allow discrimination between (b) (4). The Agency mentioned that since there is no clinical data (e.g. relative bioavailability/ bioequivalence) information supporting a (b) (4), there were two possible paths to go forward:

1. (b) (4)
2. (b) (4)

(b) (4)

The Applicant agreed to  $Q = (b) (4)$  at 30 minutes as the acceptance criterion for dissolution testing as part of the drug product specification (release and stability). The Applicant will also test for dissolution at 45 minutes (release and stability). If the mean of six tablets at 45 minutes is (b) (4) no further action is taken. However, if the mean of six tablets is (b) (4), that result will serve as a trigger to perform (b) (4) testing on the finished tablet (refer to decision tree above).

The acceptance criterion for (b) (4) by (b) (4) was not finalized during the teleconference. The tight content uniformity performance for the tablets (20 batches) and the

reasonable sensitivity of the (b) (4) method (b) (4) further supports the use of the above decision tree, which is consistent with previous actions the Agency has taken. The Applicant will provide further (b) (4) information and data they already have (but not included in the NDA) for CMC evaluation.

Based on this agreement, the revised drug product specifications were submitted to the NDA in an amendment dated 8/24/12, which includes the following changes:

- a) Tightening of the dissolution test acceptance criterion for Quality control (QC) testing to: Q= (b) (4), t=30 min with stage testing according to USP, EP, JP
- b) Testing for absence of (b) (4): dissolution after 45 min with not less than (b) (4) (mean of 6 individual samples) and without stage testing

The following is not part of the revised drug product specifications, but suggested by the Applicant as a post-approval action:

(b) (4)

The acceptability of the (b) (4) method and validation will be a review issue when the information is submitted (post-approval). The suggested (b) (4) acceptance criterion of (b) (4) in the drug product was not agreed upon during the teleconference and will need to be evaluated when submitted (post-approval)

In summary, the newly proposed dissolution acceptance criteria of Q (b) (4) at 30 minutes (QC testing), and NLT (b) (4) dissolved at 45 minutes (b) (4) are acceptable from Biopharmaceutics perspective. Based on the revised regulatory drug product specifications, if the batch does not meet the dissolution specifications, the drug product batch fails and can not be release. Review of the (b) (4) testing method and method validation and proposed acceptance criterion will be done by the CMC reviewer (post approval).

**RECOMMENDATION:**

The following dissolution method and dissolution acceptance criteria have been agreed upon with the Applicant for Regorafenib film-coated IR tablets, 40 mg (refer to submission dated Aug 24 , 2012):

USP Apparatus/RPM	Medium	Volume	Acceptance Criteria
II/75 rpm	Acetate buffer pH 4.5 containing 0.1% sodium dodecyl sulfate	900 mL	a) QC testing: Q= (b) (4) t=30 min with stage testing according to USP, EP, JP.  b) Testing for absence of (b) (4) dissolution after 45 min with not less than (b) (4) (mean of 6 individual samples) and without stage testing

From the Biopharmaceutics perspective, NDA 203-085 for Regorafenib Tablets, 40 mg is recommended for APPROVAL.

**Elsbeth Chikhale, Ph.D.**

Biopharmaceutics Reviewer  
Office of New Drug Quality Assessment

**Sandra Suarez-Sharp, Ph.D.**

Senior Biopharmaceutics Reviewer  
Office of New Drug Quality Assessment

Cc: Angelica Dorantes; Richard Lostrito

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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ELSBETH G CHIKHALE  
08/28/2012

SANDRA SUAREZ  
08/28/2012

# Office of Clinical Pharmacology

## *Filing and Review Form*

### General Information about the Submission

	Information		Information
NDA/BLA Number	203-085	Brand Name	Stivarga
OCP Division (I, II, III, IV, V)	V	Generic Name	Regorafenib
Medical Division	DOP2	Drug Class	Multiple tyrosine kinase inhibitor
OCP Reviewer	Stacy S. Shord, Pharm.D.	Indication(s)	Metastatic colorectal cancer
OCP Team Leader	Hong Zhao, PhD	Dosage Form	Film-coated tablets
Pharmacometrics Reviewer		Dosing Regimen	160 mg
Date of Submission	04/27/2012	Route of Administration	Oral
Estimated Due Date of OCP Review	08/30/2012	Sponsor	Bayer HealthCare Pharmaceuticals, Inc
Medical Division Due Date	09/27/2012	Priority Classification	Priority, expedited (5-month)
PDUFA Due Date	10/27/2012	eCTD link	<a href="\\Cdsesub1\evsprod\NDA203085\0000">\\Cdsesub1\evsprod\NDA203085\0000</a>

