

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

203085Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 203085

SUPPL # N/A

HFD # 107

Trade Name Stivarga

Generic Name regorafenib

Applicant Name Bayer HealthCare Pharmaceuticals, Inc.

Approval Date, If Known: September 27, 2012

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

N/A

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

N/A

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

N/A

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)

IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical

investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

Investigation #2

!

!

YES

! NO

Explain:

! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES

NO

If yes, explain:

=====

Name of person completing form: Monica Hughes
Title: Lead Regulatory Health Project Manager
Date: September 26, 2012

Name of Office/Division Director signing form: Patricia Keegan, M.D.
Title: Division Director DOP2/OHOP

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MONICA L HUGHES
09/26/2012

PATRICIA KEEGAN
09/26/2012

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 203085 Supplement Number: _____ NDA Supplement Type (e.g. SE5): _____

Division Name: DOP2/OHOP PDUFA Goal Date: 10/27/12 Stamp Date: 4/27/12

Proprietary Name: Under Review

Established/Generic Name: regorafenib

Dosage Form: 40mg tablet

Applicant/Sponsor: Bayer HealthCare Pharmaceuticals Inc.

Indication(s) previously approved (please complete this question for supplements and Type 6 NDAs only):

- (1) N/A
(2) _____
(3) _____
(4) _____
-

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): 1
(Attach a completed Pediatric Page for each indication in current application.)

Indication: Metastatic colorectal cancer

Q1: Is this application in response to a PREA PMR? Yes Continue
No Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #: _____ PMR #: _____

Does the division agree that this is a complete response to the PMR?

- Yes. Please proceed to Section D.
 No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW active ingredient(s) (includes new combination); indication(s); dosage form; dosing regimen; or route of administration?*

(b) No. PREA does not apply. **Skip to signature block.**

* **Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.**

Q3: Does this indication have orphan designation?

- Yes. PREA does not apply. **Skip to signature block.**
 No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
 No: Please check all that apply:
 Partial Waiver for selected pediatric subpopulations (Complete Sections B)
 Deferred for some or all pediatric subpopulations (Complete Sections C)
 Completed for some or all pediatric subpopulations (Complete Sections D)
 Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
 Extrapolation in One or More Pediatric Age Groups (Complete Section F)

(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

			Reason (see below for further detail):			
	minimum	maximum	Not feasible [#]	Not meaningful therapeutic benefit [*]	Ineffective or unsafe [†]	Formulation failed ^Δ
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

- # Not feasible:
 - Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____

* Not meaningful therapeutic benefit:

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

- Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.*)

Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for selected pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Date studies are due (mm/dd/yy): _____							

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:			
Population		minimum	maximum
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpmhs@fda.hhs.gov) OR AT 301-796-0700.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):

Population		minimum	maximum	PeRC Pediatric Assessment form attached?	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:					
Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 6/2008)



Bayer HealthCare Pharmaceuticals hereby certifies under FD&C Act, Section 306(k)(1) that it did not, and will not, use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug, and Cosmetic Act in connection with New Drug Application 203,085.

Date:

3/13/12

Signature:

John Talian, PhD

Vice President, Global Regulatory Affairs

Head of US Regulatory Affairs

Bayer HealthCare Pharmaceuticals

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 203085	NDA Supplement # N/A	If NDA, Efficacy Supplement Type:
Proprietary Name: Stivarga Established/Proper Name: regorafenib Dosage Form: Tablets, 40 mg		Applicant: Bayer HealthCare Pharmaceuticals, Inc. Agent for Applicant (if applicable): N/A
RPM: Monica Hughes		Division: Division of Oncology Products 2
<p><u>NDAs and NDA Efficacy Supplements:</u></p> <p>NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p>	<p><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u></p> <p>Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p><input type="checkbox"/> This application does not rely upon a listed drug. <input type="checkbox"/> This application relies on literature. <input type="checkbox"/> This application relies on a final OTC monograph. <input type="checkbox"/> This application relies on (explain)</p> <p><u>For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></p> <p><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></p> <p><input type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check:</p> <p>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</p>	
❖ Actions		
<ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is <u>October 27, 2012</u> 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> • Previous actions (<i>specify type and date for each action taken</i>) 		<input checked="" type="checkbox"/> None

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 5) lists the documents to be included in the Action Package.

² For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

<p>❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____</p>	<input type="checkbox"/> Received
<p>❖ Application Characteristics ³</p>	
<p>Review priority: <input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority Chemical classification (new NDAs only): Type 1</p> <p> <input checked="" type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC </p> <p> NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies </p> <p> <input type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC <input type="checkbox"/> Submitted in response to a Pediatric Written Request </p> <p> BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 601.42) Subpart H <input type="checkbox"/> Approval based on animal studies </p> <p> REMS: <input type="checkbox"/> MedGuide <input type="checkbox"/> Communication Plan <input type="checkbox"/> ETASU <input type="checkbox"/> MedGuide w/o REMS <input type="checkbox"/> REMS not required </p> <p>Comments:</p>	
<p>❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)</p>	<input type="checkbox"/> Yes, dates
<p>❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)</p>	<input type="checkbox"/> Yes <input type="checkbox"/> No
<p>❖ Public communications (<i>approvals only</i>)</p>	
<ul style="list-style-type: none"> Office of Executive Programs (OEP) liaison has been notified of action 	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> Press Office notified of action (by OEP) 	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> Indicate what types (if any) of information dissemination are anticipated 	<input type="checkbox"/> None <input checked="" type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input checked="" type="checkbox"/> Other ASCO Burst

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
<ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity? 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions. 	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. 	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). 	<input type="checkbox"/> No paragraph III certification Date patent will expire
<ul style="list-style-type: none"> [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i> 	<input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "Yes," skip to question (4) below. If "No," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (5).

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
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CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist ⁴	Yes
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included
Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Approval Letter and Approved Labeling: September 27, 2012
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> • Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	September 27, 2012
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	April 27, 2012
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	

⁴ Fill in blanks with dates of reviews, letters, etc.

<ul style="list-style-type: none"> ❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>) 	<input type="checkbox"/> Medication Guide <input checked="" type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> • Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	Attached to the PI, see PI section
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	April 27, 2012
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	
<ul style="list-style-type: none"> ❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>) 	
<ul style="list-style-type: none"> • Most-recent draft labeling 	September 21, 2012
<ul style="list-style-type: none"> ❖ Proprietary Name <ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>) • Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name. 	June 29, 2012 June 27, 2012
<ul style="list-style-type: none"> ❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>) 	<input checked="" type="checkbox"/> RPM June 25, 2012 <input checked="" type="checkbox"/> DMEPA July 25, 2012 <input checked="" type="checkbox"/> DMPP/PLT (DRISK) September 11, 2012 <input checked="" type="checkbox"/> ODPD (DDMAC) Professional: September 11, 2012 Consumer: September 12, 2012 <input type="checkbox"/> SEALD <input type="checkbox"/> CSS <input checked="" type="checkbox"/> Other reviews Maternal Health: August 29, 2012
Administrative / Regulatory Documents	
<ul style="list-style-type: none"> ❖ Administrative Reviews (<i>e.g., RPM Filing Review⁵/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>) 	June 13, 2012 (RPM Filing Review)
<ul style="list-style-type: none"> ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte 	<input checked="" type="checkbox"/> Not a (b)(2)
<ul style="list-style-type: none"> ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>) 	<input checked="" type="checkbox"/> Not a (b)(2)
<ul style="list-style-type: none"> ❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>) 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> ❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm 	
<ul style="list-style-type: none"> • Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action

⁵ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

<ul style="list-style-type: none"> ❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC <u>July 25, 2012</u> If PeRC review not necessary, explain: _____ • Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>) 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> ❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (<i>include certification</i>) 	<input checked="" type="checkbox"/> Verified, statement is acceptable
<ul style="list-style-type: none"> ❖ Outgoing communications (<i>letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons</i>) 	September 26, 2012 (uploaded September 27, 2012) September 25, 2012 September 24, 2012 September 19, 2012 September 18, 2012 August 29, 2012 August 29, 2012 August 21, 2012 August 20, 2012 August 2, 2012 July 18, 2012 Filed, Issues Identified Letter: June 25, 2012 June 8, 2012 May 31, 2012 May 15, 2012 May 10, 2012 NDA Acknowledgement Letter: May 4, 2012
<ul style="list-style-type: none"> ❖ Internal memoranda, telecons, etc. 	September 25, 2012 (uploaded September 27, 2012) September 25, 2012 (uploaded September 26, 2012) September 19, 2012 (uploaded September 21, 2012) September 13, 2012 (uploaded September 14, 2012) September 11, 2012 (uploaded September 18, 2012) September 11, 2012 (uploaded September 14, 2012) August 28, 2012 (uploaded September 18, 2012) August 28, 2012 (uploaded August 29, 2012) August 22, 2012 (uploaded August 29, 2012) August 21, 2012 (uploaded August 29, 2012) August 14, 2012 (uploaded August 29, 2012) August 14, 2012 (uploaded September 7, 2012) July 27, 2012 (uploaded August 29, 2012) July 26, 2012 Mid-Cycle Meeting

	(uploaded August 14, 2012) July 17, 2012 Monthly Team Meeting (uploaded August 27, 2012) June 12, 2012 Monthly Team Meeting (uploaded August 27, 2012) First Planning Meeting Summary: May 9, 2012, (uploaded June 13, 2012) Review Designation Memo: May 15, 2012
❖ Minutes of Meetings	
• Regulatory Briefing (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> No mtg
• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> N/A or no mtg
• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)	<input type="checkbox"/> No mtg August 23, 2011 (Minutes Issued: September 19, 2012)
• EOP2 meeting (<i>indicate date of mtg</i>)	<input type="checkbox"/> No mtg September 3, 2009 (Minutes Issued: October 2, 2009)
• Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>)	SPA Agreement Letter: January 22, 2012 Fast Track Granted Letter: June 10, 2011
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available (<i>do not include transcript</i>)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input type="checkbox"/> None September 26, 2012
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None September 19, 2012
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None September 10, 2012
PMR/PMC Development Templates (<i>indicate total number</i>)	<input type="checkbox"/> None September 26, 2012
Clinical Information⁶	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	Concurred, September 7, 2012
• Clinical review(s) (<i>indicate date for each review</i>)	September 7, 2012 (combined review) June 6, 2012: Filing Review
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None

⁶ Filing reviews should be filed with the discipline reviews.

❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	Page 15 of combined clinical Review (S. Pradhan and K. Shastri, uploaded: September 7, 2012.)
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not applicable
❖ Risk Management <ul style="list-style-type: none"> REMS Documents and Supporting Statement (<i>indicate date(s) of submission(s)</i>) REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) 	<input type="checkbox"/> None A. Vega review August 28, 2012
❖ DSI Clinical Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>)	<input type="checkbox"/> None requested September 6, 2012
Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None Concurred, August 30, 2012
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None Concurred, August 30, 2012
Statistical Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None August 30, 2012 May 21, 2012: Filing Review
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None Concurred, September 25, 2012
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None Concurred, September 25, 2012
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None September 25, 2012 Biologics Plausibility Consult: September 5, 2012 Filing Review: June 4, 2012
❖ DSI Clinical Pharmacology Inspection Review Summary (<i>include copies of DSI letters</i>)	<input type="checkbox"/> None

Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
• Supervisory Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None September 10, 2012 (Division Director and Team Leader Reviews concurred)
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	<input type="checkbox"/> None September 10, 2012 Filing Review: May 25, 2012
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	<input type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary (<i>include copies of DSI letters</i>)	<input checked="" type="checkbox"/> None requested
Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None September 14, 2012 and September 6, 2012
• Branch Chief/Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None Concurred, September 14, 2012 (DP) and August 30, 2012 (DS and DP)
• Product quality review(s) including ONDQA biopharmaceutics reviews (<i>indicate date for each review</i>)	<input type="checkbox"/> None August 30, 2012 (DP) August 30, 2012 (DP) Biopharmaceutics: August 28, 2012 Filing Review: May 29, 2012 Filing Review: May 11, 2012
❖ Microbiology Reviews <input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) (<i>indicate date of each review</i>) <input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer (<i>indicate date of each review</i>)	<input type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)	See page 66 of primary CMC review (J. Jee)
<input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>)	
<input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>)	

❖ Facilities Review/Inspection	
<input checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout) (date completed must be within 2 years of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites ⁷)	Date completed: September 5, 2012 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER (date of most recent TB-EER must be within 30 days of action date) (original and supplemental BLAs)	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation (check box only, do not include documents)	<input checked="" type="checkbox"/> Completed <input checked="" type="checkbox"/> Requested: June 7, 2012, received July 5, 2012 <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed (per review)

⁷ I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MONICA L HUGHES
09/27/2012

INTERNAL MEMORANDUM OF MEETING MINUTES

MEETING DATE: September 26, 2012
TIME: 1:00 PM ET
LOCATION: Teleconference, WO 22, Room 2327
APPLICATION: NDA 203085
DRUG NAME: Stivarga (regorafenib)

FDA ATTENDEES:

Patricia Keegan - Division Director
Steven Lemery- Clinical Team Leader
Liang Zhou - Product Assessment Lead, CMC
Nallaperumal Chidambaram- Acting Branch Chief - Branch II
Office of New Drug Quality Assessment
Josephine Jee- Product Quality Reviewer
Robert Lu- Product Quality Reviewer
Monica Hughes- Lead Regulatory Health Project Manager

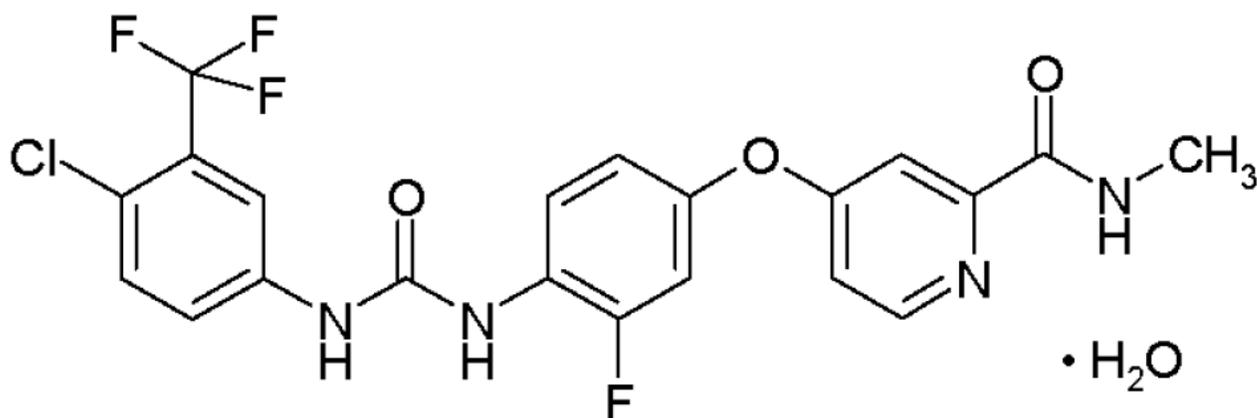
EXTERNAL CONSTITUENT ATTENDEES:

Philip Johnson, Regulatory Affairs
Robert Kelly, CMC Regulatory Affairs
Werner Heilmann, CMC Technical Development
Meni Melek, Regulatory Affairs
Alan Hassell, Labeling Regulatory Affairs

DISCUSSION POINTS: The purpose of this teleconference was to address a CMC issue that arose during the review and subsequent labeling negotiations of NDA 203085.

Bayer submitted revised product labeling on September 25, 2012, with the proposed changes to Section 11 (noted in red):

Stivarga (regorafenib) has the chemical name 4-[4-([4-chloro-3-(trifluoromethyl) phenyl] carbamoyl) amino]-3-fluorophenoxy]-N-methylpyridine-2-carboxamide **monohydrate**. Regorafenib has the following structural formula:



Regorafenib is a monohydrate and it has a molecular formula $C_{21}H_{15}ClF_4N_4O_3 \cdot H_2O$ and a molecular weight of 500.83. Regorafenib is practically insoluble in water, slightly soluble in acetonitrile, methanol, ethanol, and ethyl acetate and sparingly soluble in acetone.

Stivarga tablets for oral administration are formulated as light pink oval shaped tablets debossed with "BAYER" on one side and "40" on the other. Each tablet contains 40 mg of regorafenib in the anhydrous state, which corresponds to 41.49 mg of regorafenib monohydrate, and the following inactive ingredients: cellulose microcrystalline, croscarmellose sodium, magnesium stearate, povidone, and colloidal silicon dioxide. The film-coating contains the following inactive ingredients: ferric oxide red, ferric oxide yellow, lecithin (soy), polyethylene glycol 3350, polyvinyl alcohol, talc, and titanium dioxide.

FDA agreed with the proposed wording of the product labeling.

Bayer also proposed in the revised product labeling on September 25, 2012:

(b) (4)

FDA did not agree (b) (4) noting that regorafenib monohydrate is the form of the drug substance and therefore should be appropriately listed in the USAN. As previously communicated to Bayer on August 29, 2012, the USAN update should include structure, chemical name, CAS number, and any other relevant information but the USAN name of "Regorafenib" remains unchanged.

Bayer agreed (b) (4) (see attached email communication following this teleconference).

From: Philip Johnson [mailto:philip.johnson@bayer.com]

Sent: Wednesday, September 26, 2012 1:22 PM

To: Hughes, Monica L

Subject: RE: FDA Proposed Labeling: NDA 203085

Dear Monica –

To formally document the discussion at today's teleconference, Bayer agrees to continue with our USAN amendment for Regorafenib to represent this as a monohydrate.

Our teleconference participants today were:

Philip Johnson, Regulatory Affairs

Robert Kelly, CMC Regulatory Affairs

Werner Heilmann, CMC Technical Development

Meni Melek, Regulatory Affairs

Alan Hassell, Labeling Regulatory Affairs

When you have a chance, we would appreciate the list of FDA participants.

Best Regards,
Phil

Philip Johnson, MBA
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/s/

MONICA L HUGHES
09/27/2012

MEMORANDUM OF MEETING MINUTES

MEETING DATE: September 25, 2012

TIME: 8:30-9:00 AM ET

LOCATION: Teleconference, WO 22, RM 3266

APPLICATION: NDA 203085

DRUG NAME: Stivarga (regorafenib)

TYPE OF MEETING: Teleconference with Special Government Employee (SGE), Dr. David Kelsen, cleared for participation by CDER's Division of Advisory Committee and Consultant Management (DACCM).

FDA ATTENDEES:

Patricia Keegan - Division Director

Shan Pradhan- Clinical Reviewer

Monica Hughes- Lead Regulatory Health Project Manager

EXTERNAL CONSTITUENT ATTENDEES:

Dr. David Kelsen

BACKGROUND: Dr. David Kelsen agreed to serve and was cleared as an SGE for this NDA. Prior to this teleconference, background materials and draft product labeling were provided to Dr. Kelsen, along with three specific division questions for Dr. Kelsen to address during this teleconference. Those materials are attached to this document.

DISCUSSION POINTS:

FDA Questions for Discussion During Teleconference:

1. Does the 1.4 month improvement in median overall survival observed in the regorafenib arm of Study 14387 represent a clinically meaningful benefit?

DISCUSSION DURING TELECONFERENCE: Dr. Kelsen stated that he was familiar with this data. Dr. Kelsen stated that regorafenib demonstrated a modest, but meaningful benefit for a specific subgroup of patients not yet identified. FDA stated that identifying a specific subgroup of patients in which regorafenib treatment will have the most benefit may be difficult as it is a multiple kinase inhibitor and will affect a number of different subgroups.

2. Based upon the data in this study, does the risk-benefit ratio favor treating the proposed indicated population with regorafenib?

