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RESEARCH**

*APPLICATION NUMBER:*  
**204369Orig1s000**

**MEDICAL REVIEW(S)**

## CLINICAL REVIEW

Application Type	Efficacy Supplement
Application Number	NDA 204369/Type 9
Priority or Standard	Priority
Submit Date	August 30, 2012
Received Date	August 30, 2012
PDUFA Goal Date	February 28, 2013
Division / Office	DOP2 / OHOP

Reviewer Names	Jennie Chang, PharmD (Efficacy) Amir Shahlaee, MD (Safety)
Review Completion Date	February 1, 2013

Established Name	Regorafenib
Trade Name	Stivarga®
Therapeutic Class	Multikinase inhibitor
Applicant	Bayer Health Care Pharmaceuticals, Inc.

Formulation	40 mg tablets
Dosing Regimen	160 mg (4 tablets) once taken orally once daily for 21 days of a 28-day cycle.

Indication	Regorafenib is indicated in patients with locally advanced, unresectable, or metastatic gastrointestinal stromal tumors (GIST) who have been previously treated with imatinib and sunitinib.
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Intended Population	Adult ≥ 18 years of age
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Template Version: March 6, 2009

## Table of Contents

<b>1</b>	<b>RECOMMENDATIONS/RISK BENEFIT ASSESSMENT .....</b>	<b>8</b>
1.1	Recommendation on Regulatory Action .....	8
1.2	Risk Benefit Assessment.....	8
1.3	Recommendations for Postmarket Risk Evaluation and Mitigation Strategies .	13
1.4	Recommendations for Postmarket Requirements and Commitments .....	13
<b>2</b>	<b>INTRODUCTION AND REGULATORY BACKGROUND .....</b>	<b>14</b>
2.1	Product Information .....	14
2.2	Tables of Currently Available Treatments for Proposed Indications .....	15
2.3	Availability of Proposed Active Ingredient in the United States .....	18
2.4	Important Safety Issues with Consideration to Related Drugs.....	18
2.5	Summary of Presubmission Regulatory Activity Related to Submission .....	18
2.6	Other Relevant Background Information .....	21
<b>3</b>	<b>ETHICS AND GOOD CLINICAL PRACTICES.....</b>	<b>21</b>
3.1	Submission Quality and Integrity .....	22
3.2	Compliance with Good Clinical Practices .....	22
3.3	Financial Disclosures.....	22
<b>4</b>	<b>SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES .....</b>	<b>23</b>
4.1	Chemistry Manufacturing and Controls .....	23
4.2	Clinical Microbiology.....	23
4.3	Preclinical Pharmacology/Toxicology .....	23
4.4	Clinical Pharmacology .....	23
4.4.1	Mechanism of Action.....	23
4.4.2	Pharmacodynamics.....	23
4.4.3	Pharmacokinetics.....	23
<b>5</b>	<b>SOURCES OF CLINICAL DATA.....</b>	<b>24</b>
5.1	Tables of Studies/Clinical Trials .....	24
5.2	Review Strategy .....	24
5.3	Discussion of Individual Studies/Clinical Trials.....	25
<b>6</b>	<b>REVIEW OF EFFICACY .....</b>	<b>38</b>
	Efficacy Summary .....	38
6.1	Indication .....	39
6.1.1	Methods .....	40
6.1.2	Demographics .....	40
6.1.4	Subject Disposition.....	45
6.1.5	Protocol Violations .....	49
6.1.6	Analysis of Primary Endpoint .....	50

6.1.7	Analysis of Secondary Endpoints(s)	56
6.1.8	Other Endpoints	59
6.1.9	Subpopulations	59
6.1.10	Analysis of Clinical Information Relevant to Dosing Recommendations	62
6.1.11	Discussion of Persistence of Efficacy and/or Tolerance Effects	62
6.1.12	Additional Efficacy Issues/Analyses	62
<b>7</b>	<b>REVIEW OF SAFETY</b>	<b>62</b>
	Safety Summary	62
7.1	Methods	64
7.1.1	Studies/Clinical Trials Used to Evaluate Safety	64
7.1.2	Categorization of Adverse Events	65
7.1.3	Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence	66
7.2	Adequacy of Safety Assessments	66
7.2.1	Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations	66
7.2.2	Explorations for Dose Response	68
7.2.3	Special Animal and/or In Vitro Testing	68
7.2.4	Routine Clinical Testing	68
7.2.5	Metabolic, Clearance, and Interaction Workup	68
7.2.6	Evaluation for Potential Adverse Events for Similar Drugs in Drug Class	68
7.3	Major Safety Results	69
7.3.1	Deaths	69
7.3.2	Nonfatal Serious Adverse Events	71
7.3.3	Dropouts and/or Discontinuations	72
7.3.4	Adverse events leading to dose interruption	74
7.3.5	Adverse events leading to dose reduction	75
7.3.6	Significant Adverse Events	76
7.4	Supportive Safety Results	91
7.4.1	Common Adverse Events	91
7.4.2	Laboratory Findings	93
7.4.3	Vital Signs	94
7.4.4	Electrocardiograms (ECGs)	95
7.4.5	Special Safety Studies/Clinical Trials	96
7.4.6	Immunogenicity	96
7.5	Other Safety Explorations	96
7.5.1	Dose Dependency for Adverse Events	96
7.5.2	Time Dependency for Adverse Events	96
7.5.3	Drug-Demographic Interactions	97
7.5.4	Drug-Disease Interactions	98
7.5.5	Drug-Drug Interactions	99
7.6	Additional Safety Evaluations	99
7.6.1	Human Carcinogenicity	99

7.6.2	Human Reproduction and Pregnancy Data.....	99
7.6.3	Pediatrics and Assessment of Effects on Growth .....	99
7.6.4	Overdose, Drug Abuse Potential, Withdrawal and Rebound.....	99
7.7	Additional Submissions / Safety Issues .....	99
<b>8</b>	<b>POSTMARKET EXPERIENCE.....</b>	<b>100</b>
<b>9</b>	<b>APPENDICES .....</b>	<b>101</b>
9.1	Literature Review/References .....	101
9.2	Labeling Recommendations .....	103
9.3	Advisory Committee Meeting.....	104

## Table of Tables

Table 1. Risk Factors for Aggressive Clinical Behavior .....	9
Table 2. Currently Available Treatment for GIST .....	16
Table 3. FDA advice for revision of SAP for Trial 14874 .....	19
Table 4. Trials submitted to NDA 204369.....	24
Table 5. Protocol milestones .....	26
Table 6. Baseline Demographics .....	41
Table 7. Baseline Tumor Characteristics.....	42
Table 8. 14874 Prior GIST Treatment .....	43
Table 9. 14874 Subsequent GIST Treatment.....	44
Table 10. Summary of Patient Enrollment by Country.....	45
Table 11. Rescreened Patients .....	46
Table 12. Patient Disposition.....	48
Table 13. Disposition of All Patients who Discontinued Double-Blind Treatment .....	49
Table 14. Protocol Violations.....	50
Table 15. Progression-Free Survival by BCRR .....	51
Table 16. Comparison of Progression-free Survival between BCRR and Investigator ..	55
Table 17. Discordance between Assessments by BCRR and Investigator for Progressive Disease .....	55
Table 18. Overall Survival Based on BCRR.....	56
Table 19. Time-to-progression Based on BCRR .....	58
Table 20. Supportive Safety Studies (Pooled).....	65
Table 21. Demographics of Safety Population for GRID Trial .....	66
Table 22. Exposure during the DB Phase of the GRID Trial .....	67
Table 23. Regorafenib exposure during DB and OL Phases of the GRID Trial .....	67
Table 24. Deaths on Study 14874 (Cutoff date January, 26, 2012) .....	69
Table 25. Patients on GRID Trial who died during the Trial or within 30 days of last dose of therapy .....	70
Table 26. Non-fatal SAEs occurring in >1% of patients on the GRID Study.....	71
Table 27. AEs leading to discontinuation of study therapy during the GRID Study .....	73
Table 28. TEAEs leading to dose interruption ( $\geq 1\%$ ) in Double Blind Phase of the GRID Study .....	74
Table 29. TEAEs leading to dose reduction (>1%) during Double Blind Phase of the GRID Trial .....	75
Table 30. Dermatologic AEs reported in >1% of patients on the GRID study .....	76
Table 31. 'Severe cutaneous adverse reactions' amongst all regorafenib exposed patients (cases identified using MedDRA SMQ, narrow).....	78
Table 32. Incidence of dermatologic adverse events by race in DB Phase of the GRID Study .....	79
Table 33. Patients with Hepatobiliary Toxicity during the DB Phase of the GRID Study	80
Table 34. Patients with Hepatobiliary Toxicity during the OL Phase of the GRID Study	80
Table 35. Laboratory evaluation for Identifying cases of Hy's Law.....	82
Table 36. Adverse Events Reported for patient on DB Phase of the GRID Study.....	83

Table 37 AEs classified under the Renal SOC in the DB Phase of the GRID Study ....	85
Table 38 TEAEs classified under the Vascular SOC in the DB Phase of the GRID Study .....	87
Table 39 AEs of Hemorrhage during DB Phase of the GRID Study .....	89
Table 40 Thyroid function values during the GRID Trial .....	90
Table 41 Most common TEAEs ( $\geq 10\%$ of patients in any treatment group) by MedDRA PT during double blind phase of study 14874 .....	92
Table 42 Hematology Laboratory Evaluations on the GRID Trial .....	93
Table 43 Liver Function Evaluations on the GRID Trial .....	93
Table 44 Chemistries and Urinalysis results from the GRID Trial .....	94
Table 45 Mean Values for systolic and diastolic BP on the GRID Trial .....	94
Table 46 Reported Weight changes in Kg for patients enrolled on the GRID Trial .....	95
Table 47 AEs with a difference of $> 10\%$ between race categories for patients on regorafenib in the GRID Trial .....	98

## Table of Figures

Figure 1. Overall Trial Design.....	30
Figure 2. Safety Monitoring Schedule .....	34
Figure 3. Kaplan-Meier Curves of Progression-Free Survival at 145 PFS Events Based on BCRR .....	52
Figure 4. Forest Plot of PFS Sensitivity Analyses .....	54
Figure 5. Kaplan-Meier Curves of Overall Survival Based on BCRR .....	57
Figure 6. Time-to-progression Based on BCRR.....	58
Figure 7. PFS Results by Demographic Subgroups.....	60
Figure 8. PFS Results by Baseline Characteristic Subgroups.....	61

## 1 Recommendations/Risk Benefit Assessment

### 1.1 Recommendation on Regulatory Action

The clinical review team recommends approval of new drug application (NDA) 204369 for regorafenib tablets for the treatment of patients with locally advanced, unresectable, or metastatic gastrointestinal stromal tumors (GIST) who have been previously treated with imatinib and sunitinib.

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

### 1.2 Risk Benefit Assessment

#### **Analysis of condition**

##### **Summary of evidence**

Gastrointestinal stromal tumors represent the most common mesenchymal tumors of the gastrointestinal tract. It is estimated that the annual incidence of GIST in the United States is 7-20 cases per million population per year or approximately 4000-6000 new cases a year. These tumors most commonly affect middle age and older patients, rarely affecting patients in their forties or younger.

Gastrointestinal stromal tumors can arise from the stomach (40-60%), ileum/jejunum (25-30%), duodenum (5%) colorectum (5-15%), esophagus ( $\leq 1\%$ ) in addition to non-bowel wall portions of the GI tract such as the omentum, mesentery and peritoneum. Additionally, significant histopathological variability exists between cases of GIST. Histologically, GISTs can be divided into three primary categories: spindle cell type (70%), epithelioid type (20%) and mixed type (10%). The majority GIST tumors in adults express KIT (~95%) or platelet derived growth factor alpha (PDGFRA). In 80% of GIST cases, a KIT mutation leads to constitutive activation of this receptor. Most of the KIT mutations are in exon 11 although mutations in exons 9, 13 and 17 have also been reported. KIT mutational status and expression of the KIT protein (CD117) however do not directly correlate and approximately 10% of GIST cases do not have evidence of KIT or PDGFRA mutations. Some of these cases have mutations in the gene encoding the enzyme succinate dehydrogenase (SDH).

Significant variability has been reported in the clinical behavior of GISTs. Specifically, tumor size, location and histopathological characteristics all appear to have prognostic implications. Table 1 summarizes the effect of tumor size and mitotic count on clinical risk stratification. In addition, intestinal GISTs are reported to have more aggressive clinical behavior than gastric GISTs. Other prognostic factors include the type of KIT

mutation present in the tumor. Specifically, patients with exon 9 mutations are thought to have a more aggressive clinical course and although less responsive to imatinib therapy than exon 11 mutations, they have improved disease free survival when treated with higher doses of imatinib (800 mg vs. 400 mg).

Table 1. Risk Factors for Aggressive Clinical Behavior

	<b>Size</b>	<b>Mitotic count</b>
<b>Very low risk</b>	<2 cm	<5 per 50 HPF
<b>Low risk</b>	2-5 cm	<5 per 50 HPF
<b>Intermediate risk</b>	<5 cm	6-10 per 50 HPF
	5-10 cm	<5 per 50 HPF
<b>High risk</b>	>5 cm	>5 per 50 HPF
	>10 cm	Any mitotic rate
	Any size	>10 per 50 HPF

Source: Fletcher, CD, Berman, JJ, Corless, C, et al. Diagnosis of gastrointestinal stromal tumors: A consensus approach. Int J Surg Pathol 2002; 10:81.

The primary treatment for patients with GIST is surgical resection when possible. Historically, conventional chemotherapy and radiation have had a limited role in the treatment of patients with GIST; however, with increased evidence of the effectiveness of systemic therapy with tyrosine kinase inhibitors (TKIs), the use of these agents in the neoadjuvant, adjuvant and advanced disease setting is now the standard of care for GIST.

## **Conclusion**

Locally advanced, unresectable, or metastatic GIST is a progressive disease with a fatal outcome. Median overall survival in patients with metastatic GIST is approximately 4 years.

## **Unmet medical need**

## **Summary of evidence**

Advanced, unresectable or metastatic GIST has a high likelihood of clinical benefit with imatinib treatment. Disease progression after imatinib can be treated by dose escalation of imatinib from 400 mg to 800 mg daily. Sunitinib is approved for second-line treatment after treatment failure with imatinib. Options are limited once patients progress on imatinib and sunitinib. Other tyrosine kinase inhibitors, sorafenib, nilotinib, and dasatinib, have been shown activity; however, none are approved for GIST resistant to imatinib and sunitinib.

## **Conclusion**

Currently approved therapeutic options, imatinib and sunitinib, have been shown to provide clinical benefit and are reasonably well-tolerated; however, an unmet medical need remains in patients with disease progression on these agents.

### **Clinical benefit**

#### **Summary of evidence**

The safety and efficacy of regorafenib in GIST were evaluated in Trial 14874 (GRID trial), a randomized, double-blind, placebo-controlled, multi-center trial of regorafenib plus best supportive care (BSC) compared to placebo plus BSC in patients with metastatic and/or unresectable GIST after disease progression with imatinib and sunitinib.

One hundred ninety-nine patients were randomized 2:1 to receive regorafenib (133 patients) and placebo (66 patients). Trial 14874 enrolled 199 patients at 53 sites in 17 countries. The baseline demographics are summarized in Table 6. Two-thirds of the patients were less than 65 years old, with the mean age of 58.1 years. Sixty-four percent of patients were men and 68% of the patients were white. All patients had an ECOG performance status of 0 or 1 at the time of trial enrollment.

Trial 14874 was stratified according to geographical region, Asia versus rest of the world. As shown in Table 6, about one-quarter of patients were enrolled from countries in Asia and slightly less than 20% of patients were from North America. Fifty-seven percent of patients enrolled in Trial 14874 as third-line (after disease progression with imatinib and sunitinib) and 43% enrolled as fourth-line or more. All patients had received systemic therapy, consisting of prior imatinib and sunitinib, per trial protocol. Baseline demographics were well-balanced between the two arms.

The assessment of benefit is based on the primary endpoint of progression-free survival (PFS) by blinded central radiologic review (BCRR) and key secondary endpoint of overall survival (OS). A statistically significant, clinically meaningful median difference in PFS of 3.91 months was observed in patients randomized to receive regorafenib. Median PFS was 4.83 months in the regorafenib arm, compared to 0.92 months in the placebo arm, with a hazard ratio (HR) of 0.27 (95% CI: 0.19, 0.39; p-value <0.0001). These results were robust as they withstood numerous sensitivity analyses, and consistent with the investigator-assessed PFS results and across subgroups analyses. The results of the planned interim OS survival analysis were not mature at the time of PFS analysis. There was no statistical difference in survival between the two arms.

The FDA Guidance for Industry entitled “*Providing Clinical Evidence of Effectiveness for*

*Human Drug and Biological Products*” states that for approval, “reliance on only a single study will generally be limited to situations in which a trial has demonstrated a clinically meaningful effect on mortality, irreversible morbidity, or prevention of a disease with a potentially serious outcome, and confirmation of the result in a second trial would be practically or ethically impossible.” The reasons for the clinical review team’s recommendation of full approval for NDA 204369 are as follows: an adequate and well-controlled, double-blind, trial incorporating prospective independent radiologic review, no evidence of differential bias between treatment arms, substantial evidence of effectiveness based upon demonstration of a clinically meaningful and statistically significant and robust improvement in PFS, supported by internal consistency, and an acceptable toxicity profile.

## **Conclusion**

No other randomized, controlled trials were submitted to this NDA to support the use of regorafenib in patients with locally advanced, unresectable, or metastatic GIST who have been previously treated with imatinib and sunitinib. The single Trial 14874 demonstrates substantial evidence of efficacy based on demonstration of a clinically meaningful and statistically improvement in PFS by independent BCRR, with no evidence of differential bias between the two arms.

Currently, there are limited treatment options in this patient population that has been heavily pretreated. Overall survival with sunitinib treatment is about 15 months. A statistically significant, clinically meaningful median difference in PFS of 3.91 months was observed in patients randomized to receive regorafenib in Trial 14874. This result withstood numerous sensitivity analyses and multiple subgroup analyses and provides substantial evidence of the effectiveness.

## **Risk**

### **Summary of evidence**

The safety analysis was primarily based on the safety population of the GRID trial (132 patients treated with regorafenib and 66 treated on the placebo arm). The safety assessment was supplemented with data from the 500 patients with metastatic colorectal cancer who received regorafenib and 253 patients who received placebo in trial 14387 which was the basis for NDA 203,085. Treatment emergent adverse events (TEAEs) were reported in all patients enrolled on the regorafenib arm and 92% of the patients on the placebo arm while Grade 3 and 4 TEAEs were reported in 64% of patients on regorafenib and 26% of the patients on placebo.

The most frequently reported ( $\geq 3\%$ ) grade 3 and 4 TEAEs on the regorafenib arm were hypertension (27% on regorafenib vs. 5% on placebo), palmar-plantar erythrodysesthesia syndrome (22% vs. 2%), diarrhea (8% vs. 0), rash (5% vs. 0),

hypophosphatemia (4% vs. 0), abdominal pain (4% vs. 5%), alanine aminotransferase increased (3% vs. 2%) and fatigue (3% vs. 2%).

Seven (5%) patients on the regorafenib arm and 3 (5%) on the placebo arm of the GRID trial died during or within 30 days of the last dose of study therapy during the double blind phase of the study. An additional 7% (3/41) of the patients on the regorafenib arm and 9% (5/56) of the patients on the placebo arm died during the open-label phase of the study. Causes of death in 2 patients on regorafenib were due to TEAEs without evidence of progression. These included one patient who died of cardiac arrest and one who died of hepatic failure.

Eight patients (6%) on the regorafenib arm of the study and 5 patients (8%) on the placebo arm of the study experienced a treatment emergent adverse event (TEAE) that led to therapy discontinuation during the double blind phase of the study. TEAEs leading to discontinuation of study therapy on the regorafenib arm included posterior reversible encephalopathy syndrome (PRES), metastatic pain, elevated transaminases, hematemesis, ileus, acute hepatic failure azotemia and pneumonia each in one patient.

In addition to the adverse events identified in the GRID trial, severe cutaneous adverse reactions including Stevens Johnson Syndrome (0.045%) and Toxic epidermal necrolysis (0.091%) have been rarely reported in the overall patient population (n~2200 patients) that has been exposed to regorafenib. There were no reports of severe cutaneous adverse reactions in the GRID trial.

## **Conclusion**

In summary, there were no new safety signals in the GRID trial, and the safety profile in patients with GIST was consistent with what was seen with regorafenib in the colorectal cancer setting and with other multi-kinase inhibitors.

## **Risk management**

The risks of treatment with regorafenib are well-known to prescribers, and management advice for severe and common toxicities is included in product labeling. The risks are also managed in that this drug will be administered by oncologists who have specific training in the administration of antineoplastic drugs and in the management of toxicities related to these drugs.

## **Benefit-Risk Summary and Assessment**

Locally advanced, unresectable or metastatic GIST is an incurable disease and the standard of care is treatment with imatinib and sunitinib, followed by other tyrosine kinase inhibitors until progression or death.

The efficacy of regorafenib for the treatment of patients with metastatic colorectal carcinoma that has progressed after two lines of treatment consisting of imatinib and sunitinib was demonstrated in one single, multicenter, randomized (2:1), double-blind, placebo-controlled trial. Trial 14874 was a in 199 patients with previously treated GIST. All patients received prior treatment consisting of imatinib and sunitinib. Patients were randomized to receive 160 mg regorafenib orally once daily (n=133) plus best supportive care (BSC) or placebo (n=66) plus best supportive care for the first 21 days of each 28-day cycle. Treatment continued until disease progression, unacceptable toxicity, development of a second malignancy, or death. Patients were allowed open-label treatment with regorafenib following disease progression on blinded treatment.

Efficacy was based on the primary endpoint of PFS determined by BCRR and key secondary endpoint of OS. A statistically significant, clinically meaningful median difference in PFS of 3.91 months was observed in patients randomized to receive regorafenib. Median PFS was 4.83 months in the regorafenib arm, compared to 0.92 months in the placebo arm, with a hazard ratio (HR) of 0.27 (95% CI: 0.19, 0.39; p-value <0.0001). The planned, interim overall survival (OS) survival analysis performed at the time of PFS analysis did not cross the O'Brien-Fleming boundary and was, therefore, not mature.

There were no newly identified adverse events that were unique to the GIST patient population and the toxicity profile for regorafenib in this patient population was consistent with what has been seen in the colorectal cancer setting. Furthermore, the toxicity profile was consistent with that for other multi-tyrosine kinase inhibitors. Lastly, the adverse event profile seen in the placebo group during the double blind phase of the study suggests that the patient population enrolled on this study had very advanced disease.

The clinical review team recommends approval of regorafenib in patients with locally advanced, unresectable, or metastatic GIST, who have been previously treated with imatinib and sunitinib. Recommendation is based on a clinically meaningful and statistically significant improvement in progression-free survival, supported by internal consistency of subgroup and sensitivity analyses, and an acceptable toxicity profile.

### 1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

No REMS or Medication Guide are required for marketing of regorafenib in patients with locally advanced, unresectable, or metastatic GIST.

### 1.4 Recommendations for Postmarket Requirements and Commitments

The clinical team recommends the following Postmarketing Commitment (PMC):

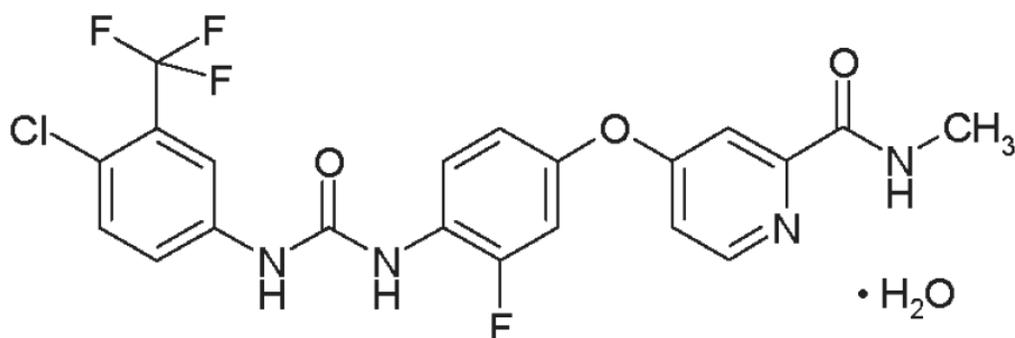
Overall Survival Assessment:

1. Submit the results of the protocol-specified final analysis of overall survival, along with datasets and analysis programs, from Trial 14874, "A randomized, double-blind, placebo-controlled phase III trial of regorafenib plus best supportive care versus placebo plus best supportive care for subjects with metastatic and/or unresectable gastrointestinal stromal tumors (GIST) whose disease has progressed despite prior treatment with at least imatinib and sunitinib."

Trial Completion Date: Month/Year: May 2015  
Final Report Submission: Month/Year: March 2016

## 2 Introduction and Regulatory Background

### 2.1 Product Information



**Established Name:** Regorafenib/BAY 73-4506

**Proprietary Name:** Stivarga

**Applicant:** Bayer HealthCare Pharmaceuticals, Inc.  
P.O. Box 1000, M1/2-1  
Montville, NJ 07045-1000

**Pharmacological Class:** Multiple-kinase inhibitor of VEGFR 1-3, TIE2, PDGFR $\beta$ , and fibroblast growth factor receptor (FGFR)1iKIT, RET, and BRAF kinases.

**Chemical Class:** Multi-targeted antineoplastic small molecule

**Proposed Indication:** "Regorafenib is indicated in patients with metastatic and/or unresectable gastrointestinal stromal tumors (GIST) who have received at least two prior therapies including imatinib and sunitinib."

**Proposed Dosage and Administration:** The recommended dose of regorafenib for patients with GIST is 160 mg (4 x 40 mg tablets) given orally once daily in repeating cycles for 21 consecutive days followed a break of 7 days.

**Drug Product:** Tablets in packages containing three bottles, with each bottle containing 28 tablets

## 2.2 Tables of Currently Available Treatments for Proposed Indications

The primary treatment for patients with GIST is surgical resection when possible. Historically, conventional chemotherapy and radiation have had a limited role in the treatment of patients with GIST; however, with increased evidence of the effectiveness of systemic therapy with tyrosine kinase inhibitors (TKIs), the use of these agents in the neoadjuvant, adjuvant and advanced disease setting is now the standard of care for GIST. Table 2 summarizes systemic therapies most commonly used in the treatment of GIST in the US.