### *Clinical Pharmacology and Biopharmaceutics Information*

	"X" if included at filing	Number of studies submitted	Critical Comments
<b>STUDY TYPE</b>			
Table of Contents present and sufficient to locate reports, tables, data, etc.	x		
Tabular Listing of All Human Studies	x		Module 5.2
HPK Summary	x		Module 2.7.2
Labeling	x		Module 1.14
Reference Bioanalytical and Analytical Methods	x		Report A59117 (module 4.2.2.1.1)
<b>I. Clinical Pharmacology</b>			
Mass balance	x	1	Study 12436 / PH-367
Isozyme characterization	x	5	PH-33760, A57473, A59099, A58506, A59022, Metabolism – CYP, UGT
Blood/plasma ratio	x	1	PH-34096
Plasma protein binding			PH-34096
Pharmacokinetics			
<b>Healthy Volunteers -</b>			
single dose	x	4	Study 14656 / Food Effect (datasets) Study 12437 / Formulation (datasets) Study 12436 / Mass Balance (datasets) Study 12435 / Ketoconazole (datasets) Study 15524 / Rifampin (datasets)
multiple dose			

<b>Patients -</b>			
single dose	x	9	Study 11650 / PH-36733, Dose escalation/intermittent (datasets) Study 11651 / PH-36742 and PH-36741, Dose escalation/continuous (datasets) Study 14814 / QT (interim) Study 13172 / Japanese (datasets) Study 14996 / Chinese (datasets) Study 11656 / DI (mFOLFOX6, FOLFIRI) (datasets) Study 12434 / DI (CYP) (interim) Study 11726 / A55873, RCC, phase 2 Study 14596 / A51601, HCC, phase 2
multiple dose	x		Study 11650 / PH-36733, Dose escalation/intermittent (datasets) Study 11651 / PH-36742 and PH-36741, Dose escalation/continuous (datasets) Study 14814 / QT (interim) Study 13172 / Japanese (datasets) Study 14996 / Chinese (datasets) Study 11656 / DI (mFOLFOX6, FOLFIRI) (datasets) Study 12434 / DI (CYP) (interim) Study 11726 / A55873, RCC, phase 2 Study 14596 / A51601, HCC, phase 2
<b>Dose proportionality -</b>	x		Study 11650 / PH-36733, Dose escalation/intermittent (datasets) Study 11651 / PH-36742 and PH-36741, Dose escalation/continuous (datasets)
<b>Drug-drug interaction studies -</b>			
in-vivo effects on primary drug	x		Study 11656 / PH-368735, FOLFIRI or mFOLFOX6 (datasets) Study 12435 / PH-36717, Ketoconazole (datasets) Study 15524 / PH-36716, Rifampin (datasets)
in-vivo effects of primary drug	x		Study 11656 / PH-368735, FOLFIRI or mFOLFOX6 (datasets) Study 12434 / PH-36721, Warfarin, Omeprazole, Midazolam (interim)
in-vitro	x	14	PH-34703, Induction – CYP PH-34364, Inhibition – CYP PH-34036, Inhibition – UGT PH-A57553, Inhibition, M2, M5 – CYP PH-35818, Inhibition, M2, M5 – UGT PH-36645, R-8644, PH-36646, A58796, PH-36201, PH-36293, A58796 and A5876, Substrate, Inhibition - PGP, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, OCT2 PH-A5064, Inhibition - DPD
<b>Subpopulation studies -</b>			
ethnicity	x		Study 13172 / A51164, Japan, solid tumors, phase 1 (datasets) Study 14996 / A51600, Hong Kong, Singapore, solid tumors, ph1 (datasets) Study 14596 / A51601, Korea, HCC, phase 2 (datasets)
gender	x	1	Pooled PK analysis
pediatrics			Requested Waiver
geriatrics			
renal impairment	x		Study 11650 / PH-36733 (mild) (datasets) Study 11726 / A55873, RCC, ph2 Pooled PK analysis
hepatic impairment	x		Study 11651 / PH-36741 (CPA, CPB) (datasets) Study 14596 / A51601, Korea, HCC, phase 2 Pooled PK analysis
<b>Pharmacodynamics</b>			
Phase 2			
Phase 3			