DISCUSSION DURING TELECONFERENCE: Dr. Kelsen stated that the risk-benefit ratio is favorable, noting that he felt that the black box warning for hepatotoxicity was appropriate and that the toxicity profile of regorafenib was acceptable with appropriate monitoring.

3. Does the proposed product label adequately inform patients and physicians of the potential risks and benefits of regorafenib treatment?

DISCUSSION DURING TELECONFERENCE: Dr. Kelsen stated that most oncologists would expect most of the observed toxicities, with the exception of hepatotoxicity. Dr. Kelsen suggested describing further, if possible, in the labeling, the subgroup of patients in which fatal hepatotoxicity occurred. Both the FDA and Dr. Kelsen discussed the finding of hepatocellular necrosis. FDA stated that there were two true Hy's-law cases noted and further stated that the risk of hepatotoxicity does seem to be higher in patients with liver metastasis and noted that physicians should monitor the patients liver tests closely in these patients.

FDA and Dr. Kelsen also discussed if Bayer should look more closely at their risk management plan and collect more data on targeted hepatotoxicity events.

Dr. Kelsen also noted that confusion may arise from the use of the CTCAE v3.0 instead of v4.0, specifically with regard to hepatotoxicity. FDA noted that the study was conducted and the data was collected using v3.0. Dr. Kelsen suggested revising the label for clarity with more specific v3.0 preferred terms.

ATTACHMENTS: Background information provided to Dr. Kelsen via facsimile on September 20, 2012.



Dr. David Kelsen
Sent via Facsimile

Dear Dr. Kelsen:

We corresponded last week regarding your assistance in the review of a new New Drug Application (NDA) 203085, submitted by Bayer Healthcare Pharmaceuticals. Please note that information concerning this application is confidential.

In this application, Bayer seeks approval of a new molecular entity, Stivarga (regorafenib), 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.

I received notification from the CDER Division of Advisory Committee and Consultant Management (DACCM) that you are cleared to serve as a Special Government Employee (SGE) for the review this new NDA.

Please review the attached written materials. We will discuss the enclosed information during a teleconference scheduled for 8:30 AM ET on September 25, 2012. We will provide toll free call in information in advance of this teleconference. Our questions we would like to discuss during this teleconference are listed below.

Following our teleconference, please return the completed Timekeeper Payroll Record (enclosed) indicating the amount of time you worked on this review via one of the following methods:

- FAX 301-796-9849: Attention Monica Hughes
- FedEx or UPS overnight delivery to:
Monica Hughes
Division of Oncology Products 2
Food and Drug Administration
WO22-2315
10903 New Hampshire Avenue
Silver Spring, MD 20903

Enclosed is a summary of the single randomized trial submitted with this application (Study 14387) and the proposed regorafenib product labeling for your review.

FDA Questions for Discussion During Teleconference:

1. Does the 1.4 month improvement in median overall survival observed in the regorafenib arm of Study 14387 represent a clinically meaningful benefit?
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?

Thank you again for your time and insights.

If you have questions, please contact me at 301-796-9225.

Sincerely,

Monica Hughes, M.S.
Lead Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosures:

1. NDA 203085 Summary Information
2. Draft regorafenib product labeling
3. Timekeeper Payroll Record

**Briefing Document for FDA Teleconference to Discuss NDA 203085
Stivarga (regorafenib), Tablets
Bayer Healthcare Pharmaceuticals**

Introduction

- On April 27, 2012, Bayer submitted NDA 203085 seeking approval of regorafenib for the treatment of patients with metastatic colorectal cancer who have been previously treated with, [REDACTED] ^{(b) (4)} fluoropyrimidine-based chemotherapy, an anti-VEGF therapy, and, if KRAS wild type, an anti-EGFR therapy.
- Regorafenib is a small molecule inhibitor of multiple kinases including BRAF, VEGFR 1/2/3, TIE2, PDGFR, FGFR, RET, and KIT.
- NDA 203085 includes data from a single randomized clinical trial, Study 14387 (also known as the CORRECT study).
- Regorafenib has been administered to over 1100 patients (including in Study 14387).

Design of Study 14387

- Study 14387 was a single, multicenter, randomized (2:1), double-blind, placebo-controlled trial that enrolled patients with previously treated mCRC.
- Patients were randomized to receive 160 mg regorafenib orally once daily (n=505) plus best supportive care (BSC), or placebo (n=255) plus best supportive care, for the first 21 days of each 28-day cycle.
 - Randomization was stratified by prior treatment with VEGF-targeting drugs (yes / no), time from diagnosis of metastatic disease (≥ 18 months / < 18 months), and geographic region.
 - Treatment continued until disease progression, unacceptable toxicity, or death.
 - The primary endpoint was overall survival and secondary endpoints were progression free survival, tumor response rate, and disease control rate.
 - Two interim analyses were planned:
 - The first interim analysis for futility was planned at 174 deaths (30%).
 - The second OS interim analysis was for efficacy and futility and was planned at 408 deaths (70%). The trial demonstrated as statistically significant effect on OS that crossed the protocol specified stopping boundary at the second interim analysis, therefore the study was stopped at that point.
- Eligibility criteria included:
 - mCRC with disease progression within 3 months after the last administration of approved standard therapies (or intolerance, and approved therapies had to include a fluoropyrimidine, oxaliplatin, irinotecan, bevacizumab, and, if KRAS wild type, cetuximab or panitumumab).
 - ECOG performance status 0-1
 - age ≥ 18 years

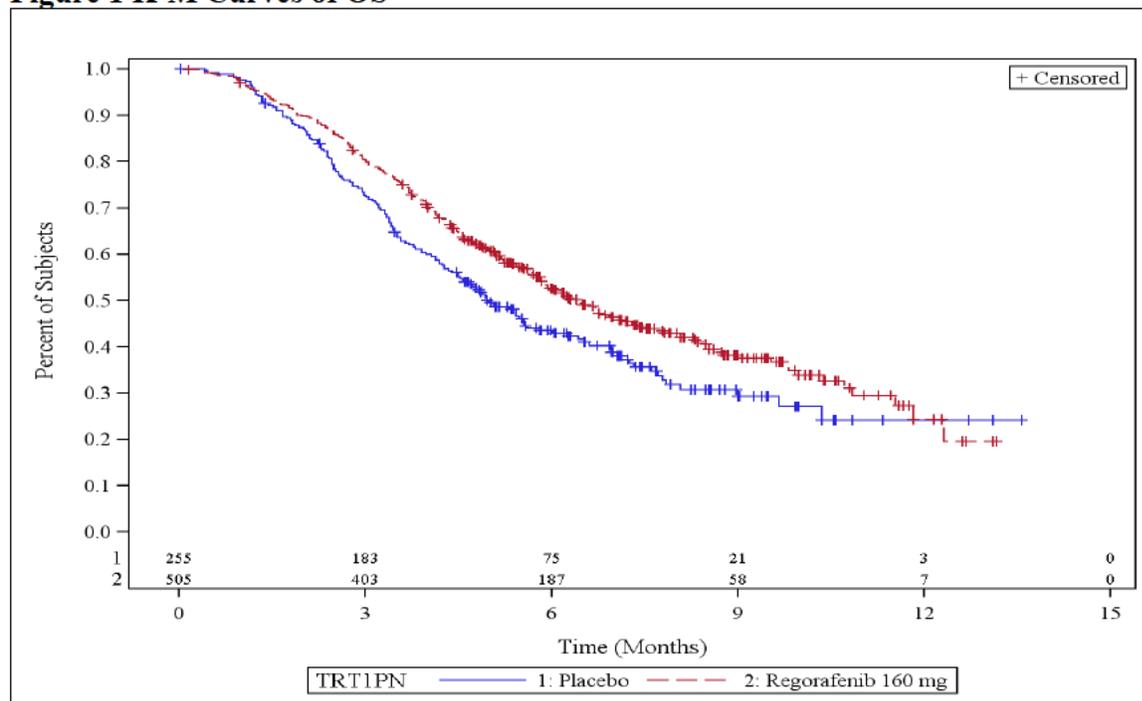
Results of Study 14387

- Baseline characteristics of enrolled patients were comparable between treatment arms.
 - Median age: 61 years
 - 78% White
 - All patients had a baseline ECOG performance status of 0 or 1.
 - Primary site of disease was colon (65%), rectum (29%), or both (6%).
 - All patients received prior treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, and bevacizumab.
 - KRAS mutation was reported in 57% of patients at study entry.
 - Of patients with a KRAS wild type tumor, all but one patient were previously treated with cetuximab and/or panitumumab.
 - There were fewer patients with a KRAS mutation in the regorafenib arm (54%) than in the placebo arm (62%).
 - Fewer patients in the regorafenib arm received systemic anti-cancer therapy during follow-up than patients in the placebo arm (30% versus 26%).

Table 1 Overall Survival

	Regorafenib N=505	Placebo N=255
Number of Events (%)	275 (55)	157 (62)
Median OS in months (95% CI)	6.4 (5.8, 7.3)	5.0 (4.4, 5.8)
HR (95% CI)	0.77 (0.64, 0.94)	
Stratified Log-Rank Test p-value	0.01	

Figure 1 K-M Curves of OS



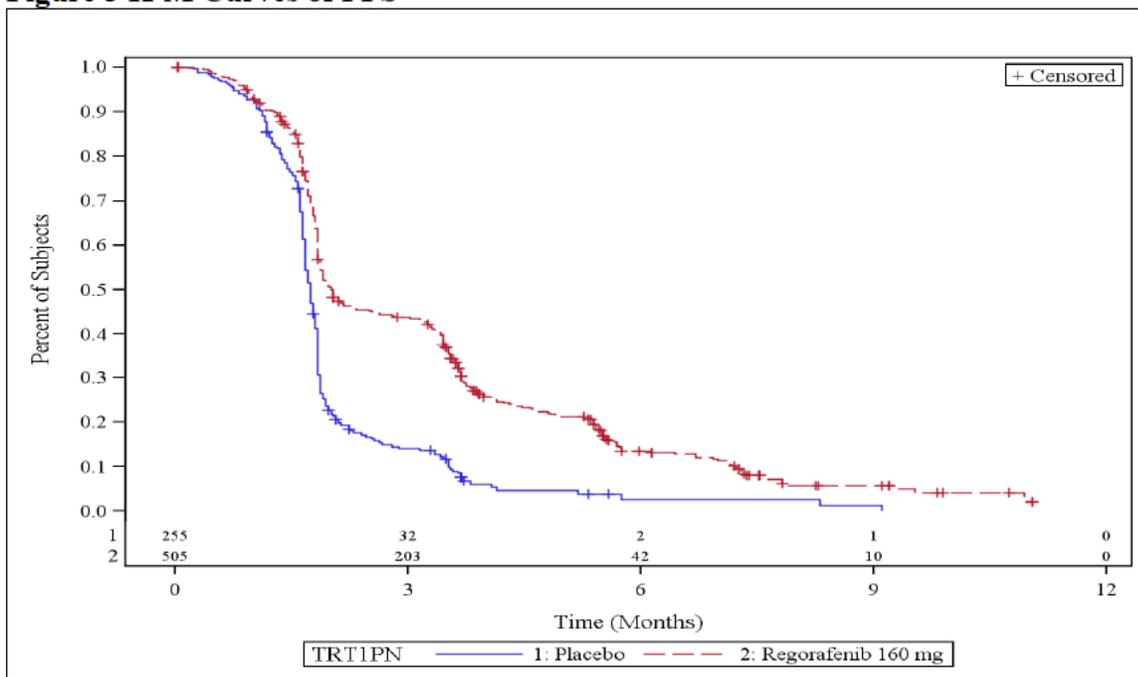
Additional Supportive Analyses of Efficacy

- One key secondary endpoint was PFS per investigator assessment.
 - FDA’s analysis of PFS excluded clinical progression events, such that PFS was defined by pathologic or radiologic findings only. Nevertheless, the final result of FDA’s analysis was almost identical to Bayer’s analysis that included clinical events as PFS events.

Table 2 Progression Free Survival - FDA's Analysis

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

Figure 3 K-M Curves of PFS



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

Table 3 Objective Response Rate

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

Analysis of Safety Data from Study 14387

- The overall toxicity profile of regorafenib appeared similar to that of other multi-kinase inhibitors.
- The mean duration of therapy was 12 weeks for the regorafenib arm compared to 8 weeks for placebo.
- Treatment-emergent adverse events resulted in dose interruptions in 61% of patients receiving regorafenib; 38% of patients required dose reduction (compared to 22% and 3%, respectively, with placebo).
- The most serious toxicities caused by regorafenib were:
 - Drug-induced liver injury
 - Hemorrhage
 - Dermatologic toxicity [palmar-plantar erythrodysesthesia (PPE) and rash]
 - Hypertension
 - Cardiac ischemic events
 - GI perforation
- Fatal hepatic failure occurred in 1.6% of patients in the regorafenib arm compared to 0.4% in the placebo arm.
- The overall incidence of hemorrhage (all grades) was 21% in regorafenib-treated patients compared to 8% with placebo.
 - Fatal hemorrhage occurred in 4 of 500 (0.8%) of patients who received regorafenib.
- The overall incidence of PPE (45% versus 7%) and the incidence of Grade 3 PPE (17% versus 0%) were increased in regorafenib-treated patients.
- Hypertension occurred in 30% of regorafenib-treated patients versus 8% with placebo.
- The incidence of myocardial ischemia and infarction was higher in regorafenib-treated patients compared to placebo (1.2% versus 0.4%).
- Adverse drug reactions observed in $\geq 30\%$ of regorafenib-treated patients were:
 - Asthenia/fatigue
 - Decreased appetite and food intake
 - PPE
 - Diarrhea
 - Mucositis
 - Weight loss
 - Infection
 - Hypertension
 - Dysphonia

TIMEKEEPER PAYROLL RECORD

Advisors and Consultants Staff

Note to Center for Drug Evaluation and Research Special Government Employee.

Use this record to submit claim for hours worked at your home, place of business, or in any FDA facility located within your commuting area. Please note any dates that you were required to travel outside of your commuting area to perform your assignment. Advisory committee members should not claim salary for hours spent on normal preparation for a committee meeting. Salary paid in response to this time sheet represents compensation in full for all services rendered and supplied by the Special Government Employee during this period.

Date(s) Hours Worked Description of Work
(Cite IND/NDA if applicable)

_____ (Sign) _____
Special Government Employee Date

Certification:

I certify that this work was done during the period(s) indicated at:

- Government furnished facility
- Employees home/office since there was no Federal office or laboratory space available at which to perform the assigned work.
- Quality and quantity of work meets performance expectations.

Center for Drug Evaluation and Research Executive Date
Secretary/Management Official Authorizing Assignment

Appears this way on original

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MONICA L HUGHES
09/27/2012



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: September 25, 2012

From: Monica Hughes, M.S., Lead Regulatory Health Project Manager DOP2/OHOP

Subject: NDA 203085: Internal Labeling Meeting

FDA reviewed and discussed Bayer's September 21, 2012, proposed labeling revisions, in response to FDA's September 19, 2012, proposal.

Attendees: Monica Hughes, Patricia Keegan, Shan Pradhan, Stacy Shord, Whitney Helms, Anwar Goheer, Karen Dowdy, James Schlick, Carole Broadnax, Karen Munoz

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MONICA L HUGHES
09/26/2012



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: September 19, 2012
From: Monica Hughes, M.S., Lead Regulatory Health Project Manager DOP2/OHOP
Subject: NDA 203085: Internal Labeling Meeting

FDA discussed the PPI during the September 19, 2012, labeling meeting.

Attendees: Kaushikkumar Shastri, Shan Pradhan, Monica Hughes, Patricia Keegan, Karen Dowdy, Barbara Fuller

Sections covered include:

- PPI
- Section 17 of the PI

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/s/

MONICA L HUGHES
09/21/2012

Meeting Summary:
NDA 203085: September 11, 2012, Monthly Team Meeting

Product: Regorafenib
Submission Date: April 27, 2012
Received Date: April 27, 2012
Goal Date: September 27, 2012
PDUFA Date: October 27, 2012

Sponsor: Bayer HealthCare Pharmaceuticals
Proposed Indication: mCRC

Attendees: Kaushikkumar Shastri, Steven Lemery, Shan Pradhan, Jade Chen, Monica Hughes, Josephine Jee, Kun He, Anwar Goheer, Whitney Helms, Stacy Shord, Hong Zhao, James Schlick, Barbara Fuller, Whitney Helms, Amarilys Vega, Robert Lu, Elsbeth Chikhale, Karen Munoz, Carole Broadnax

Meeting Purpose: We will use this team meeting to discuss review discipline specific updates as well as discuss Bayer's counter-proposed labeling submitted on September 7, 2012.

1. Review Discipline Updates:

- a. Clinical: review is complete, upcoming teleconference with SGE

Discussion During Meeting: No updates discussed, Bayer's counter-proposed labeling was discussed.

- b. Statistics: review is complete

Discussion During Meeting: No updates discussed, Bayer's counter-proposed labeling was discussed.

- c. Clinical Pharmacology: review is complete, working on PMR/PMCs

Discussion During Meeting: No updates discussed, Bayer's counter-proposed labeling was discussed.

- d. CMC: review is complete

Discussion During Meeting: No updates discussed, Bayer's counter-proposed labeling was discussed.

- e. Biopharmaceutics: review is complete

Discussion During Meeting: No updates discussed, Bayer's counter-proposed labeling was discussed.

- f. Nonclinical: review is complete

Discussion During Meeting: No updates discussed, Bayer's counter-proposed labeling was discussed.

- g. Regulatory: Labeling and PMR/PMC negotiations ongoing

Discussion During Meeting: No updates discussed, Bayer's counter-proposed labeling was discussed.

2. Consult Updates:

- a. OSE: DMEPA and DRISK: reviews are complete. Carton and Container labeling negotiations ongoing

Discussion During Meeting: No updates discussed, Bayer's counter-proposed labeling was discussed.

- b. Patient Labeling Team

Discussion During Meeting: Review is in the process of being finalized, Bayer's counter-proposed labeling was discussed.

- c. OPDP:

Discussion During Meeting: Review is in the process of being finalized, Bayer's counter-proposed labeling was discussed.

- d. Maternal Health: review is complete.

Discussion During Meeting: No updates discussed, Bayer's counter-proposed labeling was discussed.

3. Clinical site inspections: OSI review is complete.

Discussion During Meeting: No updates discussed.

4. Manufacturing inspections: Final EER acceptable.

Discussion During Meeting: No updates discussed.

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MONICA L HUGHES
09/18/2012



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: September 11, 2012
From: Monica Hughes, M.S., Lead Regulatory Health Project Manager DOP2/OHOP
Subject: NDA 203085: Internal Labeling Meeting

FDA's proposed revisions as discussed during the September 11, 2012, labeling meeting.

Attendees: Kaushikkumar Shastri, Steven Lemery, Shan Pradhan, Jade Chen, Monica Hughes, Josephine Jee, Kun He, Anwar Goheer, Whitney Helms, Stacy Shord, Hong Zhao, James Schlick, Barbara Fuller, Whitney Helms, Amariyls Vega, Robert Lu, Elsbeth Chikhale, Karen Munoz, Carole Broadnax

Sections covered include:

- Reviewed Bayer's September 7, 2012, response to our August 29, 2012, labeling comments.

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/s/

MONICA L HUGHES
09/14/2012

Hughes, Monica L

From: Martin, Jewell
Sent: Wednesday, September 05, 2012 10:29 AM
To: Hughes, Monica L
Cc: Jee, Josephine M; Lu, Donghao; Chidambaram, Nallaperum; Zhou, Liang
Subject: FW: Overall OC Recommendation NDA 203085/000 Decision: ACCEPTABLE, Decision Date: 09/05/2012, Re-evaluation Date: 02/05/2013

FYI- OC Overall Recommendation is Acceptable for NDA 203085.

