

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
204369Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 204369 (Type 9 NDA)

SUPPL #

HFD # 107

Trade Name Stivarga

Generic Name regorafenib

Applicant Name Bayer HealthCare Pharmaceuticals, Inc.

Approval Date, If Known February 25, 2013 (PDUFA Goal: February 28, 2013)

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), Type 9 NDA

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?

N/A

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# 203085

Stivarga (regorafenib)

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:

Study 14874, "A randomized, double-blind, placebo-controlled phase III study of regorafenib plus best supportive care versus placebo plus best supportive care for subjects with metastatic and/or unresectable gastrointestinal stromal tumors (GIST) whose disease has progressed despite prior treatment with at least imatinib and sunitinib".

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:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Study 14874, "A randomized, double-blind, placebo-controlled phase III study of regorafenib plus best supportive care versus placebo plus best supportive care for subjects with metastatic and/or unresectable gastrointestinal stromal tumors (GIST) whose disease has progressed despite prior treatment with at least imatinib and sunitinib".

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

!

!

IND # 75642, and 113896

YES ! NO

! Explain:

IND 75642 was administratively split out to IND 113896 following the re-organization of CDER's Office of Hematology and Oncology Products. The study was therefore, conducted under both INDs.

Investigation #2

!

!

IND #

YES ! NO

! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not

identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1
!
!
YES ! NO
Explain: ! Explain:
N/A

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, M.S.
Title: Lead Regulatory Health Project Manager
Date: February 25, 2013

Name of Office/Division Director signing form: Patricia Keegan, M.D.
Title: Director, Division of Oncology Products 2

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
02/25/2013

PATRICIA KEEGAN
02/25/2013

Hughes, Monica L

From: Hughes, Monica L
Sent: Tuesday, October 23, 2012 12:54 PM
To: Greeley, George; Suggs, Courtney
Subject: Pediatric Page for NDA 204369: Stivarga (GIST) Orphan Designation

Attachments: Pediatric Page NDA 204369 (Stivarga-GIST) orphan.doc

Hello,

I am attaching the pediatric page for NDA 204369, a Type 9 NDA that will be converted to an efficacy supplement to NDA 203085 at the time of its approval. This Type 9 NDA is for GIST and it has orphan designation.

Please let me know if you need additional information.

Thank you,
Monica



Pediatric Page NDA
204369 (Sti...

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
Email: monica.hughes@fda.hhs.gov

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 204369 (Type 9) Supplement Number: _____ NDA Supplement Type (e.g. SE5): _____

Division Name: DOP2 PDUFA Goal Date: 2/28/12 Stamp Date: 8/30/2012

Proprietary Name: Stivarga

Established/Generic Name: regorafenib

Dosage Form: tablets, 40mg

Applicant/Sponsor: Bayer HealthCare Pharmaceuticals, Inc.

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

(1) metastatic colorectal cancer (NDA 203085)

(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): _____
(Attach a completed Pediatric Page for each indication in current application.)

Indication: GIST

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).

Additional 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.

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 complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

(Revised: 6/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.



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 204,369.

Date:

7/10/12

Signature:

John Talian, PhD

Vice President, Global Regulatory Affairs

Head of US Regulatory Affairs

Bayer HealthCare Pharmaceuticals

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 204369	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>February 28, 2013, approved February 25, 2013.</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>	<p><input type="checkbox"/> Received</p>
<p>❖ Application Characteristics³</p>	
<p>Review priority: <input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority Chemical classification (new NDAs only): Type 9 (to NDA 203085)</p> <p> <input checked="" type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch <input checked="" type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch <input checked="" 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>	<p><input type="checkbox"/> Yes, dates</p>
<p>❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)</p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
<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 	<p><input checked="" type="checkbox"/> Yes <input type="checkbox"/> No</p>
<ul style="list-style-type: none"> Press Office notified of action (by OEP) 	<p><input checked="" type="checkbox"/> Yes <input type="checkbox"/> No</p>
<ul style="list-style-type: none"> Indicate what types (if any) of information dissemination are anticipated 	<p> <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 and Information Advisory) </p>