<b>PK/PD</b>			
Phase 1 and/or 2, proof of concept	x		Study 11651 / PH-36742 and PH-36741, Dose escalation/continuous, PK, biomarkers (KRAS, VEGF, DCE-MRI) Study 11762 / A51601, Korea, RCC PK, biomarkers (VEGF) Study 14814 / PH-36720, QT (interim)
Phase 3 clinical trial	x	1	Study 14387 / A53306, mCRC – PK, biomarkers (KRAS)
<b>Population Analyses</b>			None; Proposed as PMR
Data rich			
Data sparse			
<b>II. Biopharmaceutics</b>			
<b>Absolute bioavailability</b>			
<b>Relative bioavailability</b>			
solution as reference	x		Study 11650 / Report PH-36733 (datasets)
alternate formulation as reference	x		Study 11650 / Report PH-36733 (datasets) Study 12437 / Report PH-36595 (datasets)
<b>Bioequivalence</b>			None
traditional design; single/multi dose			
replicate design; single/multi dose			
<b>Food-drug interaction</b>	x		Study 14656 / Report PH-36525 (datasets)
<b>Bio-waiver request</b>			None
<b>BCS class</b>	2		Based on drug transport in Caco-2 cells and poor solubility.
<b>Dissolution - alcohol induced dose-dumping</b>			None
<b>III. Other Studies</b>			
<b>Genotype/phenotype</b>			None
<b>Pediatric development plan</b>	x		Request waiver of pediatric studies
<b>Literature references</b>			Multiple
<b>Total Number of Studies</b>		36	

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
<b>Criteria for Refusal to File (RTF)</b>					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	x			
2	Has the applicant provided metabolism and drug-drug interaction information?	x			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	x			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	x			
5	Has a rationale for dose selection been submitted?				
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	x			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	x			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	x			
<b>Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)</b>					
<b>Data</b>					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	x			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			x	
<b>Studies and Analyses</b>					
11	Is the appropriate pharmacokinetic information submitted?	x			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	x			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?		x		Applicant proposes POPPK and ER analyses as PMRs
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?		x		
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			x	Waiver Requested
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			x	Waiver Requested
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?		x		Applicant proposes ER and POPPK analyses as PMRs
<b>General</b>					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	x			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			x	

**IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? YES**

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

*The application is fileable from a clinical pharmacology perspective.*

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

*No potential review issues were identified for the 74-day letter.*

Stacy S. Shord, Pharm.D.

Reviewer

Date

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Hong Zhao, Ph.D.

Team Lead

Date

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## Clinical Pharmacology - NDA Filing Memorandum

**NDA:** 203-085\000 (eCTD 000) **IND:** 75,642  
**Compound:** Regorafenib  
**Sponsor:** Bayer HealthCare Pharmaceuticals, Inc  
**Filing Date:** June 26, 2012  
**Reviewer:** Stacy S. Shord, PharmD

### Background

Regorafenib is an oral multi-tyrosine kinase inhibitor. The applicant proposes indication for treatment of patients with metastatic colorectal cancer (mCRC) who have been previously treated with, (b) (4) fluoropyrimidine-based chemotherapy, an anti-VEGF therapy, or an anti-EGFR therapy (if KRAS wild type). The proposed drug product is available as 40 mg (b) (4) (b) (4) tablet. Regorafenib has a molecular weight of (b) (4) and it is practically insoluble in water (b) (4)

### Mechanism of Action

The applicant states in the proposed labeling that regorafenib (b) (4)

Regorafenib inhibited VEGFR2, VEGFR3, TIE2, PDGFR $\beta$ , KIT (wild-type and mutant), RET (mutant), BRAF (mutant V600E) and FGFR with IC<sub>50</sub> values ranging from ~ 3 nM to 200 nM. The activation of the MAPK pathway monitored by ERK phosphorylation was inhibited with IC<sub>50</sub> values between ~ 40 nM to 400 nM. These values appear to be at least 20-fold lower than the observed steady-state regorafenib concentrations as measured at the proposed dose in the dose escalation trial.

The preclinical pharmacology studies demonstrated that regorafenib has antitumor activity in tumor models of colorectal cancer. Its major circulating human metabolites (M2 and M5) exhibited similar anticancer activity compared to regorafenib in these models. M2 and M5 inhibited key targets, such as VEGFR2, TIE2, KIT (mutant and wild-type) and BRAF (mutant) with IC<sub>50</sub> values very similar to regorafenib. M2 and M5 were measured in the pharmacokinetic (PK) trials along with regorafenib.

### Rationale for Phase 3 Dose Selection

The proposed dose is 160 mg once daily (QD) x 21 days. Each treatment cycle = 28 days.

The maximum tolerated dose (MTD) in the first in human (FIH) trial [Study 11650] was determined to be 160 mg QD x 21 days of a 28 day cycle. The most common treatment emergent drug-related adverse events (TEAE) were grade 3 or higher hand-foot skin reaction (HFSR) and hypertension. About 58% of patients experienced disease control. The MTD was lower at 100 mg QD, when regorafenib was administered continuously with no rest as observed in a second dose escalation trial [Study 11651]. The same TEAE were identified and 37% of patients experienced disease control. The applicant selected the intermittent dosing schedule to give patients a chance to at least partially recover from toxicities and provide patients with a higher systemic exposure to regorafenib and its two pharmacologically active equipotent metabolites M2 and M5.