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Table 2. Currently Available Treatment for GIST

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Product	Approval status	Evidence of Clinical Benefit
Imatinib	Accelerated approval: 2/1/2002	<p><u>Metastatic/unresectable disease-first line</u>  <u>Accelerated approval:</u>            400 mg: ORR 33%, 600 mg: ORR 43%            Updated in 2005, pooled both arms (N=147), ORR 67% &amp; median DOR of 118 weeks.</p> <p><u>Confirmatory:</u>            Two open-label randomized studies comparing two doses of imatinib in a total of 1640 patients</p> <ul style="list-style-type: none"> <li>• Imatinib at 400 mg/day               <ul style="list-style-type: none"> <li>○ Median PFS: 18.9 months (95% CI: 17.4-21.2)</li> <li>○ Median OS: 49.0 months (95% CI: 45.3-60.0)</li> </ul> </li> <li>• Imatinib at 800 mg/day               <ul style="list-style-type: none"> <li>○ Median PFS: 23.2 months (95% CI: 20.8-24.9)</li> <li>○ Median OS: 48.7 months (95% CI: 45.3-51.6)</li> </ul> </li> </ul> <p><u>Adjuvant therapy</u>            Trial 1: A multicenter, double-blind, placebo-controlled trial randomized 713 patients to imatinib (400mg/day) vs. placebo for 12 months</p> <ul style="list-style-type: none"> <li>• Improved RFS for imatinib arm: 0.718 (95% CI: 0.531-0.971)</li> </ul> <p>Trial 2: A randomized, multicenter, open label, phase 3 trial in the adjuvant setting (Trial 2) compared 12 months of imatinib (400 mg/day) to 36 months</p> <ul style="list-style-type: none"> <li>• Improved RFS for 36 month arm: 0.46 (95% CI: 0.32, 0.65), p&lt;0.0001</li> </ul> <p>Improved OS for 36 month arm: 0.45 (95% CI: 0.22, 0.89), p=0.0187</p>
Sunitinib	Regular approval: 1/26/2006	<p><u>Metastatic/unresectable disease-second line</u>            A randomized, double-blind, placebo-controlled trial of sunitinib vs. placebo in patients intolerant of imatinib or who have progressed on imatinib, N=312</p> <ul style="list-style-type: none"> <li>• Improved median TTP: 27.3 vs. 6.4 months HR=0.33 (95% CI: 0.23-0.47), p&lt;0.00001</li> <li>• Improved median PFS: 24.1 vs. 6.0 months HR=0.33 (95% CI: 0.24-0.47), p&lt;0.00001</li> <li>• Improved ORR: 6.8 (95% CI: 3.7-11.1) vs. 0</li> </ul>
Sorafenib	No	<p><u>Metastatic/unresectable disease-third line</u>            A phase 2 multicenter trial in patients with imatinib (n=6) or imatinib and sunitinib-resistant (n=32) GIST</p> <ul style="list-style-type: none"> <li>• PR in 13% and SD in 55%</li> </ul>

		<ul style="list-style-type: none"> <li>• Median PFS: 5.2 months (95% CI: 3.4-7.4)</li> <li>• Median OS: 11.6 months (95% CI: 8.8-18.0)</li> </ul>
Nilotinib	No	<u>Metastatic/unresectable disease-third line</u> Trial 1: A single-arm, phase 2 Japanese trial One partial response observed and 23 (65.7%) patients had stable disease as the best response. <ul style="list-style-type: none"> <li>• PR in 3% and SD in 65.7%</li> <li>• Median PFS= 113 days</li> <li>• Median OS= 310 days</li> </ul> Trial 2: A phase 3 randomized trial of nilotinib vs. best supportive care <ul style="list-style-type: none"> <li>• No statistically valid improvement in median PFS or OS</li> </ul>
Dasatinib	No	<u>Metastatic/unresectable disease-third line</u> A phase 2, single arm trial of dasatinib <ul style="list-style-type: none"> <li>• 50 patients with imatinib- and sunitinib-resistant GIST</li> <li>• PR rate was 32% (15/47) by Choi criteria.</li> <li>• Progression-free &gt;6 months= 21% (10/47) of patients</li> <li>• Median PFS and OS were 2.0 months and 19 months</li> </ul>

### 2.3 Availability of Proposed Active Ingredient in the United States

Regorafenib is marketed in the United States. Regular approval was granted on September 27, 2012 for the treatment of patients with metastatic colorectal cancer who have been previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF therapy, and, if KRAS wild type, an anti-EGFR therapy..

### 2.4 Important Safety Issues with Consideration to Related Drugs

Regorafenib is a tyrosine kinase inhibitor that targets multiple pathways, VEGFR 1-3, TIE2, PDGFR $\beta$ , and FGFR1.

Class effects of tyrosine kinase inhibitors include diarrhea, hepatotoxicity, fatigue, cutaneous reactions such as rash and hand-foot syndrome.

### 2.5 Summary of Presubmission Regulatory Activity Related to Submission

**July 20, 2006: Initial trial for regorafenib entitled “Open label, phase 1 study to determine the safety, tolerability, maximum tolerated dose, pharmacokinetics, and biomarker status of BAY 73-4506 in patients with advanced malignancies” was submitted to IND 75642**

**August 25, 2010: End-of-phase 2 (EOP2) meeting (IND 75642)**

FDA advised that the revised statistical analysis plan for OS at the time of the meeting was acceptable:

Table 3. FDA advice for revision of SAP for Trial 14874

	Original Plan	Revised Plan
NDA submission	PFS + available OS data	PFS + interim OS data
Interim analysis of OS	None	Time of PFS analysis (~60 deaths)
Time of final analysis	Time of PFS analysis (~60 deaths)	136 deaths
Alpha (one-sided)	0.025	0.025
Alpha spending	None	O'Brien-Fleming
Power	Not powered	80% power to detect 66.7% increase
Long-term survival data analysis	None	Planned

Bayer stated that patients would be stratified according to two criteria, geographical region (Asia versus rest of the world), and lines of prior systemic treatment (third-line versus fourth-line or beyond). A cap will be placed on the fourth-line and beyond stratum to prevent a potential overrepresentation of heavily pre-treated-line patients.

Reviewer's comments: Following this meeting, Bayer modified the design of Trial 14874 in accordance with the discussion at the meeting, powering the trial for OS (80% power to detect a 66.7% increase) while keeping PFS as the primary endpoint, adding an interim analysis for OS, and using an O'Brien-Fleming type alpha spend to control the overall type I error rate. Stratification by geographical region is due to possible differences patient population in types of BSC treatment in Asian countries versus rest of world; however, the types of BSC were not captured by the trial.

**October 13, 2010: Submission of Trial 14874, "A randomized, double-blind, placebo-controlled phase III trial of regorafenib plus best supportive care versus placebo plus best supportive care for subjects with metastatic and/or unresectable gastrointestinal stromal tumors (GIST) whose disease has progressed despite prior treatment with at least imatinib and sunitinib", to IND 75642**

**January 12, 2011: Orphan designation granted (IND 75642)**

**February 7, 2012: Administrative split from IND 75642, submission of IND 113896 for regorafenib in GIST, resubmission of Trial 14874**

**March 9, 2012: Written correspondence to the Applicant (IND 113896)**

The FDA conveyed the following comments to the Applicant, based on the statistical analysis plan (SAP) that was submitted to IND 75642 on February 7, 2012. The SAP for protocol 14874 had not been previously submitted to the Agency.

- Primary PFS and OS analyses should be performed with 122 PFS events and 136 deaths, respectively, as originally planned. FDA did not agree that the analyses will be performed with 144 PFS events and 160 deaths since the rationale of increasing the number of events for the analyses was not clear and it would have resulted in overpowering of the trial.
- Provide the details of the difference to be detected for PFS and OS. Include the HR and the estimated medians for the treatment and control arms.
- For the OS interim analysis, provide the estimated number of deaths to perform the analysis, the corresponding O'Brien-Fleming (OBF)-boundary and alpha level.
- Disease control rate (DCR) is unlikely to be included in the label.

**March 20, 2012: Written correspondence to the Applicant (IND 113,896)**

Protocol 14874 was amended (Amendment 3, dated September 27, 2011) to change the PFS analysis so that it will be performed with approximately 144 PFS events (versus approximately 122 events with 170 randomized patients in the original protocol ) and the final OS analysis with 160 deaths (versus 136). This was due to the over-recruitment of patients into the trial. The trial was still blinded to the Bayer, so the amendment was not based on any unblinded information from the trial. One hundred forty-four PFS events had already occurred and were included in the trial database.

FDA restated that the primary analysis should be performed according to the original protocol. Modifications without convincing clinical rationale were strongly discouraged because potential bias might be introduced. Despite the fact that 29 additional subjects were enrolled, the primary analysis should be performed based on the originally planned 122 PFS events. However, if the Applicant strongly preferred to change the primary analysis from 122 PFS events to 144 PFS events, FDA would consider the primary objective fulfilled only if tests at both 122 and 144 PFS events were statistically significant.

**April 17, 2011: Fast-track designation granted (IND 113,896).**

**May 3, 2012: Pre-NDA meeting (IND 113,896)**

FDA stated that the regorafenib GIST NDA should be a separate, stand-alone submission and should only contain mCRC information if it supported the GIST application. Bayer stated that the mCRC data in the clinical trial report (CRC) played no role with respect to GIST efficacy; however, the safety information included in the ISS includes approximately 500 CRC and 100 GIST subjects and therefore would be included in the GIST NDA. The serious adverse event (SAE) information would not repeat what was in the CRC NDA; however, cross reference would be provided in the GIST NDA to the CRC NDA to ensure access to all SAE information.

FDA additionally stated that the SAP would rely on agreements reached with Bayer as stated in FDA's letters dated March 9, and 20, 2012. Bayer agreed that the study objective would only be considered to have been met if both 122 and 144 PFS events are statistically significant.

FDA stated that inclusion of any specific secondary endpoint in labeling will be a review issue.

**May 31, 2012: Initial Components (CMC and Nonclinical) of Rolling NDA submission to NDA 204369**

**August 30, 2012: Final Component (Clinical) of Rolling NDA Submission to NDA 204369**

NDA 204369 was submitted and classified as type 9, which is for a new indication to a drug product that is currently being reviewed under a different NDA. In this case, NDA 203085, which is indicated for the treatment of metastatic colorectal cancer, was under FDA review at the time of NDA 204369 was submitted. After the approval of NDA 204369, the NDA will be "administratively closed" by the FDA, and all submissions by Bayer will be made to the original "parent" NDA, NDA 203085, as a supplement.

2.6 Other Relevant Background Information

None.

### **3 Ethics and Good Clinical Practices**

### 3.1 Submission Quality and Integrity

The submission contains all required components of the eCTD and was of adequate quality and integrity to allow for review of the clinical trial pertaining to the proposed indication. The overall quality and integrity of application were reasonable as judged by a review of case report forms of 30% of the patients enrolled and comparison to datasets to confirm accuracy of data transfer. Comparison of verbatim terms for all grade 3, 4, or 5 (NCI CTCAE v.3.0) to the Medical Dictionary for Regulatory Activities (MedDRA) adverse event (AE) coding demonstrated that the safety data was adequately captured and appropriately coded.

### 3.2 Compliance with Good Clinical Practices

The applicant stated that the trial was conducted under US IND 113,896 ‘in accordance with “good clinical practice” (GCP) and all applicable regulatory requirements, and, the guiding principles of the Declaration of Helsinki. Prior to initiation of the trial, the protocol, any amendments, the informed consent form, and other information that required pre-approval were reviewed and approved by a national, regional, or investigational center institutional ethics committees (IEC) or institutional review boards (IRB).

No clinical site inspection was conducted by the Office of Scientific Investigations (DSI). There was concern that a site inspection should be conducted due to the fact that one trial was submitted to NDA 204369 to support the GIST indication. However, given the small number of patients (<10) at any one of the sites identified and the robust efficacy results, the review team determined that an audit would not significantly impact the overall trial results. Additionally, clinical inspections were conducted for the initial approval of NDA 203085 for the mCRC indication. No significant findings were found and study data collected appeared reliable.

### 3.3 Financial Disclosures

In accordance with 21 CFR 54.4, Bayer submitted the required financial certification and disclosure requirements for Trial 14874.

Financial conflict of interest and arrangements of clinical investigators (FDA Form 3454) were collected by Bayer for all principal investigators (PIs) and sub-investigators listed on a FDA Form 1572 prior to trial initiation. All investigators, except for one, had disclosed or attested to having no financial interests.

Bayer filed a financial disclosure for one of the sub-investigators, [REDACTED] (b) (6)  
His wife, [REDACTED] (b) (6)

[REDACTED] Her compensation from Bayer in 2010 was

35,839,443 yen (equivalent to \$442,000) and in 2011 was 35,837,812 yen (equivalent to \$442,000).

As a sub-investigator, (b) (6)  
The patients comprised <1.5% of total patient population enrolled; therefore, the data does not have the potential to bias the outcome and/or conclusions of the trial.

Reviewer's comment: The Applicant appears to have done due diligence with regard to financial certification and disclosure requirements. (b) (6) financial interest does not appear to impact the trial results even if these patients were excluded from the trial, as his site enrolled only (b) (6) patients (<1.5% of total).

## 4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

### 4.1 Chemistry Manufacturing and Controls

No new data submitted for review. Please refer to the review for NDA 203085.

### 4.2 Clinical Microbiology

No new data submitted for review. Please refer to the review for NDA 203085.

### 4.3 Preclinical Pharmacology/Toxicology

No new data submitted for review. Please refer to the review for NDA 203085.

### 4.4 Clinical Pharmacology

#### 4.4.1 Mechanism of Action

No new data submitted for review. Please refer to the review of NDA 203085.

#### 4.4.2 Pharmacodynamics

No new data submitted for review. Please refer to the review of NDA 203085.

#### 4.4.3 Pharmacokinetics

No new data submitted for review. Please refer to the review of NDA 203085.

## 5 Sources of Clinical Data

### 5.1 Tables of Studies/Clinical Trials

The trials submitted in support of NDA 204369 are shown below:

Table 4. Trials submitted to NDA 204369

Trial	Protocol Title	Drug Regimen/s	Number of Patients
<b>Pivotal Trial</b>			
BAY 73-4506/14874	A randomized, double-blind, placebo-controlled phase III study of regorafenib plus best supportive care versus placebo plus best supportive care for subjects with metastatic and/or unresectable gastrointestinal stromal tumors (GIST) whose disease has progressed despite prior treatments with at least imatinib and sunitinib	Regorafenib 160 mg orally once daily for three weeks of every four weeks (28 day cycle) OR placebo	Total: 199 Regorafenib: 133 Placebo: 66
<b>Supportive Trial</b>			
BAY 73-4506/14935 <sup>†</sup>	A non-randomized, open label, multi-center Phase II study evaluating the efficacy and safety of regorafenib in patients with metastatic and/or unresectable gastrointestinal stromal tumor (GIST), resistant or intolerant to at least imatinib and sunitinib	Regorafenib 160 mg orally once daily for three weeks of every 4 weeks (28 day cycle)	Total: 34 Regorafenib: 34

<sup>†</sup> George S, Wang Q, Heinrich MC, Corless CL. Efficacy and safety of regorafenib in patients with metastatic and/or unresectable GI stromal tumor after failure of imatinib and sunitinib: a multicenter phase II trial. *J Clin Oncol* 30:2401-2407.

### 5.2 Review Strategy

This review focuses on the single, randomized, placebo-controlled, multicenter phase 3 clinical trial, BAY 73-4506/14874. No Special Protocol Assessment request was submitted. During the review process, Trial BAY 73-4506/14874 was reviewed in detail, including trial reports, raw datasets, derived datasets, case report forms (CRFs) and narratives. Major efficacy and safety analyses were reproduced or audited using JMP datasets submitted electronically under the NDA. The analyses included the following:

- A survey of the current literature on diagnosis, classification, and treatment of GIST using published literature, internet, and references submitted by the Applicant;
- Review of all correspondence and meeting minutes between the Bayer and FDA;
- Applicant's presentation to FDA on September 17, 2012;

- Major efficacy and safety analyses reproduced or audited using the SAS datasets.
- Review of patient narratives in selected cases;
- Review of previous clinical review completed for the original NDA approval;
- Review of the current product labeling;
- Requests for additional information from the Sponsor;
- Evaluation of proposed labeling and revision of labeling.
- Relevant published literature; and
- The 120-day safety update

Trial 14935, a supportive phase 2 trial, was not reviewed as Bayer did not have the trial database for an investigator-initiated study; therefore, it was not submitted. Only the efficacy and safety summary data were reviewed.

### 5.3 Discussion of Individual Studies/Clinical Trials

#### 5.3.1 Clinical Trial BAY 73-4506/14874

##### **Trial title**

A randomized, double-blind, placebo-controlled phase III trial of regorafenib plus best supportive care versus placebo plus best supportive care for subjects with metastatic and/or unresectable gastrointestinal stromal tumors (GIST) whose disease has progressed despite prior treatments with at least imatinib and sunitinib

##### **Protocol milestones**

Table 5. Protocol milestones

Milestone	Date	# Patients Entered
Protocol Original Version under IND 75642	October 5, 2010	0
Amendment 1 – SDN 210 Protocol Version 2.0 (IND 75642)	February 9, 2011	4
Amendment 2 – SDN 309 Protocol Version 3.0 (IND 75642)	July 26, 2011	162
Amendment 3 – SDN 334 Protocol Version 4.0 (IND 75642)	September 27, 2011	199
Statistical Analysis Plan, version 1	January 26, 2012	199
Statistical Analysis Plan, version 1.1	March 26, 2012	199
First patient recruited	January 10, 2011	
Last patient recruited	July 28, 2011	
Trial closed to accrual	August 18, 2011	
PFS at 122 events	November 3, 2011	
PFS at 144 events	January 26, 2012	
Database lock	January 26, 2012	
Initial portion (CMC and nonclinical) of rolling NDA submission	May 31, 2012	
Final portion (clinical) of rolling NDA submission	August 30, 2012	
Clinical trial report and datasets submission	August 30, 2012	

SDN = Supporting Document Number

Reviewer's comment: Statistical Analysis Plan (SAP), version 1, dated January 26, 2012, will be used for the efficacy analyses, given that the database lock occurred on January 26, 2012. The SAP, version 1.1, was amended after the database lock.

### 5.3.2 Protocol Amendments for Trial BAY 73-4506/14874

#### **Amendment 1 – SDN 210:** February 9, 2011

Number of patients randomized: 4

1. Clarification of procedures during follow-up periods, including tumor assessment and safety assessment schedule for patients who had been on placebo and cross-over to regorafenib and discontinue treatment due to other reasons, clarification of ongoing studies in the introduction, and clarification and revision of procedures.

2. Clarification of dose reductions
  - Dose reductions to lower than 80 mg are not allowed. If the dose would need to be reduced to a dose lower than 80 mg, treatment will be discontinued.
3. Re-screening of screen failures
  - Patients may be re-screened if they were previously a screen failure. A new patient number must be assigned via IVRS/IWRS. This will be handled on a case by case basis after review by the CRO. Patients can only be re-screened once.
4. Modification of RECIST v 1.1
  - The RECIST criteria (version 1.1) will be used (modified and clarified as described below) for the primary and several of the secondary variables.
  - For this trial, following modifications to the RECIST criteria (version 1.1) will be implemented (details will be laid out in the imaging charter):
    - no lymph nodes will be chosen as target lesions. Enlarged lymph nodes will be followed as non-target lesions
    - no bone lesions may be chosen as target lesions
    - PET scan is not acceptable for radiological evaluation.

Additionally, one clarification to the RECIST criteria (version 1.1) is considered relevant for GIST tumor assessments. A progressively growing new tumor nodule within a pre-existing tumor mass must meet the following criteria to be considered as “unequivocal evidence” of progression by the modification to RECIST 1.1 that we will use consistently throughout this clinical trial:

- lesion is at least 2 cm in size and definitively a new active GIST lesion (e.g. enhancing with contrast or other criteria to rule out artifact) or
  - lesion must be expanding on at least 2 sequential imaging studies.
5. Change in exclusion criteria and change in nonpermissible concomitant medications and treatments
    - Exclude patients who have received any other approved tyrosine kinase inhibitor within 1 week or a minimum of 5 drug half-lives, whichever is longer (i.e. within 7 days for imatinib, or within 10 days for sunitinib) and any other investigational new drugs within 4 weeks or 5 drug half-lives (if drug half-life in patients is known), whichever is shorter.
    - Allow patients taking chronic erythropoietin.
    - Concomitant palliative radiation therapy of any kind is not allowed.
    - Grapefruit or grapefruit juice is not allowed.
  6. Drug diary provided to trial participants

Reviewer’s comment: The original protocol was submitted to IND 75,642 on October 5, 2010, and Amendment #1 was submitted on February 9, 2011. Applicant modified the
--

RECIST v 1.1 criteria for assessing tumor response to capture disease progression of a new nodule in a pre-existing tumor mass. A nodule within a mass is considered a sign of recurrent GIST. These modifications to RECIST are more conservative for determination of disease progression.

**Amendment 2 – SDN 309:** July 26, 2011

Number of patients randomized: 162

1. To monitor hepatic function, include weekly monitoring of AST, ALT, and bilirubin for the first two cycles of treatment.
2. Following Cycle 4, safety assessments were performed at Day 1 of each subsequent cycle; safety assessments at Day 15 were left to the discretion of the investigator. This amendment requires that safety assessments be performed at Day 15 of Cycle 5 and Cycle 6 (in addition to Day 1), and permits Day 15 safety assessments to be discretionary at Cycle 7 and subsequent cycles.
3. Clarification of hand-foot-skin reaction (HFSR). NCI CTCAE v.4 does not have a classification for HFSR. Instead, sites must select 'palmar-plantar erythrodysesthesia syndrome' for investigator HFSR verbatim terms, as this is comparable to the old HFSR definitions in CTCAE version 3.
4. Clarification of adverse events of special interest (AESI). Addition of AESIs occurring during the observation period must be reported immediately, in addition to SAEs.
5. To minimize the risk of postural hypotension and renal failure, language was added to carefully monitor patients who develop diarrhea, mucositis, anorexia or other events predisposing to fluid loss or inadequate fluid intake and rehydrate as clinically necessary.

Reviewer's comment: Amendment 2 was submitted on July 26, 2011, nine months after the trial commenced. The changes to the protocol in the amendment are all safety-related and add more safety monitoring, especially for hepatic toxicity.

**Amendment 3 – SDN 275:** September 27, 2011

Number of patients randomized: 199

1. Increase the number of PFS events required for analysis of the primary efficacy endpoint from 122 to 144 PFS events, and to increase the number of patients randomized, from approximately 170 (planned) to 199 patients, the final number of randomized patients.

2. Allow patients who are on the placebo + BSC arm to cross over to active treatment with regorafenib, if the primary endpoint trial results support a positive benefit:risk ratio.

Reviewer's comment: Bayer's rationale for increasing the primary efficacy endpoint from 122 to 144 PFS events is due to accrual much faster than anticipated, resulting in over-recruitment of 29 patients. Bayer stated that not increasing the number of PFS events would result in an increase of censored patients and a weaker characterization of PFS and hazard ratio.

Two letters, dated March 9, 2012, and March 20, 2012, were sent by FDA to Bayer in reference to the SAP submitted by Applicant on February 7, 2012. In the March 9, 2012 letter, FDA stated:

*"The primary progression free survival (PFS) analysis and the overall survival (OS) analysis should be performed with 122 PFS events and 136 deaths, respectively, as originally planned. We do not agree that the analyses will be performed with 144 PFS events and 160 deaths since the rationale of increasing the number of events for the analyses is not clear and it will result in overpowering of the study."*

On March 20, 2012, FDA reiterated its concerns regarding the statistical analysis:

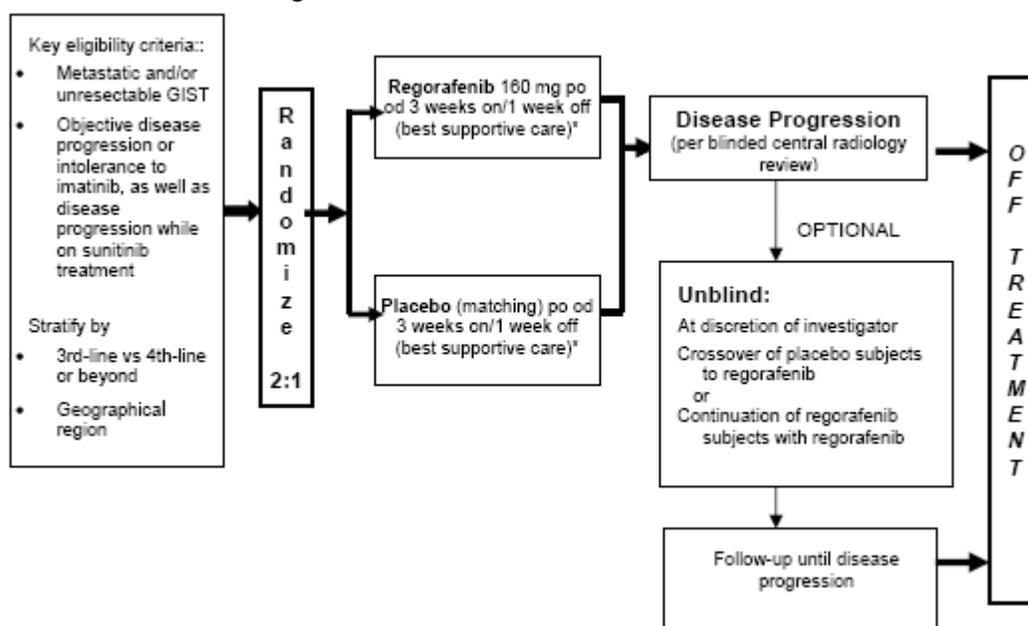
*"In well controlled and adequately conducted trials, the primary analysis should be performed according to the original protocol. Modifications without convincing clinical rationale are strongly discouraged because potential bias may be introduced. In your Phase 3 study, Protocol 14874, despite the fact that 29 additional subjects were enrolled, the primary analysis should still be performed based on the originally planned 122 PFS events. However, if Bayer strongly prefers to change the primary analysis from 122 PFS events to 144 PFS events, FDA will consider the primary objective fulfilled only if tests at both 122 and 144 PFS events are statistically significant."*

### **5.3.3 Design of Trial BAY 73-4506/14874**

BAY 73-4506/14874 was a multinational, randomized, double-blind, placebo-controlled phase 3 trial of regorafenib plus BSC versus placebo plus BSC for patients with metastatic and/or unresectable GIST whose disease had progressed despite prior treatment with at least imatinib and sunitinib. Best supportive care included any method to preserve the comfort and dignity of the patients, and excluded any disease-specific anti-neoplastic therapy such as any kinase inhibitor, chemotherapy, radiation therapy, or surgical intervention. One hundred ninety-nine patients who met eligibility criteria were randomized (2:1) to receive regorafenib or placebo. For the treatment arm, regorafenib was administered 160 mg orally once daily, three weeks on and one week off, constituting one cycle. Patients were stratified according to lines of prior treatment

(third versus fourth line or more); at least 50% of patients must have received third line therapy, and geographical region (Asia versus rest of world). Patients who received placebo were offered open-label (cross-over option) after objective tumor progression by central review, and patients could have continued treatment with regorafenib even after first progression for those who were on the regorafenib arm, or after second progression for those who crossed over.