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>)	Action(s) and date(s) Approval: 2/25/13
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. 	February 22, 2013
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	August 30, 2012 Revised labeling following NDA 203085 Approval: October 24, 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 package insert.
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	Attached to package insert.
<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>) 	Approved on 9/27/12 under NDA 203085
<ul style="list-style-type: none"> • Most-recent draft labeling 	
<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. 	Stivarga was found acceptable under the review of NDA 203085
<ul style="list-style-type: none"> ❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>) 	<input checked="" type="checkbox"/> RPM 11/9/12 <input type="checkbox"/> DMEPA <input checked="" type="checkbox"/> DMPP/PLT (DRISK) 1/14/13 <input checked="" type="checkbox"/> ODPD (DDMAC) Professional and Consumer 1/15/13 <input type="checkbox"/> SEALD <input type="checkbox"/> CSS <input checked="" type="checkbox"/> Other reviews MHT 1/9/12
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>) 	10/26/12
<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
<ul style="list-style-type: none"> ❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC _____ If PeRC review not necessary, explain: <u>Orphan designation granted for this indication.</u> • Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>) 	<input type="checkbox"/> Included

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

❖ 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
❖ Outgoing communications <i>(letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons)</i>	2/13/13 (Labeling) 2/8/13 Teleconference (uploaded 2/19/13) 2/6/13 (Labeling) 2/1/13 (CMC PMC Proposal) 1/24/13 (Labeling) 1/15/13 (PMC Proposal) 1/2/13 12/21/12 (Labeling) 11/2/12 10/29/12 10/23/12 10/5/12 10/2/12 9/26/12 9/19/12 9/7/12 9/5/12 9/5/12 8/7/12 6/18/12
❖ Internal memoranda, telecons, etc.	2/5/13 (uploaded 2/6/13) 1/28/12 Wrap-Up MTG (uploaded 2/5/13) 1/28/13 SGE Discussion (uploaded 2/4/13) 1/24/13 (uploaded 1/30/13) 1/17/13 (uploaded 1/18/13) 12/20/12 (uploaded 12/21/12) 12/13/12 (uploaded 12/21/12) 12/10/12 (uploaded 12/21/12) 12/6/12 (uploaded 12/21/12) 11/29/12 (uploaded 12/21/12) 10/25/12 (uploaded 12/14/12) 9/6/12 (uploaded 10/24/12) 9/4/12 (uploaded 10/24/12) 9/14/12
❖ Minutes of Meetings	
<ul style="list-style-type: none"> Regulatory Briefing <i>(indicate date of mtg)</i> 	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> 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
<ul style="list-style-type: none"> Pre-NDA/BLA meeting <i>(indicate date of mtg)</i> 	<input type="checkbox"/> No mtg 5/3/12 (uploaded 5/23/12)
<ul style="list-style-type: none"> EOP2 meeting <i>(indicate date of mtg)</i> 	<input type="checkbox"/> No mtg 8/25/10 (uploaded 9/23/10)
<ul style="list-style-type: none"> Other milestone meetings (e.g., EOP2a, CMC pilots) <i>(indicate dates of mtgs)</i> 	
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> Date(s) of Meeting(s) 	
<ul style="list-style-type: none"> 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 checked="" type="checkbox"/> None
Division Director Summary Review (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None 2/25/13
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
PMR/PMC Development Templates (<i>indicate total number</i>)	<input type="checkbox"/> None CMC 2/12/13 Clinical Pharmacology 1/29/13 Clinical 1/29/13
Clinical Information ⁶	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	Concurred 2/1/13
• Clinical review(s) (<i>indicate date for each review</i>)	2/1/13 Filing Review: 10/23/12
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ 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>)	Addressed in clinical review page 22
❖ 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	1/30/2013
• 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 checked="" type="checkbox"/> None
❖ DSI Clinical Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>)	<input checked="" type="checkbox"/> None requested
Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	<input 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 2/1/13
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None Concurred 1/31/13
Statistical Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 1/31/13 Filing Review: 10/9/12

⁶ Filing reviews should be filed with the discipline reviews.

Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None Concurrence of primary review 1/28/13
Clinical Pharmacology Team Leader Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None Concurrence of primary review 1/25/13
Clinical Pharmacology review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None 1/24/13 Filing Review: 10/10/12
❖ DSI Clinical Pharmacology Inspection Review Summary <i>(include copies of DSI letters)</i>	<input checked="" type="checkbox"/> None
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
• Supervisory Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None Concurred 12/20/12
• Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>	<input type="checkbox"/> None 12/19/12 Filing Review: 10/17/12
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer <i>(indicate date for each review)</i>	<input checked="" 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
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None CMC Review Concurred: 1/24/13 Biopharmaceutics Review Concurred: 11/19/12
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>	<input type="checkbox"/> None Biopharmaceutics Review: 11/19/12 Biopharmaceutics Filing Review: 10/10/12 CMC Review: 1/24/13 CMC Filing Review: 10/11/12
❖ Microbiology Reviews	<input type="checkbox"/> Not needed
<input checked="" type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i>	Micro Review: 12/11/12 Micro Filing Review: 9/18/12
<input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>	
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>	<input checked="" 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>)	CMC review: 1/24/13
<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) (<i>date completed must be within 2 years of action date</i>) (<i>only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁷</i>)	Date completed: EES email: January 29, 2013 CMC Review: 1/31/13 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER (<i>date of most recent TB-EER must be within 30 days of action date</i>) (<i>original and supplemental BLAs</i>)	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation (<i>check box only, do not include documents</i>)	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" 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
02/28/2013

INTERNAL MEMORANDUM OF MEETING MINUTES

MEETING DATE: February 8, 2013
TIME: 10:00-11:00 AM ET
LOCATION: Teleconference, WO 22, Room 4201
APPLICATION: NDA 204369
DRUG NAME: Stivarga (regorafenib)

FDA ATTENDEES:

Patricia Keegan - Division Director, DOP2
Anthony Murgu-Associate Director, OHOP
Suzanne Demko- Clinical Team Leader
Monica Hughes- Lead Regulatory Health Project Manager
Janet Jiang-Statistics
Jennie Chang-Senior Clinical Analyst
Shanee Toombs-OPDP
Carole Broadnax-OPDP

EXTERNAL CONSTITUENT ATTENDEES:

Bayer Attendees:

Darshan Wariabharaj (Regulatory Affairs, Global Regulatory Strategy)
Philip Johnson (Regulatory Affairs, Global Regulatory Strategy)
Anthony Genovese (Regulatory Affairs, Advertising and Promotion)
Lynn Bowen (Regulatory Affairs, Advertising and Promotion)
Alan Hassell (Regulatory Affairs, Labeling)
Elisa S Mandra (Regulatory Affairs, Labeling)
Aubrey Anderson (Regulatory Affairs, Labeling)
Stephanie Mondabon (Regulatory Affairs, Global Regulatory Strategy)
Sarah Schlieff (Global Safety Leader)
Christian Kappeler (Statistics)
Sibyl Anderson (Medical Affairs)
Joseph Germino (Medical Affairs)
Iris Kuss (Clinical Development)

DISCUSSION POINTS: The purpose of this teleconference was to discuss particular sections of the labeling as part of ongoing labeling negotiations associated with NDA 204369.

FDA sent proposed draft labeling to Bayer in advance of this teleconference on February 6, 2013.

On February 7, 2012, Bayer sent an email communication to FDA with the following labeling proposal and agenda items to discuss during the February 8, 2013, teleconference:

1. Bayer proposed including the range instead of the SD so the text in the label would read:

Section 6.1: “The median duration of therapy was 7.3 ((b) (4) range [0.3, 47.0]) weeks for patients receiving Stivarga.”

(b) (4) “The median duration of therapy was 22.9 ((b) (4) range [0.1, 50.9]) weeks for patients receiving Stivarga.”

The numbers cited in the range were confirmed by Bayer’s statistician.

DISCUSSION DURING TELECONFERENCE: (b) (4)

(b) (4) therefore, FDA recommended using median values. FDA acknowledged Bayer’s concerns expressed during the teleconference and agreed that the ranges could be included in product labeling. (b) (4)

2. Discuss Section 5.3: Dermatological Toxicity

FDA Proposed: “Withhold Stivarga, reduce the dose, or permanently discontinue Stivarga depending on the severity and persistence of dermatologic toxicity [see *Dosage and Administration* (2.2)]. (b) (4)

Prior to this teleconference, FDA had proposed to delete the all Bayer’s proposed language as shown above.