-----Original Message-----

From: ees_admin@fda.gov [mailto:ees_admin@fda.gov]
Sent: Wednesday, September 05, 2012 10:04 AM
To: Olagbaju, Bose*; Godwin, Francis; Martin, Jewell; Zhou, Liang; Salganik, Maria*; Biswas, Sumita *
Subject: Overall OC Recommendation NDA 203085/000 Decision: ACCEPTABLE, Decision Date: 09/05/2012, Re-evaluation Date: 02/05/2013

This is a system generated email message to notify you that the Overall Compliance Recommendation has been made for the above Application.

For general questions about how to use EES in your work, send an email to EESQUESTIONS (EESQUESTIONS@cder.fda.gov). To contact the EES technical staff, send an email to CDER EES Help (EESHELP@fda.hhs.gov). Thank you.

Meeting Summary
Wrap-Up Meeting: August 28, 2012
NDA 203085
Stivarga (regorafenib)/mCRC

Overview: Important Review Goal Dates

Review Target Due Dates:	5 Month Review	6 Month Review
<i>Primary Review Due</i>	August 30, 2012	September 29, 2012
<i>Secondary Review Due</i>	September 3, 2012	October 3, 2012
<i>DOP2 CDTL Review Due</i>	September 6, 2012	October 6, 2012
<i>DOP2 Division Director Review Due</i>	September 17, 2012	October 17, 2012
<i>OHOP Office Director Review Due/Sign-Off</i>	September 27, 2012	October 27, 2012

Internal Goal Date: September 27, 2012

PDUFA Goal Date: October 27, 2012

FDA Attendees: Monica Hughes, Josephine Jee, Elsbeth Chikhale, Steven Lemery, Shan Pradhan, Robert Lu, Liang Zhao, Nallaperum Chidambaram, Anwar Goheer, Stacy Shord, Whitney Helms, Hong Zhao, Karen Jones, Hong Zhao, Huanyu Chen, Patricia Keegan, Amir Shahlaee, Afrouz Nayernama, Karen Dowdy, Mary Dempsey, Tzu-Yun McDowell, Derek Smith, Robert Pratt, Amarylis Vega, Carole Broadnax, James Schlick,

Agenda Items and Discussion During Meeting:

1. Discipline Specific Reviews of Application
 - a. CMC: Josephine Jee and Donghao (Robert) Lu

Discussion During Meeting: Drug Substance and Drug Product reviews are complete; internal discussions ongoing to determine if a PMC is needed for the [REDACTED] (b) (4)

CMC will also provide the updated EES status following the inspection.

CMC will also ask Bayer to update the USAN information for regorafenib to reflect the drug substance as a regorafenib monohydrate. The update should include structure, chemical name, CAS number and any other relevant information but the USAN name of "regorafenib" remains unchanged. A commitment to update this should be provided to the NDA.

In addition, CMC Carton and Container labeling comments will be conveyed to Bayer shortly.

Meeting Summary
Wrap-Up Meeting: August 28, 2012
NDA 203085
Stivarga (regorafenib)/mCRC

- b. Biopharmaceutics: Elsbeth Chikhale 5 minutes

Discussion During Meeting: On August 15, 2012, a teleconference was held with Bayer to discuss the dissolution specification issues.

Post Meeting Follow-Up: FDA clarified the following with Bayer via email communication “Please note that the acceptance criterion for [REDACTED] (b)(4) [REDACTED] was not agreed upon during the teleconference on 8/15/12, and that your suggested [REDACTED] (b)(4) in the drug product will be a review issue when validated [REDACTED] (b)(4) information (including justification for the proposed acceptance criterion) is submitted.” Bayer agreed.

- c. Non-Clinical: Anwar Goheer

Discussion During Meeting: No review issues were discussed; primary, secondary, and DD reviews will be completed shortly.

- d. Clinical Pharmacology: Stacy Shord

Discussion During Meeting: Primary and secondary reviews are almost complete. PMR/PMC forms are being completed, and proposed PMR/PMCs will be conveyed to Bayer shortly along with additional comments to be conveyed to the IND.

- e. Clinical: Shan Pradhan and Kaushik Shastri

Discussion During Meeting: Primary and secondary reviews are almost complete.

- f. Statistics : Jade Chen

Discussion During Meeting: Primary and secondary review is complete; will have DD sign off shortly.

- g. OMPQ (manufacturing inspection update): Derek Smith

Discussion During Meeting: The 483 issued during the inspection in July was VAI.

- h. OSI (clinical site inspection update):

Discussion During Meeting: The final clinical site inspection was just completed; the OSI review will be completed shortly.

Meeting Summary
Wrap-Up Meeting: August 28, 2012
NDA 203085
Stivarga (regorafenib)/mCRC

2. Pending Consults

Discuss anticipated completion dates of outstanding consults:

- OSE: DMEPA and DRISK

Discussion During Meeting: DMEPA review is complete. DRISK review will be completed shortly.

- Patient Labeling Team

Discussion During Meeting: Review will be completed following receipt of substantially complete labeling from the division.

- OPDP

Discussion During Meeting: Review will be completed following receipt of substantially complete labeling from the division.

- Pediatric and Maternal Health

Discussion During Meeting: Review is complete.

3. Labeling Discussion: Clinical and Statistical will lead discussion.

- Status of labeling review
 - Labeling meetings held: July 27, August 14, 21, and 22, 2012
 - Labeling meeting scheduled: August 28, 2012
- Discuss open items with input needed from other reviewers
- Discuss need for additional meetings

Discussion During Meeting: An additional meeting will be set up during the second week of September to discuss Bayer's response to our labeling comments.

4. Discuss Postmarketing Commitments

Discussion During Meeting: There will be clinical pharmacology PMRs/PMCs to be conveyed to Bayer shortly.

Meeting Summary
Wrap-Up Meeting: August 28, 2012
NDA 203085
Stivarga (regorafenib)/mCRC

5. Discuss Postmarketing Safety Surveillance Plan Steven Lemery/Kaushik Shastri
-Clinical team will inform the Division of Pharmacovigilance what types of adverse events they should be monitoring for.
Discussion During Meeting: Adverse events following the use of regorafenib have been those typically observed after other TKI drugs such as sorafenib, sunitinib, or pazopanib.

6. Discussion of Proposed Action To Be Taken: Steven Lemery
Discussion During Meeting: All review disciplines recommend an approval action for this application.

7. Discussion of sign-off procedure and schedule: Steven Lemery
Discussion During Meeting: Final primary and secondary reviews need to be completed (by end of first week of September) in order for the CDTL and DD to complete their reviews within the planned, 5-month review timeframe. Sign-off process will continue with labeling, PMR/PMCs, and action letter.

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/s/

MONICA L HUGHES
09/18/2012



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: August 28, 2012

From: Monica Hughes, M.S., Lead Regulatory Health Project Manager DOP2/OHOP

Subject: NDA 203085: Internal Labeling Meeting

FDA's proposed revisions as discussed during the August 28, 2012, labeling meeting.

Attendees: Keegan, Patricia; Shastri, Kaushikkumar; Lemery, Steven; Pradhan, Shan; Chen, Huanyu (Jade); Hughes, Monica

Sections covered include:

- Highlights
- Section 2: Dosage and Administration

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/s/

MONICA L HUGHES
08/29/2012



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: August 22, 2012

From: Monica Hughes, M.S., Lead Regulatory Health Project Manager DOP2/OHOP

Subject: NDA 203085: Internal Labeling Meeting

FDA's proposed revisions as discussed during the August 22, 2012, labeling meeting.

Attendees: Keegan, Patricia; Shastri, Kaushikkumar; Broadnax, Carole; Shord, Stacy; Helms, Whitney; Schlick, James; Chen, Huanyu (Jade); Hughes, Monica;

Sections covered include:

- Highlights
- Section 1: Indications and Usage
- Section 17: Patient Counseling Information
- Section 6: Adverse Events

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MONICA L HUGHES
08/29/2012



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: August 21, 2012

From: Monica Hughes, M.S., Lead Regulatory Health Project Manager DOP2/OHOP

Subject: NDA 203085: Internal Labeling Meeting

FDA's proposed revisions as discussed during the August 21, 2012, labeling meeting.

Attendees: Keegan, Patricia; Shastri, Kaushikkumar; Zhou, Liang; Shord, Stacy; Helms, Whitney; Dowdy, Karen; Ceresa, Carrie M; Schlick, James; Hughes, Monica; Patel, Anuja; McDougal, Andrew

Sections covered include:

- Section 3: Dosage Forms and Strengths
- Section 11: Description
- Section 16: How Supplied/Storage and Handling
- Section 13: Nonclinical Sections
- Carton and container labeling

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MONICA L HUGHES
08/29/2012



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: August 21, 2012
From: Monica Hughes, M.S., Lead Regulatory Health Project Manager DOP2/OHOP
Subject: NDA 203085

Under the risk management plan (section 2.2) submitted on June 4, 2012, for severe drug-induced liver injury you state that an open label Phase IIIb study in up to 3000 patients with metastatic CRC (Study 15967) will be initiated. Within this study, adverse event reporting and laboratory monitoring will be used to further characterize the incidence and severity of severe DILI, and to evaluate the liver function monitoring schedule and associated dose modification scheme in standard clinical practice.

Please clarify and address the following comments/questions:

1. Confirm that this is the ongoing expanded access study, currently under the US IND 75642.
2. What are your plans regarding the study, should Regorafenib be approved while the study is ongoing?
3. What is the minimum number of subjects that will be enrolled in the study and when will the data submitted to the FDA?

Please submit your responses to our comments/questions above to me via email communication by 5:00 PM ET August 23, 2012, along with a subsequent formal submission to NDA 203085.

Please let me know if you have any questions.

Regards,

Monica Hughes, M.S.
Lead Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-9225
Fax: 301-796-9849

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/s/

MONICA L HUGHES
08/21/2012



NDA 203085

INFORMATION REQUEST

Bayer Healthcare Pharmaceuticals, Inc.
Attention: Philip Johnson, MBA
Deputy Director, Global Regulatory Affairs
P.O. Box 1000, M1/2-1
Montville, NJ 07045-1000

Dear Mr. Johnson:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for regorafenib tablet, 40 mg.

We also refer to the Agency's Information Request sent on August 07, 2012 and your responses submitted on August 13, 2012.

We are reviewing the chemistry section of your submission and have the following comments and information requests. We request a written response by August 24, 2012, in order to continue our evaluation of your NDA.

1. Adequate in-process controls are critical for the manufacturing of (b) (4). Provide the acceptance criteria for assay and impurity profile for (b) (4).
2. Propose a test and acceptance criterion for (b) (4) in the drug substance specification for regorafenib monohydrate, as the manufactured drug substance is (b) (4).
3. Justify why the color of the manufactured drug substance has (b) (4) in the drug substance specification (b) (4).
4. In S.1.2.01 01, Structural Formula section, (b) (4) may be interpreted as n H₂O. It should be changed to (dot) H₂O.

(b) (4)

If you have any questions, call Jewell Martin, Regulatory Project Manager, at (301) 796-2072.

Sincerely,

{See appended electronic signature page}

Nallaperumal Chidambaram, Ph.D.
Acting Branch Chief, Branch II
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

NALLAPERUM CHIDAMBARAM
08/20/2012



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: July 18, 2012
From: Monica Hughes, M.S., Lead Regulatory Health Project Manager DOP2/OHOP
Subject: NDA 203085

We have the following requests for information. We are requesting a response to items 1 and 2 by 5:00 PM on July 19, 2012, and the remaining items within 5 business days.

1. Please provide transport dataset(s) and the SAS program(s) with adequate document(s) for producing the results in the Ad-Hoc Statistical Analysis 1 and Ad-Hoc Statistical Analysis 2 under SN3 dated on 5/16/2012. For example, using the information in table 16.1.9.2, the statistical reviewer could not define the date of censoring for those without neither radiological PD nor death.
2. Please resubmit ADSL dataset including all of the baseline disease characteristics, medical and surgical history, and prior and concomitant therapy which had been used to generate CSR Table 8-6, 8-7, 8-9 and Appended Table 14.1/12, 14.1/20, 14.1/23.
3. Please provide SAS program(s) with adequate document(s) to duplicate the analysis variable derivation (datasets: adevtte and adevresp) including time to event endpoints: OS, PFS (including sensitivity analyses and ad-hoc analyses), and ORR.
4. Based on the submitted SAS program under SN4 dated on 5/24/12 (FDA_request_15may2012_OS_analysis.pdf), the statistical reviewer performed the OS and PFS analyses by months using attached SAS program and got the following results. Please comment on the SAS program regarding to the results in red fonts.

TYPE	TRT1PN	Censor/Events	MED_95%CI	HR_95CI_S	PV_S (2-sided)	HR_95CI_US	PV_US (2-sided)
	Placebo	98/157	5.0 (4.4, 5.8)	0.77 (0.64, 0.94)	0.0102	0.77 (0.63, 0.93)	0.0077

	Regorafenib 160 mg	230/275	6.4 (5.8, 7.3)				
PFS	Placebo	14/241	1.7 (1.7, 1.7)	0.49 (0.42, 0.58)	<.0001	0.49 (0.42, 0.58)	<.0001
	Regorafenib 160 mg	75/430	1.9 (1.9, 2.1)				

SAS program:

```

/*Get final analysis dataset*/
data der.fdaeff; set der.adevtte;
  avalm=aval/30.4375;
  label avalm= "Time (Months)";
run;

proc lifetest data = der.fdaeff;
  TITLE "OS, Un-stratified log rank test with median OS (95% CI), overall " ;
  time avalm * acenfln(1);
  strata TRT1PN / test = (logrank);
  where PARAMCD="TTD";
run;

proc lifetest data =der.fdaeff;
  TITLE "OS, stratified log rank test, overall " ;
  time avalm * acenfln(1);
  strata REGCRF VEGFNY TFMDCRF / group=TRT1PN test = (logrank);
  where PARAMCD="TTD";
run;

proc phreg data = der.fdaeff;
  TITLE "OS stratified HR, overall" ;
  model avalm * acenfln(1) = TRT1PN / risklimits ;
  strata REGCRF VEGFNY TFMDCRF;
  where PARAMCD="TTD";
run;

proc lifetest data = der.fdaeff;
  TITLE "PFS, Un-stratified log rank test with median OS (95% CI), overall " ;
  time avalm * acenfln(1);
  strata TRT1PN / test = (logrank);

```

```
        where PARAMCD="PFS";
run;

proc lifetest data =der.fdaeff;
    TITLE "PFS, stratified log rank test, overall " ;
    time avalm * acenfln(1);
    strata REGCRF VEGFNY TFMDCRF / group=TRT1PN test = (logrank);
    where PARAMCD="PFS";
run;

proc phreg data = der.fdaeff;
    TITLE "PFS stratified HR, overall" ;
    model avalm * acenfln(1) = TRT1PN / risklimits ;
    strata REGCRF VEGFNY TFMDCRF;
    where PARAMCD="PFS";
run;
```

Please let me know if you have any questions.

Regards,

Monica Hughes, M.S.
Lead Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-9225
Fax: 301-796-9849

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/s/

MONICA L HUGHES
07/18/2012

MEMORANDUM OF MEETING MINUTES

MEETING DATE: August 15, 2012
TIME: 10:30AM- 11:00AM (EST)
LOCATION: TCON/CDER WO 2560
APPLICATION: NDA 203085
DRUG NAME: Regorafenib
TYPE OF MEETING: FDA initiated TCON
MEETING CHAIR: Sandra Suarez Sharp, PhD
ONDQA Acting Biopharmaceutics Team Leader
MEETING RECORDER: Jewell Martin, Regulatory Health Project Manager
MEETING PURPOSE: The purpose of the TCON was to discuss a response to IR received from Bayer on July 5, 2012.

FDA Attendees:

Richard Lostritto, PhD, ONDQA Acting Biopharmaceutics Supervisory Lead
Elsbeth Chikhale, PhD, ONDQA Biopharmaceutics Reviewer
Josephine Jee, PhD, ONDQA CMC Reviewer
Sandra Suarez-Sharp, PhD, ONDQA Acting Biopharmaceutics Team Leader
Jewell Martin, MA, MBA, PMP, ONDQA Regulatory Health Project Manager

Bayer Attendees:

Alexander Pontius, Analytical Development -Dissolution
Christopher Wessler, Product Supply, QC
Evelin Amoulong, Global Regulatory Affairs, CMC
Robert Haydu, US Regulatory Affairs, CMC
Susanne Skrabs, Formulation and Manufacturing Process Development
Ulrich Oberdieck, Analytical Development, Drug product
Werner Heilmann, Analytical Development, Drug substance and CMC Project leader
Stephanie Mondabon, EU Regulatory Affairs
Philip Johnson, US Regulatory Affairs
Meni Melek, US Regulatory Affairs

Meeting Discussion:

The Agency informed the applicant that they lacked adequate/direct control over (b) (4) during manufacture, at release, and on stability. Instead the applicant proposed to use dissolution testing as a surrogate for (b) (4). While potentially allowable, their proposed specification of $Q = (b) (4)$ at 30 minutes would not allow discrimination between (b) (4). The Agency mentioned that since there is not clinical data (e.g. relative bioavailability/bioequivalence) information supporting a (b) (4), there were two possible paths to go forward:

1. (b) (4)

2.

(b) (4)

(b) (4)

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

The tight content uniformity performance for the tablets (20 batches) and the reasonable sensitivity of the (b) (4) method (b) (4) further supports this approach. The Applicant will provide further (b) (4) information and data they already have (but not in the NDA) for CMC evaluation by mid next week.

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/s/

JEWELL D MARTIN
08/30/2012

RICHARD T LOSTRITTO
08/30/2012

Meeting Summary
NDA 203085: August 14, 2012, Monthly Team Meeting

Product: Stivarga (regorafenib)
Submission Date: April 27, 2012
Received Date: April 27, 2012
Goal Date: September 27, 2012 (primary reviews to be completed by August 30, 2012)
PDUFA Date: October 27, 2012

Sponsor: Bayer HealthCare Pharmaceuticals

Proposed Indication: mCRC

FDA Attendees: Monica Hughes, Stacy Shord, Amarilys Vega, Steven Lemery, Whitney Helms, Anwar Goheer, Josephine Jee, Elsbeth Chickhale, Shan Pradhan, Kun He, Meredith Libeg

Meeting Purpose: This planning meeting was to discuss review discipline specific updates as well as discuss any available updates to the upcoming clinical site or manufacturing inspections.

1. Review Discipline Updates:

- a. Clinical
 - ◆ Efficacy Review
 - ◆ Safety Review

 - ◆ Discuss: Clinical site inspection sites(s) selected/Dates of inspections- Agenda item #3 below

DISCUSSION DURING MEETING: The team discussed that similar class labeling included a boxed warning for hepatotoxicity and the team discussed including one for this label. Reviews are wrapping up.

- b. Statistics

DISCUSSION DURING MEETING: No review issues were discussed, wrapping up review.

- c. Clinical Pharmacology
 - ◆ Biologics plausibility consult initiated

DISCUSSION DURING MEETING: No new clinical pharmacology review issues were discussed, the clinical pharmacology team has sent proposed PMRs and PMCs to the safety team for review.

- d. CMC
 - ◆ Discuss: Manufacturing inspection site(s) selected/drug product site inspection completed, any outcomes/updates to report: Detailed in agenda Item #4 below

DISCUSSION DURING MEETING: No review issues were discussed during this meeting. As noted in item 4 below, the manufacturing site inspection was conducted July 9-12, 2012, and the team is waiting for final review.

- e. Biopharmaceutics
 - ◆ Information requested in filing letter, Bayer emailed a preliminary response to FDA; during the last team meeting the biopharmaceutics team noted they would have a teleconference with Bayer shortly, any updates?