Regorafenib is to be administered with a low fat meal. A dedicated food effect trial [Study 14656] indicated that a high-fat breakfast decreased exposure to its metabolites M2 and M5 by 20% [90% CI: 66, 97] and 51% [90% CI: 40, 60], respectively, and increased the mean AUC of regorafenib by 48% [90% CI: 134, 164]. A low fat meal increased the AUC of regorafenib by 36% [90% CI: 123, 150] and increased the AUC for its metabolites M2 and M5 by 40% [90% CI: 115, 169] and 23% [90% CI: 101, 149], respectively. The applicant opted to administer regorafenib with a light meal in the phase 3 registration trial.

### Efficacy Evaluation in Clinical Trials

The applicant proposed an indication for the treatment of patients with mCRC who have been previously treated with, (b) (4) fluoropyrimidine-based chemotherapy, an anti-VEGFR therapy, and, if KRAS wild type, an anti-EGFR therapy. The applicant conducted a single phase 3 registrational trial [Study 14387], entitled "A randomized, double-blind, placebo-controlled phase III study of regorafenib plus BSC versus placebo plus BSC in patients with metastatic colorectal cancer who have progressed after standard therapy." The primary endpoint was overall survival (OS). Secondary endpoints were progression-free survival (PFS), objective tumor response rate (ORR) and disease control rate. In total, 760 patients were randomized 2:1 to receive oral regorafenib 160 mg (4 x 40 mg tablets) QD (n=505) plus best supportive care (BSC) or matching placebo (n=255) plus BSC QD x 21 days. Each cycle = 28 days. The mean daily regorafenib dose received was 147 mg. Patients continued therapy until disease progression or unacceptable toxicity. Most patients received less than three previous therapies for metastatic disease, including fluoropyrimidine-based chemotherapy, anti-VEGF therapy and anti-EGFR therapy if the patient was KRAS wild type.

The addition of regorafenib to BSC resulted in significantly longer survival compared to placebo plus BSC as listed in the table below. The OS and the PFS benefit were independent of age, KRAS mutation status, and the number of previous therapies.

Efficacy parameter	Hazard Ratio* (95% CI)	P-value (one-sided)	Median (95% CI)	
			Regorafenib plus BSC (n=505)	Placebo plus BSC (n=255)
Median Overall Survival	0.77 (0.64, 0.93)	0.00518	6.4 months (5.9, 7.3)	5.0 months (4.4, 5.8)
Median Progression Free Survival	0.49 (0.42, 0.58)	<0.000001	1.9 months (1.9, 2.1)	1.7 months (1.7, 1.7)

### Safety Evaluation in Clinical Trials

The most common adverse reactions ( $\geq 30\%$ ) are asthenia/fatigue, anorexia, HSRF, diarrhea, weight loss, infection, hypertension and dysphonia. Warnings and Precautions include severe liver function tests abnormalities, reversible posterior leukoencephalopathy, gastrointestinal perforation and fistulae, impaired wound healing, HFSR, and rash, as well as increased bleeding, myocardial ischemia and infarction, and hypertension. The table [courtesy application orientation meeting] lists the incidence of hepatotoxicity, including the number of Hy's law cases. Germline DNA was collected in the registration trial, but it was not analyzed for possible genetic determinants of hepatotoxicity.

Evaluation of hepatotoxicity (laboratory abnormalities) according to FDA Guidance			
	Overall	Patients with liver metastases	Patients without liver metastases
<b>Regorafenib</b>	<b>N = 500</b>	<b>N = 387</b>	<b>N = 113</b>
AST or ALT > 3x ULN, tot. bilirubin > 2x ULN	35 (7.4%)	34 (9.2%)	1 (1.0%)
Hy's Law criteria*	4 (0.8%)	2 (0.5%)	2 (2.0%)
<b>Placebo</b>	<b>N = 253</b>	<b>N = 181</b>	<b>N = 72</b>
AST or ALT > 3x ULN, tot. bilirubin > 2x ULN	17 (6.9%)	17 (9.6%)	0
Hy's Law criteria*	1 (0.4%)	1 (0.6%)	0

\*: Hy's Law criteria (AST/ALT > 3x ULN, Alk. Phosphatase < 2x ULN, tot. bilirubin > 2x ULN) – FDA Guidance, Section E.4

Study14387/data cutoff 21 Jul 2011: Table 14.3.1/3: CTD Module 5.3.5.3, Integrated Analysis, Pool 3, Table 3.3 / 8

## Assessment of the Potential for QT/QTc Interval Prolongation

Regorafenib inhibited the hERG K<sup>+</sup> current with an IC<sub>50</sub> value of 12 μM [PH-33109], but demonstrated no effect on the cardiac action potential in rabbit Purkinje fibers up to 2 μM [PH-33827] and no effect on ECG intervals in Beagle dogs after oral and intravenous administration [Reports PH-33963, PH-35619, PH-34580, PH-34182, A45739].