Following Discussion During the Teleconference: “Withhold Stivarga, reduce the dose, or permanently discontinue Stivarga depending on the severity and persistence of dermatologic toxicity [see *Dosage and Administration* (2.2)]. **Institute supportive measures for symptomatic relief** (b) (4)

DISCUSSION DURING TELECONFERENCE: FDA expressed concern that while these (b) (4) were specified in the protocol, Bayer did not verify or collect data that these recommendations were followed. FDA stated that these (b) (4) are well known in the medical community and did not want to make definitive statements in the product labeling that were

not supported by data in the application. FDA and Bayer agreed to retain the highlighted sentence above that was in the approved labeling for NDA 203085.

(b) (4)

3. Discuss Section 14.2: Overall Survival

DISCUSSION DURING TELECONFERENCE: Bayer did not agree with the statement, “There was no difference in overall survival at the time of the planned interim analysis based on 29% of the total events for the final analysis.” FDA stated that the data submitted under this application supports this as a factual statement. Bayer stated that they did not anticipate an increase in overall survival at the interim analysis, FDA stated that this is a technical disagreement between Bayer and FDA as this interim analysis was a planned analysis and if Bayer had seen an increase in overall survival at the interim analysis Bayer would have proposed including it in the product labeling. After a brief discussion, Bayer proposed revising the labeling as follows by including the highlighted “statistically significant” text and FDA accepted this proposal:

“A statistically significant improvement in PFS was demonstrated among patients treated with Stivarga compared to placebo (see Table 6 and Figure 2). There was no **statistically significant** difference in overall survival at the time of the planned interim analysis based on 29% of the total events for the final analysis.”

Bayer agreed to provide revised labeling to FDA that reflects the changes agreed upon during this teleconference.

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/s/

MONICA L HUGHES
02/19/2013



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

Memorandum

Date: February 13, 2013
From: Monica Hughes, M.S., Lead Regulatory Health Project Manager DOP2/OHOP
Subject: NDA 204369

On February 12, 2013, Bayer proposed the following change in Section 14.2 via email communication to FDA:

[REDACTED] (b) (4)

On February 13, 2013, FDA proposed the following counter-proposal to Bayer via email communication to Section 14.2:

Patients were randomized to receive 160 mg regorafenib orally once daily (N=133) plus best supportive care (BSC) or placebo (N=66) plus BSC for the first 21 days of each 28-day cycle. Treatment continued until disease progression or unacceptable toxicity. (b) (4)

(b) (4) In Study 2, the median age of patients was 60 years, 64% were men, 68% were White, and all patients had baseline ECOG performance status of 0 (55%) or 1 (45%). At the time of disease progression as assessed by central review, the study blind was broken and all patients were offered the opportunity to take Stivarga at the investigator's discretion. (b) (4) Fifty-six (85%) patients randomized to placebo and 41 (31%) patients randomized to Stivarga received open-label Stivarga. (b) (4)

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/s/

MONICA L HUGHES
02/13/2013



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

Memorandum

Date: February 5, 2013

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

Subject: NDA 204369: Internal Labeling Meeting

Attendees: Monica Hughes, Patricia Keegan, Janet Jiang, Kun He, Jason Bunting, Jennie Chang, Carol Broadnax, Anthony Murgo, Suzanne Demko

Discussion:

FDA sent Bayer a draft labeling proposal on January 24, 2013. Bayer provided a response to that proposal via email communication on January 29, 2013. During this meeting, the team reviewed and discussed Bayer's proposal.

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/s/

MONICA L HUGHES
02/07/2013



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

Memorandum

Date: February 6, 2013

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

Subject: NDA 204369

Please find attached FDA's counter proposal to your revised package insert (PI) and patient package insert (PPI) submitted via email communication on January 29, 2013, in response to our January 24, 2012, proposed revisions. We are providing this response in advance of our teleconference on February 8, 2013.

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

Attachment: FDA proposed revisions to the package insert and patient package insert

25 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/
TS) immediately following this page.