DISCUSSION DURING MEETING: The biopharmaceutics team is having a teleconference with Bayer on August 15, 2012, to discuss dissolution specifications criteria. Review is wrapping up.

- f. Nonclinical

DISCUSSION DURING MEETING: No review issues were discussed during this meeting. Review is wrapping up.

- g. Regulatory
 - ◆ Labeling meetings ongoing

DISCUSSION DURING MEETING: No review issues were discussed during this meeting. Labeling meetings are continuing and PMC/PMR language will be crafted and conveyed to Bayer.

2. **Mid-Cycle Meeting was held on July 26, 2012 (12:00-1:30)**
- ◆ Any updates following mid-cycle meeting, any information requests pending?

DISCUSSION DURING MEETING: No information requests were discussed.

3. **Clinical site inspection sites(s) selected/Dates of inspections:**

OSI update:

- Inspection at Mayo Clinic complete, preliminary VAI for minor problems with drug accountability.
- Inspection of (b) (4) (CRO for Bayer) complete- preliminary NAI.
- Inspections (2) in Italy– completed following last team meeting, any updates?
- Inspection in Belgium is scheduled 8/17 to 9/1.

DISCUSSION DURING MEETING: No updates were discussed during this meeting, clinical review team will discuss with OSI outside of this meeting.

4. Manufacturing inspection site(s) selected/Dates of inspections:
- ◆ DP inspection completed, any updates on the outcome?

Drug Product

Name and Address	Contact Person at Site	Telephone Number	Fax Number	E-mail Address	Registration Number	Stage of Manufacturing	Proposed Site NDA
Bayer Pharma AG Muellerstrasse 170-178 13353 Berlin, Germany	Clinical Supplies : Dr. Matthias Hartisch (Qualified Person)	49 30 468 192180	49 30 468 18165	matthias.hartisch@bayer.com	3002808 086	Manufacturing, primary & secondary packaging, Quality Control release and stability testing	No
Bayer Pharma AG D-51368 51368 Leverkusen, Germany	Market Supplies : Dr. Matthias Herboth (Qualified Person)	49 214 30 57430	49 214 30 9657430	matthias.herboth@bayer.com	3002806 462		Yes

DISCUSSION DURING MEETING: The manufacturing site inspection was conducted July 9-12, 2012, and the team is waiting for the final review.

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/s/

MONICA L HUGHES
09/07/2012



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: August 14, 2012

From: Monica Hughes, M.S., Lead Regulatory Health Project Manager DOP2/OHOP

Subject: NDA 203085: Internal Labeling Meeting

FDA's proposed revisions as discussed during the August 14, 2012, labeling meeting.

Attendees: Keegan, Patricia; Lemery, Steven; He, Kun; Shastri, Kaushikkumar; Pradhan, Shan; Shahlaee, Amir; Zhou, Liang; Zhao, Hong; Shord, Stacy; Helms, Whitney; Dowdy, Karen; Ceresa, Carrie M; Schlick, James; Hughes, Monica; Jarral, Vaishali

Sections covered include:

- Section 2: Dosage and Administration
- Section 14: Clinical Studies
- Section 7: Drug Interactions
- Section 8: Use in Specific Populations
- Section 12: Clinical Pharmacology
- Section 10: Overdosage
- Section 4: Contraindications

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/s/

MONICA L HUGHES
08/29/2012

NDA 203085: Stivarga (regorafenib) Mid-Cycle Meeting Summary

1. Important Goal Dates

Review Completion Goal Date: September 27, 2012

PDUFA Goal Date: October 27, 2012

2. Discipline Specific Reviews of Application

- Applicable studies/information submitted
- Status of your review of the data
- Discussion of findings so far

- a. Are there issues requiring resolution? Discuss in presentations or state no issues have been identified.

Discussion: No issues have been identified

- b. Are there any major labeling issues? Discuss in presentation or state there are no issues identified.

Discussion: A boxed warning may be needed for drug.

- c. Are there PMC and Risk Management Plan Issues? Discuss during presentation or state that there are no plans/need for PMC/PMRs/REMS.

Discussion: Clinical Pharmacology reviewer may request PMR for QTc & DDI.

- Identification of need for additional input from review team or through additional consults

Discussion: None at this time

- Information requests to be sent to sponsor

Discussion: To be determined

- Presentations

- a. Regulatory/Introduction (Steven Lemery on behalf of Monica Hughes)
- b. Clinical/Statistical (Shan Pradhan: Efficacy & Kaushik Shastri: Safety)
- c. Clinical Pharmacology (Stacy Shord)
- d. Non-Clinical (Anwar Goheer)
- e. CMC (Josephine Jee and Robert Lu)& Biopharmaceutics (Elsbeth Chickhale)

3. Pending Consults

-OSI Inspections:

- Inspection at Mayo Clinic complete (prelim VAI for minor problems with drug accountability).
- Inspection of (b) (4) (CRO for Bayer) complete (prelim NAI).
- Inspections (2) in Italy are ongoing – completed last week.

NDA 203085: Stivarga (regorafenib) Mid-Cycle Meeting Summary

- Inspection in Belgium is scheduled 8/17 to 9/1.
 - **OC/DMPQ Inspection:** DP facility in Germany completed, awaiting results.
- *For a complete list of consults, see table below.

4. Scheduled Meetings

Team Meetings: August 14 and September 11, 2012.

Wrap-Up: August 28, 2012.

Labeling: July 27, and August 14, 21, and 22, 2012.

8. Goals Remaining

Milestone	5 month review	6 month review
Send proposed labeling/PMR/PMC/REMS to applicant (Review Planner's Target date)	August 30, 2012 *Goal is to have substantially complete labeling to OPDP, PLT, etc. following final labeling meeting on August 22, 2012 meeting.	September 29, 2012
Week after the proposed labeling has been sent, discuss the Labeling/PMR/PMC with Applicant	September 6, 2012	October 6, 2012
Review Target Due Dates: <i>Primary Review Due</i> <i>Secondary Review Due</i> <i>CDTL Review Due</i> <i>Division Director Review Due</i> <i>Office Director Review Due/Sign-Off</i>	August 30, 2012 September 3, 2012 September 6, 2012 September 17, 2012 September 27, 2012	September 29, 2012 October 3, 2012 October 6, 2012 October 17, 2012 October 27, 2012
Compile and circulate Action Letter and Action Package	September 6, 2012	October 6, 2012
FINAL Action Letter Due	September 27, 2012	October 27, 2012

NDA 203085: Stivarga (regorafenib) Mid-Cycle Meeting Summary

9. Consults

OPDP	Carole Broadnax- professional reviewer Karen Munoz- consumer reviewer
OSE	Sue Kang-OSE RPM Sean Bradley-OSE RPM TL *DMEPA/CMC/DDMAC to review carton/container, and patient labeling Amarilys Vega: Risk Management Plan James Schlick-Proprietary Name Review James Schlick, OSE/DMEPA Todd Bridges, OSE/DMEPA TL Cynthia LaCivita, SE/DRISK TL Bob Pratt, OSE/DPV TL Cunlin Wang, OSE/DEPI TL
Maternal Health	Carrie Ceresa -Reviewer Melissa Tassinari
Facility/OMPQ	Mahesh Ramandhan
QT-IRT	**To be assigned when final report comes in with all data in the PMR submission in November 2012.
OSI	Janice Pohlman assigned, sites selected, site notification has begun.
Pediatric Page/PeRC	**Full Waiver Requested PeRC Meeting Date: July 25, 2012
Patient Labeling Team	*Patient Information Included Karen Dowdy, PLT Barbera Fuller, PLT (TL)
SEALD	Ann Marie Trentacosti
SGE's or Patient Representatives	Steven Lemery and Caleb Briggs working on screening: Jean Grem, Nebraska Carmen Allegra, UF David Kelsen, MSKCC
Biologics Plausibility Consult	Keith Burkhart, Predictive Safety Team, OCP Paul Zhichkin, Predictive Safety Team, OCS/OSPD Darrell Abernethy, Predictive Safety Team, OCP Naomi Kruhlak, QSAR

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/s/

MONA G PATEL
08/14/2012



NDA 203085

INFORMATION REQUEST

Bayer Healthcare Pharmaceuticals, Inc.
Attention: Philip Johnson, MBA
Deputy Director, Global Regulatory Affairs
P.O. Box 1000, M1/2-1
Montville, NJ 07045-1000

Dear Mr. Johnson:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for regorafenib tablet, 40 mg.

We also refer to your April 27, 2012, submission, containing your original New Drug Application.

We are reviewing the chemistry section of your submission and have the following comments and information requests. We request a written response by August 7, 2012, in order to continue our evaluation of your NDA.

Drug Substance

1. Provide a specification for [REDACTED] (b) (4)
2. The stability of [REDACTED] (b) (4) in the test solutions were not described in the validation report of analytical methods for impurities. Submit stability data for [REDACTED] (b) (4) in the test solutions.
3. [REDACTED] (b) (4) Revise the drug substance specification to include [REDACTED] (b) (4)

Drug Product

1. Provide appropriate test(s) to confirm [REDACTED] (b) (4)

2. Provide controls, including data, to limit the exposure to the conditions which cause [REDACTED] (b) (4) critical to assuring the quality and efficacy of this product.
3. Provide a [REDACTED] (b) (4) specification for regorafenib [REDACTED] (b) (4). Include appearance, identification, [REDACTED] (b) (4), residual solvents, heavy metals, impurities, assay, residue on ignition, physical form, particle size distribution, and bulk density.
4. Provide analytical data to demonstrate that [REDACTED] (b) (4) is maintained throughout the shelf-life of Regorafenib Tablets. This test and the corresponding acceptance criterion should be included in the specification for Regorafenib Tablets.
5. Clarify the term [REDACTED] (b) (4) described in the primary packaging system of the drug product.

If you have any questions, call Jewell Martin, Regulatory Project Manager, at (301) 796- 2072.

Sincerely,

{See appended electronic signature page}

Nallaperumal Chidambaram, Ph.D.
Acting Branch Chief, Branch II
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

NALLAPERUM CHIDAMBARAM

08/02/2012



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: July 27, 2012

From: Monica Hughes, M.S., Lead Regulatory Health Project Manager DOP2/OHOP

Subject: NDA 203085: Internal Labeling Meeting

FDA's proposed revisions as discussed during the July 27, 2012, labeling meeting.

Attendees: Keegan, Patricia; Lemery, Steven; He, Kun; Chen, Huanyu (Jade); Shastri, Kaushikkumar; Pradhan, Shan; Shahlaee, Amir; Jones, Karen; Zhou, Liang; Zhao, Hong; Shord, Stacy; Goheer, M. Anwar; Chikhale, Elsbeth G; Jee, Josephine M; Helms, Whitney; Lu, Donghao; Dowdy, Karen; Ceresa, Carrie M; Schlick, James; Brown, Janice; Broadnax, Carole; Varney, Deanne

Sections covered include:

Section 1: Indications and Usage

Section 2.1: Recommended Dose

Section 5: Warnings and Precautions

Section 14: Clinical Studies

Sponsor edits for Sections 6-12, 16 and 17, and Highlights were accepted.

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/s/

MONICA L HUGHES
08/29/2012

Meeting Summary
NDA 203085: July 17, 2012, Monthly Team Meeting

Product: Regorafenib
Submission Date: April 27, 2012
Received Date: April 27, 2012
Goal Date: September 27, 2012 (primary reviews to be completed by August 30, 2012)
PDUFA Date: October 27, 2012

Sponsor: Bayer HealthCare Pharmaceuticals

Proposed Indication: mCRC

FDA Attendees: Monica Hughes, Kaushik Shastri, Stacy Shord, Amarilys Vega, Steven Lemery, Patricia Keegan, Whitney Helms, Anthony Murgo, Anwar Goheer, Josephine Jee, Sandra Suarez, Janice Brown, Shan Pradhan, Barbara Fuller, Carrie Ceresa, Robert Lu, James Schlick, Jade Chen, Karen Dowdy, Hong Zhao, Naomi Kruhlak, Liang Zhou, Amir Shahlaee

Meeting Purpose: We will use this second planning meeting to discuss review discipline specific updates as well as discuss any available updates to the upcoming clinical site or manufacturing inspections.

Draft Agenda and Discussion Items:

1. Review Discipline Updates:

- a. Clinical
 - ◆ Efficacy Review
 - ◆ Safety Review
 - ◆ Discuss: Clinical site inspection sites(s) selected/Dates of inspections- Agenda item #3 below

DISCUSSION DURING MEETING: No updates regarding the efficacy or safety review were discussed during this meeting. Preparations for the mid-cycle presentation are underway. The clinical team noted one finding that more patients were enrolled in the mutant KRAS arm and that more mutant KRAS patients were also in the placebo arm. Discussion regarding clinical site inspections will be captured under item 3 below.

- b. Statistics

DISCUSSION DURING MEETING: The statistics reviewer noted that several stratification factors were used in the analyses provided. The statistical reviewer is working to confirm the primary and secondary results.

- c. Clinical Pharmacology

- ◆ Biologics plausibility consult initiated

DISCUSSION DURING MEETING: No new clinical pharmacology review issues were discussed, the clinical pharmacology team is working on generating language for additional PMRs/PMCs to be proposed. The clinical pharmacology reviewer has met with the biologics plausibility team.

d. CMC

- ◆ Discuss: Manufacturing inspection site(s) selected/Do we have an update for the dates of inspections: Agenda Item #4 below

DISCUSSION DURING MEETING: No review issues were discussed during this meeting. As noted in item 4 below, the manufacturing site inspection was conducted July 9-12, 2012, and the team is waiting for inspection results.

e. Biopharmaceutics

- ◆ Information requested in filing letter, Bayer emailed a preliminary response to FDA; biopharmaceutics team will have a teleconference with Bayer shortly.

DISCUSSION DURING MEETING: The biopharmaceutics team has requested that Bayer tighten some of their specifications as they are set too high and will not reject some batches, a teleconference will be held with Bayer and the biopharmaceutics team shortly.

f. Nonclinical

DISCUSSION DURING MEETING: No review issues were discussed during this meeting. Bayer has submitted several studies as part of their application that are under review.

g. Regulatory

- ◆ Revised labeling submitted
- ◆ Proprietary name approved by OSE: Stivarga

DISCUSSION DURING MEETING: Revised labeling was submitted as requested in our filing letter and the subsequent approval of their proprietary name.

2. **Preparation for upcoming Mid-Cycle Meeting on July 26, 2012 (12:00-1:30)**

a. Presentations (clarify who will be presenting at the mid-cycle meeting):

- Regulatory
- CMC & Biopharmaceutics
- Non-Clinical
- Clinical
- Statistical
- Clinical Pharmacology

DISCUSSION DURING MEETING: The mid-cycle meeting is scheduled for 1.5 hours on July 26, 2012. The review team discussed the order and allowed timing for each of the disciplines presentations. Draft slides should be sent to the CDTL and RPM on July 23, 2012.

3. **Clinical site inspection sites(s) selected/Dates of inspections:**

OSI update:

- Inspection at Mayo Clinic complete (prelim VAI for minor problems with drug accountability)
- Inspection of (b) (4) (CRO for Bayer) complete (prelim NAI)
- Inspections (2) in Italy are ongoing - should be completed this week
- Inspection in Belgium is scheduled 8/17 to 9/1.

Note: The following list was recommended to select sites from for inspection, not all of these sites will be inspected.

Site # (PI name, Address, Phone number, Email, Fax#)	Protocol ID	Number of Subjects	Indication
22001: Alberto Sobrero IRCCS A.O.U. San Martino e IST Oncologia Medica Largo R. Benzi, 10 16132 Genova ITALY	14387	40	Top enrollment; number of protocol deviations (26).
22004: Alfredo Falcone A.O.U. Pisana Oncologia Medica 2 S.O. Santa Chiara Via Roma, 67 56100 Pisa ITALY	14387	29	High enrollment; number of protocol deviations (23).
22005: Salvatore Siena A.O. Osp Niguarda Ca' Granda Oncologia Medica Falck Piazza Ospedale Maggiore, 3 20162 Milano ITALY	14387	36	High enrollment; top number of protocol deviations (31).

Site # (PI name, Address, Phone number, Email, Fax#)	Protocol ID	Number of Subjects	Indication
<u>28001:</u> Eric Van Custem UZ Leuven Gasthuisberg Herestraat 49 3000 LEUVEN BELGIUM +32 16 344 218 eric.vancutsem@uzleuven.be	14387	34	High enrollment; number of protocol deviations (29).
<u>16001:</u> Marc Ychou AURELLE-MONTPPELLIER Centre Val d'Aurelle Service d'Oncologie digestive 208 rue des Apothicaires 34298 MONTPPELLIER FRANCE +33.4.67.61.30.66 mychou@valdorel.fnclcc.fr	14387	25	High enrollment; number of protocol deviations (23).
<u>14001:</u> Axel Grothey Mayo Clinic - Rochester Divison of Medical Oncology 200 First Street, SW Rochester, Minnesota 55905 UNITED STATES +1-507-284-2511 grothey.axel@mayo.edu	14387	22	Top enrolling US site; number of protocol deviations (23).

DISCUSSION DURING MEETING: The team reviewed the OSI update note above. We will discuss updates at the next team meeting.

4. Manufacturing inspection site(s) selected/Dates of inspections:

- ◆ Has the inspection been scheduled?

Drug Product

Name and Address	Contact Person at Site	Telephone Number	Fax Number	E-mail Address	Registration Number	Stage of Manufacturing	Proposed Site NDA
Bayer Pharma AG Muellerstrasse 170-178 13353 Berlin, Germany	Clinical Supplies : Dr. Matthias Hartisch (Qualified Person)	49 30 468 192180	49 30 468 18165	matthias.hartisch@bayer.com	3002808 086	Manufacturing, primary & secondary packaging, Quality Control release and stability testing	No
Bayer Pharma AG D-51368 51368 Leverkusen, Germany	Market Supplies : Dr. Matthias Herboth (Qualified Person)	49 214 30 57430	49 214 30 9657430	matthias.herboth@bayer.com	3002806 462		Yes

DISCUSSION DURING MEETING: The manufacturing site has been inspected; we will discuss updates at the next team meeting.

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/s/

MONICA L HUGHES
08/27/2012

Meeting Summary
NDA 203085: June 12, 2012, Monthly Team Meeting

Product: Regorafenib
Submission Date: April 27, 2012
Received Date: April 27, 2012
Goal Date: September 27, 2012 (primary reviews to be completed by August 30, 2012)
PDUFA Date: October 27, 2012

Sponsor: Bayer HealthCare Pharmaceuticals

Proposed Indication: mCRC

FDA Attendees: Monica Hughes, Kaushik Shastri, Stacy Shord, Amarilys Vega, Steven Lemery, Patricia Keegan, Whitney Helms, Anthony Murgo, Anwar Goheer, Josephine Jee, Elsbeth Chickhale, Janice Brown, Shan Pradhan, Barbara Fuller, Carrie Ceresa, Robert Lu, James Schlick, Jade Chen, Liang Zhou, Amir Shahlaee, Karen Jones

Meeting Purpose: This first planning meeting was to discuss review discipline specific updates as well as discuss any available updates to the upcoming clinical site or manufacturing inspections.

Draft Agenda and Discussion Items:

1. Review Discipline Updates:

- a. Clinical
 - ◆ Efficacy Review
 - ◆ Safety Review
 - ◆ Discuss: Clinical site inspection sites(s) selected/Dates of inspections- Agenda item #2 below

DISCUSSION DURING MEETING: No updates regarding the efficacy or safety review were discussed during this meeting. Discussion regarding clinical site inspections will be captured under item 2 below.

No REMS was submitted as part of this application, DRISK will review the risk management plan submitted as part of the application.

- b. Statistics

DISCUSSION DURING MEETING: No updates were discussed during this meeting.