The applicant included an interim analysis of the QT/QTc intervals completed on 25 patients enrolled into a dedicated cardiovascular safety trial [Study 14814] and an analysis of ECG changes from baseline by visit in at least 279 patients enrolled into the registration trial Study 14387. The proposed labeling states that (b) (4)

The final study report for the dedicated cardiovascular safety study will be submitted to address a planned post marketing requirement (PMR) in November 2012. A QT-IRT consult will not be placed until the final study report for this cardiovascular safety trial is received.

## Human Pharmacokinetic Data

A total of approximately 1,145 cancer patients, including 621 patients with CRC, were treated with regorafenib in completed and ongoing clinical trials and a total of 124 healthy volunteers were administered regorafenib. Regorafenib PK were evaluated following oral administration of single doses to healthy volunteers, as well as single and multiple doses to cancer patients.

The applicant summarized the PK as follows:

- The mean peak plasma level (C<sub>max</sub>) is 2.5 μg/mL after a single oral dose. The C<sub>max</sub> increases to 3.9 μg/mL (8.1 μM) at steady-state. The accumulation at steady-state is about 2-fold.
- The t<sub>max</sub> is 3 hrs to 4 hrs after a single oral dose.
- Regorafenib undergoes enterohepatic circulation. Secondary and tertiary maximal plasma concentrations were observed at 6 hrs to 8 hrs and then 24 hrs after the dose.
- Regorafenib is highly bound (99.5%) to human plasma proteins; the main binding protein was albumin.
- The partition coefficients between erythrocytes and plasma ranges from 0.16 to 0.26.
- Regorafenib is metabolized primarily in the liver by CYP3A4 and UGT1A9.
- The mean elimination half-life (t<sub>1/2</sub>) ranges from 20 hrs to 30 hrs.
- About 71% of the dose is excreted in feces (47% as regorafenib, 24% as metabolites) and about 19% of the dose is excreted in urine.
- The systemic exposure of regorafenib at steady-state increases with dose proportionally at doses < 60 mg and less than proportionally at doses > 60 mg.
- The interpatient variability is about 43% at steady-state.

The main circulating metabolites at steady-state are M2 and M5. These metabolites are pharmacologically active and have similar concentrations as regorafenib at steady-state (about 92% and 84% of regorafenib concentrations, respectively). The applicant summarized the PK as follows:

- The steady-state concentrations ( $C_{ss}$ ) for M2 were 3.3  $\mu\text{g/mL}$  (6.6  $\mu\text{M}$ ) and for M5 was 2.9  $\mu\text{g/mL}$  (6.0  $\mu\text{M}$ ).
- The protein binding of M2 and M5 is 99.8% and 99.9%, respectively.
- The mean  $t_{1/2}$  for M2 ranges from 20 hrs to 30 hrs, similar to that of parent drug.
- The mean  $t_{1/2}$  for M5 ranges from 40 hrs to 100 hrs.

### Comparability

The proposed commercial tablet dosage form is identified as a (b) (4) tablet. The patients enrolled into the dose escalation trial Study 11650 were administered an oral solution dosage form (20 mg/mL solution), an immediate release tablet dosage form (20 mg tablet) or a (b) (4) tablet dosage form (20 mg or 100 mg tablets). The relative bioavailability of the (b) (4) tablets was compared to the oral solution in the fasted state. Compared with an oral solution, the 20 mg (b) (4) tablet (at a dose of 60 mg) demonstrated a relative bioavailability of about 70% and a  $C_{max}$  about 60% for the parent compound; the 100 mg (b) (4) tablet demonstrated a relative bioavailability about 83% and a  $C_{max}$  about 55%.

The applicant conducted a dedicated relative bioavailability trial to compare the PK of regorafenib administered as the initial (b) (4) tablet with (b) (4) film coating dosage form to the “to be marketed” (b) (4) tablet with (b) (4) coating dosage form [Study 12437]. The geometric mean ratio (GMR) and 90% confidence intervals (CI) of the  $C_{max}$  [GMR 111%; 90% CI: 101, 122] and AUC [GMR 100%; 90% CI: 93, 107] for regorafenib suggest that these tablet dosage forms are bioequivalent.