Figure 1. Overall Trial Design



Adapted from Figure 1. Overall trial design, Section 3, Trial Design, Statistical Analysis Plan, Version 1.1, p. 8.

### **Objectives:**

1. Primary objective: compare treatment groups using PFS per central radiology review, according to modified RECIST criteria.
2. Secondary objectives: compare regorafenib and placebo treatment groups in terms of overall survival (OS), time to progression (TTP), disease control rate (DCR), tumor response rate (RR), duration of response (DOR), and safety of regorafenib.
3. Exploratory objectives: compare treatment groups in terms of health-related quality of life (HRQoL), to describe the pharmacokinetics of regorafenib, and to conduct a biomarker evaluation of regorafenib.

The primary endpoint as stated in the SAP submitted on February 7, 2012, and per agreement with FDA in letters dated March 9, 2012 and March 20, 2012, was PFS based on BCRR. Final analysis was to be performed as originally planned at 122 PFS events; however, Bayer changed the primary analysis from 122 PFS events to 144 PFS

events, per Amendment 3. FDA stated that the primary objective would be fulfilled only if tests at both event analyses were statistically significant. The power to detect an improvement in PFS of 100% would be increased from 90% to 94%.

Randomized therapy was administered daily until disease progression or withdrawal from therapy, e.g., unacceptable toxicity, withdrawal of consent, death. Safety assessments were performed on days 1 and 15 of each cycle for the first six cycles and beyond cycle 6, day 15 safety assessments were at the discretion of the investigator. Efficacy assessments were every four weeks (or less, if clinically indicated) for the first 3 months, every six weeks (or less, if clinically indicated) for the next three months (through month 6), and every 8 weeks (or less, if clinically indicated) until the end of treatment (> 6 months of treatment). Tumor assessments were performed until objective tumor progression per central radiology review.

**Eligibility criteria:**

Inclusion criteria:

1. Signed informed consent form (ICF) obtained before any trial specific procedures.
2. Male or female patients  $\geq$  18 years of age.
3. Histologically confirmed metastatic and/or unresectable GIST.
4. At least imatinib and sunitinib as prior treatment regimens, with objective disease progression or intolerance to imatinib, as well as disease progression while on sunitinib therapy. Additionally, disease progression or intolerance to other systemic therapies, as well as investigational new agents, was allowed, except prior treatment with any other vascular endothelial growth factor receptor (VEGFR) inhibitor.
5. Patients must have had at least one measurable lesion according to modified RECIST, version 1.1. A lesion in a previously irradiated area was eligible to be considered as measurable disease as long as there was objective evidence of progression of the lesion prior to trial enrollment.
6. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1.
7. Adequate bone marrow, liver, and renal function, as assessed by the following laboratory requirements conducted within 7 days of starting trial treatment.
8. Recovery to NCI-CTCAE v4.0 Grade 0 or 1 level or recovery to baseline preceding the prior treatment from any previous drug/procedure-related toxicity (except alopecia, anemia, and hypothyroidism).

Exclusion criteria:

1. Prior treatment with regorafenib. Patients permanently withdrawn from trial participation were not allowed to re-enter the trial.
2. Prior treatment with any vascular endothelial growth factor receptor (VEGFR) inhibitor except sunitinib.
3. Patients who received:
  - a. any other approved tyrosine kinase inhibitor within 1 week or a minimum of 5 drug half-lives, whichever is longer (i.e. within 7 days for imatinib, or within 10 days for sunitinib).
  - b. any other investigational new drugs within 4 weeks or 5 drug half-lives (if drug half-life in patients is known), whichever is shorter.
4. Cancer other than GIST within 5 years prior to randomization except for curatively treated cervical cancer in situ, non-melanoma skin cancer, and superficial bladder tumors (Ta [Non-invasive tumor], and Tis [Carcinoma in situ]).
5. Major surgical procedure, open biopsy, or significant traumatic injury within 28 days before start of trial medication.
6. Congestive heart failure New York Heart Association (NYHA)  $\geq$  class 2.
7. Unstable angina or myocardial infarction (MI) within the past 6 months before start of trial medication.
8. Cardiac arrhythmias requiring anti-arrhythmic therapy (beta blockers or digoxin are permitted).
9. Uncontrolled hypertension (systolic blood pressure  $>$  140 mm mercury (Hg) or diastolic pressure  $>$  90 mmHg despite optimal medical management).
10. Arterial thrombotic or embolic events, or venous thrombotic events.
11. Patients with evidence or history of bleeding diathesis. Any hemorrhage or bleeding event  $>$  NCI-CTCAE version 4.0 grade 3 or higher within 4 weeks prior to the start of trial drug.
12. Interstitial lung disease with ongoing signs and symptoms at the time of screening.
13. Persistent proteinuria of NCI-CTCAE version 4.0 grade 3 or higher.
14. Close affiliation with the investigational site, e.g., a close relative of the investigator or dependent person (e.g., employee of or student at the investigational site who would have access to trial records and case report form [CRF] data).
15. Left ventricular ejection fraction (LVEF)  $<$  50% or below the lower limit of normal (LLN) for the institution (whichever is higher).

Reviewer's comment: Applicant changed inclusion criteria #5 to use *modified* RECIST criteria, version 1.1, per Amendment 1 (refer Section 5.3). Additionally, exclusion criteria #3 was added for a washout period for other investigational new drugs. The original protocol only provided a washout period for other tyrosine kinase inhibitors.

**Randomization and stratification:**

Patients received treatment according to a 2:1 randomization schema, regorafenib+ BSC or placebo + BSC. Patients were identified by a unique subject number. The protocol stated that at least 50% of the patients will have had only imatinib and sunitinib as prior treatment for GIST, making regorafenib the third-line treatment for these patients. This was accomplished via an Interactive Voice Response System (IVRS)/Interactive Web Response System (IWRS). All centers were notified when the maximum number patients in the 4<sup>th</sup>-line or beyond stratification group were recruited into the trial. All further patients had to be from the stratification group receiving third-line treatment.

Patients were stratified at randomization according to:

- Third-line versus fourth-line or more; at least 50% of patients must be third-line
- Geographical region (Asia versus rest of world)

**Monitoring**

Figure 2. Safety Monitoring Schedule

Study Periods	Screening Period (Assessments can be completed in one or more visits, as long as they are completed within the time frames.)			Treatment Period						Survival Follow-up Period
	Within 28 days	Within 14 days	Within 7 days	Cycle 1 (4 weeks)		Cycle 2+ (4 weeks)		End of Treatment	Safety Follow-up	
Procedures and Assessments	Within 28 days	Within 14 days	Within 7 days	Day 1	Day 15	Day 1	Day 15 <sup>a</sup>	Within 14 days	Within 30 days	Every 3 months
Informed consent	X									
Inclusion/exclusion criteria checked		X		X						
Demographics	X									
Diagnosis confirmation	X									
Past tumor specific therapy (including radiotherapy and surgery)	X									
Complete medical history	X									
Tumor assessment <sup>b</sup>		X				X <sup>b</sup>		X		
Bone scan (if bone metastases are suspected)	X									
Head CT or MRI (if brain metastases are suspected)	X									

Study Periods	Screening Period (Assessments can be completed in one or more visits, as long as they are completed within the time frames.)			Treatment Period						Survival Follow-up Period
	Within 28 days	Within 14 days	Within 7 days	Cycle 1 (4 weeks)		Cycle 2+ (4 weeks)		End of Treatment	Safety Follow-up	
Procedures and Assessments	Within 28 days	Within 14 days	Within 7 days	Day 1	Day 15	Day 1	Day 15 <sup>a</sup>	Within 14 days	Within 30 days	Every 3 months
12-lead ECG	X			X		X <sup>c</sup>		X		
Echocardiography or MUGA (LVEF assessment)	X <sup>d</sup>			X <sup>d</sup>						
Adverse events & toxicities				X <sup>e</sup>						
Concomitant medications				X						
ECOG performance status		X		X		X		X		
Physical examination		X		X		X		X		
CBC with differential			X	X <sup>f</sup>	X	X	X <sup>a</sup>	X		
Chemistry & electrolyte panel			X	X <sup>f</sup>	X	X	X <sup>a</sup>	X		
Urinalysis			X	X <sup>f</sup>	X	X	X <sup>a</sup>	X		
Thyroid function test (TSH, T3, T4)			X	X <sup>f</sup>		X				
Coagulation panel (PT/PT-INR, PTT)			X	X <sup>g</sup>		X		X		
Pregnancy test (if applicable)			X							
Pharmacokinetic sampling							X <sup>h</sup>			

Clinical Review  
 Jennie Chang and Amir Shahlaee  
 NDA 204369/Type 9  
 Stivarga (regorafenib)

Study Periods	Screening Period (Assessments can be completed in one or more visits, as long as they are completed within the time frames.)			Treatment Period						Survival Follow-up Period
	Within 28 days	Within 14 days	Within 7 days	Cycle 1 (4 weeks)		Cycle 2+ (4 weeks)		End of Treatment	Safety Follow-up	
Procedures and Assessments				Day 1	Day 15	Day 1	Day 15 <sup>a</sup>	Within 14 days	Within 30 days	Every 3 months
Blood biomarker sampling			X <sup>i</sup>	X <sup>i</sup>	X <sup>i</sup>		X <sup>i</sup>	X <sup>i</sup>		
Tumor biopsy biomarker sampling	X <sup>i</sup>									
Randomization				X						
Blood pressure monitoring		X			X <sup>j</sup>					
Patient-reported Quality of Life Questionnaires				X		X <sup>k</sup>		X		
Drug dispensing				X		X				
Drug accountability					X	X	X <sup>a</sup>	X		
Anti-cancer medications									X	X
Survival assessment										X

- a After 4 cycles, Day 15 assessments can be done at the discretion of the investigator. After individual subject unblinding, safety assessments for subjects who continue on regorafenib will be performed on day 1 (+/- 7 days) of each cycle, and for subjects who crossed-over to regorafenib additional safety assessments will be performed on day 15 (+/- 7 days) for the first 4 cycles (for cycles thereafter, conducting the day 15 assessments is at the discretion of the investigator).
- b **Tumor assessments:** Tumor assessment during the screening period must be performed within 14 days of starting study drug (definitely within no longer than 21 days). Tumor assessment will be every 4 weeks (or less weeks, if clinically indicated) for the first 3 months, every 6 weeks (or less weeks, if clinically indicated) for the next 3 months (through month 6), and every 8 weeks (or less weeks, if clinically indicated) until the end of treatment (> 6 months on treatment). Tumor assessments will be performed until progressive disease (per blinded central radiology review).
- c **12-lead electrocardiogram (ECG):** After 6 cycles, ECG can be performed based on the investigator's discretion.
- d **Echocardiogram or MUGA (LVEF assessment):** An echocardiogram or MUGA is mandatory during screening. During treatment, an echocardiogram or MUGA should only be performed if clinically indicated.
- e **Adverse events and toxicities:** AE assessment to be started after signing of informed consent until 30 (± 7) days after last study treatment.
- f **Laboratory evaluations:** The laboratory evaluations are not required at Day 1 of Cycle 1 if these were completed within 7 days of starting study drug treatment. Laboratory values for study result analyses will be those provided by the study central laboratory. The investigators may use local laboratory values for subject treatment decisions. Any relevant local laboratory results should be recorded in the CRF.
- g **Coagulation panel (PT/PT-INR, PTT):** If a subject is on warfarin with stable PT/INR at baseline, the PT/INR should be assessed on Day 5. If value is above the acceptable range, the dose should be modified and the assessment should be repeated weekly until it is stable. This information will be recorded in the CRF.
- h **Pharmacokinetic sampling:** One pre-dose sample from all subjects at selected study sites on Day 15 of Cycle 2.
- i **Biomarker sampling:** Archived and fresh tumor biopsies will be collected during screening. Archived biopsies will be collected from subjects who consent to the collection and use of archived biopsy material for biomarker analyses. Fresh biopsies will be collected from subjects who consent to the collection and use of the fresh biopsy material for biomarker analyses and for whom the biopsy procedure is deemed safe and appropriate. It is preferred that tumor biopsies be submitted for biomarker analysis as formalin fixed paraffin-embedded (FFPE) blocks; however freshly prepared unstained slides are also acceptable (at least 12 slides, if possible), as is frozen tissue. A whole blood sample will be collected during screening (within 7 days prior to start of study drug) from subjects who provide consent for the collection and use of the blood sample for genetic biomarker analyses. Plasma samples will be collected at screening (within 7 days prior to start of study drug), Cycle 1/Day 1 (prior to start of study drug), Cycle 1/Day 15, Cycle 2/Day 15, Cycle 3/Day 15 and end of treatment from subjects who provide consent for the collection and use of the plasma samples for biomarker analyses.
- j **Blood pressure monitoring:** At least weekly, or more frequently, for first 6 weeks of treatment. Blood pressure can be measured by the treating physician or designee and entered into the CRF on the required visits or measured by the subject and entered into a subject diary. In the latter case, the subject should be instructed to contact the physician in the event of systolic ≥ 140 mmHg and/or diastolic ≥ 90 mmHg. The physician should confirm the reading before recording it into the CRF.
- k **Patient reported QoL questionnaires:** The European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 and EuroQoL five dimension questionnaire (EQ-5D) should be self-administered by the subject at the start of the visit before the subject sees the physician and before any study related procedures are done so that any interaction between the subject and physician or other health care provider will not influence the responses to the questionnaires. Questionnaires should be administered at baseline (Day 1 of Cycle 1), Day 1 of Cycles 2-4, then Day 1 of every other cycle (Cycles 6, 8, etc) thereafter, and at the end of treatment visit. The site personnel should complete the Patient Reported Outcomes Information Sheet.

ECG = electrocardiogram; PT = prothrombin time

Adapted from Table 7-1: Schedule of procedures and assessments (as of Amendment 2), in Section 7.1.1, Tabulated overview, Clinical Study Protocol, No. BAY 73-4506/14874

Reviewer's comment: Modified RECIST and additional safety monitoring were added in Amendment 2. A Data Monitoring Committee (DMC) was used to monitor ongoing safety of patients and the operation was guided by a DMC charter. Tumor assessments were performed every 4 weeks for the first 3 months, then every 6 weeks for the next 3 months (through month 6 on-trial) and every 8 weeks until end of trial drug administration.

**Endpoints:**

1. Primary:
  - Progression-free survival (PFS), per blinded central radiology review, using modified RECIST v 1.1.
  
2. Secondary:
  - Overall survival
  - Time to progression
  - Disease control rate
  - Tumor response rate
  - Duration of response
  
3. Exploratory
  - Secondary PFS after progression
  - Health-related quality of life (HRQoL)
  - Health utility values
  - Pharmacokinetics of regorafenib
  - Biomarker evaluation of regorafenib

Reviewer's comment: Bayer amended the tumor assessment criteria to *modified* RECIST v1.1 in Amendment 1. Bayer was informed in a letter from FDA dated March 20, 2012 that DCR is unlikely to be included in the label, as this is not considered a regulatory endpoint. HRQoL and healthy utility values will be measured using the European Organization for Research and Treatment of Cancer (EORTC) Core Quality of Life Questionnaire (QLQ-C30) version 3.0 and EuroQol five dimensions questionnaire (EQ-5D).

**Statistical Analysis Plan (SAP):**

The primary population for efficacy analysis was the intent-to-treat population, which consisted of all randomized patients. For the safety analysis, the population consisted of all patients who received at least one dose of trial medication.

The primary efficacy endpoint was PFS in the intent-to-treat per BCRR; the analysis was to be performed when approximately 122 PFS events were observed in

approximately 170 patients in the ITT population. Based on the over-recruitment of 29 patients (199 patients randomized), the target number of PFS events was increased to 144 to maintain the grade of maturity of the trial, as modified in Amendment 3. The power to detect an improvement in PFS of 100% would be increased from 90% to 94%.

The two arms were compared using a stratified log-rank test with a one-sided alpha of 0.01 stratified by lines of prior systemic therapy and geographical region, at randomization. The null hypothesis that both treatment arms had the same PFS distribution was tested against the alternative hypothesis that the distribution of PFS times in the regorafenib arm was different from the control arm according to the Lehmann alternative.

Assuming a one-sided alpha of 0.01, a power of 90%, a 100% increase in median time to PFS, and an allocation ratio of 2:1 between the experimental and the control arm, 144 events were required.

With the additional assumptions:

- Patients enrolled at a rate of 20 per month
- An exponential distribution of the PFS event times
- Median time of PFS in the control group of 6 weeks
- Five percent drop-out rate of patients evaluable for PFS
- Four months of enrollment ramp-up period

An interim analysis of OS was performed at the time of PFS analysis. A final analysis of OS was planned when approximately 160 events had occurred. Because of the increase in the enrollment of patients to 199, the number of survival events increased from 136 events to 160 events, by the same ratio as the number of PFS events. This would provide an 84% power to detect a 67% increase in median time to death from 6 months in the placebo plus BSC arm to 10 months in the regorafenib arm with a one-sided alpha of 0.025. The O'Brien-Fleming boundary was used for determination of the significance thresholds.

### **Efficacy variables**

Progression-free survival (PFS): measured from the date of randomization until the date of radiological progression or death (if death occurs before progression). Patients without tumor progression or death at the time of analysis will be censored at their last date of radiological tumor assessment. The date of disease of progression will be the date of first observation of progression.

Overall survival (OS): date of randomization until the date of death due to any cause. If a patient is alive at the date of database cutoff then it will be censored at the database cutoff date.

Time to progression (TTP): date of randomization until the date of radiological progression. Patients without tumor progression at the time of analysis will be censored at their last date of radiological tumor assessment. The date of progression will be the date of first observation of progression.

Tumor response rate: defined as the proportion of patients with the best overall tumor response of partial response (PR) or complete response (CR) according to modified RECIST criteria (version 1.1) that is achieved during treatment or within 30 days after termination of trial medication.

Duration of response (DOR): number of days from the date of first documented objective response of PR or CR, whichever is noted earlier, to first disease progression or death before progression. Patients without progression or death before progression at the time of analysis will be censored at the date of their last tumor assessment.

## 6 Review of Efficacy

*Please refer to statistical review conducted by Xiaoping (Janet) Jiang, Ph.D., statistical reviewer, Division of Biometrics V, Office of Biostatistics, for this application review, under separate cover. Unless otherwise stated, the descriptive analyses were conducted by the clinical reviewer for efficacy (J. Chang).*

### **Efficacy Summary**

The efficacy of regorafenib in metastatic and/or unresectable GIST after disease progression with imatinib and sunitinib was evaluated in a multicenter, double-blind, randomized, placebo-controlled phase 3 comparison of regorafenib plus BSC versus BSC in trial 14874. Patients with histologically confirmed metastatic and/or unresectable GIST were randomized in 2:1 to receive regorafenib or placebo. Treatment consisted of regorafenib 160 mg orally once daily, three weeks on and one week off, with matching placebo. Stratification factors were prior line of treatment (third-versus fourth-line) and geographical region (Asia versus rest of world). Treatment continued until patients experienced disease progression, death, development of a second malignancy, pregnancy, unacceptable toxicity, noncompliance, or withdrew consent. Patients randomized to placebo were permitted to crossover to open-label Stivarga at time of progression, and patients randomized to Stivarga were permitted to continue treatment based on investigator's judgment upon evidence of progression. Radiographic assessments of response were performed every 4 weeks for the first 3 cycles, then every 6 weeks for cycles 4-6, and after cycle 6, every 8 weeks.

The primary endpoint was originally PFS in a planned sample size of 170 randomized patients and approximately 122 PFS events for the final analysis, based on improvement in median PFS of 100%, from six weeks to 12 weeks. The one-sided type I error was set to 0.01, power was 0.90. However, the primary endpoint was changed in

Amendment 3 (September 27, 2011) increased the number of PFS events required for analysis of the primary efficacy endpoint from 122 to 144 PFS events, and number of patients randomized, from approximately 170 (planned) to 199 patients, the final number of randomized patients.

Assessment of efficacy was based on the primary endpoint of PFS assessed by BCRR and the key secondary endpoint of OS. The clinical reviewer's (J. Chang) recommendation for approval was based on review of clinical data, which supported the conclusion that regorafenib prolonged progression-free survival in a patient population that had failed imatinib and sunitinib, a population for whom no other therapy was approved. A statistically significant, clinically meaningful median difference in PFS of 3.91 months was observed in patients randomized to receive regorafenib. Median PFS was 4.83 months in the regorafenib arm, compared to 0.92 months in the placebo arm, with a hazard ratio of 0.27 (95% CI: 0.19, 0.39; p-value <0.0001). Although there was a concern that a single study is not adequate to establish clinical efficacy, the results of Trial 14874 were robust as they withstood numerous sensitivity analyses, and were consistent with investigator-assessed PFS results and across patient subsets. Interim OS survival analysis was not mature at the time of PFS analysis.

Currently, no FDA-approved therapy exists for patients with heavily pretreated GIST. An open-label, phase 2 study (n=33) by George et al., initially provided evidence of clinical activity of regorafenib in patients with metastatic or unresectable GIST after failure of imatinib and sunitinib. The results were confirmed in Trial 14874. Although the overall survival results are not mature and will most likely be confounded given the crossover, the aforementioned efficacy results provide evidence that regorafenib has a role as third-line treatment for this patient population, after failure of imatinib and sunitinib with a durable median PFS of 4.83 months. Furthermore, results of subgroup analyses reveal that regorafenib is effective in patients regardless of age, gender, geographical location, ECOG performance status, or KIT mutational status.

The clinical reviewer (J. Chang) concludes that Trial 14874 demonstrated adequate evidence of clinical benefit to support the proposed indication, modified in Section 6.1 Indication.

## 6.1 Indication

The indication is, "Stivarga is a kinase inhibitor indicated for the treatment of patients with locally advanced, unresectable, or metastatic gastrointestinal stromal tumor (GIST) who have been previously treated with imatinib mesylate and sunitinib malate."

Reviewer's comment: "Locally advanced" was added to better characterize the patient population enrolled in Trial 14874. Additionally, "and" was removed from "unresectable and/or metastatic" as it was determined to be unnecessary.

### 6.1.1 Methods

This review focused primarily on the efficacy results of the single randomized, placebo-controlled, phase 3 trial, Trial 14874. For information on 14874 trial design, see section 5.3.1.

The original trial protocol and protocol amendments were reviewed for accuracy, and compared to the advice provided by FDA in meeting minutes and written correspondence. The efficacy results provided in Trial 14874 were analyzed for consistency, by comparing central radiological review and investigator-assessed review, by verifying the accuracy of documented tumor measurements reported in case report forms (CRFs) and recorded in datasets. The CRFs were also reviewed for completeness of data.

With the statistical reviewer's assistance, discrepancies in evaluation of tumor lesions between the central radiological review and investigator were also inspected. Factors that might affect the efficacy analyses, such as withdrawal from trial, intolerable toxicities, and missing or imbalanced efficacy assessments, were evaluated. Statistical analyses were performed by the statistician and clinical reviewer for efficacy and were compared to the applicant's trial reports. Multiple subgroup and sensitivity analyses were conducted to confirm the robustness of the primary outcome measure.

### 6.1.2 Demographics

Trial 14874 enrolled 199 patients at 53 sites in 17 countries. The baseline demographics and tumor characteristics are summarized in Table 6 and Table 7. Two-thirds of the patients were less than 65 years old, with the mean age of 58.1 years. Sixty-four percent of patients were men and 68% of the patients were white. All patients had an ECOG performance status of 0 or 1 at the time of trial enrollment. The predominant primary tumor site was the stomach (37%) and over 60% had metastatic disease at time of study entry. All patients had been previously treated with imatinib and sunitinib, and in 57% of patients, enrollment into the study was considered third-line treatment. Fifty-three percent of patients were positive for the KIT exon 11 mutation.

Table 6. Baseline Demographics

Parameter	Regorafenib + BSC, N=133 (%)	Placebo + BSC, N=66 (%)	Total N=199 (%)
Gender			
Female	48 (36)	24 (36)	72 (36)
Male	85 (64)	42 (64)	127 (64)
Age (years)			
Median	60	61	60
Mean	58	58	58
Range	18-82	25-87	18-87
Race			
White	90 (68)	45 (68)	135 (68)
Asian	34 (26)	16 (24)	50 (25)
Black or African American	0	1 (2)	1 (1)
Not reported	7 (5)	4 (6)	11 (6)
Missing	2(2)	0	2 (1)
ECOG Performance Status, n			
0	73 (55)	37 (56)	110 (55)
1	60 (45)	29 (44)	89 (45)
Ethnicity			
Hispanic			
Non-Hispanic/Unknown			
Geographical region			
Asia	32 (24)	15 (23)	47 (24)
Rest of world	101 (76)	51 (77)	152 (76)
North America	22 (17)	14 (21)	36 (18)
Non-North America	111 (84)	52 (79)	163 (82)

Extracted from DM dataset and ADSL dataset and from Table 8-10, Baseline demographic and disease characteristics (FAS), p. 110, Clinical Study Report, A59137

Table 7. Baseline Tumor Characteristics

Tumor characteristic	Regorafenib, N=133 (%)	Placebo + BSC, N=66 (%)	Total N=199 (%)
Primary tumor site location			
Colon ascending	1 (1)	0	1 (<1)
Colon sigmoid	2 (2)	0	2 (1)
Duodenum	11 (8)	4 (6)	15 (8)
Ileum	16 (12)	7 (11)	23 (12)
Jejunum	22 (17)	10 (15)	32 (16)
Mesentery	5 (4)	2 (3)	7 (4)
Omentum	0	1 (2)	1 (<1)
Rectum	4 (3.0)	1 (2)	5 (3)
Stomach	50 (38)	23 (35)	73 (37)
Undetermined	20 (15)	14 (12)	34 (17)
Extent of disease at diagnosis			
Metastatic	85 (64)	37 (56)	122 (61)
Unresectable	5 (4)	10 (15)	15 (8)
Metastatic and unresectable	33 (25)	12 (18)	45 (23)
Multifocal, but confined to stomach	7 (5)	3 (5)	10 (5)
Missing	3 (2)	4 (6)	7 (4)
Histology			
Epitheloid	12 (9)	4 (6)	16 (8)
Mixed	18 (14)	10 (15)	28 (14)
Spindle cells	66 (50)	30 (46)	96 (48)
Unknown	32 (24)	18 (27)	50 (25)
Missing	5 (4)	4 (6)	9 (5)
Number of tumor sites			
1	16 (12)	9 (14)	25 (13)
2	31 (23)	20 (30)	51 (26)
3	39 (29)	13 (20)	52 (26)
4	21 (16)	9 (14)	30 (15)
≥5	26 (20)	15 (23)	41 (21)
Prior anti-cancer drug group			
Third line	74 (56)	39 (59)	113 (57)
Fourth line and beyond	59 (44)	27 (41)	86 (43)
Any mutation	60 (45)	36 (55)	96 (48)
KIT mutation			
Exon 9	9 (15)	6 (17)	15 (16)
Exon 11	34 (57)	17 (47)	51 (53)
Not assessed	73 (55)	30 (46)	103 (52)

Source: FA, ADBCC, ADSL.xpt, and ADXP.xpt datasets

Reviewer's comment: Baseline demographics were well-balanced between treatment and control arms. Age and gender were representative of the overall GIST population.