- c. Clinical Pharmacology

DISCUSSION DURING MEETING: Discussion regarding clinical pharmacology PMRs submitted as part of the application was discussed along with the potential need for additional PMRs, if needed; clinical pharmacology will work to have draft language in August.

d. CMC

- ◆ Discuss: Manufacturing inspection site(s) selected/Dates of inspections-
Agenda Item #3 below

DISCUSSION DURING MEETING: No updates were discussed during this meeting. Discussion regarding manufacturing site inspections will be captured under item 3 below.

e. Biopharmaceutics

DISCUSSION DURING MEETING: No updates were discussed during this meeting.

f. Nonclinical

DISCUSSION DURING MEETING: No updates were discussed during this meeting.

g. Regulatory

DISCUSSION DURING MEETING: The clinical team noted that Bayer's request for a full waiver of pediatric studies also included deferral language which is confusing. The RPM will contact Bayer and ask them to resubmit their request for waiver of pediatric studies that removes the confusing language.

2. **Clinical site inspection sites(s) selected/Dates of inspections:**

This application includes a phase 3 pivotal study sponsored by Bayer, the CORRECT study (Study 14387). Study 14387 was a randomized, double-blind, placebo-controlled trial of regorafenib plus best supportive care versus placebo plus best supportive care in patients with metastatic colorectal cancer. The study was conducted in North America, Europe (including Eastern Europe), Israel, Australia, Japan, and China.

Note: The following list was developed to recommend select sites from for inspection, not all of these sites will be inspected as part of this application.

Site # (PI name, Address, Phone number, Email, Fax#)	Protocol ID	Number of Subjects	Indication
22001: Alberto Sobrero IRCCS A.O.U. San Martino e IST Oncologia Medica Largo R. Benzi, 10 16132 Genova ITALY +39-010- 5553301 alberto.sobrero@hsanmartino.liguria.it	14387	40	Top enrollment; number of protocol deviations (26).
22004: Alfredo Falcone A.O.U. Pisana Oncologia Medica 2 S.O. Santa Chiara Via Roma, 67 56100 Pisa ITALY +39-050-992466 a.falcone@med.unipi.it	14387	29	High enrollment; number of protocol deviations (23).
22005: Salvatore Siena A.O. Osp Niguarda Ca' Granda Oncologia Medica Falck Piazza Ospedale Maggiore, 3 20162 Milano ITALY +39-02- 64442290 salvatore.siena@ospedaleniguarda.it	14387	36	High enrollment; top number of protocol deviations (31).

Site # (PI name, Address, Phone number, Email, Fax#)	Protocol ID	Number of Subjects	Indication
<u>28001:</u> Eric Van Custem UZ Leuven Gasthuisberg Herestraat 49 3000 LEUVEN BELGIUM +32 16 344 218 eric.vancutsem@uzleuven.be	14387	34	High enrollment; number of protocol deviations (29).
<u>16001:</u> Marc Ychou AURELLE-MONTPPELLIER Centre Val d'Aurelle Service d'Oncologie digestive 208 rue des Apothicaires 34298 MONTPPELLIER FRANCE +33.4.67.61.30.66 mychou@valdorel.fnclcc.fr	14387	25	High enrollment; number of protocol deviations (23).
<u>14001:</u> Axel Grothey Mayo Clinic - Rochester Divison of Medical Oncology 200 First Street, SW Rochester, Minnesota 55905 UNITED STATES +1-507-284-2511 grothey.axel@mayo.edu	14387	22	Top enrolling US site; number of protocol deviations (23).

DISCUSSION DURING MEETING: Clinical site inspections are being scheduled and conducted. The team discussed the potential delay of Dr. Eric Van Custem’s site that may not occur until the end of August. The team agreed to discuss updates at the next team meeting.

3. Manufacturing inspection site(s) selected/Dates of inspections:

Drug Product

Name and Address	Contact Person at Site	Telephone Number	Fax Number	E-mail Address	Registration Number	Stage of Manufacturing	Proposed Site NDA
Bayer Pharma AG Muellerstrasse 170-178 13353 Berlin, Germany	Clinical Supplies : Dr. Matthias Hartisch (Qualified Person)	49 30 468 192180	49 30 468 18165	matthias.hartisch@bayer.com	3002808 086	Manufacturing, primary & secondary packaging, Quality Control release and stability testing	No
Bayer Pharma AG D-51368 51368 Leverkusen, Germany	Market Supplies : Dr. Matthias Herboth (Qualified Person)	49 214 30 57430	49 214 30 9657430	matthias.herboth@bayer.com	3002806 462		Yes

DISCUSSION DURING MEETING: The Drug Product manufacturing site noted above will be the only site inspected as part of this application. The inspection is currently being scheduled and the team will discuss updates at the next meeting.

Additional Discussion Items (not part of the agenda):

4. The team discussed the potential of evaluating the OS population based on biomarkers (e.g., VEGF) as a means to pull out patients for future trials. The clinical pharmacology team noted that VEGF data was collected as part of the Phase 3 study, the team noted asking Bayer to submit available data.
5. The team discussed involving the biologics plausibility team as a consult for this application to examine the breakdown products and potential adverse events. The clinical pharmacology team will review and discuss with their CRADA.

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/s/

MONICA L HUGHES
08/27/2012



NDA 203085

**METHODS VALIDATION
MATERIALS RECEIVED**

Bayer HealthCare Pharmaceuticals Inc.
Attention: Philip Johnson
Deputy Director, Global Regulatory Affairs
P.O. Box 1000
Montville, NJ 07045-1000

Dear Philip Johnson:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Stivarga® (Regorafenib) Tablets, 40 mg and to our June 7, 2012, letter requesting sample materials for methods validation testing.

We acknowledge receipt on July 5, 2012, of the sample materials and documentation that you sent to the Division of Pharmaceutical Analysis (DPA) in St. Louis.

If you have questions, you may contact me by telephone (314-539-3815), FAX (314-539-2113), or email (Michael.Trehy@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

Michael L. Trehy
MVP Coordinator
Division of Pharmaceutical Analysis, HFD-920
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

MICHAEL L TREHY
07/05/2012



NDA 203085

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Bayer Healthcare Pharmaceuticals, Inc.
P.O. Box 1000
Montville, NJ 07045-1000

ATTENTION: Philip Johnson, MBA
Deputy Director, Global Regulatory Affairs

Dear Mr. Johnson:

Please refer to your New Drug Application (NDA) dated April 27, 2012, and received April 27, 2012, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Regorafenib Tablets, 40 mg.

We also refer to your April 30, 2012, correspondence, received April 30, 2012, requesting review of your proposed proprietary name, Stivarga. We have completed our review of the proposed proprietary name, Stivarga and have concluded that it is acceptable.

The proposed proprietary name, Stivarga, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you. If **any** of the proposed product characteristics as stated in your April 30, 2012, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Sue Kang, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4216. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Monica Hughes at (301) 796-9225.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
06/29/2012



NDA 203085

FILING COMMUNICATION

Bayer Healthcare Pharmaceuticals, Inc.
Attention: Philip Johnson, MBA
Deputy Director, Global Regulatory Affairs
P.O. Box 1000, M1/2-1
Montville, NJ 07045-1000

Dear Mr. Johnson:

Please refer to your New Drug Application (NDA) dated April 27, 2012, received April 27, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for regorafenib film-coated tablet, 40mg.

We also refer to your amendments dated May 3, 16, and 24, 2012, and June 4 and 7, 2012.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Priority**. Therefore, the user fee goal date is October 27, 2012.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, midcycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by September 28, 2012.

During our filing review of your application, we identified the following potential review issues:

1. In consultation with the CDER/SEALD, we have identified several issues with the proposed package insert that need to be addressed. Please see the attached package insert that contains our comments and suggested revisions as well as the detailed comments below. Please note that the comments/suggested revisions were applied to your

originally submitted package insert. Please incorporate these revisions in the most recent version of the package insert submitted on June 4, 2012.

2. The provided dissolution data support a tighter acceptance criterion for your product. Please implement a dissolution acceptance criterion of $Q = \text{[REDACTED]}^{(b) (4)}$ at 30 minutes for your product at release and on stability. Nevertheless, it must be recognized that some batches may require Stage 2 and, occasionally, Stage 3 testing. Revise the dissolution acceptance criterion accordingly and submit the updated specifications table for the drug product. Please submit this information by July 10, 2012.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

During our preliminary review of your submitted labeling, we have identified the following labeling format issues:

3. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading. Please delete the space.
4. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: [(Product) is a (name of class) indicated for (indication)].” Please revise this statement to read as follows “[PTN] is a kinase inhibitor indicated for mCRC.”
5. All subsection headings must be indented, not bolded, and in title case. Please ensure that all subsection headings are in title case.
6. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) should not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval. Please revise as FDA-Approved Patient Labeling should not be a subsection of Section 17.
7. Section 17 of the package insert currently states “ *See 17.8 for FDA Approved Patient Labeling*”, please revise to state “See FDA-approved patient labeling (Patient Information)”

We request that you submit labeling that addresses these issues by July 13, 2012. The resubmitted labeling will be used for further labeling discussions. Please incorporate these revisions into your most recent version of the package insert submitted on June 4, 2012. In addition, please provide an updated annotated version of the package insert with hyperlinks to the specific sections referenced in the application.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI), and patient PI. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), and patient PI, and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a full waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

If you have any questions, call Monica Hughes, M.S., Lead Regulatory Project Manager, at 301-796-9225.

Sincerely,
{See appended electronic signature page}
Patricia Keegan, M.D.
Director
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ATTACHMENTS: FDA Proposed Labeling Revisions

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

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/s/

PATRICIA KEEGAN
06/25/2012



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: June 8, 2012

From: Monica Hughes, M.S., Lead Regulatory Health Project Manager DOP2/OHOP

Subject: NDA 203085

On May 16, 2012, Philip Johnson of Bayer emailed the following information and requested FDA's response:

"As we are planning the ordering of packaging materials for Regorafenib, we would appreciate your feedback on a question relating to (b) (4)

[Redacted]

[Redacted] (b) (4)

On May 24, 2012, Philip Johnson of Bayer emailed the following additional information and request for FDA comments on the May 16, 2012, pictograms:

(b) (4)

We have reviewed the above proposed (b) (4) and have the following comments:

We acknowledge your comments regarding (b) (4). However, despite the rationale, we still find (b) (4) ambiguous and unclear. (b) (4)

In addition, we recommend you add the statement 'Push Down and Turn' on the bottle cap and the statement 'Do Not Eat' to the desiccant.

Please let me know if you have any questions.

Regards,

Monica Hughes, M.S.
Lead Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-9225
Fax: 301-796-9849

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/s/

MONICA L HUGHES
06/08/2012



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: May 31, 2012
From: Monica Hughes, M.S., Lead Regulatory Health Project Manager DOP2/OHOP
Subject: NDA 203085

We have the following request for additional information to be submitted to the regorafenib NDA 203085:

1. For the nonclinical micronucleus study (Study No. T 3074309, Report No. PH-33682), please submit the clinical observation and body weight data for each animal in the study. If any other data are available regarding exposure or toxicity (e.g. plasma concentrations) that was not provided in the original study report, please provide these data as well.

We are requesting that you submit this information to NDA 203085 as soon as possible.

Please let me know if you have any questions.

Regards,

Monica Hughes, M.S.
Lead Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-9225
Fax: 301-796-9849

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/s/

MONICA L HUGHES
05/31/2012



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: May 15, 2012
From: Monica Hughes, M.S., Lead Regulatory Health Project Manager DOP2/OHOP
Subject: NDA 203085

We are currently reviewing your new NDA submitted on April 27, 2012, and have the following request for information:

Due to limited information in the Define.pdf and Statistical Analysis Plan Associated document Analysis Datasets Programming Specification.pdf, the statistical reviewer was not able to duplicate the CSR OS analyses.

The reviewer used following SAS codes to get listed SAS results. Please submit detailed instructions on how to conduct the efficacy analysis. The SAS programs including called macros can be submitted as reference programs.

In addition, we need the main efficacy analysis datasets ADEVTTE (all Time to event efficacy analysis data) and ADEVRESP (Response efficacy analysis data) in the wide format (one observation per patients) instead of long format (multiple observations per patient).

FDA SAS program

```
proc lifetest data = der.adevtte;  
    time aval * ACUTOFLN(1);  
    strata TRT1PN / test = (logrank);  
    where PARAMCD="TTD";  
run;  
  
proc phreg data = der.adevtte ;  
    model  aval * ACUTOFLN(1) = TRT1PN / risklimits  
ties=Efron;  
    strata REGCRF VEGFNY TFMDCRF;  
    where PARAMCD="TTD";  
run;
```

FDA SAS results

Obs	TYPE	TRT1PN	NUM	MED_CI	HR_CI_S	PV1	HR_CI_US	PV2
1	OS overall	Placebo	89/166	149.0 (130.0, 169.0)	0.75 (0.62, 0.91)	0.029	0.74 (0.61, 0.90)	0.0021
2	OS overall	Regorafenib 160 mg	224/281	191.0 (175.0, 214.0)				

CSR OS results

Table 9-2 Primary analysis of overall survival (ITT)

	Placebo + BSC (N = 255)	Regorafenib + BSC (N = 505)
Number of patients (%) with event	157 (61.6)	275 (54.5)
Number of patients (%) censored	98 (38.4)	230 (45.5)
Median overall survival (days)	151	196
95% CI for median	134, 177	178, 222
Range (days, without censored values)	13-315	5-375
Range (days, including censored values)	(1** – 413**)	(5 – 401**)
Overall survival rate at		
Month 3 (95% CI)	0.727 (0.672, 0.782)	0.803 (0.768, 0.838)
Month 6 (95% CI)	0.435 (0.371, 0.498)	0.525 (0.479, 0.571)
Month 9 (95% CI)	0.308 (0.238, 0.378)	0.382 (0.329, 0.435)
Month 12 (95% CI)	0.240 (0.151, 0.330)	0.243 (0.155, 0.331)
Hazard ratio (regorafenib/placebo) ^a		0.774
95% CI for hazard ratio		0.636, 0.942
One-sided p-value from log rank test		0.005178

Abbreviations: ** – censored observation; CI – confidence interval; ITT – intent to treat

a. A Hazard ratio < 1 indicates superiority of regorafenib over placebo.

Note: Stratification based on CRF data. The hazard ratio and its 95% CI was based on Cox Regression Model, stratified by prior treatment with anti-VEGF drugs (yes/no), time from diagnosis of metastatic disease (≥18 months vs <18 months) and geographical region 1 (North America, Western Europe, Israel and Australia) versus region 2 (Asia) versus region 3 (South America, Turkey and Eastern Europe).

Source: [Table 14.2/1](#), [Table 14.2/2](#)

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/s/

MONICA L HUGHES
05/15/2012



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: May 10, 2012
From: Monica Hughes, M.S., Lead Regulatory Health Project Manager DOP2/OHOP
Subject: NDA 203085 (regorafenib)

We are currently reviewing your new NDA submitted on April 27, 2012, and have the following request for information:

1. Please resubmit the data definition.pdf file for derived efficacy and safety datasets Please see example in the Table FDA.adevtte, and provide the following information in your define file:
 - a. Adequate comment for variable labels. For example, variable ACENFLN's label is "censoring flag". Based on the variable label, it is not clear that this variable should be used the censoring flag for OS or PFS for primary analysis or sensitivity analysis?
 - b. Adequate comment(s) for data format decode of categorical and numerical variable(s).
 - c. Adequate comment(s) in the comment column, including algorithm to derive new variable from raw data and raw variable(s)

Table: FDA.ADEVTTE

variable name	variable LABEL	variable type AND length	variable format	Format decodes	Origin	Role	Comment
ACENFLN	Censoring Flag, N	Num 8			derived		

2. Please provide detailed information for sample size calculation including software (version), snap shot of sample size calculation results and updated alpha allocation for the 2nd interim efficacy analysis on OS based on the proportion of death information (74.2%=actual number of death event (432)/number of project final death events (582)).
3. Please provide the SAS programs with adequate document for producing the results in CSR section 8 tables 8-2, 8-3, 8-5, 8-6, 8-7, 8-8, 9-1, 9-2, 9-3, 9-4, 9-5, 9-6, 9-7, 9-8, 9-9, 9-10, 9-14, 9-15, 9-16, and 9-17; and in Appendix tables 14.1/12, 14.1/20, 14.1/23, and 14.2/29.

Please let me know if you have any questions.

Regards,

Monica Hughes, M.S.
Lead Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-9225
Fax: 301-796-9849

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/s/

MONICA L HUGHES
05/10/2012

1st Planning Meeting Summary
May 9, 2012

NDA: 203085

Product: Regorafenib
Submission Date: April 27, 2012
Received Date: April 27, 2012
Sponsor: Bayer HealthCare Pharmaceuticals

Proposed Indication: mCRC

Current Review Team for NDA 203085:

Patricia Keegan, M.D., Director DOP2	ATTENDED MEETING
Monica Hughes, M.S., Lead RPM	ATTENDED MEETING
Karen Jones (CPMS)	ATTENDED MEETING
Shan Pradhan, M.D., Medical Officer (Efficacy Review)	ATTENDED MEETING
Kaushik Shastri, M.D., Medical Officer (Safety Review)	ATTENDED MEETING
Steve Lemery, M.D., Medical Officer (TL and CDTL)	ATTENDED MEETING
Huanyu (Jade) Chen, Ph.D., Statistics	ATTENDED MEETING
Kun He, Ph.D., Statistics (TL)	ATTENDED MEETING
Stacy Shord, Ph.D., Clinical Pharmacology	ATTENDED MEETING
Hong Zhao, Ph.D, Clinical Pharmacology (TL)	ATTENDED MEETING
M.A. Goheer, Ph.D., Non-Clinical	ATTENDED MEETING
Andrew McDougal, Ph.D., Non-Clinical (acting TL)	ATTENDED MEETING
Whitney Helms, Ph.D., Non-Clinical TL	ATTENDED MEETING
Josephine Jee, Ph.D., Product	ATTENDED MEETING
Liang Zhou, Ph.D., Product (TL)	ATTENDED MEETING
Sarah Pope Miksinski, Ph.D., Product TL	
Janice Brown, Ph.D., TL	ATTENDED MEETING
Jewell Martin, Product (ONDQA RPM)	
Angelica Dorantes, Ph.D., Biopharmaceutics TL	
Elsbeth Chikhale, Ph.D., Biopharmaceutics Reviewer	ATTENDED MEETING
James Schlick, OSE Proprietary Name Reviewer	
Mahesh Ramandhan, OMPQ	
Vipul Dholakia, OMPQ	ATTENDED MEETING
Janice Polman, OSI	ATTENDED MEETING
Carol Broadnax, OPDP Professional Reviewer	
Karen Munoz, OPDP, Consumer Reviewer	
Karen Dowdy, PLT	
Barbera Fuller, PLT (TL)	
Carrie Ceresa, PMHT	
James Schlick, OSE/DMEPA	
Todd Bridges, OSE/DMEPA TL	
Cynthia LaCivita, SE/DRISK TL	

Bob Pratt, OSE/DPV TL
Cunlin Wang, OSE/DEPI TL

Additional Attendees:

Jeff Summers
Anthony Murgio
Richard Pazdur
Michael Axelson
Vipul Dholakia

A standard **reminder** that all team members should notify the RPM, the CDTL, their team leader and other team members as soon as issues arise during the review process, instead of waiting until the next scheduled meeting to discuss.

Agenda Items and Discussion During Meeting:

1. **Review Status:**

- Priority Review requested, discussion to expedite review clock
- Categorical Exclusion requested
- Requested full waiver of pediatric studies
- The clinical development of regorafenib for mCRC has been conducted under IND 75642.