### Exposure Response (ER) Analyses

The applicant conducted a dose- and concentration-response analysis as part of Study 11650 for biomarkers, clinical activity and safety. No relationship was observed between exposure of regorafenib as well as its metabolites M2 and M5 and safety or clinical activity. The applicant proposes to submit an E-R analysis for the registration Study 14387 as a proposed PMR in November 2012.

### Population Pharmacokinetic (PPK) Analyses

The applicant completed an integrated univariate analysis of PK parameters of regorafenib and its metabolites across phase 1 and 2 trials in patients with cancer. No apparent relationship was identified between regorafenib PK and age, gender or body weight. The applicant proposes to submit a PPK analysis inclusive of the registration trial as a planned PMR in November 2012.

The PK of regorafenib and its metabolites were measured in three separate trials in which Asian patients were enrolled: Study 13172 [Japanese], Study 14996 [Chinese] and Sty14596 [Korean]. The applicant states that no differences in regorafenib exposure (as measured by  $C_{max}$  and AUC) were apparent when comparing all Asians to Whites. The applicant states that a trend toward lower metabolites concentrations in Asians was observed relative to Whites. The clinical significance is unknown.

## Assessment of the Effect of Organ Impairment

The applicant did not conduct a dedicated hepatic or renal impairment trial, but the applicant conducted post-hoc analyses in patients with impaired organ impairment enrolled in the dose escalation trials. The exposure of regorafenib and its metabolites M2 and M5 does not appear comparable in 14 patients with mild hepatic impairment (Child-Pugh A) and 4 patients with moderate hepatic impairment (Child-Pugh B) relative to patients with normal hepatic function after a single 100 mg dose of regorafenib [Study 11651] based on the 90% CIs. The GMR for the  $AUC_{0-24hr}$  was 82% [90% CI: 54, 124] for patients with mild hepatic impairment and 101% [90% CI: 56, 182] for patients with moderate hepatic impairment. The PK of regorafenib has not been studied in patients with severe hepatic impairment (Child-Pugh C). A dedicated PK trial in patients with mild and moderate hepatic impairment might be warranted.

It appears the steady-state exposure of regorafenib at a dose of 160 mg is not comparable in patients with mild renal impairment compared to patients with normal renal function. Eighteen patients with normal renal function, 10 patients with mild renal impairment and one patient with moderate renal impairment were included in Study 11650. The GMR for  $AUC_{0-24hr,ss}$  was 66% [90% CI: 45, 99] for patients with mild renal impairment relative to patients with normal renal function using the Cockcroft-Gault formula to determine renal function, but it was 91% [90% CI: 59, 140] using the Modified Diet in Renal Disease formula. The applicant states that limited data from phase 1 and 2 trials indicates that the range of exposure in patients with moderate renal impairment is comparable to that seen in patients with normal renal function; however, the applicant did not conduct a PPK analysis. The PK of regorafenib has not been studied in patients with severe renal impairment or end-stage renal disease. A dedicated PK trial in patients with renal impairment might be warranted.

## Assessment of the Potential for Drug Interactions

Regorafenib undergoes metabolism by CYP3A4 and UGT1A to several metabolites as illustrated in the figure below. Metabolites M2 and M5 were found in the plasma and metabolites M7 and M8 were found in the urine of patients enrolled in Study 11650 after administration of repeated daily doses.

The applicant completed two separate PK trials to evaluate the effects of a strong inhibitor and an inducer on the PK of regorafenib and its metabolites. The administration of ketoconazole (400 mg QD x 18 days) with a single dose of regorafenib (160 mg on day 5) increased the mean regorafenib AUC by approximately 33% [90% CI: 121, 146] and decreased the mean exposure of M2 and M5 by approximately 90%. The applicant concluded that CYP3A4 inhibitors are unlikely to have a relevant effect on the safety and efficacy of regorafenib.

The administration of rifampin (600 mg QD x 9 days) with a single dose of regorafenib (160 mg on day 7) reduced the mean regorafenib AUC by 50% [90% CI: 45, 56] and the  $C_{max}$  by 20% [90% CI: 68, 96]. The GMR for the M5 AUC was 364% [90% CI: 290, 456] and for the M2 AUC was 91% [90% CI: 78, 106]. The applicant concluded that strong inducers of CYP3A4 should be avoided, or selection of an alternate concomitant medicinal product, with no or minimal potential to induce CYP3A4 should be considered.