All patients, except for one, enrolled in Trial 14874 had received prior surgery. Less than ten percent of patients had received prior radiation. All patients had received systemic therapy, consisting of prior imatinib and sunitinib, per trial protocol. About half of the patients had received the maximum dose of imatinib at 800 mg daily. Between 20-30% of patient were also treated with other tyrosine kinase inhibitors, nilotinib and dasatinib.

Table 8. 14874 Prior GIST Treatment

Treatment	Regorafenib, N=133 (%)	Placebo, N=66 (%)
Prior surgery	132	66 (100)
Prior radiation	4 (6)	5 (3.8)
Prior Systemic Therapy		
Imatinib	133 (100)	66 (100)
Imatinib 400 mg	43 (32)	20 (30)
Imatinib 800 mg	68 (51)	34 (52)
Sunitinib	133 (100)	66 (100)
Nilotinib	29 (22)	20 (30)
Other tyrosine kinase inhibitor	2 (2)	1 (2)
mTOR inhibitor	3 (2)	1 (2)
Cytotoxic chemotherapy	13 (10)	2 (3)
Other	5 (4)	1 (2)

Source: ADCM.xpt and ADXP.xpt datasets and response to information request from Bayer, dated October 2, 2012 (prior imatinib daily dose).

**Reviewer's comments:** More patients in the regorafenib arm were exposed to systemic therapy after imatinib and sunitinib, consisting of nilotinib and cytotoxic chemotherapy. Therefore, these patients may have had more treatment-resistant disease. Additionally, about half of the patients had failed treatment with imatinib 800 mg daily. Patients often initiate dosing at 400 mg daily, but may benefit from dose escalation to 800 mg daily if patients present with KIT exon 9 mutation, or have disease progression.

As shown in Table 9, both arms were well-balanced in terms of the number of patients who received systemic anti-cancer therapy during follow-up. Slightly more patients in the placebo arm continued to receive tyrosine kinase inhibitors after trial treatment. In some cases, the same tyrosine kinase inhibitor, imatinib and sunitinib, as prior systemic therapy, was re-administered.

Table 9. 14874 Subsequent GIST Treatment

	<b>Regorafenib, N=133 (%)</b>	<b>Placebo, N=66 (%)</b>
Number of patients	20 (15)	10 (15)
Types of anti-cancer therapy		
Tyrosine kinase inhibitor	22 (17)	14 (21)
Imatinib	9 (7)	4 (6)
Nilotinib	4 (3)	0
Pazopanib	1 (1)	0
Sorafenib	6 (5)	5 (8)
Sunitinib	2 (2)	1 (2)
Other <sup>†</sup>	4 (3)	1 (2)
Investigational agents	2 (2)	3 (5)

<sup>†</sup> Other includes doxorubicin, dacarbazine, cyclophosphamide, everolimus, dovotininb  
 Source: ADCM.xpt dataset.

The trial was stratified according to geographical region, Asia versus rest of the world. As shown in Table 6, about one-quarter of patients were enrolled from countries in Asia and slightly less than 20% of patients were from North America. Thirteen percent of enrolled patients were from the US and the largest group of patients from any one country was from Germany, which comprised 16% of the patients. Fifty-three sites enrolled patients from 17 countries. No site enrolled more than patients each. The two highest accruing sites were in Poland (Centrum Onkologii - Instytut im. M.Sklodowskiej-Curie) and Japan (National Cancer Center Hospital East), each enrolling 10 patients. The highest accruing sites in the US were in Philadelphia, PA (Fox Chase Cancer Center, n=7), Portland, Oregon (Oregon Health and Science University, n=4) and Boston, MA (Dana-Farber Cancer Institute, n=4).

Table 10. Summary of Patient Enrollment by Country

Country	Regorafenib + BSC, N=133 (%)	Placebo + BSC, N=66 (%)	Total N=199 (%)	Number of Centers
Austria	2 (2)	0	2 (1)	2
Belgium	4 (3)	2 (3)	6 (3)	1
Canada	7 (5)	3 (5)	10 (5)	3
China	7 (5)	4 (6)	11 (6)	4
Germany	20 (15)	12 (18)	32 (16)	6
Spain	2 (2)	2 (3)	4 (2)	2
Finland	1 (<1)	0	1 (<1)	1
France	14 (11)	5 (8)	19 (10)	4
United Kingdom	8 (6)	3 (5)	11 (6)	3
Israel	1 (1)	0	1 (<1)	1
Italy	12 (9)	8 (12)	20 (10)	3
Japan	12 (9)	5 (8)	17 (9)	6
South Korea	10 (8)	6 (13)	16 (8)	4
Netherlands	7 (5)	3 (5)	10 (5)	2
Poland	8 (6)	2 (3)	10 (5)	1
Singapore	3 (2)	0	3 (2)	1
United States	15 (11)	11 (17)	26 (13)	9

Source: DM dataset.

Reviewer's comment: Representation of patients was from Europe, Asia and North America. There was under-representation of patients who were of African American (< 1%) and of Hispanic descent. This may be attributable to the fact that most patients enrolled were from Europe. A higher percentage of patients from North America were enrolled in the placebo arm compared to the regorafenib arm.

#### 6.1.4 Subject Disposition

Trial 14874 was conducted internationally at 53 sites, in 17 countries. A total of 240 patients were screened and 41 patients failed screening, with 199 patients randomized to 14874. Of the 199 patients, 133 were randomized to regorafenib arm and 66 to placebo arm. Patients were allowed to be rescreened once if they failed initial screening. Per information provided by Bayer on October 2, 2012, seven patients were rescreened and five patients were randomized to the trial at second screening. Reasons for second screening are as follows:

Table 11. Rescreened Patients

Subject number	Previous Subject Number (if any)	Reason for 1st Screening Failure	Reason for 2nd Screening Failure (if any)	Comments
260031002	260030002	Eligibility criteria not met (ANC)	Eligibility criteria not met (serum creatinine)	Screen failed (SF) twice – 1 <sup>st</sup> SF ANC, 2 <sup>nd</sup> SF Creatinine
540071004	540070004	Eligibility criteria not met (ANC)	N/A (randomized and treated)	1 <sup>st</sup> SF ANC, 2 <sup>nd</sup> screening completed and found eligible
220010001	Not entered in CRF	see comment	N/A (randomized and treated)	Per PRA/CoreLabs: Image Quality Acquisition (IQA) was not established until >28 days from initial baseline IQA submission thus violating the screening window (28 days). Once IQA was obtained, subject was randomized.
200021002	200020002	AE (intestinal obstruction)	N/A (randomized and treated)	1 <sup>st</sup> SF due to AE intestinal obstruction which resolved and subject was re-screened after recovery and screening completed and found eligible.
200031003	200030003	Eligibility criteria not met (Hgb)	Eligibility criteria not met (Hgb)	Screen failed twice – Hgb both times
200081001	200080001	Eligibility criteria not met (ANC)	N/A (randomized and treated)	1 <sup>st</sup> SF ANC, 2 <sup>nd</sup> screening completed and found eligible
140051004	Not entered in CRF	see comment	N/A (randomized and treated)	Per PRA: The subject signed consent and was screened in IXRS on 07 June. The subject then went on vacation. He didn't want to go through screening procedures or take IP while on vacation. The site screen failed the subject in IXRS. The subject had an appointment on 11 July 2011 and the site had the subject re-sign the ICF. The subject was again entered in IXRS as a re-screen (140051004) and screening procedures were completed.

Source: Response to information request from Bayer, dated October 2, 2012.

**Reviewer's comments:** Reasons for failing initial screening do not appear to have impacted the trial, and the number of patients, 5 of 199 (2.5%) rescreened patients, are small.

Table 12 below describes the disposition of patients in Trial 14874. All patients randomized, except for one in the regorafenib arm, received treatment. As of the data cut-off of January 26, 2012, more patients (40%) in the regorafenib arm are still receiving treatment than in the placebo arm (5%). The reasons for treatment discontinuation are similar between both arms; however, more patients in the regorafenib arm had radiologic disease progression in the regorafenib arm (15%), compared to the placebo arm (3%).

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Table 12. Patient Disposition

	Regorafenib N=133 (%)	Placebo N=66 (%)
<b>Disposition in double-blind treatment period</b>		
Rescreened and randomized	3 (2)	2 (2)
Double-blind treatment period		
Randomized	133 (100)	66 (100)
Regorafenib not administered	1 (1)	0
Started double-blind treatment	132 (99)	66 (100)
Ongoing	53 (40)	3 (5)
Discontinued therapy*	39 (29)	7 (11)
Death	2 (2)	0
Progression-clinical	2 (2)	1 (2)
Progression-radiologic	20 (15)	2 (3)
Withdrawal by patient	4 (3)	0
AE associated with clinical disease progression	5 (4)	4 (6)
AE not associated with clinical disease progression	3 (2)	0
Protocol violation	0	0
Lack of efficacy	1 (1)	0
Noncompliance	2 (2)	0
Open-label treatment with regorafenib	41 (31)	56 (85)
<b>Disposition in open-label treatment</b>		
Open-blind treatment period	41 (31)	56 (85)
Ongoing	26 (20)	34 (52)
Discontinued therapy	15 (11)	22 (33)
Death	1 (1)	1 (2)
Progression-clinical	0	2 (3)
Progression-radiologic	12 (9)	11 (17)
Withdrawal by patient	0	5 (8)
AE associated with clinical disease progression	2 (2)	0
AE not associated with clinical disease progression	0	3 (5)
Physician decision	2 (2)	0

Source: ADDS.xpt dataset

\* Did not receive any open-label treatment.

Reviewer's comments: A higher percentage of patients discontinued therapy in the regorafenib arm, compared to placebo, due to radiologic progression and a higher percentage of patients pursued open-label treatment with regorafenib following disease progression in the placebo arm. Open-label treatment with regorafenib may dilute the magnitude of overall survival, which is a secondary endpoint of this trial; therefore, the results will be difficult to interpret.

**Table 13** lists the reasons for discontinuing double-blind treatment in a total of 86 patients, 56 (42%) in the regorafenib arm and 30 (45%) in the placebo arm. The reasons for treatment discontinuation were well-balanced, except patient withdrawal was higher in the placebo arm (17%) versus regorafenib arm (7%). The primary reason for discontinuation as radiological disease progression in both arms, 57% for regorafenib and 43% for placebo.

Table 13. Disposition of All Patients who Discontinued Double-Blind Treatment

Reason	Regorafenib, n=133 (%)	Placebo, N=66 (%)
Total	56 (42)	30 (45)
Adverse event associated with clinical disease progression	7 (13)	5 (17)
Adverse event not associated with clinical disease progression	3 (5)	3 (10)
Death	3 (5)	1 (3)
Lack of efficacy	1 (2)	0
Non-compliance with study drug	2 (4)	0
Physician decision	2 (4)	0
Clinical disease progression	2 (4)	3 (10)
Radiological disease progression	32 (57)	13 (43)
Patient withdrawal	4 (7)	5 (17)

Source: ADDS.xpt dataset

### 6.1.5 Protocol Violations

Seventy-four percent of patients in the placebo arm and 80% of patients in the regorafenib arm had protocol violations. Types of protocol violations were categorized as inclusion/exclusion criteria, procedure deviations, time schedule deviations, and treatment deviations. Overall, the numbers of protocol violations were equally balanced between both arms.

There were a greater number of patients in the regorafenib arm than the placebo arm that had protocol violations for inclusion/exclusion criteria, eleven patients in the regorafenib arm and one patient in the placebo arm. These were all classified as minor for both arms. In the regorafenib arm, the protocol violations included a history of elevated blood pressure or uncontrolled hypertension, intolerance to sunitinib, < 10 day washout period with sunitinib, no CT screening prior to enrollment, history or seizures, and ECOG performance status > 0 or 1. In the placebo arm, one patient had a history of prostate cancer at the time of enrollment.

The largest number of protocol violations involved procedure deviations and were minor. These involved mostly laboratory assessments and ECGs, completion of quality of life (QOL) questionnaires, and missing pharmacokinetic and biomarker samples. The

time schedule deviations were due to procedures and assessments performed outside the scheduled window of +/- days. Most were performed after the window of assessments; however, several patients had their efficacy assessments performed early due to the change in timing of tumor assessments from every four weeks (+/- 7 days) after first 3 months to every six weeks (+/- 7 days) for subsequent 3 months through month six. Evaluation of treatment deviations revealed minor violations that involved taking the incorrect administration of study medication.

Table 14. Protocol Violations

Protocol Violation	Regorafenib	Placebo	Total
Number of patients	107 (80%)	49 (74%)	156 (78%)
Types	489	268	722
Inclusion/exclusion criteria	26 (5%)	3 (1%)	29 (4%)
Procedure deviations	327 (67%)	166 (62%)	493 (68%)
Time schedule deviations	51 (10%)	24 (9%)	75 (10%)
Treatment deviations	85 (17%)	45 (17%)	125 (17%)

Source: ADDV.xpt dataset

Reviewer's comment: An additional (b) (6) patients at trial site (b) (6) (refer to Section 3.3 Financial Disclosures) were identified by the clinical reviewer as a having a protocol violation. The protocol violation involved exclusion criteria (see Section 5.3), "Close affiliation with the investigational site, e.g., a close relative of the investigator or dependent person (e.g., employee of or student at the investigational site who would have access to trial records and case report form [CRF] data)." The sub-investigator was the husband of a Bayer employee.

The percentage of protocol violations was balanced between the two arms. Overall, the protocol violations were relatively minor and do not appear to have compromised the integrity of Trial 14874.

#### 6.1.6 Analysis of Primary Endpoint

The primary endpoint of Trial 14874 was progression-free survival, defined as the date of randomization until the date of radiological progression or death (if death occurs before progression). The CRFs for 30% of the patients were audited by the clinical reviewer for efficacy (J. Chang) to verify that the data transmitted in the datasets were an accurate representation of the patient information documented in the CRFs. An additional PFS event was identified for patient ID 200021002.

On March 13, 2012, Bayer communicated to FDA that 42 new patients entered screening in the final week of recruitment, and the final number of patients randomized was 199, 29 more patients than originally planned. Bayer stated that the analysis of PFS would be based on approximately 144 events and the protocol was amended (#4) on September 27, 2011 accordingly. The trial was still blinded to Bayer. FDA

responded on March 20, 2012, and stated that, “if Bayer strongly prefers to change the primary analysis from 122 PFS events to 144 PFS events, FDA will consider the primary objective fulfilled only if tests at both 122 and 144 PFS events are statistically significant.”

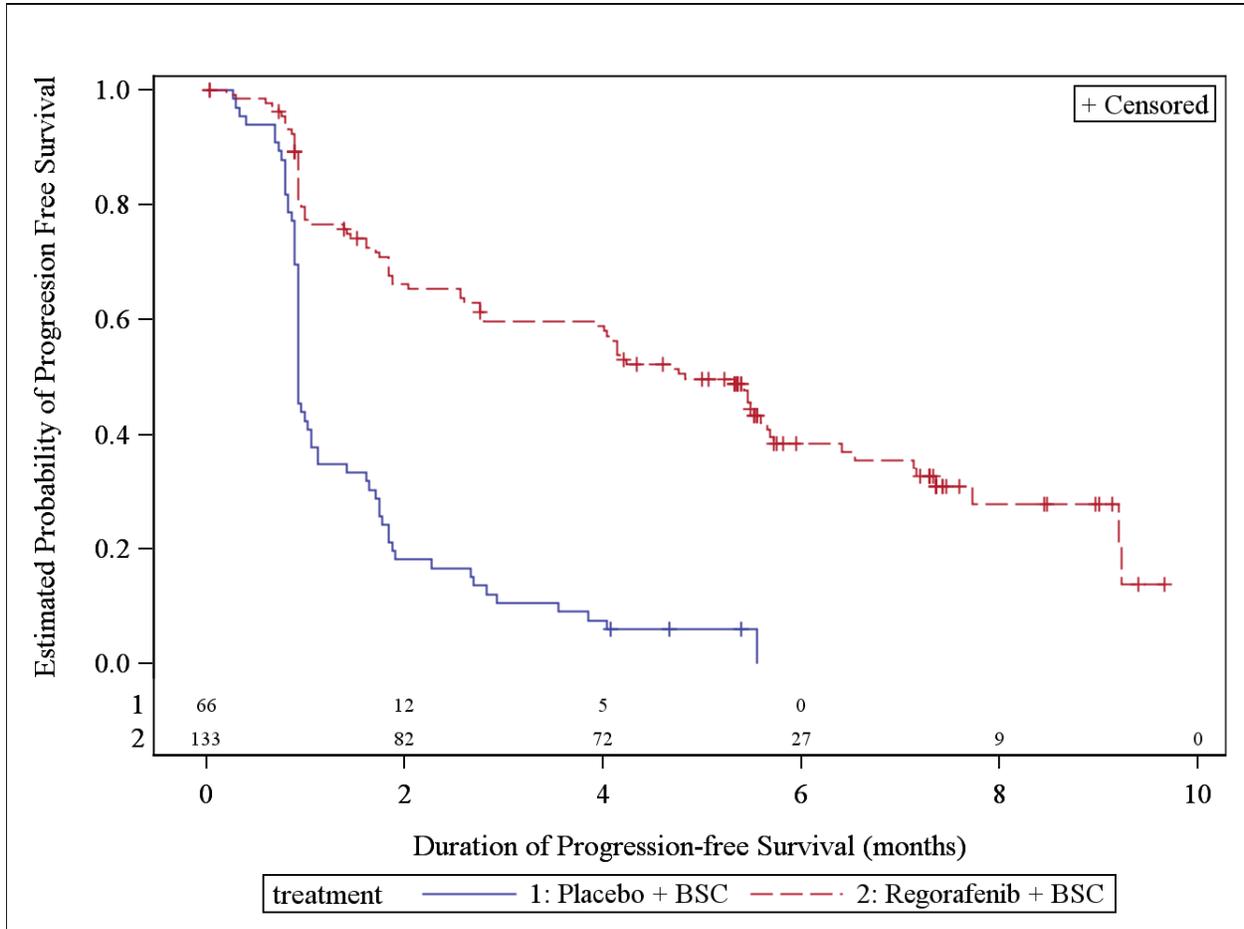
Due to the increased power and maturity of the data and the additional PFS event, results of PFS at 145 events, with a database lock date of January 26, 2012, are considered the primary analysis by FDA. The results of the PFS analysis at 123 and 145 events are presented below.

A statistically significant, clinically meaningful prolongation in PFS was observed with regorafenib; median PFS of 4.83 months (95% CI: 3.91, 5.65) in the regorafenib arm compared to 0.92 months (95% CI: 0.92, 1.05) in the placebo arm, with a hazard ratio of 0.27 (95% CI: 0.19, 0.39;  $p < 0.0001$ ). The 73% risk reduction in disease progression is clinically meaningful in the proposed patient population, given that no other therapy is approved for the third-line indication. Overall survival data were not mature at the time of PFS analysis, refer to Section 6.1.7 Analysis of Secondary Endpoints(s).

Table 15. Progression-Free Survival by BCRR

	145 Events		123 Events	
	Placebo (n=66)	Regorafenib (n=133)	Placebo (n=66)	Regorafenib (n=133)
Censored (%)	3 (5)	51 (38)	7 (11)	70 (52)
Events (%)	63 (96)	82 (62)	59 (89)	64 (48)
Progression	62	76	58	58
Death	1	5	1	5
Median PFS in days (95% CI)	28 (28, 32)	147 (119, 172)	28 (28, 32)	129 (85, 199)
Median PFS in months (95% CI)	0.9 (0.9, 1.1)	4.8 (3.9, 5.7)	0.9 (0.9, 1.1)	4.2 (2.8, 6.5)
Hazard ratio (95% CI)	0.27 (0.19, 0.39)		0.27(0.19, 0.40)	
p-value (stratified log-rank)	<0.0001		<0.0001	

Figure 3. Kaplan-Meier Curves of Progression-Free Survival at 145 PFS Events Based on BCRR



Source: Xiaoping (Janet) Jiang, Ph.D., statistical reviewer

Reviewer's comments: Patient 200021002 died within 30 days of withdrawing from trial. Bayer censored this patient; however, the reviewer has counted this patient as a PFS event due to hepatic failure not related to clinical disease progression, given that the patient was unblinded before progression. The patient was randomized on May 17, 2011 and underwent one imaging assessment on June 13, 2011. Patient ended treatment on [REDACTED] (b) (6) and died [REDACTED] (b) (6)

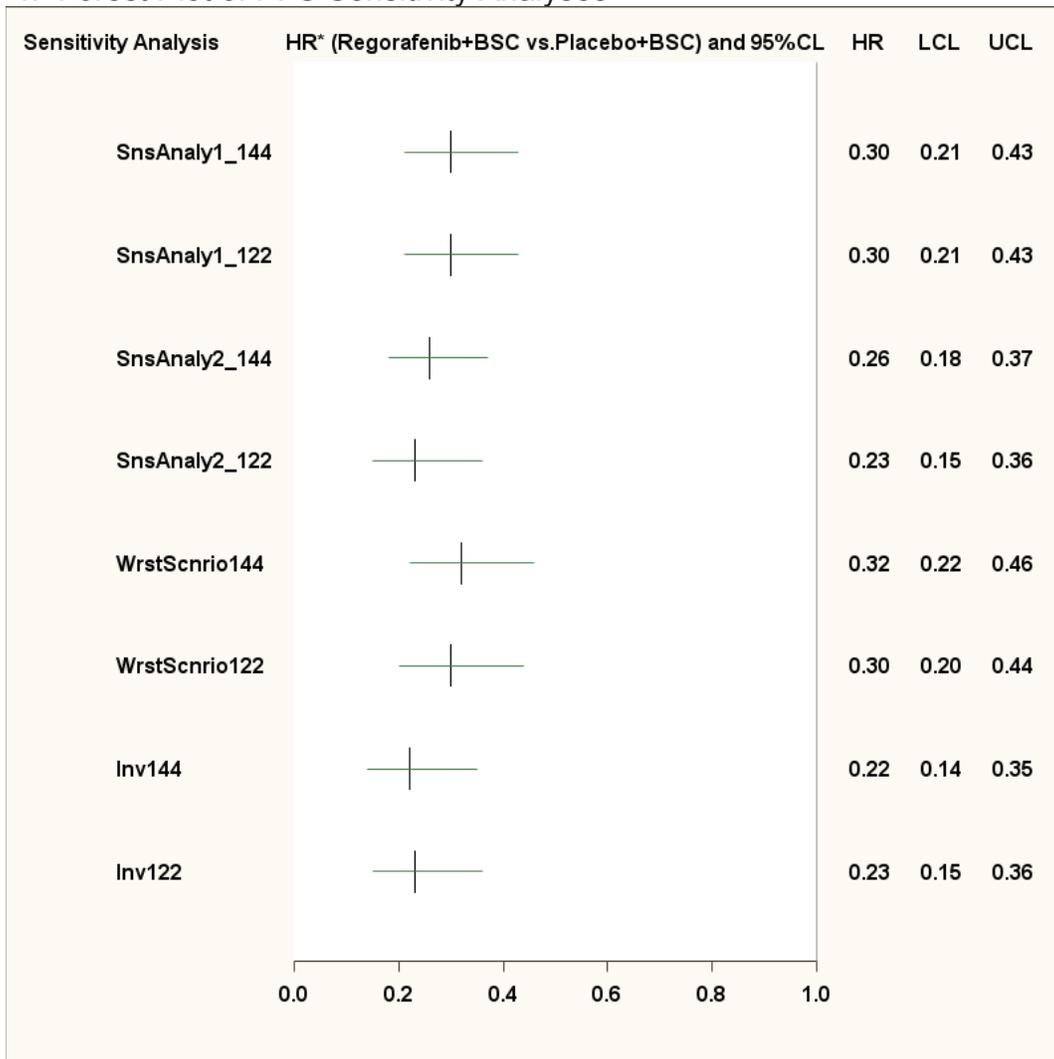
Per Dr. Jiang, SAP v1.0 dated January 25, 2012 was used for the final statistical analysis, before the database lock. The SAP v1.1 was dated March 22, 2012, after the database lock. The censoring rule, "For subjects who are unblinded prior to observing progression, PFS will be censored at the date of the last scan performed prior to unblinding," appears in SAP 1.1, but does not in SAP 1.0. Additionally, FDA does not agree with the censoring rule to censor PFS for the patients who were unblinded prior to observing progression, as noted in censoring rules in the Guidance for Industry, "Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics" (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071590.pdf>).

The choice of PFS as the primary endpoint for Trial 14874 is appropriate, given the endpoints used in past for approval of imatinib and sunitinib. Accelerated approval for imatinib in the metastatic setting was based on ORR, and confirmed by PFS and OS. For sunitinib, regular approval was based on PFS and TTP. Although PFS is a surrogate for OS, the lack of treatment options in patients with unresectable or metastatic GIST resistant to imatinib and sunitinib preclude other options. Additionally, robustness of PFS in this trial is supported by the sensitivity analyses and patient subsets as discussed below.

### **Sensitivity Analyses**

Multiple sensitivity analyses were performed by Dr. Jiang. As shown in Figure 4, Sensitivity Analysis 1 was conducted based on using the minimum PFS of investigator and BCRR and Sensitivity Analysis 2 was conducted using unstratified log-rank test (stratified log-rank test was the primary analysis). Bayer conducted the Worst Case Scenario, whereby the PFS date was moved for unscheduled tumor assessments to the previous estimated tumor assessment for the regorafenib arm and for the placebo arm, to the next tumor assessment. Sensitivity analyses were also conducted with investigator-assessed PFS at 144 and 122 events.

Figure 4. Forest Plot of PFS Sensitivity Analyses



INV=investigator

Source: Xiaoping (Janet) Jiang, Ph.D., statistical reviewer

Reviewer's comment: The multiple sensitivity analyses demonstrate that the results are robust and consistent with the primary analysis.