DISCUSSION DURING MEETING: Priority review will be granted, discussion noted below to expedite that review clock further. RPM will send pediatric waiver information to the PeRC.

2. **Dates Milestone Letters Must Issue (differences between a 6-month priority review clock and potentially completing the review in 5 months):**

Milestone	5 month review	6 month review
Acknowledgment Letter	May 11, 2012 *Issued 5/4/12	May 11, 2012 *Issued 5/4/12
Filing Action Letter •Do we have any filing issues that we should discuss today? •Do we need to have teleconference with the Applicant before the filing meeting? •If the filing issues are not identified, we will need to send a “Notification of Review Status” letter.	June 26, 2012	June 26, 2012

Milestone	5 month review	6 month review
Deficiencies Identified Letter (74 Day Letter)	July 10, 2012	July 10, 2012
Send proposed labeling/PMR/PMC/REMS to applicant (Review Planner's Target date)	August 30, 2012	September 29, 2012
Week after the proposed labeling has been sent, discuss the Labeling/PRM/PMC with Applicant	September 6, 2012	October 6, 2012
Review Target Due Dates: <i>Primary Review Due</i> <i>Secondary Review Due</i> <i>CDTL Review Due</i> <i>Division Director Review Due</i> <i>Office Director Review Due/Sign-Off</i>	August 30, 2012 September 3, 2012 September 6, 2012 September 17, 2012 September 27, 2012	September 29, 2012 October 3, 2012 October 6, 2012 October 17, 2012 October 27, 2012
Compile and circulate Action Letter and Action Package	September 6, 2012	October 6, 2012
FINAL Action Letter Due	September 27, 2012	October 27, 2012

DISCUSSION DURING MEETING: The review team and managers discussed expediting the review of this application to less than 6 months. The teams agreed to discuss internally and convey possible expedited review timeframes to Drs. Keegan and Pazdur.

No potential filing issues were discussed at this meeting. No pre-filing meeting, teleconference is needed with the sponsor at this time.

3. Potential Consults/Collaborative Reviewers Needed:

OPDP	Carole Broadnax- professional reviewer Karen Munoz- consumer reviewer Olga Salis – RPM
OSE	Sue Kang-OSE RPM Sean Bradley-OSE RPM TL *DMEPA/CMC/DDMAC to review carton/container, and patient labeling

	<p>*Risk Management Plan-To be assigned</p> <p>James Schlick-Proprietary Name Review James Schlick, OSE/DMEPA Todd Bridges, OSE/DMEPA TL Cynthia LaCivita, SE/DRISK TL Bob Pratt, OSE/DPV TL Cunlin Wang, OSE/DEPI TL</p>
Maternal Health	<p>Tammie BrentHoward-Reviewer Melissa Tassinari Carrie Ceresa</p>
Facility/OMPQ	<p>Mahesh Ramandhan</p>
QT-IRT	<p>**To be assigned when final report comes in with all data in the PMR submission in November 2012.</p>
OSI	<p>Janice Pohlman assigned, need to select sites.</p>
Pediatric Page/PeRC	<p>**Full Waiver Requested PeRC Meeting Date: July 25, 2012</p>
Patient Labeling Team	<p>*Patient Information Included Karen Dowdy, PLT Barbera Fuller, PLT (TL)</p>
SEALD	<p>Ann Marie Trentacosti</p>
SGE's or Patient Representatives	<p>Steven Lemery and Caleb Briggs working on screening the following potential SGEs: Jean Grem Nebraska, Carmen Allegra UF, David Kelsen MSKCC.</p>

DISCUSSION DURING MEETING: The group reviewed and discussed consults already requested and those remaining to be assigned. Post meeting follow up items are highlighted in the table above. The pediatric waiver discussion for this application will be held on July 25, 2012. Dr. Lemery and ACS are working on screening the potential SGEs noted above.

4. Upcoming/TBD Internal Team Meetings:

- **Filing Meeting:** Scheduled for May 29, 2012.
**Please bring Filing review (TL signature) and Interim Deliverables
 - a. Please be prepared to identify significant filing issues for day 74 letter. The template is available on the 21st Century website.
<http://inside.fda.gov:9003/ProgramsInitiatives/Drugs/21stCenturyReview/ucm034190.htm>

DISCUSSION DURING MEETING: Reminder was given to the team to bring their draft filing memos to the filing meeting, all filing review memos must be uploaded in DARRTs prior to the June 26, 2012, filing date.

- **Mid-Cycle Meeting:** Scheduled for July 26, 2012.

DISCUSSION DURING MEETING: The review team stated that a practice session would not be required for the mid-cycle meeting. No further discussion occurred.

- **Labeling Meetings (suggested section groupings to facilitate discussion): When should we begin labeling meetings?**
 - a. Clinical Sections: Indications and Usage, Adverse Reactions, Warnings and Precautions
 - b. Clinical Sections: Dosage and Administration, Clinical Studies, Drug Interactions, Use in Specific Populations, Overdosage, Contraindications, References
 - c. Dosage Forms and Strengths, Description, How Supplied/Storage and Handling, Nonclinical Sections, Clinical Pharmacology, Nonclinical Toxicology

**Include OSE/CMC during this labeling meeting to review carton and container.
 - d. Highlights, Indications and Usage, Patient Counseling Information

DISCUSSION DURING MEETING: The group agreed to begin labeling meetings after the mid-cycle meeting and will work on the draft agenda above as the RPM will set up 4 labeling meetings that will identify which sections will be reviewed during the meeting and who will be required to attend.

- **Team Meetings and PMR/PMC Working Meetings:**
 - **Do we want to schedule monthly team meetings?**
 - **Do we want to schedule separate PMC/PMR meetings?**

DISCUSSION DURING MEETING: The review team requested that monthly team meetings be set up. PMC/PMR meetings will be set up as needed.

- **Wrap- Up Meeting:** TBD, By September 29, 2012 (based on 6 month review).

DISCUSSION DURING MEETING: The wrap up meeting will be scheduled, no discussion occurred.

5. **Applicant Orientation Presentation:** Held on May 8, 2012.

DISCUSSION DURING MEETING: No discussion occurred.

6. **ODAC Needed/Not Needed: If needed, Target AC date: August-September 2012 (month 4-5)**

If not needed, for an original NME or BLA application, include the reason in the RPM filing review memo. For example:

- *this drug/biologic is not the first in its class*
- *the clinical study design was acceptable*
- *the application did not raise significant safety or efficacy issues*
- *the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease*

If needed, we plan on going to Advisory Committee- we will need a planning meeting and practice sessions.

DISCUSSION DURING MEETING: The review team and management do not see a need to discuss this application at an ODAC meeting, noting that the application does not raise significant safety or efficacy issues.

7. **Miscellaneous Items or Issues:**

- a. OSI inspections are needed, when does clinical/stats team need to pick the sites that will be inspected. **Do we need any preclinical study site audits?

DISCUSSION DURING MEETING: The clinical reviewer is working with OSI to select clinical sites for inspection. The non-clinical review team will discuss if any preclinical sites will require an inspection and we will discuss the team's decision at the upcoming filing meeting.

- b. CMC/Jewell Martin will assist with the following consults:

- **Establishment (EES)/Coordinate Inspections**
- **Environmental Analysis: Request for Categorical Exclusion**
- **Labeling**

DISCUSSION DURING MEETING: One manufacturing site will be inspected (drug product), however, the inspection has not yet been scheduled. The team will discuss any updates during the filing meeting.

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/s/

MONICA L HUGHES
06/13/2012



NDA 203085

NDA ACKNOWLEDGMENT

Bayer Healthcare Pharmaceuticals, Inc.
Attention: Philip Johnson, MBA
Deputy Director, Global Regulatory Affairs
P.O. Box 1000, M1/2-1
Montville, NJ 07045-1000

Dear Mr. Johnson

We have received your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: regorafenib tablet, 40 mg

Date of Application: April 27, 2012

Date of Receipt: April 27, 2012

Our Reference Number: NDA 203085

Proposed Use: For the treatment of patients with metastatic colorectal cancer (CRC) who have been previously treated with, (b) (4) fluoropyrimidine-based chemotherapy, an anti-VEGF therapy, and, if KRAS wild type, an anti-EGFR therapy.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on June 26, 2012, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncology Products 2
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call Monica Hughes, M.S., Lead Regulatory Health Project Manager, at (301) 796-9225.

Sincerely,

{See appended electronic signature page}

Karen D. Jones
Chief, Project Management Staff
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

KAREN D JONES
05/04/2012



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 075642

**SPECIAL PROTOCOL ASSESSMENT –
NO AGREEMENT**

Bayer Healthcare Pharmaceuticals, Inc.
Attention: Andrew Jiang, Deputy Director
Global Regulatory Affairs
P.O. Box 1000
Montville, NJ 07045-1000

Dear Mr. Jiang:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for BAY 734506 (Kinase Inhibitor).

We also refer to your December 8, 2009, request, received on December 9, 2009, for a special protocol assessment of a clinical protocol. The protocol is titled "A Randomized, Double-blind, Placebo-controlled Phase III Study of Regorafenib Plus BSC versus Placebo Plus BSC in Patients with Metastatic Colorectal Cancer (CRC) Who Have Progressed after Standard Therapy."

Special protocol assessment is designed to evaluate an individual protocol primarily in response to specific questions posed by the sponsor. Our assessment does not address your overall development strategy. Based on our review of your questions in the context of other submitted information, we have determined that the design and planned analysis of your study do not adequately address the objectives necessary to support a special protocol assessment.

We also have the following responses to your questions.

LIST QUESTIONS AND RESPONSES

Question 1

At the September 3 End-of-Phase 2 meeting the FDA recommended overall survival (OS) as a primary endpoint of the study. The revised protocol takes into account the Division's recommendation. The statistical design has been modified to include overall survival as a primary endpoint and futility analyses for OS.

For further details please refer to the study protocol and statistical analysis plan (SAP).

Does the FDA agree that the statistical study design, the planned interim and final analyses of the primary efficacy endpoint as outlined here and described in detail in the study protocol and SAP are acceptable ?

FDA Response: No.

a. We recommend that you plan a futility interim analysis earlier than (b) (4) information fraction (per meeting discussion) and conduct a single interim analysis for efficacy. Your proposed first OS interim analysis at (b) (4) information fraction is too late for futility purposes and too early for an efficacy claim if an accurate and robust estimate of the treatment effect size will be targeted.

b. Whether a 1.5 month increment in median overall survival would be clinically significant in this patient population will be a review issue.

Question 2

In the study, the following subgroup analyses are planned. Descriptive statistics and hazard ratio estimates with 95% CI for OS and PFS will be provided at least within each category of the following variables, provided there is a sufficient number of events in total within the subgroup across the treatment arms:

- Demographic information like race, sex, age group (<65yr, ≥65yr)
- Region: region 1 (US, Western EU, Australia and New Zealand), region 2 (Asia), and region 3 (South America, South Africa, Turkey and Eastern EU)
- Time from diagnosis of metastatic disease (≥ 18 months and < 18 months)
- Prior systemic anti-cancer therapies:
 - prior anti-VEGF therapy (Yes and No),
 - prior anti-cancer drugs, categorized in following four groups:
 - Fluoropyrimidine, oxaliplatin, irinotecan;
 - Fluoropyrimidine, oxaliplatin, irinotecan, bevacizumab;
 - Fluoropyrimidine, oxaliplatin, irinotecan, anti-EGFR antibody;
 - Fluoropyrimidine, oxaliplatin, irinotecan, bevacizumab, anti-EGFR antibody;
 - number of treatment lines
- KRAS mutation status (using the information given by the investigator in the CRF)
- Further important baseline cancer characteristics (for example ECOG performance status (0 and 1))

Does the FDA agree that the planned subgroup analyses as outlined are acceptable?

FDA Response: Yes. However, the trial must be successful in its overall primary efficacy endpoint for any subgroup analyses to be meaningful. Subgroup analyses will be considered exploratory and may not be included in the intended labeling of your product.

Question 3

At the September 3 End-of-Phase 2 meeting the FDA stated that patients should have failed all approved therapies for metastatic colorectal cancer (i.e., fluoropyrimidine, oxaliplatin, irinotecan, bevacizumab and cetuximab/panitumumab if KRAS WT) before joining the study. The possibility of including patients from countries where bevacizumab and/or cetuximab/panitumumab are not approved and thus patients have not been pretreated with each of these agents, was discussed with the FDA and has been considered as an acceptable approach.

The inclusion criterion has been modified to meet these requirements and is based on the recommendation by the Phase 3 Study Steering Committee:

Progression during or within 3 months following the last administration of approved standard therapies. Depending on the approval status in each of the participating countries, these must include fluoropyrimidine, oxaliplatin, irinotecan, bevacizumab and cetuximab or panitumumab (if KRAS WT) if approved in the respective country. A list of approved standard therapies for the anticipated participated countries is attached as appendix to the study protocol.

Patients who have withdrawn from standard treatment due to unacceptable toxicity warranting discontinuation of treatment and precluding retreatment with the same agent prior to progression of disease will also be allowed into the study. Patients treated with oxaliplatin in an adjuvant setting should have progressed during or within 6 months of completion of adjuvant therapy.

If unacceptable toxicity is the reason for premature discontinuation of standard therapy, the investigator will be instructed to provide information on the unacceptable toxicity in the CRF.

Does the FDA agree that the definition of patient population is acceptable?

FDA Response: Yes.

Question 4

At the September 3 End-of-Phase 2 meeting, Bayer presented stratification factors to the FDA. After further consultation with the Steering Committee members, the stratification factors have been modified and are proposed below:

- prior treatment with VEGF targeting drugs (yes/no)

Rationale: Targeted therapies have proven to significantly improve the therapeutic efficacy in metastatic colorectal cancer and have shown to prolong overall survival in patients with metastatic CRC. Patients who have not received targeted therapies might have a different overall survival. Since anti-VEGF treatment is independent of the KRAS mutational status of the tumor, prior anti-VEGF therapy has been chosen as a stratification factor to minimize such potential influence.

- time from diagnosis of metastatic disease (≥ 18 months vs < 18 months)

Rationale: Time from diagnosis of metastatic disease is considered to be a prognostic factor for both PFS and overall survival. Patients who will be included in this trial have been treated with several lines of palliative therapy since diagnosis of metastatic disease. The length of treatment and response to these previous treatments will have an influence on the time since diagnosis of metastatic disease at randomization. A cut off of 18 months is suggested as a stratification factor as different outcomes for these two patient groups are expected.

- geographical region (Region 1 (US, Western EU, Australia/New Zealand) vs. Region 2 (Asia) vs. Region 3 (South America, South Africa, Turkey, Eastern EU). In order to maintain a balanced representation of each of the three regions, Asia (Region 2) is not planned to randomize more than 250 patients.

Rationale: The proposed clinical trial is planned to be global with inclusion of all major regions of the world. Based on regional variances in the practice to treat colorectal cancer, including 1) availability of drugs to treat colorectal cancer 2) usage of follow up treatments after disease progression and 3) inclusion in follow up clinical trials, differences in overall survival are expected. Therefore stratification according to regions is suggested.

The treatment paradigms in Asia (eg China) are expected to differ at a relevant level from US/Western Europe/Australia/New Zealand. In addition patients' treatment options in South America, South Africa, Turkey and Eastern Europe are considered to differ from those in the two other regions. Therefore stratification according to 3 regions is planned (Region 1 (US, Western EU, Australia/New Zealand) vs. Region 2 (Asia) vs. Region 3 (South America, South Africa, Turkey, Eastern EU).

Are the proposed stratification factors acceptable for patient randomization and the stratified analysis of the primary efficacy endpoint OS?

FDA Response: Please clarify what percentage of patients will be enrolled in the United States. You will need to provide a plan for enrolling a population that is representative of the U.S. population with adequate representation of minority groups.

Question 5

(b) (4)

RECIST 1.1 is seen to add value especially in the assessment of small lesions and bone lesions. It is also starting to be implemented as the standard in oncology trials.

Does the FDA agree to the use of RECIST 1.1 for tumor response assessments?

FDA: Yes.

Question 6

The effect of food is currently being evaluated in a study entitled "A Phase 1, Randomized, Open Label, 3-Way Cross-Over Study to Determine the Effect of a High-Fat Breakfast, a Low-Fat Breakfast and Fasting State on the Pharmacokinetics of a Single Oral Dose of 160 Mg Regorafenib (BAY 73-4506) in Healthy Volunteers". In this study, the effect of a low fat or high fat breakfast vs fasting on the pharmacokinetics of regorafenib and its major metabolites will be characterized. Final pharmacokinetic data for this study is expected in early March, 2010. Based on the results of this study, the Phase 3 study protocol may be amended from administration of study drug with a low fat meal to administration of regorafenib with food and/or fasting.

Does the FDA agree that a modification to the directions for regorafenib administration with respect to food will not affect the Agency's assessment of the Phase 3 study protocol, and therefore prior agreement with the Agency on such a modification is not necessary?

FDA Response: Yes, it is acceptable. However, the effect of food on exposure of your drug has not been reviewed by the Agency.

It is not certain how a modification in administration with respect to food will influence exposure response for safety and efficacy. We recommend that instructions of administration with or without food should be consistent throughout the trial.

In addition, we have the following comments.

1. The secondary endpoints listed on page 6 of the SPA request are different from the protocol.

2. You proposed to test PFS, ORR and DCR [REDACTED] (b) (4)

3. DCR defined as [REDACTED] (b) (4) **is unlikely to be included in the label.**

Although we do not agree on the issues you posed, this does not preclude you from conducting this study under your IND.

If you choose to submit a revised protocol for special protocol assessment prior to study initiation, it should address all the issues itemized above and should be submitted as a new request for special protocol assessment.

If you wish to discuss our responses, you may request a meeting. Such a meeting will be categorized as a Type A meeting (refer to the Guidance for Industry: Formal Meetings with Sponsors and Applicants for PDUFA Products). This meeting would be limited to discussion of this protocol.

If you have any questions, call Diane Hanner, Regulatory Project Manager, at (301) 796-4058.

Sincerely,

{See appended electronic signature page}

Robert L. Justice, M.D., M.S.
Director
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
IND-75642	ORIG-1	BAYER HEALTHCARE PHARMACEUTICA LS INC	BAY 734506 (KINASE INHIBITOR)

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/s/

ROBERT L JUSTICE
01/22/2010



**FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B (Teleconference)
Meeting Category: Pre-NDA
Meeting Date and Time: August 23, 2011 1:00 p.m.
Meeting Location: Bldg. 22, Room 3201
Application Number: IND 075642
Product Name: Regorafenib (BAY 73-4506)
Indication: Metastatic colorectal cancer
Sponsor/Applicant Name: Bayer Health Care Pharmaceuticals
Meeting Request Date: May 6, 2011
Meeting BGP date: July 22, 2011
Meeting Chair: John R. Johnson, M.D., Lead Medical Officer
Meeting Recorder: Diane Hanner, M.P.H., M.S.W.