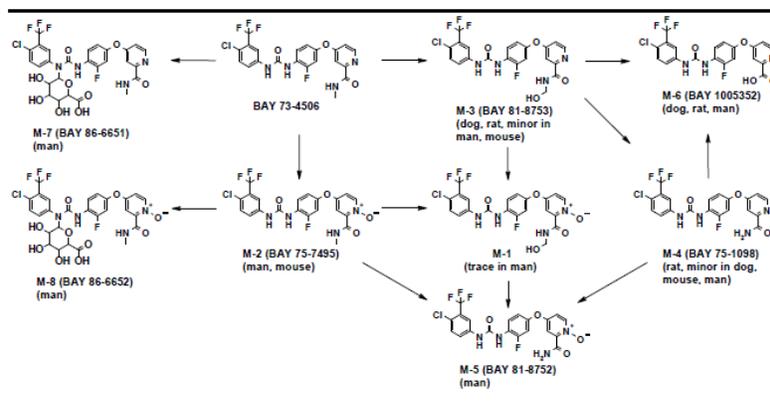


Figure 5-1: Proposed metabolic pathways of regorafenib *in vitro* and *in vivo*

Regorafenib exhibited no inductive potential on CYP1A2, CYP2B6, CYP2C19 and CYP3A4 after repeated exposure of up to 1000 ng/mL. Although the applicant did not provide sufficient information to calculate R3 values as defined in the 2012 draft Guidance for Industry regarding drug interaction studies, it is unlikely regorafenib will induce these enzymes as the enzyme activity following application of regorafenib appears comparable to basal activity in absence of an inducer or inhibitor in three donor hepatocytes. No studies were conducted to determine the ability of its M2 and M5 metabolite to induce these enzymes.

Regorafenib and its metabolites M2 and M5 inhibited CYP2B6, CYP2C9, CYP2C8, CYP2C19, CYP2D6 and/or CYP3A4 *in vitro*. The R values calculated using the maximal concentration of regorafenib or its M2 or M5 metabolite suggest that a drug interaction trial is warranted with a sensitive substrate of CYP2B6, CYP2C19, CYP2C8, CYP2C9, CYP2D6, and CYP3A4. The applicant is currently conducting a trial with a substrate of CYP2C19, CYP2C9, and CYP3A4. The final study report will be submitted as a planned PMR in November of 2012.

Regorafenib inhibited UGT1A9 and UGT1A1 *in vitro*. The steady-state plasma concentrations are approximately 3.8- to 4.9-fold higher than the  $K_i$  values. The applicant states that M2 and M5 inhibit UGT with a similar potency. It appears that regorafenib might inhibit UGT1A1 in humans; the PK of irinotecan and its metabolite SN-38 were measured in 11 patients administered FOLFIRI (days 1 and 15) in combination with regorafenib at a dose of 160 mg on days 4-10 and 18-24 [Study 11656]. The mean SN-38 AUC increased by 44% (90% CI: 120%, 184%) and the mean irinotecan AUC increased by 28% (90% CI: 107%, 154%) when irinotecan was administered five days after regorafenib (C2D1) compared to those without regorafenib (C1D1). The applicant concluded that the clinical significance of these findings is unknown.

Regorafenib showed a high permeability across Caco-2 cells. It appears regorafenib is a BCS class II compound with high permeability and low solubility. Regorafenib is not a substrate for human P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3 and OCT2 *in vitro*. Regorafenib inhibited P-gp and BCRP *in vitro*. The R values calculated for the blood and the gut suggests that a drug interaction trial is warranted with a sensitive P-gp substrate. The applicant does not plan to conduct a drug interaction trial. Regorafenib did not inhibit OATP1B1, OATP1B3, OAT1, OAT3 and OCT2 *in vitro*.

Regorafenib will be administered as monotherapy. However, a PK sub-study indicated that an interaction with oxaliplatin and fluorouracil might occur [Study 11656]. The ratio of the geometric mean  $C_{max}$  and AUC was 89% and 106% for fluorouracil (mFOLFOX6), was 117% and 119% for unbound platinum and was 109% and 139% for total platinum, respectively. The

90% CIs were not within the default no effect bounds within these small patient cohorts and substantial interpatient variability was observed.

### **Analytical Methods**

The applicant provided a report that describes methods used to determine regorafenib, M2, M3, M4 and M5 in human plasma and regorafenib, M2, M7, and M8 in human urine using LC/MS/MS. The LLOQ for the determination of regorafenib in plasma was 2 ng/mL using sample volumes of 100  $\mu$ L and 4 ng/mL using sample volumes of 50  $\mu$ L. The interday precision (coefficient of variation) was less than 12% and the bias of accuracy ranged between -4% and +9%. The LLOQ in urine was 10 ng/mL using sample volumes of 100  $\mu$ L for the determination of regorafenib. The precision (coefficient of variation) was less than 7% and the bias of accuracy ranged between -5% and -1%. Regorafenib, M2 and M5 are stable in plasma at 37°C for at least 4 hrs, at room temperature for at least 24 hrs, and at  $\leq$  -15°C for at least 18 months.