Additionally, sensitivity analysis of PFS between the BCRR and investigator's assessment was performed, as shown below:

Table 16. Comparison of Progression-free Survival between BCRR and Investigator

	BCRR		Investigator	
	Placebo (n=66)	Regorafenib (n=133)	Placebo (n=66)	Regorafenib (n=133)
Events (%)	63 ( 96)	81 ( 61)	51( 77)	48 (36)
Censored (%)	3 ( 5)	52 ( 39)	15 (23)	85 (64)
Median PFS in days (95% CI)	28 ( 28, 32)	147 (122, 173)	52 (29, 56)	224 (195, not reached)
Median PFS in months (95% CI)	0.92 (0.92, 1.05)	4.82 (4.01, 5.68)	1.71 (0.95, 1.84)	7.36 (6.41, not reached)
Hazard Ratio* (95% CI)	0.27 (0.19 – 0.39)		0.22 (0.14 – 0.35)	
p-value (stratified log rank)	<0.0001		<0.0001	

Source: Xiaoping (Janet) Jiang, Ph.D., statistical reviewer

Table 17. Discordance between Assessments by BCRR and Investigator for Progressive Disease

Investigator	BCRR					
	Placebo			Regorafenib		
	PD (%)	No PD (%)	Total (%)	PD (%)	No PD (%)	Total (%)
Progressive disease	50 (100)	0	50	40 (91)	4 (9)	44
No progressive disease	12 (80)	3 (20)	15	37 (44)	48 (56)	85

Reviewer's comment: Although the total number of PFS events is 145, not 144, for the purpose of comparison of PFS between BCRR and investigator, PFS at 144 events was used. Assessment of PFS according to BCRR and investigator, and are internally consistent with HRs ranging from 0.22 to 0.27 and median differences ranging from 4.8 months to 7.4 months, based on 144 events. These data indicate that the results of the trial are robust and clinically meaningful. The results as determined by investigators

demonstrated a greater difference in median PFS; however, investigator bias often accounts for such differences..

As shown in Table 17, the discordance for PD by investigator was 80% with BCRR in the placebo arm and 44% in the regorafenib arm. Reasons for discordance include alternative interpretation of lesions, selection of different lesions. Additionally, investigator assessment can be influenced by knowledge of the clinical status of a patient, resulting in assessment bias. This occurs when an investigator labels a borderline case stable disease if the patient is doing well clinically but would not do so if the patient is deteriorating clinically. Despite the discordance, the consistency and robustness of the PFS results withstood numerous sensitivity analyses.

### 6.1.7 Analysis of Secondary Endpoints(s)

The prespecified secondary endpoints of the trial were to compare the regorafenib and placebo treatment groups in terms of overall survival, time-to-progression, disease control rate, response rate, and duration of response in hierarchical order.

#### Overall Survival Based on BCRR

As of the January 26, 2012 data cut-off, a total of 46 events had occurred, the OS analysis was performed, comprising 43% of the events planned at the final analysis. Overall survival was defined as the time from date of randomization to date of death due to any cause.

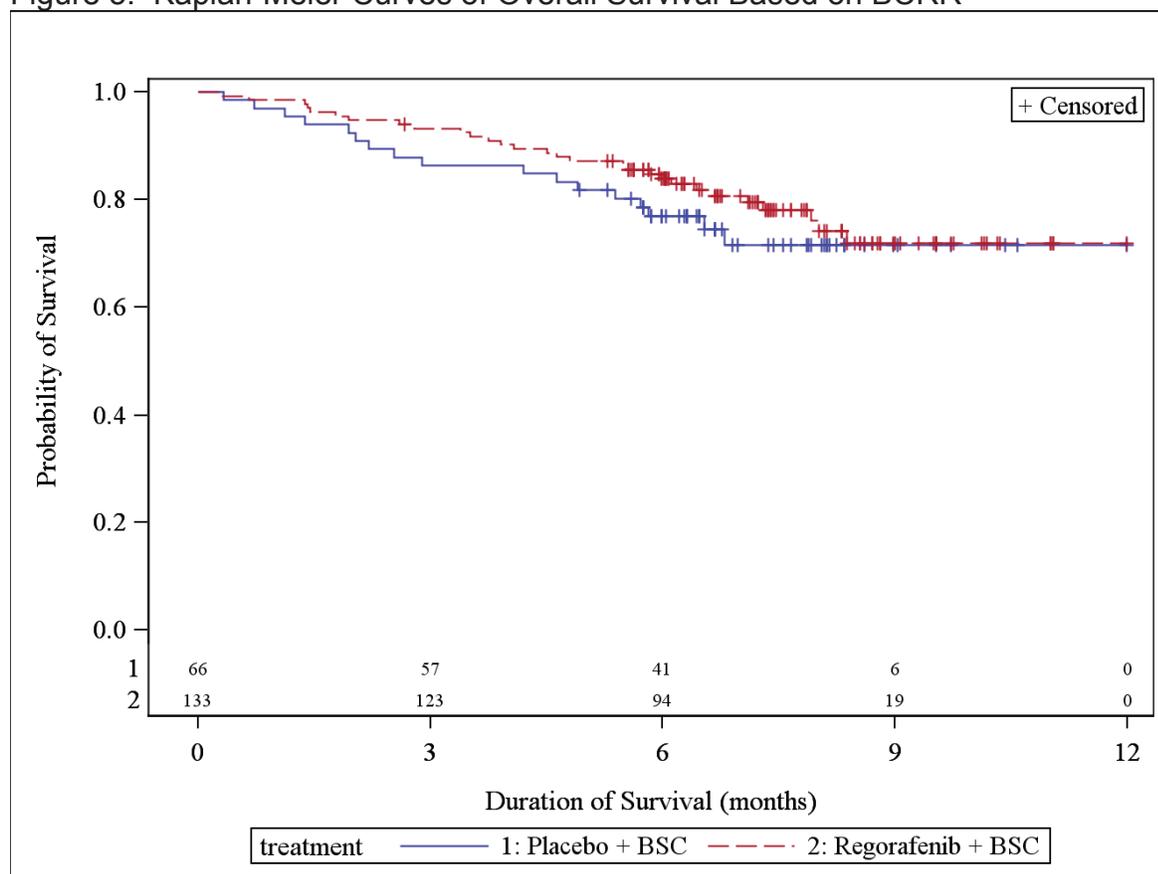
Table 18. Overall Survival Based on BCRR

	<b>Placebo, N=66</b>	<b>Regorafenib, N=133</b>
Events	17 (26%)	29 (22%)
Censored	49 (74%)	104 (78%)
Median OS in months (95% CI)	not reached	not reached
Hazard Ratio (95% CI)	0.77 (0.42, 1.41)	
p-value (stratified log-rank)	0.1989	

na=not applicable

Source: Xiaoping (Janet) Jiang, Ph.D., statistical reviewer

Figure 5. Kaplan-Meier Curves of Overall Survival Based on BCRR



Source: Xiaoping (Janet) Jiang, Ph.D., statistical reviewer

Reviewer’s comments: The planned, interim overall survival (OS) analysis performed at the time of PFS analysis did not cross the O’Brien-Fleming boundary and was, therefore, not mature.

Note also that open-label treatment with regorafenib was allowed after disease progression, and this may dilute the magnitude of overall survival. However, a lack of treatment options exist for patients in the placebo arm after the failure of imatinib and sunitinib and treatment with regorafenib provides clinical benefit for these patients.

Time to Progression Based on BCRR

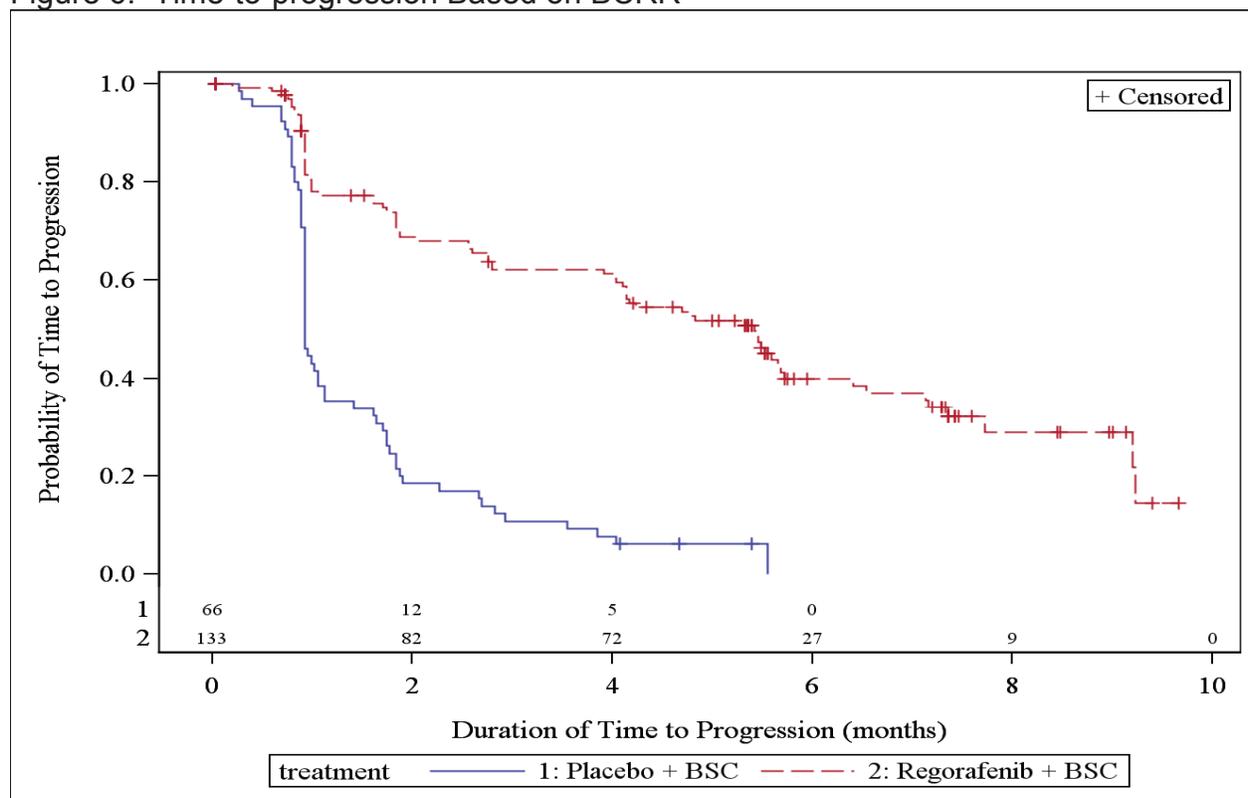
Time to progression was defined as date of randomization until date of radiological progression.

Table 19. Time-to-progression Based on BCRR

	Placebo, n=66 (%)	Regorafenib, n=133 (%)
Number of events	62 (94)	76 (57)
Number censored	4 (6)	57 (43)
Median TTP, months (95% CI)	0.9 (0.9, 1.1)	5.4 (4.1, 5.7)
Hazard ratio (95% CI)	0.25 (0.17, 0.36)	
p-value (stratified log-rank)	<0.0001	

Source: Xiaoping (Janet) Jiang, Ph.D., statistical reviewer

Figure 6. Time-to-progression Based on BCRR



Source: Xiaoping (Janet) Jiang, Ph.D., statistical reviewer

### Tumor Response Rate and Duration of Response

Tumor response rate was defined as the percentage of patients with a complete response (CR) or partial response (PR), and duration of response was defined as time from first documented CR or PR, whichever is observed first, to disease progression or death in responders only. Six (5%) patients in the regorafenib arm and one patient (2%)

in the placebo arm had a confirmed partial response by BCRR review. No complete response was observed in either arm. The median duration of response per BCRR was 99 days (range: 42-99) in the regorafenib arm and 30 days in the placebo arm.

Reviewer's comment: Disease control rate is not considered a regulatory endpoint, refer to written correspondence to Bayer, dated March 9, 2012.

The low response rate observed with regorafenib is consistent with other approved TKIs for GIST, imatinib and sunitinib.

#### 6.1.8 Other Endpoints

No additional efficacy endpoints for Trial 14874 were considered for regulatory decision-making.

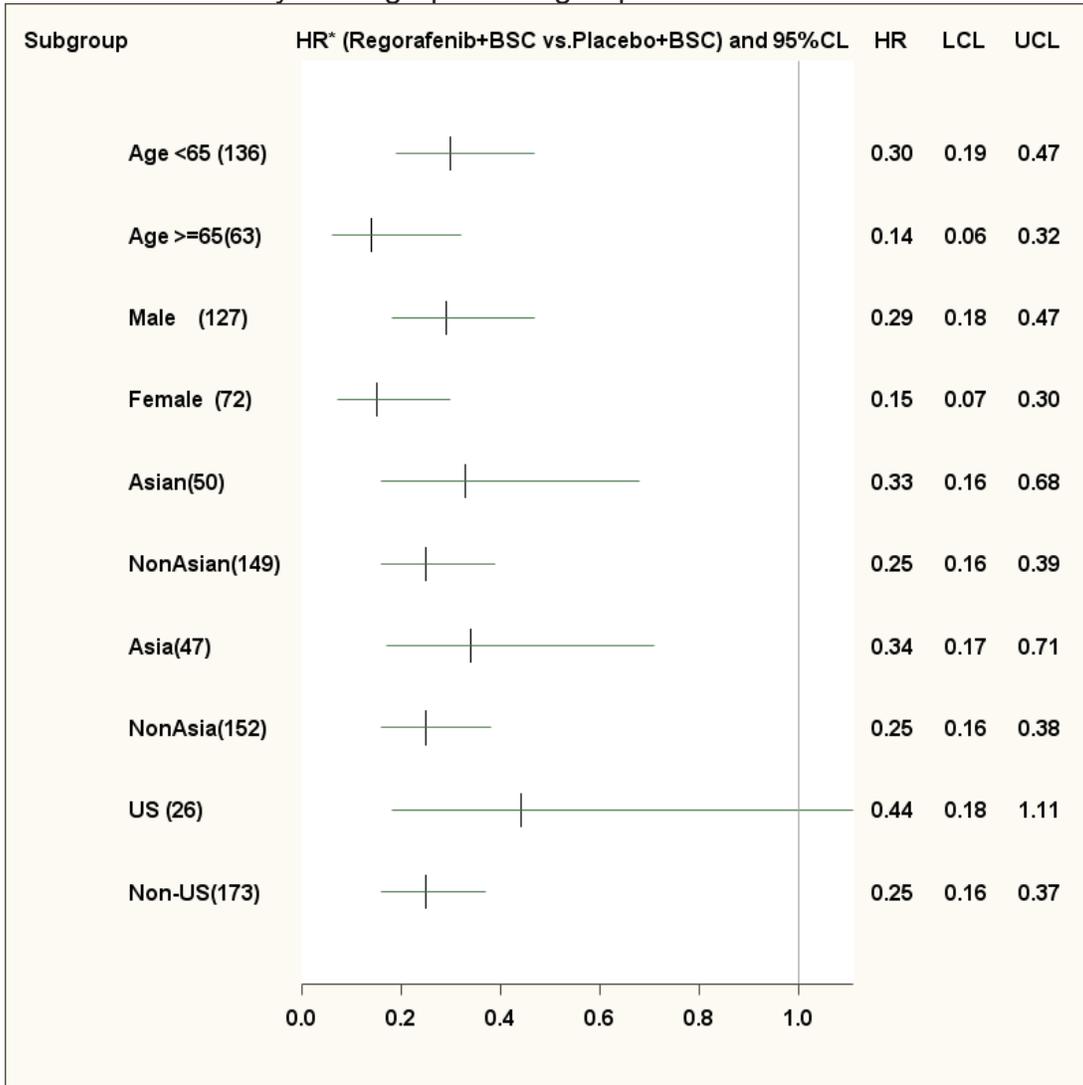
#### 6.1.9 Subpopulations

Exploratory subgroup analyses of PFS were evaluated by Dr. Jiang. The subgroups that were evaluated, as shown in Figure 7 and Figure 8, include age, gender, geographical region, number of lines of prior therapy, duration of prior imatinib therapy, KIT exon mutations, and baseline ECOG performance status. Overall, the results of the subgroup analyses were consistent with those of the primary analysis for Trial 14874.

Patients with KIT exon 11 or exon 9 mutations had a similar reduction in the risk of disease progression, 73% (HR=0.27, 95% CI: 0.12, 0.59) and 68% (HR=0.32, 95% CI: 0.07, 1.39), respectively.

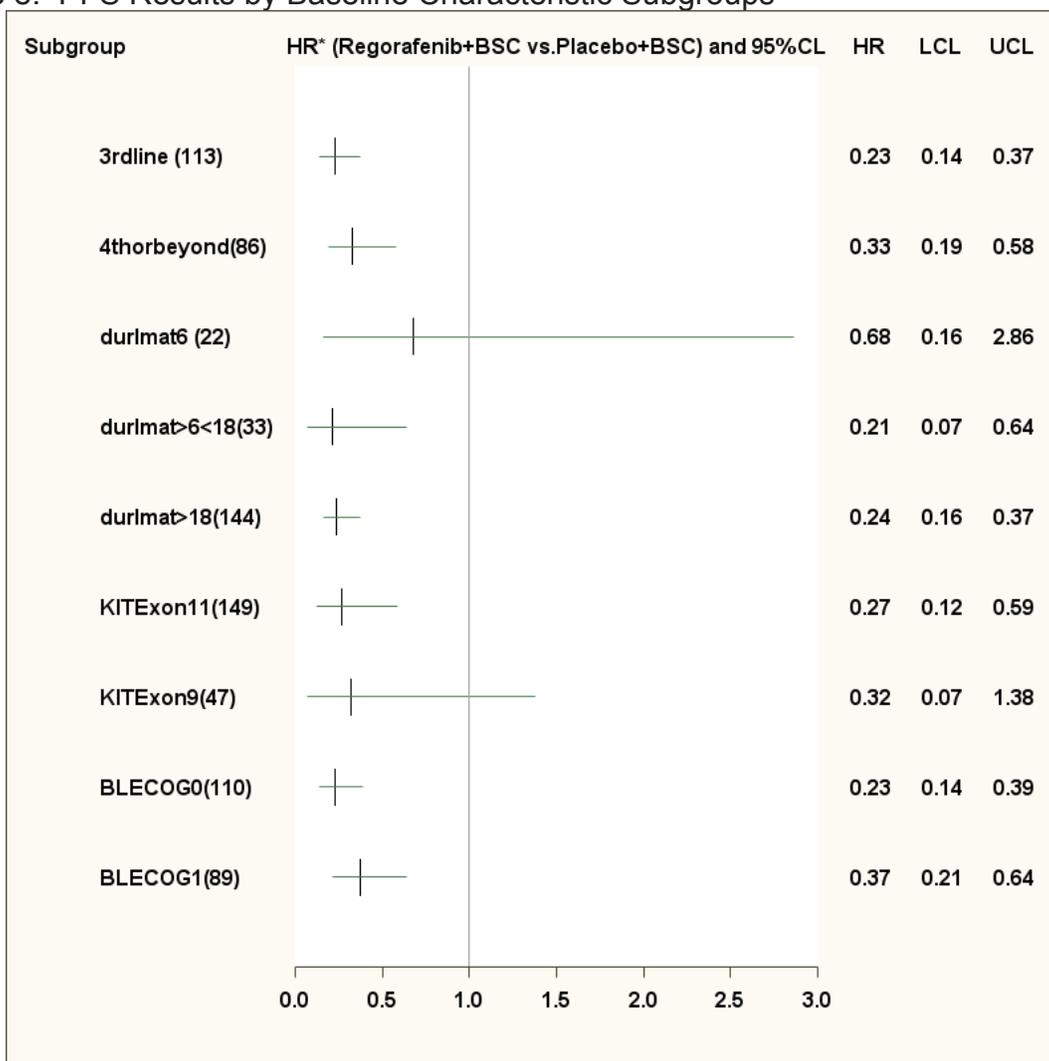
Although not described in Trial 14874 protocol in terms of imatinib resistance or imatinib tolerance per se, PFS results were explored in patients according to duration of prior imatinib treatment (< 6 months, > 6 to < 18 months, > 18 months). As shown in Figure 8, treatment with regorafenib in patients > 6 to < 18 months of imatinib treatment had a more favorable relative risk reduction of disease progression or death compared to patients with < 6 months of imatinib treatment, 79% (HR=0.21, 95% CI: 0.07, 0.64) versus 32% (HR=0.68, 95% CI: 0.16, 2.86), respectively. For patients with > 18 months, the relative risk reduction of disease progression or death was 76% (HR=0.24, 95% CI: 0.16, 0.37).

Figure 7. PFS Results by Demographic Subgroups



Source: Xiaoping (Janet) Jiang, Ph.D., statistical reviewer

Figure 8. PFS Results by Baseline Characteristic Subgroups



Source: Xiaoping (Janet) Jiang, Ph.D., statistical reviewer

Reviewer's comment: The multiple subgroup analyses based upon age, gender, ECOG performance status, prior therapies, and geographical region provide confirmation of the robustness of the primary PFS results. In terms of prognostic factors, KIT mutational status was not predictive of benefit from regorafenib treatment.

Although not defined as imatinib-resistant or imatinib-tolerant in Trial 14874 protocol, primary resistance to imatinib is defined as clinical progression developing during the first 6 months of imatinib therapy (see 2012 NCCN guidelines for GIST). As shown in Figure 8, patients with < 6 months of imatinib treatment had a lower risk reduction of disease progression or death compared to patients who were treated with imatinib > 6 months, which is defined as secondary imatinib-resistance, after initial response followed by progression.

The hazard ratios for the subgroup analyses were generally below 1; however, the upper confidence limit of the hazard ratios for KIT exon 9 and duration of imatinib < 6 months were above 1. The large confidence intervals may be attributable to the small number of events in the subgroups; therefore, interpretation of these results must be taken with caution.

#### 6.1.10 Analysis of Clinical Information Relevant to Dosing Recommendations

No new data submitted for review. Please refer to the review of NDA 203085.

#### 6.1.11 Discussion of Persistence of Efficacy and/or Tolerance Effects

No new data submitted for review. Please refer to the review of NDA 203085.

#### 6.1.12 Additional Efficacy Issues/Analyses

None.

## 7 Review of Safety

### **Safety Summary**

The safety data in patients with GIST was primarily derived from the 198 patients treated with regorafenib in the safety population of the GRID trial (# 14874). One-hundred and thirty two patients received regorafenib at an oral dose of 160 mg for the first 3 weeks of each 4 week cycle and 66 patients received the corresponding placebo. The placebo-control allowed us to assess the safety of regorafenib against background adverse events that occur in this population with advanced and metastatic GIST. The safety assessment was supplemented with data from the 500 patients with metastatic colorectal cancer who received regorafenib and 253 patients who received placebo in trial 14387 which was the basis for NDA 203,085. Additional safety data was provided from patients in phase I and II studies, and pharmacovigilance information (deaths and serious adverse events) from the applicant's ongoing studies, providing overall safety assessment from over 1200 patients with cancer exposed to regorafenib. Considering the rarity of GIST and the third line indication in patients with metastatic and locally advanced disease, the available information was appropriate for this safety assessment.

In the GRID trial, the mean duration of therapy was 20 weeks (median of 22.9 weeks) for patients receiving regorafenib and 9.1 weeks (median of 7.0 weeks) for patients receiving placebo. The duration of therapy correlated with the median PFS at 21 and 4 weeks (4.8 and 0.9 months) for regorafenib and placebo, respectively. Dose

interruptions for adverse events were required in 58% of the patients receiving regorafenib and 50% of the patients had their dose reduced. Drug-related adverse reactions that resulted in treatment discontinuation were reported in 2.3% of regorafenib-treated patients compared to 1.5% of patients who received placebo. Although the duration of therapy is brief, considering the short duration of study enrollment of the patients on the placebo arm and the rarity of this life threatening disease, this duration of therapy is acceptable when performing a risk to benefit analysis.

The most significant toxicities caused by regorafenib included drug induced liver injury (section 7.3.6.2), hemorrhage (section 7.3.6.6), dermatologic toxicity (palmar-plantar erythrodysesthesia, rash and severe cutaneous adverse reactions) (section 7.3.6.1), hypertension (section 7.3.6.5), cardiac ischemic events (section 7.3.6.3) and gastrointestinal perforation (section 7.3.6.8).

The current labeling for regorafenib includes a boxed warning for episodes of severe and fatal drug induced liver injury. One patient (0.8%) in the regorafenib arm of the GRID study experienced fatal drug induced liver toxicity. This patient did not have any evidence of liver metastasis and this finding was consistent with findings in the colorectal cancer study.

The overall incidence of episodes of hemorrhage (Grades 1-4) was 11% in regorafenib treated patients compared to 3% in placebo-treated patients in the GRID trial. No episodes of fatal hemorrhage were reported in this trial.

Regorafenib caused an increased incidence of adverse reactions involving the skin and subcutaneous tissues (78% versus 24%), including hand-foot skin reaction (67% vs. 12%) also known as palmar-plantar erythrodysesthesia (PPE), and severe rash frequently requiring dose modification. Grade 3 rash was reported in 7% of regorafenib treated patient in contrast to no patients in the placebo arm. Serious adverse reactions of erythema multiforme (0.2% vs. 0% in study 14387) and Stevens Johnson Syndrome (0.2% vs. 0% in study 14387) were not seen in the regorafenib treated patients in the GRID trial. Toxic epidermal necrolysis was occurred in 0.17% of 1200 regorafenib-treated patients across all clinical trials but was not reported in the GRID trial.

Hypertension occurred in 59% of regorafenib-treated patients vs. 27% of patients who received placebo in the GRID trial. The onset of hypertension occurred during the first 2 cycles of treatment in most patients.

Gastrointestinal perforation or fistula occurred in 0.6% of 1200 patients treated with regorafenib across clinical trials including 0.5% (4/188) of all patients who were treated with regorafenib during the blinded or open-label portion of the GRID trial. Two of the cases of gastrointestinal perforation observed during the GRID trial were fatal.

There only case of reversible posterior leukoencephalopathy among the database of 1200 patients who have received regorafenib occurred during the GRID trial.

The most frequently observed adverse drug reactions ( $\geq 20\%$ ) in patients receiving regorafenib in the combined metastatic colorectal and GIST populations are asthenia/fatigue, HFSR/PPE, diarrhea, decreased appetite/ and food intake, hypertension, mucositis, dysphonia, and infection, pain (not otherwise specified), weight decreased weight, gastrointestinal and abdominal pains, rash, fever, constipation and nausea (section 7.4.1).

There were no reported episodes of QTc prolongation in the GRID trial (section 7.4.4). The applicant provided an interim report from the completely enrolled but ongoing dedicated cardiac safety study (study 14814) and the full study report has been requested as part of a PMR. Although the final results of this safety study are pending, based on the available evidence, there does not appear to be an increased risk of QTc prolongation with regorafenib.

In summary, the safety profile of regorafenib is consistent with other multi-kinase inhibitors and what was previously identified during the review of NDA 203085 for the metastatic colorectal cancer indication. The PFS advantage seen with regorafenib in the patients with GIST whose disease had progressed through imatinib and sunitinib provides a favorable benefit:risk assessment for regorafenib in this patient population.