FDA ATTENDEES

- Robert Justice, M.D., M.S., Director DDOP
- Amna Ibrahim, M.D., Deputy Division Director, Medical Officer Team Leader
- John R. Johnson, M.D., Lead Medical Officer
- Amy McKee, M.D., Medical Officer
- Anthony Murgo, M.D., M.S., FACP, Associate Director OODP IO, Acting Deputy Director DDOP
- CDR Diane Hanner, M.P.H., M.S.W., Senior Program Management Officer
- Haripada Sarker, Ph.D., CMC Lead, ONDQA, DNDQA I
- Pengfei Song, Ph.D., Clinical Pharmacology Reviewer, DCP5
- Rosane Charlab Orbach, Ph.D., Genomics Reviewer
- Lijun Zhang, Ph.D., Mathematical Statistician, DB 5

SPONSOR ATTENDEES

- Gerhard Schlueter, Ph.D., Global Regulatory Affairs
- Meni Melek, Ph.D., Global Regulatory Affairs
- Laura Park, Global Regulatory Affairs
- Dietmar Berger, M.D., Clinical Development
- Dirk Laurent, M.D., Clinical Development
- Andrea Wagner, M.D., Clinical Development
- Olaf Christensen, M.D., Clinical Pharmacology
- Chetan Lathia, Ph.D., Clinical Pharmacology
- Richard Nkulikiyinka, M.D., Global Pharmacovigilance
- Kirstin Meyer, Ph.D., Toxicology

- Minghua (Michael) Shan, Ph.D., TA Expert Statistician
- Frank Cihon, Clinical Statistician
- Patricia Hegarty, Statistical Programming
- Sabine Fiala-Buskies, Integrated Analysis
- Rita Darkow, Ph.D., Project Management
- Ulrike Schmalfuss, Ph.D., Project Management

1.0 BACKGROUND

Regorafenib is a promiscuous kinase inhibitor with targets such as VEGFR-1-3, TIE2, PDGFR- β , FGFR1, KIT, RET and B-RAF. These kinases are involved in a number of the pathways thought to initiate and maintain tumor growth, including angiogenesis and proliferation. *In vivo* xenograft models of breast, colon, renal, non-small cell lung, melanoma, pancreatic, thyroid and ovarian cancers have been inhibited by regorafenib.

The proposed use for regorafenib is in patients with metastatic colorectal carcinoma (mCRC) after failure of standard therapy. For patients with metastatic disease, standard first- and second-line treatment is FOLFOX or FOLFIRI \pm bevacizumab and cetuximab or panitumumab (if KRAS WT). There are multiple additional single agents or combination regimens that also can be used as second-line therapy in the metastatic setting. For patients who have progressive disease on all of these standard therapies, there are no approved therapies. Clinical trials or best supportive care is the standard approach for such patients.

2.0 DISCUSSION

Question 1

Does the Agency agree that the nonclinical development program (including primary and secondary pharmacology, safety pharmacology, pharmacokinetics and toxicology studies) described in the briefing document under Section 12 is adequate and sufficient to support marketing authorization for the treatment of cancer patients with regorafenib?

All nonclinical reports previously submitted to the IND will be formatted according to eCTD standards and re-submitted with the NDA. Please confirm that this is acceptable.

FDA Response:

Your non-clinical program is generally acceptable. A final decision will be made after review of data submitted with the NDA. Your proposal to re-submit all nonclinical reports previously submitted to the IND and formatted according to eCTD standards is acceptable.

Bayer Response:

No further discussion is needed.

Question 2

As required by the FDA, Bayer will be submitting an Integrated Summary of Efficacy (ISE) and Integrated Summary of Safety (ISS) in Module 5.3.5.3 of the eCTD.

In the FDA “Guidance for Industry, Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Documents” (April 2009), it is described that if the narrative portion of the ISE or ISS is suitable for use in section 2.7.3 or 2.7.4, the narrative portion should be submitted only once and referenced in both Module 2, section 2.7.3 or 2.7.4 and Module 5, section 5.3.5.3 (i.e., provide leaf elements in both locations).

Therefore, we propose to write Module 2, section 2.7.3 or 2.7.4 and Module 5, section 5.3.5.3 as follows:

- Module 5, section 5.3.5.3 for ISS and ISE
 - Textual part
 - Refers FDA to 2.7.3 and 2.7.4 for text portion
 - Tables, Figures & Appendices
 - Datasets
- Module 2, section 2.7.3 and 2.7.4
 - Textual part & possibly Tables, Figures
 - Refers FDA to 5.3.5.3 for appendices and datasets

An overview of all clinical pharmacology and clinical studies to be part of eCTD is listed in Appendix 16.1 together with the type of data we plan to include in the NDA.

Please confirm that this is acceptable:

FDA Response: Yes.

Bayer Response:

No further discussion is needed.

Question 3

As discussed in Section 15.1, in view of the limited number of clinical studies included in the dossier (one single Phase 3 study), does the Agency concur with the proposal that a pooled analysis for efficacy will not be performed?

FDA Response: Yes.

Bayer Response:

No further discussion is needed.

Question 4

As discussed in Section 15.2, Bayer intends to include three major analysis sets (phase 1 and 2 studies with continuous dosing, phase 1 and 2 studies with intermittent dosing, and the data from the Phase III study) in the integrated summary of safety (ISS), combining data from cancer patients treated at similar dose levels across the different studies. Sub-group analyses within each dataset will be carried out by dose level, ethnicity/race, indication, age, sex, BMI, and baseline renal function and hepatic function, as outlined in the statistical analysis plan for the ISS. Bayer does not intend to include available data from studies combining regorafenib with other anti-cancer therapies or data from non-company sponsored studies. Data from healthy volunteer studies, which were done with single dose regorafenib administration only, are not planned to be part of the ISS either.

Does the Agency concur with this proposed strategy for the ISS?

FDA Response: No. If there was a serious adverse event or death in the healthy volunteer studies or the combination studies which was deemed to be related to regorafenib, this data must be submitted.

Bayer Response:

Bayer accepts FDA's recommendation. For the healthy volunteer studies and the combination studies, if there are regorafenib related SAEs including deaths, these studies will be included as part of the Integrated Summary of Safety (ISS). SAE's for these types of studies will not be pooled with any of the three major analysis sets above, but will be presented separately.

Meeting Discussion: This is acceptable.

Question 5

The eCTD submission will contain 2 types of datasets, both to be submitted electronically in SAS Version 5 transport file format with corresponding documentation:

SDTM datasets (version 3.1.2) with define.xml documentation [.xml style sheet, and the annotated CRF (blankcrf.pdf)]

Bayer analysis datasets (ADS) with define.pdf documentation

SDTM Datasets

To assist in medical review of the eCTD, Bayer will submit data in SDTM (version 3.1.2) format for the following clinical study:

- 14387 Phase 3 CRC, 160 mg (dosing schedule: 3 weeks on/1 week off)

Bayer Analysis Datasets (ADS)

Analysis datasets will be provided for the following clinical studies:

- 14387 Phase 3 CRC, 160 mg (dosing schedule: 3 weeks on/1 week off)
- 11726 Phase 2 Renal cell cancer, 160 mg (dosing schedule: 3 weeks on/1 week off)

- 14596 Phase 2 Hepatocellular cell cancer, 160 mg (dosing schedule: 3 weeks on/1 week off)
- 11650 Phase 1 in patients with advanced solid tumors, dose escalation (dosing schedule: 3 weeks on/1 week off)
- 11651 Phase 1 in patients with advanced solid tumors, dose escalation (dosing schedule: continuous dosing)
- 13172 Phase 1 in Japanese patients with advanced solid tumors, 160 mg (dosing schedule: 3 weeks on/1 week off)
- 14996 Phase 1 in Chinese patients with advanced solid tumors, 160 mg (dosing schedule: 3 weeks on/1 week off)
- 11656 Phase 1 regorafenib in combination with mFOLFOX6 or FOLFIRI in patients with advanced, metastatic colorectal cancer, 160 mg (dosing schedule: sequential)
- 12437 Phase 1 study to Evaluate the Relative Bioavailability of 160 mg of BAY 73-4506 Administered as 1 x 100 mg + 3 x 20 mg Tablets and 4 x 40 mg Tablets in healthy volunteers (dosing schedule: single dose)
- 14656 Phase 1 study to Determine the Effect of a High-Fat Breakfast, a Low-Fat Breakfast and Fasting State on the Pharmacokinetics of a Single Oral Dose of 160 Mg Regorafenib (BAY 73-4506) in healthy volunteers
- 12435 Phase 1 study to determine the effect of Ketoconazole on the pharmacokinetics of a Single Oral Dose of Regorafenib (BAY 73-4506) in healthy volunteers (final PK data will be provided, safety data provided if available)
- 15524 Phase 1 study to determine the effect of Rifampin on the pharmacokinetics of a Single Oral Dose of 160 Mg Regorafenib (BAY 73-4506) in Healthy Volunteers
- 12436 Phase 1 mass balance study of 120 mg ^[14C]BAY 73 4506 (regorafenib) after single dose oral administration in healthy volunteers

The Bayer analysis datasets contain all raw data as it was collected from the clinical trial CRFs as well as additional derived variables, observations, and derived datasets created specifically to support study analysis. All statistical programs written in SAS for statistical table generation utilized these Bayer analysis datasets as input.

In addition, integrated safety analyses will be performed. An integrated safety pool will be provided containing data from all Phase 1 and 2 studies conducted in cancer patients where regorafenib was administered as a single agent (11650, 11651, 13172, 14996, 11726, 14596). For studies not realized in CDISC- standard (11650, 11651, 13172, 11726), the analysis datasets are created for the integrated safety pool only. Analysis datasets will be provided for these

pooled safety analyses. The define.xml document - describing the origin of these data – delivered, refers to studies conducted in CDISC- standard (14596, 14996).

Does the Agency agree with the proposal outlined above regarding the scope, format, and documentation of the electronic datasets to be submitted?

FDA Response: Yes.

Bayer Response:

No further discussion is needed.

Question 6

Bayer is intending to submit CRFs in electronic format only, in accordance with FDA guidance on electronic submissions, and to include CRFs and patient narratives from pivotal clinical study (no. 14387) for only those patients who died during the course of the study (during treatment or within 30 days after last administration of study drug), who discontinued from study treatment due to an adverse event not associated with clinical disease progression or who experienced an adverse event of special interest meeting the definition of serious adverse event. All other case report forms will be available upon request.

Please confirm that this is acceptable.

FDA Response: No; CRFs for all serious adverse events, regardless of whether it is an adverse event of special interest, should be submitted.

Bayer Response:

Bayer accepts FDA's recommendation that CRFs for all serious adverse events should be submitted. Bayer would like to seek confirmation on patient narratives. As requested, Bayer proposes to provide patient narratives from pivotal clinical study (no. 14387) for only those patients who died during the course of the study (during treatment or within 30 days after last administration of study drug), who discontinued from study treatment due to an adverse event not associated with clinical disease progression or who experienced an adverse event of special interest meeting the definition of serious adverse event.

Meeting Discussion: FDA requests that narratives be submitted for all serious adverse events except those related to disease progression.

Question 7

Bayer intends to use MedDRA for the presentation of safety data in the US PI Adverse Reaction section. Please confirm that this is acceptable

FDA Response: Yes.

Bayer Response:

No further discussion is needed.

Question 8

At the time of NDA submission, it is expected that several company-sponsored studies (b) (4) will still be ongoing. To satisfy the FDA requirement for an update on safety in ongoing studies, Bayer will provide SAE listings from the Global Safety Database up to the cut-off off December 31, 2011. The cut-off was chosen to be as close as possible to the date of finalization of the submission package, taking into account the time needed for internal review and quality checks.

Please confirm that this is acceptable.

FDA Response: No; as you have indicated below, you intend to submit the clinical portion of the NDA sometime in Q1 or Q2 of 2012. If the clinical data were submitted in the second quarter of 2012, a database cutoff of December 31, 2011 would not be sufficient. The differential should not be greater than 6 months between the data cut-off and the submission of the safety update.

Bayer Response:

Bayer would like to seek confirmation that the differential should not be greater than 6 months between the data cut-off for the 120-day safety update and the submission of the 120-day safety update.

Meeting Discussion: FDA confirmed that the differential should not be greater than 6 months between the data cut-off for the 120-day safety update and the submission of the 120-day safety update.

Question 9

Bayer proposes to provide financial certification and disclosure information for investigators who participated in the pivotal Phase 3 Study no. 14387 only as we rely on this “covered clinical study” to establish that the product is effective.

Please confirm that this is acceptable.

FDA Response: Yes.

Bayer Response:

No further discussion is needed.

Question 10

As discussed in Section 13, the Clinical Pharmacology Development program was presented and discussed with the Agency at the End of Phase II meeting (September 3, 2009). Based on this, the clinical pharmacology/clinical studies and analysis that are planned to be included in the NDA are included in Table 13-1.

Please note, that for the studies 12434 (“A Phase I, non-randomized open-label study to evaluate the effect of BAY 73-4506 (regorafenib) on probe substrates of CYP 2C9 (warfarin), 2C19 (omeprazole) and 3A4 (midazolam) in a cocktail approach (Group A) and on a probe substrate of CYP 2C8 (rosiglitazone, Group B) in patients with advanced solid tumors”) and 14814 (“An open-label, non-randomized Phase I study of regorafenib (BAY 73-4506) to evaluate cardiovascular safety, tolerability, pharmacokinetics and anti-tumor activity in patients with advanced solid tumors”) the patient recruitment is not completed yet, as the enrolment for the pivotal phase 3 study was faster than expected. Therefore interim PK and QTc reports for patients who have completed the primary analysis in the study, will be provided for the aforementioned 2 studies. (b) (4)

Does the Agency consider this clinical pharmacology package acceptable for submission?

FDA Response: Yes, your proposal appears generally acceptable. However, we recommend that you make your best efforts to submit final study reports at NDA submission. We strongly recommend that you submit the QT study with the NDA.

Bayer Response:

Bayer will make best efforts to include the study report for the QTc study in the initial NDA submission.

Question 11

Mutations in specific proto-oncogenes have been identified in CRC, the most prevalent being KRAS (mutated in ~40-50%), PIK3CA (mutated in ~10-15%) and BRAF (mutated in ~5-10%). Determining tumor mutational status is important from a therapeutic perspective since this information may guide the decision of which drug to administer to a particular patient. For example, it has been determined that CRC tumors that harbor an activating KRAS mutation are unlikely to respond to anti-EGFR antibody therapy and thus this form of therapy is no longer recommended for the treatment of CRC patients with KRAS-mutant tumors.

In Phase 3 study (no. 14387), potential correlations between tumor mutational status and clinical outcome will be evaluated. Tumor-associated mutations in KRAS, PIK3CA and BRAF will be examined in baseline plasma and available tumor tissue specimens using a highly sensitive and specific mutation-detection technology called BEAMing (Inostics, GmbH). The goal of this biomarker analysis is to determine whether the tumor mutational profile of the patients enrolled in Phase 3 study (no. 14387) influences their response to regorafenib therapy. Statistical analyses will be performed to determine whether the population of subjects whose specimens are used in the biomarker analysis are representative of the overall study population with regards to

clinical outcome and to determine whether the mutational status of KRAS, BRAF or PIK3CA (or combinations thereof) influence clinical outcome in either a predictive or prognostic manner. If the mutational status of any particular gene or gene combination appears to be predictive of clinical response to regorafenib, this finding may warrant prospective evaluation in future clinical trials. Since the retrospective biomarker analysis proposed for Phase 3 study (no. 14387) is considered exploratory and does not constitute a primary or secondary endpoint of this clinical study, it is Bayer's position that the corresponding biomarker report does not need be part of the initial NDA but rather can be submitted to the regulatory agency approximately 12 months after the end of this clinical study.

Does the agency concur with this timeline?

FDA Response: Your plan appears acceptable for these exploratory analyses, however we encourage you to include the biomarker report in the initial NDA submission.

Bayer Response:

Bayer acknowledges the Division's comment.

Question 12

(b) (4)

Please confirm if this is acceptable.

FDA Response: Yes.

Bayer Response:

No further discussion is needed.

Question 13

Does the Agency agree with the submission of electronic CTD format as outlined in the Table of Contents for Modules 1, 2, 4 and 5 included in the Appendix 16.2?

FDA Response: Yes.

Bayer Response:

No further discussion is needed.

Question 14: Request for a Submission of portions of an Application

Bayer has received an approval of Fast Track Designation for metastatic Colorectal Cancer (CRC) on June 15, 2011. Therefore, the following timeline is proposed to submit portions of an Application:

- Target submission date for CTD Module 2.4, 2.6 and 4: January 2012 (exact date will be communicated to the Division upon available)
- Target submission date for a complete NDA for metastatic CRC: 1 – 2Q, 2012 (exact date will be communicated to the Division upon available)

Please confirm that this is acceptable.

FDA Response: Yes.

Bayer Response:

Bayer would like to provide an update to the Division with the most current target submission date for a complete NDA for metastatic CRC. It is estimated that the NDA will likely be submitted in July 2012; it is also anticipated that a submission of portions of an Application will not be required.

Question 15: CRC Pediatric Waiver

A waiver of the requirement for studies in pediatric patients is requested in Appendix 16.6 as colorectal cancer is not an indication with a substantial number of pediatric patients.

Please confirm that this is acceptable.

FDA Response: You will need to submit your request with the NDA for review by PeRC.

Bayer Response:

No further discussion is needed.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

No issues identified requiring further discussion.

4.0 ACTION ITEMS

No issues identified requiring further actions.

5.0 ATTACHMENTS AND HANDOUTS

There were no attachments or handouts for the meeting minutes.

Meeting Chair

{See appended electronic signature page}

John R. Johnson, M.D., Lead Medical Officer

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JOHN R JOHNSON
09/19/2011



FOOD AND DRUG ADMINISTRATION

Meeting Date and Time: September 3, 2009 4:00 p.m.
Meeting Type: Type B
Meeting Category: End of Phase 3 Colorectal cancer
Meeting Location: Bldg. 22, Room 1309
Application Number: IND 75,642
Product Name: Regorafenib (BAY 73-4506)
Received Briefing Package August 3, 2009
Sponsor Name: Bayer HealthCare
Meeting Requestor: Hua (Andrew) Jiang, M.S., M.B.A.
Meeting Chair: Ann Farrell, M.D.
Meeting Recorder: Diane Hanner, M.P.H., M.S.W.
Meeting Attendees:
BAYER

<u>Name</u>	<u>Title & Line Function</u>
Andrea Wagner, M.D.	Global Clinical Lead Colorectal Cancer, Clinical Development
Dirk Laurent, M.D.	Vice President, Head Clinical Development Oncology 2
Lisa Cupit, M.D.	Medical Expert Colorectal Cancer, Medical Affairs
MingHua (Michael) Shan, Ph.D.	Senior Director, Statistics, Oncology
Olaf Christensen, M.D.	Deputy Director, Clinical Pharmacology
Chetan Lathia, Ph.D.	Senior Director, Clinical Pharmacology
Tiffany Lin, Pharm.D.	Assistant Director, Clinical Pharmacology
Louis Mylecraine, PhD, DABT	Senior Director, Toxicology
Ulrike Schmalfluss, Ph.D.	Global Project Leader, Global R&D Project Management

Oliver Bokel Herde, Ph.D. Assistant Director, Global Regulatory Affairs
John Talian, Ph.D. Vice President, US Head, Global Regulatory Affairs
Hua (Andrew) Jiang, MS, MBA Deputy Director, Global Regulatory Affairs

FDA Attendees

<u>Name</u>	<u>Title & Line Function</u>
Ann Farrell, M.D.	Deputy Division Director, DDOP
Edvardas Kaminskas, M.D.	Clinical Reviewer, DDOP
Qi Liu, Ph.D.	Acting Clinical Pharmacology Team Leader, DCP5
Hua Lillian Zhang, Ph.D.	Clinical Pharmacology Reviewer, DCP5
Huanyu, Chen, Ph.D.	Biostatistics Reviewer, DBV
Diane Hanner, M.P.H., M.S.W.	Senior Program Management Officer, DDOP

DISCUSSION

Question 1

Does the FDA agree that [REDACTED] ^{(b) (4)} for the planned Phase 3 clinical trial is acceptable for marketing authorization?

FDA Response: No. We recommend OS as the primary efficacy endpoint.

Other considerations:

- 1) You should consider a smaller Phase 2 trial to get a better idea of the effectiveness of regorafenib before embarking on a large Phase 3 trial.
- 2) Alternatively, we recommend early stopping rules for futility.