### **Biomarker Analysis**

Biomarker analysis included evaluation of KRAS mutational status [Study 11650, Study 14387], VEGF and VEGFR2 plasma levels [Study 11650, Study 11726] and DCE-MRI [Study 11650]. The applicant concluded that KRAS mutant positive status does exhibit an effect on clinical activity or survival based on these limited exploratory analyses and demonstrated that sVEGFR2 levels decreased following administration of regorafenib supporting the proposed mechanism of action that regorafenib affects VEGF signaling. Other plasma proteins were measured in addition to VEGF and VEGFR2 in Study 11726. In Study 11650, a decrease in the iAUC60 for the gadolinium curve as measured by DCE-MRI was observed with more pronounced effects for doses  $\geq$  120 mg. The applicant suggest that regorafenib-mediated changes in the level of specific plasma proteins correlated with clinical activity, but stated these preliminary findings require confirmation in a large prospective clinical trial. It appears biomarkers were included in other trials as noted in the tabular listing of the trials in Modules 2.7.2 and 5.2.

Of note, germline DNA collection was included in Study 14387. The protocol states that DNA could be used to evaluate single nucleotide polymorphisms in genes of interest (e.g., VEGF and VEGFR2). Germline DNA analysis was not included in the clinical study report.

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/s/  
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STACY S SHORD  
06/04/2012

HONG ZHAO  
06/04/2012  
I concur.

## PRODUCT QUALITY - BIOPHARMACEUTICS FILING REVIEW

<b>NDA Number</b>	203-085
<b>Submission Date</b>	4/27/12
<b>Product name, generic name of the active</b>	Regorafenib
<b>Dosage form and strength</b>	Film Coated Tablet - 40 mg/tablet
<b>Route of Administration</b>	Oral
<b>Applicant</b>	Bayer Healthcare Pharmaceuticals, Inc.
<b>Clinical Division</b>	Division of Oncology Products
<b>Type of Submission</b>	Original NDA – 505(b)(1)
<b>Biopharmaceutics Reviewer</b>	Elsbeth Chikhale, Ph.D.
<b>Biopharmaceutics Team Leader</b>	Angelica Dorantes, Ph.D.

The following parameters for the ONDQA's Product Quality-Biopharmaceutics filing checklist are necessary in order to initiate a full biopharmaceutics review (i.e., complete enough to review but may have deficiencies).

<b>ONDQA-BIOPHARMACEUTICS</b>				
<b>A. INITIAL OVERVIEW OF THE NDA APPLICATION FOR FILING</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
1.	Does the application contain dissolution data?	x		
2.	Is the dissolution test part of the DP specifications?	x		3.2.P.5.2.02-01 Proposed; Method: Apparatus 2, 900 mL of acetate buffer pH 4.5 with 0.1% SDS at 37 °C, at 75 rpm Acceptance Criteria: Q <span style="background-color: #cccccc;">(b) (4)</span> at 30 min
3.	Does the application contain the dissolution method development report?	x		3.2.P.5.3.21 The report appears to have all required information.
4.	Is there a validation package for the analytical method and dissolution methodology?	x		3.2.P.5.3
5.	Does the application include a biowaiver request?		x	Not needed.
6.	Does the application include an IVIVC model?		x	
7.	Is information such as BCS classification mentioned, and supportive data provided?	x		Applicant states that regorafenib is a BCS Class II compound
8.	Is information on mixing the product with foods or liquids included?		x	
9.	Is there any <i>in vivo</i> BA or BE information in the submission?	x		

## PRODUCT QUALITY - BIOPHARMACEUTICS FILING REVIEW

B. FILING CONCLUSION				
	Parameter	Yes	No	Comment
10.	<b>IS THE BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?</b>	x		
11.	If the NDA is not fileable from the product quality-biopharmaceutics perspective, state the reasons and provide <b>filing</b> comments to be sent to the Applicant.			NA
12.	If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide <b>filing</b> comments to be sent to the Applicant.			NA
13.	Are there any <b>potential review</b> issues to be forwarded to the Applicant for the 74-day letter?		x	

*{See appended electronic signature page}*

Elsbeth Chikhale, Ph.D.  
Biopharmaceutics Reviewer  
Office of New Drug Quality Assessment

5/29/12  
Date

*{See appended electronic signature page}*

Angelica Dorantes, Ph.D.  
Biopharmaceutics Team Leader  
Office of New Drug Quality Assessment

5/29/12  
Date

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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ELSBETH G CHIKHALE  
05/29/2012

ANGELICA DORANTES  
05/29/2012