## 7.1 Methods

### 7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Regorafenib received approval for treatment of metastatic CRC in the third line on September 27, 2012. The NDA for the CRC indication was submitted to the FDA on April 27, 2012, approximately 4 months prior to submission of the current application in GIST. As such, the majority of the safety data from studies with regorafenib were recently reviewed by the FDA and there is limited postmarketing safety data that is currently available for review. Therefore, the primary focus of the current review is based on the safety findings of the GRID Trial. No data from a phase 2 trial in GIST, trial 14935, were submitted as this trial was investigator initiated. The results of the phase 2 trial however were published recently and the publication was available for review. This publication was reviewed and all relevant findings were incorporated into this safety review. These studies are summarized in Table 4. Updated supportive data from the randomized colorectal cancer study and other studies used in original approval of NDA 203,085 were also reviewed. These studies are summarized in Table 20.

Table 20. Supportive Safety Studies (Pooled)

Study	Regorafenib Dose	Study Type/Phase	Population	Total patients
14387	160 mg every 3/4 wks	Controlled Phase 3	Colorectal Cancer	753 (500 received regorafenib)
11726	160 mg every 3/4 wks	Uncontrolled phase 2	Renal Cancer	49
14596	160 mg every 3/4 wks	Uncontrolled phase 2	Hepatocellular Cancer	36
11650	10-220 mg every 3/4 wks	Phase I dose escalation	Advanced solid tumors	76
11651	20-140 mg continuous dosing	Phase I dose escalation	Advanced solid tumors	84
13172	160 mg every 3/4 wks	Uncontrolled phase 2	Advanced solid tumors	16
14996	160 mg every 3/4 wks	Uncontrolled phase 2	Advanced solid tumors	12

As discussed previously, 240 patients were enrolled on the GRID trial, 199 of whom were randomized in a 2 to 1 fashion to regorafenib (n=133) vs. placebo (n=66), respectively. One hundred and ninety eight of the 199 patients received at least one dose of regorafenib (n=132) or placebo (n=66) and are part of the safety analysis subset.

This study was designed to allow patients receiving placebo to cross-over and receive therapy with regorafenib in an open-label fashion. Fifty-six of the 66 patients (85%) randomized to placebo eventually received open label therapy with regorafenib. Additionally, 41 (31%) of the 198 patients who received regorafenib in the double-blind (DB) phase of the study, continued to receive therapy after progression. The safety findings of the double-blind phase of this study represent the core of this review. Data from the open label phase (OL) of the study were analyzed in addition to the safety findings from the double-blind phase of the study. In total, 188 (94%) of the 199 patients who were randomized eventually received regorafenib at some point during the course of the GRID study.

The data cutoff for the original submission was March 31, 2012 while the cutoff for the 90-day safety update was July 31, 2012.

#### 7.1.2 Categorization of Adverse Events

Adverse events (AEs) reported from the GRID study were classified using the National Cancer Institute (NCI) Common Terminology Criteria Adverse Event (CTCAE), version 4.0. These AEs were subsequently coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 14.1. The coding of verbatim terms was compared to the reported MedDRA preferred terms and no major discrepancies were noted.

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

The data from the GRID trial in addition to study 14387 (NDA 203,085) which was the basis of the approval for the metastatic colorectal cancer indication was pooled together by comparing safety data from all patients treated with regorafenib to data from patients treated with placebo by the applicant. This pooled analysis was reviewed separately from the results of the GRID trial in order to confirm the safety findings. The data from this pooled analysis was appropriate for confirming the findings of the GRID trial. Additionally, the information from the uncontrolled Phase I and II studies was used for assessments of select adverse events of interest during this review.

## 7.2 Adequacy of Safety Assessments

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

In the GRID trial, 132 patients received regorafenib at a dose of 160 mg, orally, each day for 3 weeks of every 4 week (28-day) cycle (intermittent dosing: 3 weeks on/1 week off treatment) while 66 were randomized to receive matching placebo during the double blind phase (DB). Table 21 provides an overview of the demographics of this safety population.

Table 21 Demographics of Safety Population for GRID Trial

		<b>Regorafenib (n=132)</b>	<b>Placebo (n=66)</b>
<b>Race</b>	White	89 (67%)	45 (68%)
	Asian	34 (26%)	16 (24%)
	Black OR African American	0	1 (2%)
	Not Reported	7 (5%)	4 (6%)
	Missing	2 (2%)	0
<b>Gender</b>	F	48 (36%)	24 (36%)
	M	84 (64%)	42 (64%)
<b>Age</b>	Median (range)	60 (18-82)	61 (25-87)
	<65 years	89 (67%)	46 (70%)
	≥65 years	43 (33%)	20 (30%)
<b>ECOG Score</b>	0	72 (55%)	37 (56%)
	1	60 (45%)	29 (44%)

During the DB phase of the GRID trial, the mean treatment duration ( $\pm$ SD) on the regorafenib arm was 20.22 ( $\pm$ 11.62) weeks with a median of 22.94 weeks and a mean daily dose was 139.79 mg ( $\pm$ 22.94). This data is summarized in Table 22.

Table 22 Exposure during the DB Phase of the GRID Trial

	<b>Regorafenib (n=132)</b>	<b>Placebo (n=66)</b>
<b>Overall time under treatment</b>		
Mean $\pm$ SD (weeks)	20.22 $\pm$ 11.62	9.08 $\pm$ 5.89
Median	22.94	6.98
<b>Cycles of Therapy</b>		
Mean $\pm$ SD (cycles)	5.5 $\pm$ 2.8	2.9 $\pm$ 1.4
Median	6.0	2.5
<b>Actual daily dose (mg)*</b>		
Mean $\pm$ SD	139.79 $\pm$ 22.94	159.49 $\pm$ 2.99
Median	146.83	160.00

\* Interruptions/days off therapy excluded.

During the DB phase of the trial, 95 patients (72%) who received regorafenib had a dose modification: 50 (38%) of these patients had a dose interruption/delay, 34 (26%) had dose interruption/delay and a dose reduction, 11 (8%) had a dose reduction only. Seventeen patients (26%) on the placebo arm had a dose interruption/delay with no dose reductions.

In addition to the patients who received regorafenib during the DB phase of the study, 56 patients in the placebo arm crossed over to receive regorafenib in the open-label phase of the study while 41 patients on the regorafenib arm continued to receive regorafenib after progression. Table 23 summarizes the exposure in the two treatment arms when the OL phase of the study is also considered.

Table 23 Regorafenib exposure during DB and OL Phases of the GRID Trial

	<b>Regorafenib (n=132)</b>	<b>Placebo (n=56)</b>
<b>Overall time under treatment</b>		
Mean $\pm$ SD (weeks)	23.65 $\pm$ 12.25	15.27 $\pm$ 9.11
Median	24.79	14.96
<b>Cycles of Therapy</b>		
Mean $\pm$ SD (cycles)	6.6 $\pm$ 3.16	4.66 $\pm$ 2.33
Median	7	5
<b>Actual daily dose (mg)*</b>		
Mean $\pm$ SD	137.82 $\pm$ 23.93	146.19 $\pm$ 20.51
Median	144.71	160.00

Forty (73%) of the 56 patients who crossed over from the placebo had to have a dose modification while receiving regorafenib: 29 (52%) had a dose delay/interruption, 9 (16%) had a dose delay/interruption and a dose reduction and 2 (4%) dose reductions only. In the patients randomized to regorafenib, 98 patients (74%) had a dose modification when considering the DB and OL phases of the study. Forty-eight (36%)

had a dose interruption/delay, 38 (29%) had a dose interruption/delay and a dose reduction and 12 (9%) had a dose reduction only.

Although the overall duration of therapy for most patients is brief, considering the short duration of study enrollment of the patients on the placebo arm and the rarity of this life threatening disease, this duration of therapy is acceptable when performing a risk to benefit analysis.

#### 7.2.2 Explorations for Dose Response

The GRID trial, which forms the basis of this application, was conducted using a fixed dose of 160 mg regorafenib daily for 3 weeks of each 4 week treatment cycle. This represents the currently approved dose of regorafenib for the metastatic colorectal cancer indication. This dose was originally determined based on the Phase I dose escalation trial (study 11650) in which adult patients with advanced solid tumors refractory to standard treatment were given oral regorafenib in a 21 days on / 7 days off schedule in repeated cycles, until discontinuation due to toxicity or tumor progression. No further explorations of dose response have been performed and this application did not contain pharmacologic drug level data (pop PK) or analyses for such exploration from study 14874.

#### 7.2.3 Special Animal and/or In Vitro Testing

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

#### 7.2.4 Routine Clinical Testing

The routine clinical testing of patients, as summarized in section 5.3.3.Discussion of Individual Studies/Clinical Trials, was appropriate including efforts to elicit adverse event data and monitoring of laboratory parameters, vital signs and ECGs.

#### 7.2.5 Metabolic, Clearance, and Interaction Workup

No new information was submitted to this NDA since the original approval of regorafenib for the colorectal indication on September 27, 2012. Please refer to the clinical pharmacology review for that NDA for details.

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

Regorafenib is a small molecule inhibitor of multiple kinases including BRAF, VEGFR 1/2/3, TIE2, PDGFR, FGFR, RAF-1, KIT and RET. Other multi-kinase inhibitors that target at least 3 main tyrosine kinases include regorafenib (VEGFR, PDGFR and KIT) include sorafenib (Nexavar), sunitinib (Sutent) and pazopanib (Votrient).

Potentially serious adverse events have been described with this class of agents include hepatotoxicity, cardiac ischemia/infarction, left ventricular dysfunction, QT prolongation, hemorrhage, hypertension, dermatologic toxicity, GI perforation, elevation in INR when taking warfarin, wound healing complications, arterial and venous thrombotic events, RPLS, hypothyroidism, proteinuria, infection and fetal harm.

The applicant performed an adequate assessment of the above noted adverse events. The risk to benefit analysis of regorafenib remains unchanged since original approval.

### 7.3 Major Safety Results

#### 7.3.1 Deaths

There were 46 deaths reported in patients enrolled on the GRID trial before the data cutoff date of January 26, 2012. One patient (#26004-0002), enrolled on the regorafenib arm, died prior to receiving any study therapy and hence was not part of the safety population. Eighteen patients (9%) in the safety population died within 30 days of receiving the last dose of study drug; 10 (5%) died during the double blind phase of the study and 8 (4%) during the open label phase of the study. The remaining 27 (14%) patients died > 30 days following the last dose of study therapy. These results are summarized in Table 24.

Table 24 Deaths on Study 14874 (Cutoff date January, 26, 2012)

<b>Study Arm</b>	<b>Days since study therapy</b>	<b>Double Blind Phase</b>	<b>Open Label Phase</b>
Regorafenib (n=132)	≤ 30	7 (5%)	3 (2%)
	> 30	14 (11%)	4 (3%)
Placebo (n=66)	≤ 30	3 (5%)	5 (8%)
	> 30	3 (5%)	6 (9%)

Twelve (67%) of the deaths that occurred within 30 days of last dose of study drug were in the setting of progressive disease. The cause of death in 6 (33%) patients however, could not definitively be attributed to progressive disease. These patients are described in Table 25.

Table 25 Patients on GRID Trial who died during the Trial or within 30 days of last dose of therapy

Patient ID	Study Arm	Phase	Cause of death <sup>a</sup>	CTCAE Term <sup>a</sup>
140020002	Regorafenib	DB	AE without progression	Cardiac arrest
200021002	Regorafenib	DB	AE without progression	Hepatic failure
560010004	Regorafenib	DB	Other	Acute Kidney Injury <sup>b</sup>
140010004	Placebo	OL	Other	Colonic perforation
160010007	Regorafenib	OL	Other	ARDS <sup>c</sup>
100040006	Placebo	OL	Unknown	Acute Kidney Injury
100010002	Regorafenib	DB	Progressive Disease	GI disorders-other
100050001	Placebo	DB	Progressive Disease	Death NOS
160010004	Placebo	DB	Progressive Disease	Fatigue
160040001	Regorafenib	DB	Progressive Disease	Peritoneal necrosis
180010001	Regorafenib	DB	Progressive Disease	Ileus
300020001	Placebo	DB	Progressive Disease	Death NOS
560040002	Regorafenib	DB	Progressive Disease	Death NOS
120020001	Placebo	OL	Progressive Disease	General disorders and administrative site conditions - other
120030001	Regorafenib	OL	Progressive Disease	Obstruction-gastric
180010002	Placebo	OL	Progressive Disease	Thromboembolic event
280010001	Placebo	OL	Progressive Disease	Multi-organ failure
680010003	Regorafenib	OL	Progressive Disease	Sepsis

<sup>a</sup> As determined by investigator

<sup>b</sup> In the setting of progression and rhabdomyolysis

<sup>c</sup> Patient with NF1. Evidence of cardiopulmonary failure.

<sup>d</sup> No significant discrepancies were noted in assigned causes of death.

One additional patient, #24004-0001, was originally treated with placebo but then crossed over to receive open-label regorafenib. This patient developed “neurological decompensation” 23 days after stopping open-label therapy and died of this AE on day 33 post therapy. MRI findings were inconclusive although they had evidence of diffuse parenchymal atrophy in addition chronic/old ischemic changes.

Reviewer’s note: Two additional patients (#100040008 and #540020001) were reported to have died within 30 days of the last dose of study drug but after the data cut off of 1/26/12. Further information regarding these patients’ outcomes was requested from the sponsor. Both patients died due to progression of their disease. At the time of the 90 day safety update 2 additional deaths were reported: Patient 045515 died of disease progression while patient 073122 died of “kidney and liver failure” that was attributed to progression. The remainder of deaths (18) were in patients with CRC. These cases were reviewed and no new safety signals were noted.

### 7.3.2 Nonfatal Serious Adverse Events

Twelve (20%) patients on the placebo arm and 34 (26%) patients on the regorafenib arm of the GRID study experienced a non-fatal SAE. The SAEs occurring in >1% of subjects in either arm of the study are summarized in Table 26.

Table 26 Non-fatal SAEs occurring in >1% of patients on the GRID Study

SAEs by MedDRA PT	Placebo (n=66)	Regorafenib (n=132)
Abdominal pain	3 (4.5%)	5 (3.8%)
Dehydration	1 (1.5%)	3 (2.3%)
Ascites	0	3 (2.3%)
Pyrexia	0	3 (2.3%)
Asthenia	1 (1.5%)	2 (1.5%)
General physical health deterioration	1 (1.5%)	2 (1.5%)
Diarrhea	0	2 (1.5%)
Pulmonary embolism	0	2 (1.5%)
Tumor hemorrhage	0	2 (1.5%)
Fatigue	1 (1.5%)	1 (0.8%)
Hepatic function abnormal	1 (1.5%)	1 (0.8%)
Nausea	1 (1.5%)	1 (0.8%)
Cholecystectomy	1 (1.5%)	0
Hyperglycemia	1 (1.5%)	0
Mania	1 (1.5%)	0
Mental status changes	1 (1.5%)	0
Non-cardiac chest pain	1 (1.5%)	0
Rebound effect	1 (1.5%)	0

The only SAEs occurring more frequently (>2% difference) in the regorafenib arm of the study are ascites and pyrexia.

Non-fatal SAEs were also evaluated in the patient population consisting of all patients who received regorafenib in the double-blind or the open-label phase (n=188) phase of the study. Overall non-fatal SAEs occurred in 56 (30%) patients who received regorafenib in the two phases of the study. SAEs occurring in >1% of patients included abdominal pain (3.7%), pyrexia (2.1%), tumor hemorrhage (2.1%), ascites (1.6%), back pain (1.6%), dehydration (1.6%), fatigue (1.6%), pulmonary embolism (1.6%), asthenia (1.1%), deep venous thrombosis (1.1%), diarrhea (1.1%), general physical health deterioration (1.1%) and nausea (1.1%). The SAE profile in this population was not significantly different from the regorafenib arm in the DB phase of the study with the exception of the increased rate of tumor hemorrhage.

Reviewer's note:

1) Pyrexia (3%), abdominal pain (2.4%) and diarrhea (2%) are SAEs that were also noted to occur in  $\geq 2\%$  of patients enrolled on the regorafenib arm of the CRC trial.

2) Three patients on the regorafenib arm, #560020001, #200050003 and #100010007, were reported to have SAEs of nephropathy (Grade 2), renal impairment (Grade 2) and acute renal failure (Grade 3). Review of the case narratives suggests that these cases were related to dehydration. An additional 3 patients on the regorafenib arm, #180010007, #140100001 and #140010006, were reported to have SAEs of grade 3 dehydration. Only 1 patient on the placebo arm, #160020004, had an SAE of grade 3 dehydration. All of the events on the regorafenib arm had the event during the double blind phase except patient #100010007.

3) Three patients (#220030004, #120030001 and #200050003) on the regorafenib arm were reported to have an SAE of pulmonary embolism. In two of these cases the event happened after discontinuation of therapy. There were no reports of pulmonary embolism SAEs on the placebo arm. In the first two patients the SAE was reported during DB phase while in the third patients the SAE occurred in safety follow up after the OL phase.

4) Seven patients (#160050002, #160050003, #200030002, #260010003, #540070003, #540070005, #680010002) had a hemorrhagic SAE. All patients were on the regorafenib arm of the study. Three patients had the SAE in the DB phase, 1 in OL phase and 3 during safety follow up. Three events were grade 4 and three were grade 3. All events involved the GI tract or were events of tumor hemorrhage.

5) At the time of the 90-day safety update, 117 new non-fatal SAEs were reported for all patients treated on studies with regorafenib. A review of these SAEs did not identify any new safety concerns. SAEs of special interest including hepatic disorders, cardiac failure, hemorrhage, acute renal failure and GI perforation were reviewed and no changes to current identified safety profile were noted.

### 7.3.3 Dropouts and/or Discontinuations

Eight patients (6%) on the regorafenib arm of the study and 5 patients (8%) on the placebo arm of the study experienced a treatment emergent adverse event (TEAE) that led to therapy discontinuation during the double blind phase of the study. TEAEs that were considered to be drug related occurred in 4 patients (3%) on the regorafenib arm and 1 patient (2%) on the placebo arm during the double blind phase of the study. An additional 8 patients (8%) out of the 97 that received open-label regorafenib had a TEAE leading to discontinuation of therapy. Five of the patients experiencing TEAEs leading to discontinuation that were considered to be drug related during the open label phase. The TEAEs leading to discontinuation of therapy are summarized in Table 27.

Table 27 AEs leading to discontinuation of study therapy during the GRID Study

ID#	Arm	Phase	AE by MedDRA PT	Causality*	Grade
100050001	Placebo	DB	Gastrointestinal stromal tumor	N	5
140050006	Placebo	DB	Ascites	N	3
160010004	Placebo	DB	Asthenia	Y	1
160020004	Placebo	DB	Dehydration	N	3
200050002	Placebo	DB	Hepatic function abnormal	N	3
100010007	Regorafenib	DB	Posterior reversible encephalopathy Syndrome	Y	4
100030004	Regorafenib	DB	Metastatic pain	N	2
140060003	Regorafenib	DB	Alanine aminotransferase increased	Y	3
			Aspartate aminotransferase increased	Y	3
160050002	Regorafenib	DB	Hematemesis	N	4
180010001	Regorafenib	DB	Ileus	N	5
200021002	Regorafenib	DB	Acute hepatic failure	Y	4
560010004	Regorafenib	DB	Azotaemia	N	5
560020001	Regorafenib	DB	Pneumonia	N	3
140010004	Placebo	OL	Large intestine perforation	Y	4
180010002	Placebo	OL	Deep vein thrombosis	Y	5
200030004	Placebo	OL	Drug eruption	Y	3
			Platelet count decreased	Y	4
560010007	Placebo	OL	Palmar-plantar erythrodysesthesia Syndrome	Y	3
120030001	Regorafenib	OL	Obstruction gastric	N	5
440010001	Regorafenib	OL	Hypertension	Y	2
			Diarrhoea	Y	2
540070003	Regorafenib	OL	Tumour haemorrhage	N	4
560010011	Regorafenib	OL	Abdominal pain	N	1

The only TEAEs that led to discontinuation in more than one patient receiving regorafenib were liver related events (14006003 and 200021002), hemorrhagic events (160050002 and 540070003) and skin related events (200030004 and 560010007).

Reviewer's note: Five additional patients on the regorafenib arm of the GRID trial had an AE that led to study therapy discontinuation at the time of the 90 day safety update. AEs that led to discontinuation included diarrhea, fatigue, decreased appetite, cerebral hemorrhage, palmar-plantar erythrodysesthesia syndrome and GIST. These AEs are consistent with the known safety profile for regorafenib.

### 7.3.4 Adverse events leading to dose interruption

Seventy-seven patients (58%) on the regorafenib arm and 11 patients (17%) on the placebo arm had a TEAE that led to a dose interruption. Forty-three patients (33%) on the regorafenib arm and 6 patients (9%) on the placebo arm had  $\geq 2$  TEAEs that led to dose interruption. The TEAEs most commonly leading to dose interruption included palmar-plantar erythrodysesthesia syndrome, hypertension and diarrhea. This is consistent with the previous experience with regorafenib although the incidence of hypertension appears to be slightly higher than previous experiences.

Table 28 TEAEs leading to dose interruption ( $\geq 1\%$ ) in Double Blind Phase of the GRID Study

TEAEs by MedDRA PT	Regorafenib		Placebo	
	N	%	N	%
Palmar-plantar erythrodysesthesia syndrome	33	25.0	0	0
Hypertension	14	10.6	2	3.0
Diarrhoea	8	6.1	0	0
Rash	6	4.5	0	0
Fatigue	5	3.8	2	3.0
Blood bilirubin increased	4	3.0	1	1.5
Alanine aminotransferase increased	3	2.3	0	0
Hypophosphataemia	3	2.3	0	0
Aspartate aminotransferase increased	2	1.5	0	0
Asthenia	2	1.5	0	0
Neutropenia	2	1.5	0	0
Platelet count decreased	2	1.5	0	0
Proteinuria	2	1.5	0	0
Pyrexia	2	1.5	0	0
Rash maculo-papular	2	1.5	0	0
Tumour haemorrhage	2	1.5	0	0
Abdominal pain	1	0.8	1	1.5
Nausea	0	0	2	3.0
Anaemia	0	0	1	1.5
Gastrointestinal stromal tumour	0	0	1	1.5
Hepatotoxicity	0	0	1	1.5
Hyperglycaemia	0	0	1	1.5
Hyperuricaemia	0	0	1	1.5
Mania	0	0	1	1.5
Non-cardiac chest pain	0	0	1	1.5
Rebound effect	0	0	1	1.5
Venous thrombosis	0	0	1	1.5

In the 97 patients who received open-label therapy with regorafenib, 45 experienced a TEAE that led to a dose interruption. The most common AEs ( $\geq 2$  patients) leading to dose interruption in the OL phase were palmar-plantar erythrodysesthesia syndrome (15.5%), hypertension (9.3%), alanine aminotransferase increased (4.1%), aspartate aminotransferase increased (3.1%), fatigue (3.1%), rash (3.1%), asthenia (2.1%), blood bilirubin increased (2.1%), neutrophil count decreased (2.1%) and pyrexia (2.1%). These were generally consistent with the findings in the regorafenib arm during the double-blind phase of the study.

### 7.3.5 Adverse events leading to dose reduction

Sixty-six patients (50%) on the regorafenib arm had an AE that led to a dose reduction during the double blind phase of the GRID study while only 2 patients (3%) in the placebo arm had a dose reduction. The pattern of TEAEs leading to dose reduction was consistent with the general pattern of TEAEs of this study. These TEAEs are summarized in Table 29.

Table 29 TEAEs leading to dose reduction ( $>1\%$ ) during Double Blind Phase of the GRID Trial

AE by MedDRA PT	Regorafenib (N=132)		Placebo (N=66)	
	N	%	N	%
Palmar-plantar erythrodysesthesia syndrome	44	33.3	1	1.5
Diarrhoea	6	4.5	0	-
Blood bilirubin increased	3	2.3	0	-
Hypertension	3	2.3	0	-
Rash	3	2.3	0	-
Alanine aminotransferase increased	2	1.5	0	-
Erythema	2	1.5	0	-
Fatigue	2	1.5	0	-
Mucosal inflammation	2	1.5	0	-
Rash maculo-papular	2	1.5	0	-
Hepatotoxicity	0	-	1	1.5
Hyperglycaemia	0	-	1	1.5

Twenty-five of the 97 patients (26%) that received open-label therapy experienced a TEAE leading to dose reduction. The most common TEAEs ( $\geq 2$  patients) leading to dose reduction in the open-label phase of the study included palmar-plantar erythrodysesthesia syndrome (15.5%), asthenia, fatigue and rash (all at 2.1%).

### 7.3.6 Significant Adverse Events

#### 7.3.6.1 Dermatologic Toxicity:

Adverse events that were classified under the skin and subcutaneous tissue MedDRA SOC were reported in 103 patients (78%) on the regorafenib arm and 16 patients (24%) on the placebo arm. Thirty-eight patients (29%) from the regorafenib arm had a grade 3 AE in contrast to only 1 patient (2%) on the placebo arm. The most common dermatologic AE reported was palmar-plantar erythrodysesthesia syndrome, followed by rash and alopecia. Table 30 summarizes all dermatologic AEs reported in > 1% of the patients in either arm of the study during the DB phase. The incidence of dermatologic AEs in patients on placebo arm who crossed over to receive open label regorafenib was generally similar to the patients on the regorafenib arm.

Table 30 Dermatologic AEs reported in >1% of patients on the GRID study

AEs by MedDRA PT	Regorafenib (N=132)				Placebo (N=66)			
	Grade 1-3		Grade 3		Grade 1-3		Grade 3	
	N	%	N	%	N	%	N	%
Palmar-plantar erythrodysesthesia syndrome	87	65.9	29	22.0	10	15.2	1	1.5
Rash	34	25.8	7	5.3	2	3.0	0	0
Alopecia	32	24.2	2	1.5	1	1.5	0	0
Pruritus	11	8.3	1	0.8	8	12.1	0	0
Erythema	8	6.1	2	1.5	1	1.5	0	0
Dry skin	6	4.5	0	0	0	0.0	0	0
Rash maculo-papular	5	3.8	2	1.5	0	0.0	0	0
Hyperhidrosis	4	3.0	0	0	2	3.0	0	0
Pain of skin	3	2.3	0	0	0	0.0	0	0
Dermatitis acneiform	2	1.5	0	0	0	0.0	0	0
Skin exfoliation	2	1.5	0	0	0	0.0	0	0
Skin hyperpigmentation	2	1.5	0	0	0	0.0	0	0
Skin reaction	1	0.8	0	0	1	1.5	0	0
Urticaria	1	0.8	0	0	1	1.5	0	0
Skin hypopigmentation	0	0	0	0	1	1.5	0	0
Yellow skin	0	0	0	0	1	1.5	0	0

If all MedDRA terms for “rash” are combined, the overall incidence of rash was 33% (42 patients) and the incidence of grade 3 rash 7% (9 patients) in the regorafenib arm during the double blind phase of the study. Only 2 patients (3%) on the placebo arm had an AE of grade 1 rash.