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/s/

MONICA L HUGHES
02/06/2013

Internal Meeting Summary
Wrap-Up Meeting: January 28, 2013
NDA 204369 (Type 9)
Stivarga (regorafenib)/GIST

Overview: Important Review Goal Dates

Review Target Due Dates:	6 Month Review
<i>Primary Review Due</i>	February 4, 2013
<i>Secondary Review Due</i>	February 7, 2013
<i>DOP2 Division Director Review Due/Sign-Off</i>	February 28, 2013

PDUFA Goal Date: February 28, 2013

FDA Attendees: Monica Hughes, Josephine Jee, Elsbeth Chikhale, Suzanne Demko, Amir Shahlaee, Jennie Chang, Anwar Goheer, Stacy Shord, Whitney Helms, Hong Zhao, Karen Jones, Janet Jiang, Kun He, Patricia Keegan, Tzu-Yun McDowell, Derek Smith, Jason Bunting, Carole Broadnax, Jeff Summers, Richard Pazdur, Anthony Murgo, Ali Al Hakim, Peter Waldron

Agenda Items and Discussion During Meeting:

1. Discipline Specific Reviews of Application

- a. CMC: Josephine Jee and Donghao (Robert) Lu: review complete in DARRTs 1/24/13

Discussion During Meeting: CMC review is complete, no additional discussion occurred.

- b. Biopharmaceutics: Elsbeth Chikhale: review complete in DARRTs 11/19/12

Discussion During Meeting: Biopharmaceutics review is complete, no additional discussion occurred.

- c. CMC Microbiology: Vinayak Pawar: review complete in DARRTs 12/11/12

Discussion During Meeting: CMC microbiology review is complete, discussion regarding the need for a PMC for CMC a CBE supplement to include the addition of a microbial purity test as a drug product specification. Additional internal discussions are needed.

- d. Non-Clinical: Anwar Goheer: review complete in DARRTs 12/20/12

Discussion During Meeting: Non-clinical review is complete, no additional discussion occurred.

Internal Meeting Summary
Wrap-Up Meeting: January 28, 2013
NDA 204369 (Type 9)
Stivarga (regorafenib)/GIST

- e. Clinical Pharmacology: Stacy Shord

Discussion During Meeting: Clinical pharmacology review is complete and is in the process of signed-off on, clinical pharmacology PMC template will be uploaded in DARRTs for sign-off.

- f. Clinical: Jennie Chang and Amir Shahlaee

Discussion During Meeting: Clinical review is in the process of being finalized, clinical PMC template will be uploaded in DARRTs for sign-off.

- g. Statistics: Janet Jiang

Discussion During Meeting: Statistics review is in the process of being finalized, no additional discussion occurred.

- h. OMPQ (API manufacturing inspection update): Derek Smith

-API inspection conducted in December 2012, no 483 issued. We still need the final EER recommendation of approval.

Discussion During Meeting: Two Bayer sites were inspected, both sites were NAI and no 483 was issued. The overall OC recommendation is still pending.

2. Pending Consults

Discuss anticipated completion dates of outstanding consults:

- OSE: DRISK (Risk Management Plan), Review pending

Discussion During Meeting: Risk management plan review from DRISK is in the process of being finalized. DRISK noted the potential need for skin rash related adverse events to be more prominent in the label has been discussed internally and may be suggested in the final review. DOP2 will review DRISK suggestions once the finalized review is received.

- Patient Labeling Team: Review complete in DARRTS 1/14/13

Discussion During Meeting: No additional discussion occurred.

- OPDP: both consumer and professional reviews are complete in DARRTS 1/15/13

Discussion During Meeting: No additional discussion occurred.

Internal Meeting Summary
Wrap-Up Meeting: January 28, 2013
NDA 204369 (Type 9)
Stivarga (regorafenib)/GIST

- Pediatric and Maternal Health- No proposed labeling changes, review is complete in DARRTs 1/9/13.

Discussion During Meeting: No additional discussion occurred.

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

- Status of labeling review
 - Labeling meetings held: December 6, 10, 13, 2012 and January 17, 24, 2013.
 - Sent first round of labeling comments on 12/21/12
 - Sent second round of labeling comments on 1/24/13, expect a response this week: potential follow-up teleconference with Bayer if needed.
 - Labeling meeting scheduled: none currently, will schedule on receipt of Bayer's next response.
- Discuss any open items with input needed from other reviewers
- Discuss need for additional meetings

Discussion During Meeting: Additional labeling meetings and a potential teleconference will be scheduled with Bayer following receipt and review of their counter-proposed labeling.

4. Discuss Postmarketing Commitments

-PMC negotiations are ongoing; two PMCs have been requested: (1) Clinical PMC for Overall Survival Data; and, (1) Clinical Pharmacology PMC for exposure-response analysis. Reviewers will need to upload PMC templates in DARRTs for Deputy Director for Safety in DOP2 sign off.