Bayer Response: We thank the FDA for the comment. Based on your recommendation, overall survival will be used as the primary endpoint with early stopping rules for futility in the proposed Phase 3 study.

Question 2

Does the FDA agree that placebo plus best supportive care is acceptable as the control arm in this trial?

FDA Response: Placebo plus BSC would be acceptable as treatment in the control arm, if the study subjects had failed all approved drugs or drug combinations for this indication. Otherwise, patients in the control arm should be treated with an approved drug, which they had not failed.

Bayer Response: Bayer acknowledges the response that placebo plus BSC would be acceptable as control arm in the proposed study.

Regarding the definition of the target population please refer to our response to question 8.

Question 3

[Redacted] (b) (4)

Does the FDA agree with the statistical assumption for this trial?

FDA Response: There should be an interim analysis for futility, as well as for safety. See response to question # 1.

Bayer Response: We thank the FDA for the comments. Please find our suggestion for a statistical study design with overall survival (OS) as primary endpoint and futility analysis:

[Redacted] (b) (4)

[Redacted] (b) (4)

In addition one interim analysis for futility is planned. Details of the futility analysis will be provided in the DMC Charter. Furthermore, the DMC will review safety data approximately every 6 months.

Meeting Discussion: This appears acceptable.

Question 4

Does the FDA agree to the use of RECIST version (b)(4) for tumor response assessments?

FDA Response: Yes.

Question 5

We plan to submit for FDA's review and comment the Phase 3 protocol and statistical analysis plan (SAP) through Special Protocol Review (SPA). Does the FDA agree that this approach is acceptable?

FDA Response: Yes. Please make use of our comments in this meeting in designing the protocol.

Question 6

Regorafenib is proposed as a monotherapy for treatment of patients with metastatic carcinoma of the colon or the rectum (b)(4).

Does the FDA agree that the proposed one Phase 3 study, supported by Phase 1 and Phase 2 data in over 180 patients with different types of advanced cancer including 45 colorectal carcinoma (CRC) patients, will be sufficient for the registration of regorafenib as a monotherapy treatment of patients with metastatic carcinoma of the colon or the rectum (b)(4)?

FDA Response: No. Please see our response to question #1. (b)(4)

As noted in answer to question #1, the number of mCRC patients in Phase 1 and 2 is very small and only 3 PRs were recorded. Thus, any approval would be based on the results of one Phase 3 trial and a risk/benefit analysis. As noted above, a Phase 2 study is advisable prior to embarking on a large Phase 3 trial.

For a single randomized trial to support an NDA, the trial should be well designed, well conducted, internally consistent and provide statistically persuasive efficacy findings so that a second trial would be ethically or practically impossible to perform. We strongly suggest that you conduct two adequate and well-controlled trials to support the proposed indication.

We refer you to the FDA guidance “Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products.”

Bayer Response: We acknowledge FDA’s comments that for a single trial to support an NDA, the trial results need to be persuasive.

Question 7

For randomization, the Phase 3 study will be stratified according to [REDACTED] (b) (4) [REDACTED] and geographical region (Region 1 (US, EU, South America, Australia/New Zealand) vs. Region 2 (Asia)).

Does the FDA agree with the stratification plan for randomization?

FDA Response: Provide your justification for each of your stratification factors.

Bayer Response: Please find the following justification for the proposed stratification factors:

[REDACTED] (b) (4)

- Region:

Based on regional variances in the practice to treat colorectal cancer, including 1) availability of drugs to treat colorectal cancer 2) usage of follow up treatments after disease progression and 3) inclusion in follow up clinical trials, differences in the overall survival is expected. Therefore stratification according to regions is suggested. The planned phase 3 is planned to be conducted globally with inclusion of Asia. The treatment paradigms in Asia (eg China) are expected to differ at a relevant level from US/Europe, therefore a stratification US/Europe/South America/ Australia/New Zealand vs Asia was chosen for the trial.

The preliminary analysis of this PK data showed no difference in AUC or Cmax between patients with CRC and those with any solid tumors.

The pharmacokinetics of regorafenib will be evaluated in the proposed Phase 3 monotherapy study to assess exposure in those tumor-types, identify clinically relevant covariates, and characterize exposure-response relationships.

Sparse samples (1 to 3 samples/patient on Cycle 1, Day 15) will be collected and pooled with dense data from Phase 1 studies with the goal of performing a population PK analysis.

Does the FDA agree with the population pharmacokinetic analysis plan for the proposed Phase 3 study in patients with CRC?

(Note: although the question is appearing in this section, we consider the issue to be important from both a clinical development perspective and a clinical pharmacology perspective, and we would appreciate that FDA address the question from both perspectives.)

FDA Response: It appears acceptable.

The clinical pharmacology development plan, in order to support the approval and labeling for the indication colorectal carcinoma, is presented in detail in Section 11. Table 11-1 shows a summary of ongoing or planned studies and analyses contributing to the clinical pharmacology development plan.

The questions below pertain to some, but not all of the listed studies and include proposed study designs for the corresponding studies.

Question 10

The effect of food on the pharmacokinetics of regorafenib has not been formally evaluated. A single-dose, cross-over pharmacokinetic study in healthy volunteers is proposed to evaluate the effect of regorafenib administration fasted or with a high-fat breakfast (800-1000 calories, ~50% fat) as compared to administration of regorafenib with a low-fat breakfast (300-500 calories, <30% fat) on the pharmacokinetics of regorafenib.

Does the FDA agree that the proposed study will provide information about the potential effect of food on the exposure of regorafenib when administered with a high fat meal or fasting as compared to with a low fat meal, suitable for inclusion in the package insert?

FDA Response: We recommend that you not only evaluate pharmacokinetics of regorafenib but also the pharmacokinetics of the active metabolites such as M2 and M5. We recommend that you submit the study protocol for FDA review prior to starting the study.

This is a review issue as to whether the information from the proposed study would be suitable for inclusion in the package insert regarding food effect.

Bayer Response: We thank the FDA for their comments. We plan to evaluate the pharmacokinetics of all major active metabolites. We will submit the study protocol for FDA review.

Question 11

In vitro evaluations in human hepatocytes have shown that regorafenib is primarily metabolized by CYP 3A4. A clinical study to evaluate the effect of a strong CYP 3A4 inhibitor (ketoconazole) on the pharmacokinetics of regorafenib will be conducted.

Does the FDA agree that the proposed study will provide information about the maximum potential increase in exposure of regorafenib when administered with compounds inhibiting CYP 3A4 metabolism, suitable for providing instruction in the package insert?

FDA Response: You should use 400 mg QD of ketoconazole for multiple days to obtain the maximum effect. In addition, you should not only evaluate pharmacokinetics of regorafenib but also the pharmacokinetics of the active metabolites such as M2 and M5.

When you plan the pharmacokinetic sampling scheme, you should take into consideration any potential pharmacokinetic change (e.g., increase in elimination half-lives) due to potential drug-drug interactions.

Please make sure that your sampling schedule can adequately characterize the pharmacokinetic profiles of regorafenib as well as active metabolites. We recommend that you submit the study protocol for FDA review prior to starting the study.

A final decision on what information on drug-drug interaction and/or dose adjustment include in the package insert will depend on the review of the study submitted with the NDA.

Bayer Response: We will incorporate FDA's suggestions into the study protocol and will submit the protocol for FDA review.

Question 12

In vitro evaluations in human hepatocytes have shown that regorafenib is primarily metabolized by CYP 3A4. A clinical study to evaluate the effect of a strong CYP 3A4 inducer (rifampicin) on the pharmacokinetics of regorafenib will be conducted.

Does the FDA agree that the proposed study will provide information about the maximum potential decrease in exposure of regorafenib when administered with compounds inducing CYP 3A4 metabolism, suitable for providing instruction in the package insert?

FDA Response: See response to question # 11.

Bayer Response: We will incorporate FDA's suggestions into the study protocol and will submit the protocol for FDA review.

Question 13

In vitro experiments showed that regorafenib is a moderate inhibitor of CYP 2C19 [$K_i = 16.4$] and CYP 3A4 [$K_i = 11.1$], and a strong inhibitor of CYP 2C9 [$K_i = 4.7$].

In order to assess the potential of regorafenib to inhibit metabolism by CYP2C19, CYP3A4 and CYP2C9 pathways, a study will be performed in patients with advanced, metastatic cancer who are refractory to standard treatment. Approximately 20 patients will be enrolled into the study to ensure a number of 12 patients with evaluable pharmacokinetic data. The pharmacokinetics of the probe substrates will be evaluated alone on Day -7 and co-administered with regorafenib on Cycle 1, Day 21.

Does the FDA agree with the study design for this study and that it will adequately characterize the effect of regorafenib on the probe substrates of CYP2C19, CYP3A4 and CYP2C9?

FDA Response: Please note that positive results from this study may warrant further clinical evaluation to confirm the interaction(s). Please take into consideration any potential pharmacokinetic change (e.g., increase in elimination half-lives) due to potential drug-drug interactions and make sure that your sampling schedule can adequately characterize the pharmacokinetic profiles of the probe substrates.

We recommend extending sampling times beyond 12 hours for midazolam and beyond 96 hours for warfarin. We recommend that you submit the study protocol for FDA review prior to starting the study.

As CYP2C8 demonstrated the largest $[I]/K_i$ value among the CYP enzymes tested *in vitro*, we recommend that you conduct a clinical drug-drug interaction study using repaglinide or rosiglitazone as the probe substrate of CYP2C8 to determine the effect of regorafenib on pharmacokinetics of the substrate chosen.

Bayer Response: We thank the FDA for the comments on the probe substrate study and will incorporate FDA's comments into the protocol before submitting it for FDA review.

We thank the FDA for the recommendation to conduct a clinical drug-drug interaction study to evaluate the effect of regorafenib on the pharmacokinetics of a clinically relevant CYP 2C8 substrate. We will assess the possibility of conducting such a study.

Meeting Discussion: None.

Question 14

Preclinical studies evaluating regorafenib and two major metabolites (M2, M5) showed no substantial effects on cardiovascular function and ECG in dogs at exposures (C_{max}) approximately 2 times greater for regorafenib and 8-9 times greater for the metabolites, than those reached in humans at the 220 mg dose. Regorafenib is not an inhibitor of the hERG K⁺ current in-vitro. However, the M2 (BAY 75-7495) and M5 (BAY 81-8752) metabolites are irreversible inhibitors of the hERG K⁺ current in-vitro at unbound concentrations about 20-fold higher than those reached in humans.

In order to assess the effect of regorafenib on cardiovascular safety parameters (QT_c, LVEF) a study will be performed in patients with advanced, metastatic cancer who are refractory to standard treatment. Approximately 50 patients will be enrolled into the study to ensure a number of 30 patients with evaluable cardiovascular assessments (QT_c, LVEF). The QT assessments will be performed at baseline and on Cycle 1, Day 21.

The effect of regorafenib on LVEF will be evaluated at baseline, Cycle 2, Day 21, and Cycle 5, Day 21, and every three month thereafter.

Does the FDA agree with the study design for this study and that it will adequately characterize the effect of regorafenib on the cardiovascular parameters being evaluated (QT_c, LVEF)?

FDA Response: Final determination of the acceptability of your study design will require our review of your protocol.

For QT evaluation, please submit the following documents for FDA IRT review: QT evaluation protocol, data analysis plan, investigator's brochure, table of clinical pharmacology highlights, as well as all the available clinical and non-clinical QT information. Please indicate in the cover letter that the submission is for IRT review.

Bayer Response: We will submit the QT evaluation protocol and other requested documents for IRT review.

Question 15

Preclinical information shows that regorafenib is eliminated primarily by the hepato-biliary route, and that less than 7% of the administered IV dose and less than 2% of the administered oral dose is excreted in rat urine.

The effect of renal impairment on the pharmacokinetics of regorafenib has also been explored in the Phase 1 dose escalation study 11650. Further characterization of the extent of renal elimination of regorafenib will be explored in a mass balance study. The three clinical studies or analyses are described below:

1. A comparison of patients from Phase 1 study 11650 who were dosed at either 120, 160, or 220 mg daily (21-day on/7-day off) with mild or moderate renal impairment to those with no renal impairment showed that there are no consistent or significant difference in AUC or C_{max} between patients with mild or moderate renal impairment and those with no renal impairment.
2. The amount excreted in urine (A_{ur}) in 6 patients showed that less than 5% of the administered dose was excreted in urine as parent or metabolite at the 160 mg 3 wk on/1 wk off dosing regimen.
3. A single-dose mass balance study in 3-4 healthy volunteers will be performed to characterize the routes of excretion in man.

Given the evaluations already performed, does the FDA agree that a renal impairment study does not need to be performed unless the mass balance study shows that greater than 20% of the administered dose is excreted in urine?

FDA Response: We remind you that you should not only assess the pharmacokinetics of regorafenib but also the pharmacokinetics of active metabolites. In your #1 and #2 analyses, you only evaluated pharmacokinetics of regorafenib. We recommend that you submit the mass balance study protocol for FDA review prior to starting the study.

Bayer Response: The exposure of metabolites M2 and M5 have also been evaluated in patients with normal, mild or moderate renal impairment in analysis #1 and were not included in the briefing book because they were similar to the results from the analysis of the parent compound. Attempts will be made to evaluate the urinary excretion of the active metabolites in analysis #2 (A_{ur}). All results will be reported to the FDA. We will submit the mass balance protocol for FDA review prior to starting the study.

Question 16

Preclinical data indicate that regorafenib is metabolized/eliminated by the hepato-biliary route and is likely to be primarily eliminated by the hepato-biliary route in man.

In an ongoing study using continuous dosing of 100 mg regorafenib daily, full profile PK data are being obtained after a single dose and at steady-state in at least 6 Child-Pugh A and 6 Child-Pugh B patients with hepatocellular carcinoma. These will be compared to data collected from patients with other solid tumors besides hepatocellular carcinoma at the 100 mg dose level in the dose escalation and expansion portions of the study. The potential correlation between PK data and measures of hepatic function such as bilirubin, albumin, and INR will also be explored.

Sparse samples will be collected in the proposed Phase 3 studies. In the population pharmacokinetic analysis, measures of hepatic function such as bilirubin, albumin, and INR will be considered as covariates.

Does the FDA agree that the pharmacokinetic data from hepatically impaired HCC patients will be adequate to characterize the effect of hepatic impairment on the pharmacokinetics of regorafenib?

FDA Response: No. The hepatic impairment study should be designed to guide potential dose adjustment for this special population. There are potential issues with your current proposal that need to be addressed:

- a. It is uncertain whether the pharmacokinetics of regorafenib will be different between the HCC patients and non-HCC patients in the same Child-Pugh category.
- b. As more than proportional increase in exposure for metabolites M-2 and M-5 was observed in Studies 11650 and 11651, the effect of hepatic impairment following the 160 mg QD 3 week on, 1 week off dosing schedule may not be extracted appropriately from the results obtained at the 100 mg QD continuous dosing schedule.

Bayer Response: We accept the recommendation to evaluate the effect of hepatic impairment at the 160 mg dose. Consistent with the FDA hepatic impairment guidance, a single dose study in healthy volunteers and subjects with Child-Pugh A and B liver impairment will be conducted to evaluate the effect of hepatic impairment on the pharmacokinetics of regorafenib. The results of this study will be included in the label to provide guidance on potential dose adjustments in cancer patients with hepatic impairment. We will submit the protocol for FDA review.

Meeting Discussion: The Agency raised a concern about the study design proposed by the Sponsor. The Sponsor is going to take the Agency's comments into consideration. The Agency suggested that the Sponsor may want to consider a hepatic impairment study in cancer patients with multiple doses in the dose escalations setting.

Examples can be found in the Ixempra® label and Gleevec® label. Another source of information can be found at the NCI hepatic impairment study protocol template which is used to establish the maximum tolerated dose (MTD) and dose-limiting toxicity (DLT) of the drug in groups of patients with varying degrees of hepatic dysfunction (mild, moderate, severe, and liver transplant) in order to provide appropriate dosing recommendations in such patients

(see http://ctep.cancer.gov/protocolDevelopment/docs/hepatic_dysfunction_v3.doc).

Question 17

In addition to the above mentioned studies, these additional studies and analyses will be performed to characterize the pharmacokinetics of regorafenib:

1. The effects of race, body weight, age, and gender on the PK of regorafenib will be explored using pharmacokinetic data from the Phase 1 studies, as well as in the planned population pharmacokinetic analyses in the Phase 3 studies.
2. The effect of Asian race on the pharmacokinetics of regorafenib will be evaluated in a Phase 1 study in Japanese cancer patients at the 160 mg 21-day on/7-day off dose.

Does the FDA agree that the aforementioned studies/evaluations will be adequate to provide the complete clinical pharmacology package necessary to support the approval and labeling of monotherapy regorafenib in CRC?

FDA Response: Your proposal appears generally acceptable, assuming that the design, conduct, and results of the studies are adequate. In addition, conduct an *in vitro* study to determine whether regorafenib is an inhibitor of P-gp if you have not already done so.

Bayer Response: An *in vitro* study to determine if regorafenib is an inhibitor of P-gp was conducted and found that the $[I]/IC_{50}$ of regorafenib towards P-gp is 3.7 and the IC_{50} is 2-3 μ M. Multiple dose studies of regorafenib can only be conducted in cancer patients due to the potential of toxicities in healthy volunteers. There is a paucity of p-glycoprotein substrates (see FDA Draft Guidance for Industry: Drug Interaction Studies- Study Design, Data Analysis, and Implications for Dosing and Labeling) that are considered acceptable for use in cancer patients. In addition, there is very limited experience in conducting studies with p-glycoprotein substrates in cancer patients. More importantly, most pure p-glycoprotein substrates (which are not anti-cancer agents) do not appear to have a narrow therapeutic index (for eg. fexofenadine, loperamide), necessitating a dose adjustment. Digoxin, a narrow therapeutic index p-glycoprotein substrate, and colchicine are not considered clinically relevant in the metastatic CRC setting. There are no plans to combine regorafenib with anti-cancer drugs which are p-glycoprotein substrates. Based on this, currently there is no plan to evaluate the effect of regorafenib on the pharmacokinetics of P-gp substrates. Bayer, however, agrees that the *in vitro* p-glycoprotein inhibition data should be stated in the package insert.

Meeting Discussion: This appears acceptable.

Additional FDA Comments:

- You established a recommended Phase 2 dose in Phase 1 Study 11650 as 160 mg daily for 21 days every 28 days, and in Phase 1 Study 11651 as 100 mg daily given continuously during a 21-day cycle. Were the two regimens developed on the basis of PK data?

Bayer Response: The two regimens were not developed on the basis of PK data. The first in human study (study #11650) was started with the 21 days on / 7 days off administration in order to have a safe and tolerable administration schedule. After safety data from study #11650 were available, a second study (study #11651) was started where regorafenib has been administered continuously.

- You have used the 21/28 day regimen in the RCC trial and plan to use it in the mCRC trial. A positive correlation between responses and PK parameters in the prospective trial would be helpful for future trials and for clinical use of the drug.

Bayer Response: We plan to explore the exposure-response correlation in the prospective mCRC trial. Please refer to Question 9 in the list of questions.

- The secondary endpoint of QoL is unlikely to be included in the label. Regarding QoL outcome measures, the results may not be interpretable if there are substantial missing data, imbalances in missing information between treatment arms and multiplicity issues. Also please refer to FDA draft guidance on patient reported outcome measures with respect to content validity of the instruments.

Bayer Response: We acknowledge FDA's comment.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
IND-75642	GI-1	BAYER HEALTHCARE PHARMACEUTICA LS INC	BAY 734506 (KINASE INHIBITOR)
IND-75642	GI-1	BAYER HEALTHCARE PHARMACEUTICA LS INC	BAY 734506 (KINASE INHIBITOR)

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/s/

ANN T FARRELL
10/02/2009