There were no reports of SAEs or grade ≥4 skin toxicities for any patients on the GRID study. Additionally there were no reports of any severe cutaneous adverse reactions

such as Stevens Johnson Syndrome, Toxic epidermal necrolysis or exfoliative dermatitis on the GRID study. However, 7 cases were identified in the overall population of regorafenib exposed patients using the MedDRA SMQ of “severe cutaneous adverse reactions”. These are summarized in Table 31.

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Table 31 'Severe cutaneous adverse reactions' amongst all regorafenib exposed patients (cases identified using MedDRA SMQ, narrow)

Study #	Center/Patient #	Race/Gender	Dermatologic AE	Outcome
11726	12003/0002	Caucasian, Female	Exfoliative rash(s)	Resolved. Drug discontinued.
11726	12001/0012	Black, Female	Exfoliative rash(s)	Resolved. Drug interrupted. Resumed at lower dose.
14387	22004/0004	Caucasian, Female	Erythema multiforme Pyrexia Rash Stomatitis Fatigue	Resolved. Corticosteroids. Drug discontinued.
14387	22004/0020	Asian, Female	Stevens-Johnson syndrome	Resolved. Systemic steroids. Discontinued. Confounded.
14387	?? /0003	Asian, Female	Erythema multiforme	Resolved. Topical steroids. Dose interruption. Positive re-challenge. Discontinued.
14387	20017/0006	Asian, Female	Erythema multiforme	Stomatitis and tongue margin nodules. Resolved. Dose interruption. Positive re-challenge. Discontinued.
14387	20006/0004	Asian, Female	Erythema multiforme	Resolved x 2. Dose interruption x 2. Oral steroids. Discontinuation.

The incidence of adverse events in the skin and subcutaneous SOC, in addition to the incidence of events of "palmar plantar erythrodysesthesia syndrome" and "rash" was higher in the patients who were classified as Asian. This data is summarized in Table 32.

Table 32 Incidence of dermatologic adverse events by race in DB Phase of the GRID Study

Race	White (n=89)	Asian (n=34)	Black (n=0)	Not reported (n=7)	Missing (n=2)
Patients with Dermatologic Toxicity	66 (74%)	32 (94%)	0	3 (43%)	2 (100%)
Patients with HFSR	53 (60%)	30 (88%)	0	3 (43%)	1 (50%)
Patients with Rash	26 (29%)	13 (38%)	0	0	1 (50%)

Reviewer’s note: At the time of the 90-day safety update two cases of toxic epidermal necrolysis (TEN) were identified in patients with colorectal cancer on study 15967. These cases are also considered “severe cutaneous adverse reactions” and are summarized below:

- 1) 2012-092453: This patient was a 71-year old who developed red and thick papules over 80% of the body surface area without any mucosal involvement. The patient was diagnosed with Lyell syndrome by a dermatologist. The case was confounded by the concomitant medicine lansoprazole. Patient was treated with intravenous immunoglobulin, methylprednisolone, ranitidine hydrochloride and omeprazole.
  - 2) 2012-094298: This patient was a 58-year old who was diagnosed with “grade 3 toxidermia” after two weeks of therapy with regorafenib. Patient responded to discontinuation of therapy and topical corticosteroids with recovery 3 days later.
- A third case was also reported but upon closer review was considered to be more consistent with a generalized rash than with TEN.

The labeling for regorafenib will be amended appropriately to include the risks of severe cutaneous adverse reactions. None of these events were reported in GIST patients.

#### 7.3.6.2 Hepatic Toxicity

During the DB Phase of the GRID study, 8 patients (6%) on the regorafenib arm and 2 patients (3%) on the placebo arm had a TEAE that was classified under the MedDRA hepatobiliary SOC. Three patients (2%) on the regorafenib arm experienced an SAE as compared to 1 patient (2%) on the placebo arm. These patients are summarized in Table 33.

Table 33 Patients with Hepatobiliary Toxicity during the DB Phase of the GRID Study

Patient #	Study Arm	MedDRA Preferred Term	CTCAE Grade	SAE
200050002	Placebo	Hepatic function abnormal	3	Y
160010009	Placebo	Hepatotoxicity	4	N
200030001	Regorafenib	Cholecystitis	1	N
540070001	Regorafenib	Cholecystitis	1	N
		Hepatic cyst	1	N
540070003	Regorafenib	Hepatic cyst	1	N
200050003	Regorafenib	Hepatic function abnormal	2	Y
560010001	Regorafenib	Hyperbilirubinaemia	2	N
560010004	Regorafenib	Hyperbilirubinaemia	2	N
160010008	Regorafenib	Cytolytic hepatitis	3	Y
200021002	Regorafenib	Acute hepatic failure	4	Y
		Acute hepatic failure	5	Y

An additional 5 patients had a TEAE classifiable under the hepatobiliary SOC during the OL phase of the study while 2 patients had TEAEs during both phases raising the total number of patients who received regorafenib and had a TEAE under the hepatobiliary SOC to 13 (7%). These patients are summarized in Table 34.

Table 34 Patients with Hepatobiliary Toxicity during the OL Phase of the GRID Study

Patient #	Study Arm	MedDRA Preferred Term	CTCAE Grade	SAE
200030004	Placebo	Hepatic function abnormal	1	N
260010004	Placebo	Hepatic pain	2	N
120010001	Placebo	Bile duct stenosis	3	Y
200010002	Placebo	Jaundice	3	Y
		Jaundice	3	N
280010006	Regorafenib	Hepatic failure	1	N
560010001	Regorafenib	Hyperbilirubinaemia	2	N
		Hyperbilirubinaemia	3	Y
200050003	Regorafenib	Hepatic failure	3	Y
		Hepatic failure	3	N

The narratives for patients who experienced an SAE of hepatic toxicity are summarized below:

200050002: This patient was a 49 year old Asian male who received treatment on the placebo arm. The patient experienced progression after 1 cycle of treatment and at the same time was noted to have increases in blood bilirubin, GGT, ALP, ALT and AST levels. This was attributed to disease progression or alternatively to a concomitant medication, loxoprofen. Patient did not receive therapy with regorafenib and died of progressive disease.

200050003: This patient was a 47-year-old Asian man with history of liver metastasis. Patient had received previous hepatectomy in addition to hepatic microwave coagulation therapy, hepatic radiofrequency ablation, hepatic transcatheter arterial infusion, hepatic transcatheter chemoembolization and previous therapy with sunitinib. After approximately one month of therapy patient was noted to have abnormal hepatic function in addition to renal impairment which responded to hydration. This led to study drug interruption and resumption after recovery. The patient continued to receive therapy for an additional 5 months, including OL therapy after progression, at which time the patient experienced events of pulmonary embolism in addition to grade 3 hepatic failure, hyperammonemia and hepatic encephalopathy. The event of hepatic failure was thought to be due to liver metastasis and progression.

160010008: This patient was a 74-year-old Caucasian man, randomized to the regorafenib arm of the study, who developed elevated transaminase and bilirubin levels that improved after drug interruption and resumption at a lower dose. The patient did have liver metastasis and an elevated alkaline phosphatase level at baseline. The patient continued to receive regorafenib for an additional 6 months.

200021002: This patient was a 49-year old Asian male randomized to the regorafenib arm of the study who developed fulminant hepatic failure halfway through his second cycle of therapy and subsequently died of the complications of hepatic failure including multisystem failure. This patient's past history included routine alcohol use but the SAE of fulminant hepatic failure was attributed to study therapy.

120010001: This patient was a 52-year-old Caucasian male, randomized to regorafenib, who was in the 6<sup>th</sup> month of regorafenib therapy when he was noted to have "an increase in the volume of the subject's porta hepatis, lymphadenopathy and increasing biliary tree dilation secondary to metastatic deposit at liver hilum." The patient had grade 3 elevated liver function tests in addition to the SAE of "biliary duct stenosis". Patient was treated with supportive care and study drug was interrupted. This SAE subsequently resolved.

200010002: This patient was a 46-year-old Asian male who was randomized to receive placebo. Patient did have hepatic metastases. The patient experienced an event of tiredness and somnolence attributed to liver injury while on placebo. After progression patient received OL treatment and had an elevated baseline total bilirubin level at 2.7 when regorafenib therapy started. Total bilirubin increased to 3.4 on day 4 of therapy and led to interruption of therapy. The patient's total bilirubin continued to increase despite interruption of therapy and patient was noted to have evidence of progression. Bilirubin levels did trend down again with supportive therapy but remained elevated. Patient did not receive any further therapy with regorafenib. His jaundice was attributed to progressive disease.

560010001: This subject was a 35-year-old Asian man who had multiple hepatic metastases at baseline and was randomized to the regorafenib arm of the study. This patient was treated with regorafenib and developed hyperbilirubinemia. Ultrasound did show evidence of biliary sludging in addition to a “gall bladder stone” which was thought to contribute to the presentation. Study therapy was discontinued and the patient showed evidence of improvement of hyperbilirubinemia with supportive care.

In addition to the review above, the laboratory values for all patients in the safety population were reviewed to identify any cases that satisfied Hy’s Law criteria. The only patient whose laboratory findings met the criteria for Hy’s law was patient #200021002 who died of fulminant liver failure. An additional patient, #390010001, had elevations in serum total bilirubin and transaminase levels that partially satisfied the criteria; however there was no documentation of an alkaline phosphatase level and the patient had hepatic metastasis. The results of this analysis are summarized in Table 35. In addition to evaluation of all laboratory values during the DB phase, all values during OL phase were also reviewed and no additional cases of Hy’s law were identified.

Table 35 Laboratory evaluation for Identifying cases of Hy's Law

	Regorafenib		Placebo	
	Patients with Liver Mets (n=104)	Patients without Liver Mets (n=28)	Patients with Liver Mets (n=57)	Patients without Liver Mets (n=9)
AST/ALT >3x ULN	7/103 (6.8%)	4/28 (14.3%)	5/57 (8.8%)	0
TBili ≥ 2x ULN	9/93 (9.7%)	1/27 (3.7%)	2/56 (3.6%)	0
AST/ALT >3x ULN & TBili ≥ 2x ULN	1/93 (1.1%)	1/27 (3.7%)	1/56 (1.8%)	0
Hy’s Law	0	1/27 (3.7%)	0	0

Reviewer’s note: At the time of the 90-day safety update, one additional case of “kidney and liver failure” was identified in the GRID study. Patient #073122 was originally enrolled on the placebo arm of the study and then went on to receive regorafenib in the OL phase of the study. This patient went on to develop fatal “kidney and liver failure” that was attributed to progressive disease. Overall, the risk of fulminant hepatotoxicity after exposure to regorafenib in the GIST population is similar to the risks observed in the CRC population.

### 7.3.6.3. Cardiac Toxicity

Twelve patients (9%) on the regorafenib arm and 1 patient (1.5%) on the placebo arm had an AE that was classified under the Cardiac SOC. The only AE that occurred in more than one patient was palpitations. The majority of these AEs were low grade with

only 1 patient having a grade 4 (#260010003) and 1 patient (#140020002) a grade 5 AE. These AEs are summarized in Table 36. These events were also the only cardiac SAEs on this study: patient #260010003 had an extensive history of coronary disease prior to study enrollment and experienced events of “acute coronary syndrome” and “arteriosclerosis coronary artery” while on study while patient #140020002 experienced sudden death after complaining of back pain.

In addition to the patients who experienced a cardiac AE during the DB phase of the study, two additional patients experienced cardiac AEs during the OL (Open Label) phase of the study. These were patient #100040006 who experienced an event of grade 1 sinus tachycardia and patient #540071004 who experienced an event of grade 1 Myocardial ischemia. Both patients were originally on placebo arm.

Table 36 Adverse Events Reported for patient on DB Phase of the GRID Study

MedDRA PT	Regorafenib (n=132)				Placebo (n=66)			
	Grade 1-5		Grade 3-5		Grade 1-5		Grade 3-5	
	N	%	N	%	N	%	N	%
Acute coronary syndrome	1	0.8	1	0.8	0	0	0	0
Arteriosclerosis coronary artery	1	0.8	1	0.8	0	0	0	0
Atrial fibrillation	1	0.8	0	0	0	0	0	0
Bradycardia	1	0.8	1	0.8	0	0	0	0
Cardiac arrest	1	0.8	1	0.8	0	0	0	0
Hypertensive heart disease	1	0.8	0	0	0	0	0	0
Left ventricular hypertrophy	1	0.8	0	0	1	1.5	0	0
Myocarditis	1	0.8	0	0	0	0	0	0
Palpitations	3	2.3	0	0	0	0	0	0
Pericardial effusion	1	0.8	0	0	0	0	0	0
Sinus bradycardia	1	0.8	0	0	0	0	0	0
Supraventricular extrasystoles	1	0.8	1	0.8	0	0	0	0
Supraventricular tachycardia	1	0.8	0	0	0	0	0	0
Tachycardia	1	0.8	0	0	0	0	0	0

Three categories of AEs under the cardiac SOC were further analyzed in order to better evaluate the cardiac toxicity of regorafenib in the GRID study:

Ischemia/infarction: Only 1 patient, #260010003, on the regorafenib arm had adverse events that could be grouped under this category during the DB phase of the study as discussed above. This patient had a history of hypercholesterolemia, angina pectoris and angioplasty at the time of study enrollment. Additionally, patient #140020002 died of presumed cardiac arrest although further information was not provided. One additional patient, #540071004, had an event “myocardial ischemia” during the open label phase of the study.

Reviewer's note: The risk of infarction/ischemia does not appear to be higher in patients with GIST who are treated with regorafenib in comparison to previous data from CRC study. The limited number of cases and the confounding factors do not allow any definitive conclusions.

Arrhythmias: Seven patients (5%) on the regorafenib arm and no patients on placebo were reported to have experienced a cardiac arrhythmia or palpitations under the cardiac SOC during the DB phase of the study. All events were low grade with the exception of patient #590010001 who experienced grade 3 events of "bradycardia" and "supraventricular extrasystoles." Only one additional patient, # 100040006, had an arrhythmia of grade 1 sinus tachycardia during the OL phase of the study.

In addition to the events reported under the cardiac SOC, all events under the investigations SOC were reviewed. Two patients (1.5%), #260030003 (QRS Axis abnormal) and #560010008 (Electrocardiogram QT prolonged), on the regorafenib arm and 1 patient (1.5%), #280010001 (Electrocardiogram QT prolonged), on the placebo arm had reported EKG abnormalities. Both events on the regorafenib arm were grade 1 in nature. Two additional patients, both from the regorafenib arm, had AEs of "Electrocardiogram QT prolonged" during the OL period.

Reviewer's note: The overall incidence of arrhythmias and EKG abnormalities was higher in the regorafenib arm however, only 1 patient had grade 3 events and two patients were only reported as having palpitations. This finding is consistent with findings in CRC setting and does not suggest a significant risk.

Congestive heart failure: There were no reports of cardiac failure on the GRID study. Additionally, there was no increase in the incidence edema/peripheral edema with 9 patients on placebo and 7 on regorafenib having events reported during the DB phase.

Reviewer's note: No additional cases of CHF were identified in the overall population of patients exposed to regorafenib when compared to previous analysis at time of CRC review and the risk remains unchanged.  
No additional cases of CHF were identified at the time of the 90 day safety update.

#### 7.3.6.4 Renal Toxicity

During the DB phase of the GRID study, 22 patients (16.7%) on the regorafenib arm had an AE that was reported under the renal SOC as opposed to 3 patients (4.5%) on the placebo arm. The most commonly AE was proteinuria reported in 9 patients (6.8%) on the regorafenib arm. Additionally, most of the AEs were grade 1 or 2 as can be seen in Table 37.

Table 37 AEs classified under the Renal SOC in the DB Phase of the GRID Study

MedDRA PT	Regorafenib (n=132)				Placebo (n=66)			
	Grade 1-5		Grade 3-5		Grade 1-5		Grade 3-5	
	N	%	N	%	N	%	N	%
Azotaemia	1	0.8	1	0.8	0	0	0	0
Bladder spasm	0	0	0	0	1	1.5	0	0
Dysuria	2	1.5	0	0	0	0	0	0
Haematuria	2	1.5	0	0	1	1.5	0	0
Nephrolithiasis	1	0.8	0	0	0	0	0	0
Nephropathy	1	0.8	0	0	0	0	0	0
Pollakiuria	4	3.0	0	0	1	1.5	0	0
Proteinuria	9	6.8	1	0.8	1	1.5	0	0
Renal cyst	1	0.8	0	0	0	0	0	0
Renal failure acute	2	1.5	1	0.8	0	0	0	0
Renal impairment	1	0.8	0	0	0	0	0	0
Strangury	1	0.8	0	0	0	0	0	0
Urinary incontinence	1	0.8	0	0	0	0	0	0
Urine odour abnormal	0	0	0	0	1	1.5	0	0

Overall, 5 patients, all on the regorafenib arm had an AE consistent with some degree of renal dysfunction. Four of these patients had an event that was considered an SAE. These patients are discussed below:

#560020001: This patient was a 69-year-old Asian man with history of hypertension and type two diabetes mellitus in addition to GIST at baseline. This patient did develop fever in the setting of worsening ascites and received systemic antibiotics. This patient was reported to have episodes of grade 1 and 2 “Nephropathy” with increases in creatinine. This patient subsequently responded to hydration (TPN) and was never dose reduced. Patient continued to receive regorafenib for an additional two months and eventually died of disease progression.

#280010004: This patient was a 68-year-old Caucasian man who was treated with regorafenib for 2 months. Eight days after stopping regorafenib, patient presented with progression, increasing ascites and an increase in serum creatinine and was reported as having an AE of “renal failure acute”. Patient did have 9 liters of ascites removed and the AE of renal failure was subsequently reported to have resolved. The patient did not receive further regorafenib and died of progression.

#200050003: This patient was a 47-year-old Asian man who after one month of therapy with regorafenib presented with fever, abnormal hepatic function and grade 2 “renal impairment” that was responsive to “B-fluid infusion”. The event of renal impairment did resolve and patient did continue to receive further therapy with regorafenib. The patient

did eventually stop regorafenib therapy due to worsening hepatic function attributed to disease progression.

#100010007: This patient was a 68-year-old Caucasian man who experienced an episode of Reversible posterior leucoencephalopathy syndrome (RPLS) one day after starting regorafenib. This AE led to ICU admission during which patient had AE of severe hypertension. Upon resolution of hypertension and admission to general wards the patient was reported to have an episode of elevated creatinine and an AE of “renal failure acute” was reported. The patient was treated with IVFs with resolution of this AE. This AE occurred 3 weeks after discontinuation of regorafenib. This patient did not receive any further regorafenib and subsequently died of progressive disease.

#560010004: This patient was a 54-year-old Asian man who experienced AEs of right sided weakness and tongue deviation that were attributed to skull metastasis. This patient presented with SAEs of fatal “azotemia” and “metabolic acidosis” approximately 2 months following the start of therapy. The patient’s azotemia was attributed to “rhabdomyolysis” and disease progression.

During the OL phase of the study, 22 patients were reported to have a renal AE. Twelve of these patients experienced events of proteinuria with only 3 patients who had an event of impaired renal function. These are summarized below:

#200040002: This patient was a 60-year-old Asian male randomized to regorafenib who 2 weeks after end of OL therapy was reported as having grade 1 renal impairment. No further information is available on this case.

#180010005: This patient was a 62-year-old Caucasian female randomized to placebo who was reported to have grade 3 and 2 AEs of “Renal failure chronic” during OL therapy with regorafenib. These events were reported have resolved with any dosing changes and patient continued to receive therapy for an additional 2 months.

#100040006: This patient is an 80-year-old Caucasian man who was originally randomized to placebo. This patient received OL regorafenib for 2 months following progression and presented with to the hospital with abdominal and back pain, poor oral intake, dehydration and grade 3 infection (unknown source). He was treated with systemic antibiotics and developed grade 5 renal failure. The cause of renal failure and death was reported as “unknown” by the investigator. Progression and infection may have potentially contributed to the event of renal failure.

<p>Reviewer’s note: Most of the cases of renal impairment appear to have been pre-renal in etiology and responded to hydration. However, the etiology of fatal renal failure in two patients receiving regorafenib remains unclear and the contribution of regorafenib to these events cannot be ruled out.</p>
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As noted earlier, an additional case of fatal “renal and liver failure” was reported in a patient originally randomized to placebo, in the OL phase of the study at the time of the 90 day safety update. This case was attributed to progressive disease. No further information was provided.

### 7.3.6.5 Vascular Toxicity

During the DB phase of the GRID Study, 80 patients (61%) on the regorafenib arm and 18 patients (27%) on the placebo arm were reported to have a TEAE that was classified under the Vascular SOC. These TEAEs are summarized in Table 38.

Table 38 TEAEs classified under the Vascular SOC in the DB Phase of the GRID Study

MedDRA PT	Regorafenib (N=132)				Placebo (N=66)			
	Grade 1-3		Grade 3-4		Grade 1-3		Grade 3	
	N	%	N	%	N	%	N	%
Hypertension	78	59.1	37	28.0	18	27.3	3	4.5
Flushing	2	1.5	0	0	0	0	0	0
Hot flush	2	1.5	0	0	0	0	0	0
Hypotension	2	1.5	0	0	0	0	0	0
Thrombosis	2	1.5	0	0	0	0	0	0
Arteriosclerosis	1	0.8	0	0	0	0	0	0
Haematoma	1	0.8	0	0	0	0	0	0
Peripheral coldness	1	0.8	0	0	0	0	0	0
Venous thrombosis	0	0	0	0	1	1.5	0	0

The most commonly reported TEAE was hypertension that was reported in 59% of the patients in the regorafenib arm and 27% of the patients in the placebo arm. Only 1 patient, #100010007, had a grade 4 TEAE of hypertension. This also represented the only SAE of hypertension and the only patient on this study to have an episode of RPLS.

During the DB phase of the study, 2 patients (1.5%) experienced a TEAE of “thrombosis” on the regorafenib arm, both of which were grade 2 and neither resulted in a change in regorafenib dosing. Only one patient (1.5%) in the placebo arm had an event of “venous thrombosis” that was also grade 2 in nature.

Two additional patients had a TEAE of “deep venous thrombosis” during the OL phase of the study. Both patients experienced SAEs and are further discussed below:

#180010002: This patient was a 62-year-old Caucasian female who was originally randomized to placebo. This patient received OL therapy for 1 cycle after evidence of progression. She presented to the hospital with evidence of progression, deteriorating

mental status, evidence of left lower extremity edema and decreasing renal function. Imaging revealed that the popliteal vein, superficial femoral vein, common femoral vein, deep vein of the thigh and the end part of external iliac vein were all obstructed and filled completely with thrombus. Also the tibial vein had extensive thrombotic lesions. The patient subsequently died. Death was considered to be due to deep venous thrombosis in the setting of progression. Although confounded, contribution from regorafenib cannot be ruled out.

#140040001: This patient is a 66-year-old Caucasian man who was treated on the placebo arm and then received regorafenib during the OL phase of the study. This patient experienced an SAE of portal vein thrombosis that responded to therapy with enoxaparin and warfarin and did not lead to any dosing changes for regorafenib. Relationship to study therapy could not be ruled out. This patient also experienced an SAE of pneumonia and an SAE of line infection.

In addition to the thromboembolic events identified under the vascular SOC, 3 patients (2.3%) on regorafenib and 1 patient (1.5%) on placebo were reported to have episodes of “pulmonary embolism” on the DB phase of the study. There were no additional patients with PE during the OL phase of the study. All cases on the regorafenib arm were confounded and in the setting of progressive disease.

Reviewer’s note: Overall, the number of patients with any thromboembolic event on during the DB phase of the GRID study was 5 with 2 patients on the placebo arm. This does not suggest a higher incidence of thromboembolic phenomena due to regorafenib.
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#### 7.3.6.6. Hemorrhage

The incidence of adverse events of bleeding was evaluated using the MedDRA SMQ hemorrhage terms. Overall, 15 (11%) patients in the regorafenib arm and 2 (3%) patients in the placebo arm were reported to have a bleeding event during the DB phase. These are summarized in Table 39.

There were no episodes of fatal bleeding, however, 5 patients on the regorafenib arm did have SAEs of tumor hemorrhage (2 patients), lower GI hemorrhage, hematemesis and GI hemorrhage. In addition 14 (7%) had TEAEs of bleeding during the OL phase of the study. Eleven of these patients had grade 1 TEAEs with two patients who had grade 3 and 4 tumor hemorrhage and one with grade 3 petechiae.

Table 39 AEs of Hemorrhage during DB Phase of the GRID Study

MedDRA PT	Placebo (N=66)		Regorafenib (N=132)			
	Grade 1		Grade 1-4		Grade 3-4	
	N	%	N	%	N	%
Epistaxis	0	0	3	2	0	0
Lower gastrointestinal haemorrhage	0	0	3	2	1	1
Gingival bleeding	0	0	2	2	0	0
Haematuria	1	2	2	2	0	0
Tumour haemorrhage	0	0	2	2	1	1
Gastrointestinal haemorrhage	0	0	1	1	1	1
Haematemesis	0	0	1	1	1	1
Haematochezia	0	0	1	1	0	0
Haematoma	0	0	1	1	0	0
Melaena	0	0	1	1	0	0
Rectal haemorrhage	0	0	1	1	0	0
Pulmonary haemorrhage	1	2	0	0	0	0

Reviewer's note: Two additional cases of hemorrhage were identified in patients receiving regorafenib at the time of the 90-day safety update. In the first case, patient #053877 had an event of grade 3 intra-abdominal hemorrhage while receiving OL regorafenib. This patient did have evidence of progressive disease including liver metastases which were thought to have contributed to this presentation. The second patient experienced an event of grade 4 cerebral hemorrhage while receiving regorafenib. This patient however was receiving concomitant subcutaneous heparin. These additional cases do not alter the current risk:benefit analysis.

### 7.3.6.7 Hypothyroidism

During the DB phase of the GRID study, 17 patients (13%) on the regorafenib arm and 2 patients (3%) on the placebo arm had a reported adverse event of hypothyroidism. All events were ≤ grade 2 in nature. An additional 3 patients (2%) on the regorafenib arm 1 patient (2%) on the placebo arm had an adverse event of "blood TSH increased" reported as an AE.

The mean thyroid stimulating hormone level also increased for patients on the regorafenib arm as compared to patients on the placebo arm during the course of the study however no significant changes were noted in other thyroid hormones. This is summarized in Table 40.