Discussion During Meeting: Reviewers will upload the PMC templates in DARRTs, no additional discussion occurred.

5. Discuss Postmarketing Safety Surveillance Plan Jennie Chang/Amir Shahlaee

-Clinical team will inform the Office of Surveillance and Epidemiology (OSE)/Division of Pharmacovigilance (DPV) what types of adverse events they should be monitoring for.

Discussion During Meeting: DOP2 recommended that DPV monitor closely for reported hepatotoxicity events, along with dermatological toxicities including severe cutaneous rashes, keratoacanthomas, and squamous cell carcinoma events.

Internal Meeting Summary
Wrap-Up Meeting: January 28, 2013
NDA 204369 (Type 9)
Stivarga (regorafenib)/GIST

6. Discussion of Proposed Action To Be Taken: Suzanne Demko/Anthony Murgo

*SGE teleconference with Dr. Ephraim Casper occurred earlier this morning, on January 28, 2013.

Discussion During Meeting: Dr. Casper was provided with a background document and draft product labeling in advance of our teleconference. Dr. Casper agreed that the data in the application appears to demonstrate a clinically meaningful benefit of a 3.9 month improvement in median PFS and he agreed that the risk-benefit ratio appeared to favor treating the proposed patient population with regorafenib. No additional discussion occurred.

7. Discussion of sign-off procedure and schedule: Suzanne Demko/Anthony Murgo

*Final primary and secondary reviews need to be completed (by end of first week of February) in order for the CDTL to review and ultimately for the DD to complete her review within the planned, 6-month review timeframe. Sign-off process will continue with labeling, PMR/PMCs, and action letter.

*Draft ASCO Burst is circulating

*Draft Press Release and Information Advisory are circulating

Discussion During Meeting: Outstanding primary reviews must be completed by February 4, 2013, and secondary reviews by February 7, 2013. All press-related documents are circulating. The action package and draft final action letter will begin circulating shortly. No additional discussion occurred.

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/s/

MONICA L HUGHES
02/05/2013

MEMORANDUM OF INTERNAL MEETING MINUTES

MEETING DATE: January 28, 2013
TIME: 9:00-9:30 AM ET
LOCATION: Teleconference, WO 22, RM 2327
APPLICATION: NDA 204369
DRUG NAME: Stivarga (regorafenib)
TYPE OF MEETING: Teleconference with Special Government Employee (SGE), Dr. Ephraim Casper, cleared for participation by CDER's Division of Advisory Committee and Consultant Management (DACCM).

FDA ATTENDEES:

Patricia Keegan - Division Director
Amir Shahlaee- Clinical Reviewer
Suzanne Demko-Clinical Team Leader
Anthony Murgu- Associate Director OHOP
Monica Hughes- Lead Regulatory Health Project Manager

EXTERNAL CONSTITUENT ATTENDEES:

Dr. Ephraim Casper

BACKGROUND: Dr. Ephraim Casper 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. Casper, along with three specific division questions for Dr. Casper to address during this teleconference. Those materials are attached to this document.

DISCUSSION POINTS:

In this application, Bayer seeks the approval of Stivarga (regorafenib), for the treatment of patients with locally advanced, unresectable or metastatic gastrointestinal stromal tumors (GIST) who have been previously treated with imatinib mesylate and sunitinib malate. Stivarga (regorafenib) was approved for mCRC in September of 2012.

FDA Questions for Discussion During Teleconference:

1. Does the 3.9-month improvement in median progression-free survival (PFS) observed in the regorafenib arm of Study 14874 represent a clinically meaningful treatment effect?

DISCUSSION DURING TELECONFERENCE: Dr. Casper stated that the data in the application appears to demonstrate a clinically meaningful benefit based on a 3.9 month improvement in median PFS.

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. Casper commented that he weighed the efficacy data presented in the application against the potential toxicities associated with regorafenib, which he noted were not trivial. He noted that the relatively high adverse event rate in the placebo group suggests a considerable number of the events in the regorafenib arm are probably related to the underlying disease. Dr. Casper agreed that the risk-benefit ratio for regorafenib appeared favorable for the treatment of the proposed population.