Table 40 Thyroid function values during the GRID Trial

Laboratory Parameter	Mean		Median	
	Regorafenib	Placebo	Regorafenib	Placebo
TSH, mU/L				
Baseline	4.37 (± 7.12)	3.97 (± 3.97)	2.18 (0, 45.4)	2.23 (0, 32.9)
Cycle 3	8.79 (± 27.2)	3.14 (± 4.38)	2.43 (0.02, 254.6)	2.01 (0, 31.0)
Maximum Value	13.6 (± 29.8)	5.59 (± 8.84)	3.74 (0.1, 254.6)	3.16 (0, 62.4)
Thyroxine, free, ng/dL				
Baseline	0.94 (± 0.26)	0.94 (± 0.23)	0.9 (0.39, 2.02)	0.85 (0.5, 1.8)
Cycle 3	1.06 (± 0.31)	0.96 (± 0.28)	1.01 (0.54, 2.41)	0.9 (0.5, 2.2)
Minimum Value	0.87 (± 0.23)	0.84 (± 0.18)	0.85 (0.47, 2.02)	0.85 (0.5, 1.2)
Triiodothyronine, free, pg/mL				
Baseline	6.20 (± 1.73)	5.98 (± 1.74)	6.5 (2, 10.2)	6.3 (2.4, 9.9)
Cycle 3	6.55 (± 1.89)	6.14 (± 1.92)	6.8 (1.8, 13.1)	6.55 (2.3, 9.9)
Minimum Value	5.40 (± 1.61)	5.38 (± 1.71)	5.7 (1.8, 10.0)	5.9 (2.1, 8.5)

Finally, 23 patients (17%) on the regorafenib arm received thyroxine supplementation as compared to 5 patients (8%) on the placebo arm. Sixteen patients on the placebo arm and 30 on regorafenib were placed on thyroid supplementation on or before the start day of study therapy. Additionally, in patients who had baseline TSH levels <ULN and were not on T4 supplementation at baseline, 18% of the patients in Stivarga arm and 7% of the patients in placebo arm had a rising TSH (>ULN) during treatment.

#### 7.3.6.8 Gastrointestinal Toxicity

Adverse events classified under the gastrointestinal SOC were reported in 107 patients (81%) on the regorafenib arm and 40 patients (61%) of patients on the placebo arm during the DB phase of the GRID study. The most common GI adverse events (>10%) reported in the regorafenib arm of the GRID study during the DB phase included diarrhea (46.2% vs. 9.1%), constipation (28.0% vs. 22.7%), abdominal pain (23.5% vs. 18.2%), stomatitis (23.5% vs. 6.1%), nausea (19.7% vs. 12.1%) and vomiting (16.7% vs. 7.6%). The majority of the GI adverse events were low grade with 26 patients (20%) on the regorafenib arm and 6 patients (9%) on the placebo arm experiencing CTCAE grade ≥ 3 adverse events.

The only grade 5 GI adverse events during the DB phase of the study was an event ileus reported in patient #18010001 on the regorafenib arm. This event was confounded due to the presence of progressive intra-abdominal disease. In addition, two patients were reported to have adverse events of fatal GI perforation. These included patient #16004001 with peritoneal necrosis and occurring during the DB phase of the study and patient #14001004 with event of colonic perforation during the OL phase of the study.

Reviewer's note: GI perforation is a well-known adverse event associated with regorafenib and current labeling was updated to include these cases.

#### 7.3.6.9 Infections

Forty-two patients (32%) on the regorafenib arm and 3 patients (4.5%) on the placebo arm had an adverse event that was classified under the MedDRA infections SOC. The three most common reported infectious adverse events were nasopharyngitis (7.6% vs. 0), upper respiratory tract infection (6.1% vs. 0) and urinary tract infection (5.3% vs. 1.5%). The incidence of SAEs (5.3% vs. 0) and CTCAE grade 3-5 AEs (5.3% vs. 0) were higher in the regorafenib arm of the study although the incidence of specific SAEs or grade 3-5 AEs were not notably increased.

Reviewer's Note: There were no significant changes in the adverse events of wound healing impairment or Reversible Posterior Leukoencephalopathy Syndrome (RPLS) and the risks of these labeled adverse events remains unchanged.

#### 7.3.7 Submission Specific Primary Safety Concerns

None.

#### 7.4 Supportive Safety Results

##### 7.4.1 Common Adverse Events

The most common reported TEAEs seen in the double-blind phase of study 14874 are summarized in Table 41. The only AEs more commonly reported in the placebo group were pruritis and peripheral edema.

Table 41 Most common TEAEs ( $\geq 10\%$  of patients in any treatment group) by MedDRA PT during double blind phase of study 14874

TEAEs by MedDRA PT	Placebo (n=66)		Regorafenib (n=132)	
	Grade 1-4%	Grade 3-4%	Grade 1-4%	Grade 3-4%
Palmar-plantar erythrodysesthesia syndrome	15	2	66	22
Hypertension	27	5	59	28
Diarrhea	9	0	46	8
Dysphonia	9	0	38	0
Fatigue	29	2	37	3
Decreased appetite	21	3	31	<1
Constipation	23	0	28	<1
Rash	3	0	26	5
Alopecia	2	0	24	2
Abdominal pain	18	5	23	4
Stomatitis	6	2	23	0
Pyrexia	11	2	21	0
Nausea	12	2	20	2
Mucosal inflammation	2	0	17	2
Vomiting	8	0	17	<1
Asthenia	11	0	16	<1
Headache	9	0	15	0
Muscle spasms	3	0	14	0
Weight decreased	8	0	14	0
Hypothyroidism	3	0	13	0
Myalgia	9	0	12	<1
Pain in extremity	8	1	11	0
Anemia	6	1	11	2
Back pain	8	0	10	2
Pruritus	12	0	8	<1
Edema peripheral	11	2	4	0

Most common TEAEs were also evaluated for the 56 patients on the placebo arm who went on to receive open label regorafenib. When TEAEs were evaluated for the entire cohort of patients on 14874 that were exposed to regorafenib, the list TEAEs was generally unchanged. TEAEs that occurred in  $\geq 10\%$  of patients in this bigger cohort (n=188) included cough (22, 12%), aspartate aminotransferase increased (20, 11%) and blood bilirubin increased (18, 10%).

#### 7.4.2 Laboratory Findings

Hematologic Laboratory Evaluation: Changes in the hematological parameters based on routine blood counts are shown below as the worst toxicity grade (CTCAE version 4.0) observed in the study:

Table 42 Hematology Laboratory Evaluations on the GRID Trial

Parameter	Regorafenib (n=132)			Placebo (N=66)		
	Grade			Grade		
	All %	3 %	4 %	All %	3 %	4 %
Anemia	75	3	0	73	2	0
Thrombocytopenia	13	1	0	2	0	2
Neutropenia	16	2	0	12	3	0
Lymphopenia	30	8	0	24	3	0
Increased INR	9	2	0	13	5	0

Liver Function Tests: Changes in the liver function test parameters based on routine blood tests are shown below as the worst toxicity grade (CTCAE version 4.0) observed in the study. Liver function tests that met the Hy's law criteria are discussed in section 7.3.6.2.

Table 43 Liver Function Evaluations on the GRID Trial

Parameter	Regorafenib (n=132)			Placebo (N=66)		
	Grade			Grade		
	All %	3 %	4 %	All %	3 %	4 %
Hyperbilirubinemia	33	3	1	12	2	0
Increased AST	58	3	1	47	3	0
Increased ALT	39	4	1	39	2	0
ALP increased	44	1	0	52	5	0
Hypoalbuminemia	50	2	0	32	3	0

Changes in other routine laboratory metabolic tests are shown below as the worst toxicity grade (CTC AE version 4.0) observed in the study:

Table 44 Chemistries and Urinalysis results from the GRID Trial

Parameter	Regorafenib (n=132)			Placebo (N=66)		
	Grade			Grade		
	All %	3 %	4 %	All %	3 %	4 %
Hypocalcemia	17	2	0	5	0	0
Hypokalemia	21	3	0	3	0	0
Hyponatremia	19	5	0	18	5	0
Hypophosphatemia	55	20	2	18	5	0
Elevated Creatinine	10	0	0	15	0	0
Proteinuria	39	2	0	39	3	0
Increased Lipase	14	0	1	5	0	0

Thyroid function test results were previously reviewed in Section 7.3.6.7  
 Hypothyroidism.

#### 7.4.3 Vital Signs

There were no significant changes in mean systolic or diastolic BPs for patients in either arm of the GRID trial in the first 3 cycles of therapy. These results are summarized in Table 45 and are consistent with previous findings in study 14387 in patients with colorectal cancer.

Table 45 Mean Values for systolic and diastolic BP on the GRID Trial

Systolic BP	Regorafenib		Placebo	
	N	Mean	N	Mean
Baseline	132	128.6	65	126.8
Cycle 1	132	126.8	65	125.6
Cycle 2	122	129.3	57	126.9
Cycle 3	103	127.0	34	124.6
Diastolic BP				
Baseline	132	77.9	65	78.4
Cycle 1	132	75.7	65	78.3
Cycle 2	122	76.0	57	76.4
Cycle 3	103	75.6	34	77.1

Overall 67 (51%) patients on the regorafenib arm and 19 (29%) on placebo arm had an increase in diastolic blood pressure of  $\geq 10$  points to a diastolic BP of  $\geq 80$  (CTCAE grade  $\geq 1$ ). Eighteen (14%) patients on the regorafenib arm and 5 (8%) on the placebo arm had a CTCAE grade 3 increase in diastolic blood pressure following a 10 point increase.

Sixty (45%) patients on the regorafenib arm and 9 (14%) patients on the placebo arm had an increase in the systolic blood pressure of  $\geq 20$  points to a systolic BP of  $\geq 120$  (CTCAE grade  $\geq 1$ ). Twenty-three (17%) patients on the regorafenib arm and 4 (6%) on the placebo arm had a CTCAE grade 3 increase in their systolic blood pressure following a 20 point increase.

Clinically significant increases in blood pressure were reported as adverse events and no episodes of hypertensive crisis were reported. The data analysis above is consistent with the adverse event reporting by the investigators as increases of 10 on diastolic blood pressure and 20 on systolic blood pressure were used in above analysis.

Weight changes for patients enrolled on the GRID trial were also reviewed. This data suggests that patient enrolled on the regorafenib arm had a median weight loss of between 1.0 and 2.8 kg in the first 5 cycles of therapy as compared to 0 to 1.0 for patients on placebo. This data is summarized in Table 46. This is consistent with the adverse event reporting of weight loss in  $> 20\%$  of patients on regorafenib in the pooled data from the GRID trial and the randomized trial in metastatic colorectal cancer.

Table 46 Reported Weight changes in Kg for patients enrolled on the GRID Trial

	Regorafenib					Placebo				
	N	Mean	SD	Median	Range	N	Mean	SD	Median	Range
<b>BL</b>	131	69.9	17.5	67.0	(37, 135)	65	72.1	16.4	69.0	(39, 124)
	Change from Baseline									
<b>C1, D1</b>	131	-0.1	1.5	0.0	(-8, 4)	64	0.0	1.6	0.0	(-7, 6)
<b>C2, D1</b>	119	-1.6	2.6	-1.0	(-12, 6)	55	0.3	2.7	0.0	(-7, 10)
<b>C3, D1</b>	99	-2.1	2.8	-2.0	(-10, 6)	34	0.4	4.1	0.3	(-10, 13)
<b>C4, D1</b>	90	-2.5	3.2	-2.4	(-11, 7)	18	1.4	4.2	0.5	(-5, 10)
<b>C5, D1</b>	82	-2.6	3.2	-2.8	(-12, 7)	13	1.0	4.6	1.0	(-8, 10)

There were no patients on the GRID trial that experienced a temperature of  $>38$  degrees Celsius at baseline. Three (2%) patients on the regorafenib arm and 3 (5%) on the placebo arm had a reported temperature of  $>38$  degrees during the study. This is not consistent with the reported rate of the adverse event of fever which was reported in 21% of patients on regorafenib and 11% of patients on placebo.

No significant changes in mean heart rate were noted in patients treated with regorafenib between cycles.

#### 7.4.4 Electrocardiograms (ECGs)

EKGs were performed on day 1 of the first 6 cycles of therapy in the GRID study. No clinically relevant changes were observed for any of the ECG parameters. These findings were similar to the findings in the colorectal trial, #14387.

#### 7.4.5 Special Safety Studies/Clinical Trials

Please see clinical pharmacology review. The applicant has completed enrollment in cardiac safety study (Study 14814) to evaluate QTc prolongation, if any, and left ventricular ejection fraction. An interim analysis based on assessment in 25 patients was submitted at the time of the original NDA. No new data was submitted to this supplement however the finalized results of study 14814 will be submitted to satisfy a PMR (#1925-1) issued at the time of the original NDA.

#### 7.4.6 Immunogenicity

Not applicable to this small molecule.

### 7.5 Other Safety Explorations

#### 7.5.1 Dose Dependency for Adverse Events

The placebo controlled, international multicenter trial (the GRID trial: 14874), that forms the basis of this application for the treatment of patients with metastatic and unresectable GIST was conducted with a fixed dose of 160 mg regorafenib daily for 3 weeks of each 4 week treatment cycle. No clear relationship to cumulative dose can be established as common adverse events such as hypertension and HFSR are most commonly reported in the first 2 to 3 cycles (please see Section 7.5.2 Time Dependency for Adverse Events

No clear relationship between exposure and selected indices of safety was observed for regorafenib, M2, or M5 in the dose escalation trial (Study 11650) as described in the Clinical Pharmacology Review under NDA 203-085. The applicant did not provide the pharmacokinetic data collected as part of Study 14874. A Post Marketing Commitment to submit exposure-response analyses for regorafenib and its metabolites using relevant available data collected in patients with metastatic or unresectable GIST will be included in the action letter.

#### 7.5.2 Time Dependency for Adverse Events

More than half of the treatment-emergent common adverse events occurred during the first two cycles of the treatment in either arm of the study (67.5% on regorafenib vs. 71.1% on placebo). This should be considered in the context of median number of cycles on therapy which were 6.0 cycles on the regorafenib arm and 2.9 cycles on the placebo arm.

The onset of AEs of special interest such as HFSR (89.7% on regorafenib arm and 70% on placebo arm) and hepatotoxicity (75.6% on regorafenib arm and 38% on placebo arm) also primarily occurred within the first 2 cycles of therapy.

These findings are consistent with the findings in the study 14387 which formed the basis for the colorectal approval.

### 7.5.3 Drug-Demographic Interactions

#### 7.5.3.1 Adverse Events by Age

In the DB portion of the GRID trial, the overall incidence of AEs in the placebo group were 91.3% and 95.0%, respectively, for patients <65 and ≥65 years of age while the overall incidences of AEs in the regorafenib group were 100% for patients in both age categories. The incidence of grade 3-5 AEs in placebo patients were 34.8% and 40.0%, respectively, for patients <65 and ≥65 years of age while overall incidences of grade 3-5 AEs in the regorafenib group were 70.8% and 88.4%, respectively, for patients <65 and ≥65 years of age. The AEs occurring at an incidence of >10% in patients ≥65 years of age treated with regorafenib include fatigue (46.5% vs. 32.6%), diarrhea (53.5% vs. 42.7%) and dyspepsia (14.0% vs. 2.2%). The AEs occurring at an incidence of >10% in patients <65 years of age include palmar-plantar erythrodysesthesia syndrome (70.8% vs. 55.8%), vomiting (20.2% vs. 9.3%) and abdominal pain (27.0% vs. 16.3%). Additionally, the incidence of grade ≥3 hypertension was 10.2% higher in the ≥65 year age group with all but one of the events being grade 3 in nature. These differences do not appear to be of any clinical significance.

#### 7.5.3.2 Adverse Events by Gender

In the DB portion of the GRID trial, the overall incidence of AEs in the placebo group were 90.5% and 95.8%, respectively, for male and female patients while the overall incidences of AEs in the regorafenib group were 100% for patients of both genders. The incidence of grade 3-5 AEs in placebo patients were 35.7% and 37.5%, respectively, for male and female patients while overall incidences of grade 3-5 AEs in the regorafenib group were 71.4% and 85.4%, respectively, for male and female patients. AEs in the DB phase that occurred at an incidence of >10% in males included constipation (32.1% vs. 20.8%), mucosal inflammation (21.4% vs. 10.4%) and dysphonia (42.9% vs. 29.2%). AEs in the DB phase that occurred at an incidence of >10% in females included diarrhea (56.3% vs. 40.5%), nausea (29.2% vs. 14.3%), pyrexia (29.2% vs. 16.7%), alopecia (39.6% vs. 15.5%), rash (37.5% vs. 19.0%) and headache (20.8% vs. 11.9%). Dysphonia (38.3% vs. 22.6%) was more frequently seen in males when the entire population of cancer patients exposed to regorafenib was evaluated and rash (28.6% vs. 16.0%) more frequent in females. The majority of these events, however, were grade 3 or less and do not alter the risk to benefit considerations in either population.

### 7.5.3.3 Adverse Events by Race

In the GRID trial, the most commonly enrolled race of patients was Caucasian (134) followed by Asian (50). Only 1 patient was African-American with 11 patients whose race was not reported. Considering the limited number of African-American patients, no definitive conclusions can be reached regarding this patient population.

The overall incidence of AEs (100% in both groups) and SAEs (73.5% vs. 77.5%) was similar in Asian and non-Asian patients respectively. However, differences were noted in the pattern of specific AEs reported. AEs with a difference in incidence of > 10% between Asian and Non-Asian populations are summarized in Table 47. It has to be noted that the incidence of liver enzyme elevations is significantly higher in patients of Asian ethnicity. Similar differences do exist in the patients treated with placebo. Regardless, cases of DILI have been reported in both race categories and the current labeling has a boxed warning.

Table 47 AEs with a difference of > 10% between race categories for patients on regorafenib in the GRID Trial

AE by MedDRA PT	Placebo (%)		Regorafenib (%)	
	Asian N=16	Non-Asian N=46	Asian N=34	Non-Asian N=89
Palmar-plantar erythrodysesthesia syndrome	25.0	8.7	88.2	59.6
Aspartate aminotransferase increased	12.5	2.2	26.5	3.4
Decreased appetite	25.0	19.6	44.1	22.5
Stomatitis	6.3	4.3	35.3	18.0
Alopecia	0	0	35.3	22.5
Alanine aminotransferase increased	6.3	0	14.7	3.4
Hypertension	18.8	30.4	50.0	61.8
Asthenia	0	13.0	2.9	15.7
Mucosal inflammation	0	2.2	5.9	22.5
Constipation	25.0	19.6	14.7	32.6
Diarrhoea	6.3	6.5	29.4	51.7
Hypoalbuminemia	0	0	14.7	0
Proteinuria	6.3	0	26.5	0

### 7.5.4 Drug-Disease Interactions

No new information has been submitted since the original NDA approved in September 2012. Please see the Clinical Pharmacology Review of NDA 203085 for further details.

#### 7.5.5 Drug-Drug Interactions

No new information has been submitted since the original NDA approved in September 2012. Please see the Clinical Pharmacology Review of NDA 203085 for further details.

#### 7.6 Additional Safety Evaluations

##### 7.6.1 Human Carcinogenicity

No new information has been submitted since the original NDA approved in September 2012. Please see the Clinical Pharmacology Review of NDA 203085 for further details.

##### 7.6.2 Human Reproduction and Pregnancy Data

No new information has been submitted since the original NDA approved in September 2012. Please see the Clinical Pharmacology Review of NDA 203085 for further details.

##### 7.6.3 Pediatrics and Assessment of Effects on Growth

Not applicable.

##### 7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

No new information has been submitted since the original NDA (#203085) approved in September 2012.

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

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

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

#### 7.7 Additional Submissions / Safety Issues

None.

## **8 Postmarket Experience**

No postmarketing data is available as this agent was recently approved. An Empirica Signal search of postmarketing reports from the FAERS database was attempted, but no data were retrieved.

## 9 Appendices

### 9.1 Literature Review/References

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## 9.2 Labeling Recommendations

Regorafenib received approval for treatment of metastatic colorectal cancer in September 2012 (NDA 203085).

The dose of regorafenib used in the GIST study was 160 mg, orally, once a day for the first 21 days of every 28 day cycle. This dose was based upon a phase 1 trial (11650) in patients with advanced solid tumors discussed in Section 7.2.2 Explorations for Dose Response and Section 7.5 Other Safety Explorations. This dose is the accepted maximum tolerated dose for regorafenib and is the approved dose in metastatic CRC. A post marketing commitment was issued for evaluation of exposure-response relationships in GIST.

The clinical team recommended the following key labeling changes:

### *Indications and Usage*

- Changed the indication from treatment of patients with [REDACTED] (b) (4) [REDACTED] to “Locally advanced, unresectable and or metastatic gastrointestinal stromal tumor (GIST) who have been previously treated with imatinib mesylate and sunitinib malate.” This reflects the trial that is supportive of the approval of regorafenib in GIST.

### *Warnings and Precautions*

- This section was updated to include data from the GRID trial.

- Section 5.3 was updated to include data regarding episodes of severe cutaneous skin toxicity such as Stevens Johnson Syndrome, toxic epidermal necrolysis and erythema multiforme.
- Section 5.3 was updated to remove any reference to supportive measures for management of HFSR as no definitive data exists that supports the institution of these measures.
- Section 5.7 was updated to include reports of episodes of fatal gastrointestinal perforation in the GRID trial and the overall experience in cancer patients.

#### *Adverse Reactions*

- This section was updated to include a list of all adverse events occurring in >20% of patients treated with regorafenib on the controlled metastatic CRC trial and the GRID trial.

#### *Clinical Studies*

- Revised indication to reflect the data from Study 14874 for GIST.
- Added stratification factors for randomization to describe Trial 14874 more clearly
- Revised text and data presented in the Table 6. Efficacy Results for Study 2 to reflect 145 PFS events
- Revised Kaplan-Meier Curves for PFS at 145 PFS events.
- Deleted Kaplan-Meier Curves for OS as the interim survival data were not mature.

#### *Patient Counseling Information*

- Added language about the GIST patient population for regorafenib treatment, a rare stomach, bowel, or esophagus cancer called GIST (gastrointestinal stromal tumors) “that cannot be treated with surgery or that has spread to other parts of the body and for which they have received previous treatment with certain medicines.”
- Added “severe” to describe more accurately the severity of skin rash.
- Provide more context by describing in greater detail the severity of gastrointestinal perforation.
- Re-ordered the adverse reactions for consistency with the Highlights and Section 6 of the PI.

### 9.3 Advisory Committee Meeting

No Oncology Drugs Advisory Committee (ODAC) meeting was convened for this application. The efficacy results demonstrated a favorable benefit:risk profile for regorafenib in subjects with GIST.

A special government employee with expertise in GIST, Dr. Ephraim Casper of Memorial Sloan Kettering Cancer Center however was identified and the results of the study were discussed with him via teleconference on 1/28/13.

The following 3 questions were posed to Dr. Casper:

1. Does the 3.9-month improvement in median progression-free survival observed in the regorafenib arm of Study 14874 represent a clinically meaningful treatment effect?
2. Based upon the data in this study, does the risk-benefit ratio favor treating the proposed indicated population with regorafenib?
3. Does the proposed product label adequately inform patients and physicians of the potential risks and benefits of regorafenib treatment?

Dr. Casper indicated that considering the advanced stage of disease of the patients enrolled on this study and the frequency of adverse events seen in the placebo group, the risk to benefit considerations for use of regorafenib are favorable and recommended the approval of this agent.

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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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JENNIE T CHANG  
02/01/2013

AMIR SHAHLAEE  
02/01/2013

SUZANNE G DEMKO  
02/01/2013

I have read and discussed the contents of this review with the primary review team and agree with the recommendations contained therein.

# CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

**NDA/BLA Number:** 204369

**Applicant:** Bayer

**Stamp Date:** 8/30/2012

**Drug Name:** Regorafenib (Stivarga®) **NDA/BLA Type:** Efficacy supplement

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

	Content Parameter	Yes	No	NA	Comment
<b>FORMAT/ORGANIZATION/LEGIBILITY</b>					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			Electronic CTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
<b>LABELING</b>					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			On initial review, the label appears to be in acceptable PLR format.
<b>SUMMARIES</b>					
8.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?			X	505(b)(1)
<b>DOSE</b>					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)? <b>Study Number:</b> 11650 and 11651 <b>Sample Size:</b> 76, 84 <b>Arms:</b> Dose levels ranging from 10-220 mg and continuous and intermittent dosing was evaluated <b>Location in submission:</b> Module 2, Summary of Clinical Efficacy	X			
<b>EFFICACY</b>					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application?  <b>Pivotal Study:</b> Study 14874 entitled, "A randomized,	X			

File name: 5\_Clinical Filing Checklist for NDA\_BLA or Supplement 010908

## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	<p>double-blind, placebo-controlled phase III study of regorafenib plus best supportive care versus placebo plus best supportive care for subjects with metastatic and/or unresectable gastrointestinal stromal tumors (GIST) whose disease has progressed despite prior treatments with at least imatinib and sunitinib (GRID Study)".</p> <p><u>Indication:</u> Patients with metastatic and/or unresectable gastrointestinal stromal tumors (GIST) who have received at least two prior therapies including imatinib and sunitinib</p> <p><b>Supportive Study:</b> Study 14935 entitled, "A non-randomized, open-label, phase 2 study evaluating the safety and efficacy of regorafenib in patients with metastatic and or unresectable GIST, resistant and or intolerant to at least imatinib and sunitinib".</p> <p><u>Indication:</u> Metastatic and or unresectable GIST, resistant and or intolerant to at least imatinib and sunitinib.</p>				
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?	X			
<b>SAFETY</b>					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?	X			Based on review of CRC NDA, results of the QT study will be submitted as PMR 1925-1.
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure <sup>1</sup> ) been exposed at the dose (or dose range) believed to be efficacious?			X	
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been	X			

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

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	exposed as requested by the Division?				
23.	Has the applicant submitted the coding dictionary <sup>2</sup> used for mapping investigator verbatim terms to preferred terms?	X			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
<b>OTHER STUDIES</b>					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			X	
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?			X	
<b>PEDIATRIC USE</b>					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			This indication has orphan status.
<b>ABUSE LIABILITY</b>					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
<b>FOREIGN STUDIES</b>					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?	X			
<b>DATASETS</b>					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
<b>CASE REPORT FORMS</b>					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			Additional ones were requested and have been submitted.
<b>FINANCIAL DISCLOSURE</b>					
38.	Has the applicant submitted the required Financial	X			

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

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	Content Parameter	Yes	No	NA	Comment
	Disclosure information?				
<b>GOOD CLINICAL PRACTICE</b>					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

**IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? \_\_\_X\_\_\_**

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

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

Jennie Chang and Amir Shahlaee October 22, 2012  
 \_\_\_\_\_  
 Reviewing Medical Officers Date

Suzanne Demko October 22, 2012  
 \_\_\_\_\_  
 Clinical Team Leader 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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JENNIE T CHANG  
10/22/2012

AMIR SHAHLAEE  
10/22/2012

SUZANNE G DEMKO  
10/23/2012