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

DISCUSSION DURING TELECONFERENCE: Dr. Casper agreed that the proposed draft product label appears to adequately inform patients and physicians of the potential risks and benefits of regorafenib.

ATTACHMENTS: Background information provided to Dr. Casper via a password protected file, secure email communication on January 23, 2013.



Dr. Ephraim Casper
Sent via Email Communication

Dear Dr. Casper:

We had a teleconference with you on October 5, 2012, regarding the possibility of your assistance in the review of a New Drug Application (NDA) 204369, submitted by Bayer Healthcare Pharmaceuticals. Please note that information concerning this application is confidential.

In this application, Bayer seeks approval of Stivarga (regorafenib), for the treatment of patients with locally advanced, unresectable or metastatic gastrointestinal stromal tumors (GIST) who have been previously treated with imatinib mesylate and sunitinib malate.

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 NDA.

Please review the attached written materials. We will discuss the enclosed information during a teleconference scheduled for 9:00 AM ET on January 28, 2013. We will provide toll-free call in information in advance of this teleconference. The 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 14874 (the GRID study), and the proposed regorafenib product labeling for your review.

FDA Questions for Discussion during Teleconference:

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

Thank you again for your time and insights.

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

Sincerely,

{See appended electronic signature page}

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 204369 Summary Information
2. Timekeeper Payroll Record
3. Draft regorafenib product labeling

**Briefing Document for FDA Teleconference to Discuss NDA 204369
Stivarga (regorafenib), Tablets
Bayer Healthcare Pharmaceuticals**

I. Introduction

- On August 30, 2012, Bayer submitted NDA 204369 seeking approval of regorafenib for the treatment of patients with locally advanced, unresectable, or metastatic gastrointestinal stromal tumors (GIST) who have been previously treated with imatinib mesylate and sunitinib malate.
- Regorafenib is a small molecule inhibitor of multiple kinases including BRAF, VEGFR 1/2/3, TIE2, PDGFR, FGFR, RET, and KIT.
- NDA 204369 includes data from a single, randomized clinical trial, Study 14874, entitled “A randomized, double-blind, placebo-controlled phase III study of regorafenib plus best supportive care versus placebo plus best supportive care for subjects with metastatic and/or unresectable gastrointestinal stromal tumors (GIST) whose disease has progressed despite prior treatments with at least imatinib and sunitinib”, also known as the GRID study.
- Regorafenib has been administered to over 1200 patients, including those in Study 14874, and is currently approved for the treatment of patients with metastatic colorectal cancer who have been previously treated with, or are not considered candidates for, fluoropyrimidine-based chemotherapy, an anti-VEGF therapy, and, if KRAS wild type, an anti-EGFR therapy.

II. Design of Study 14874

- Study 14874 was a multicenter, international, randomized (2:1), double-blind, placebo-controlled trial that enrolled patients with metastatic or unresectable GIST, previously treated with imatinib or sunitinib.
- Patients were randomized to receive 160 mg regorafenib orally once daily (n=133) or placebo (n=66) every 21 days of a 28-day cycle.
- Patients were stratified at randomization according to:
 - Administration of study drug as 3rd-line versus $\geq 4^{\text{th}}$ -line treatment
 - Geographical region (Asia versus rest of world)
- At the time of disease progression, the study blind was broken for individual patients; at the investigator’s discretion, patients on both treatment arms were offered the opportunity to take open-label regorafenib.
- The primary endpoint was progression-free survival and secondary endpoints were overall survival, tumor response rate, and time-to-tumor progression. All tumor-based endpoints were to be based on determinations made by a blinded central radiologic review (BCRR).
- No interim analyses were performed.
- Eligibility criteria included:
 - Age ≥ 18 years
 - Histologically confirmed metastatic or unresectable GIST.
 - At least imatinib and sunitinib as prior treatment regimens, with objective disease progression or intolerance to imatinib, as well as disease progression while on sunitinib therapy. Additionally, disease progression or intolerance to other systemic

- therapies, as well as investigational new agents, was allowed, except prior treatment with any other vascular endothelial growth factor receptor (VEGFR) inhibitor.
- Patients must have at least one measurable lesion according to modified RECIST, version 1.1, in which lymph nodes and bone lesions were not target lesions and a progressively growing new tumor nodule within a pre-existing tumor mass was progression.
 - Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1.

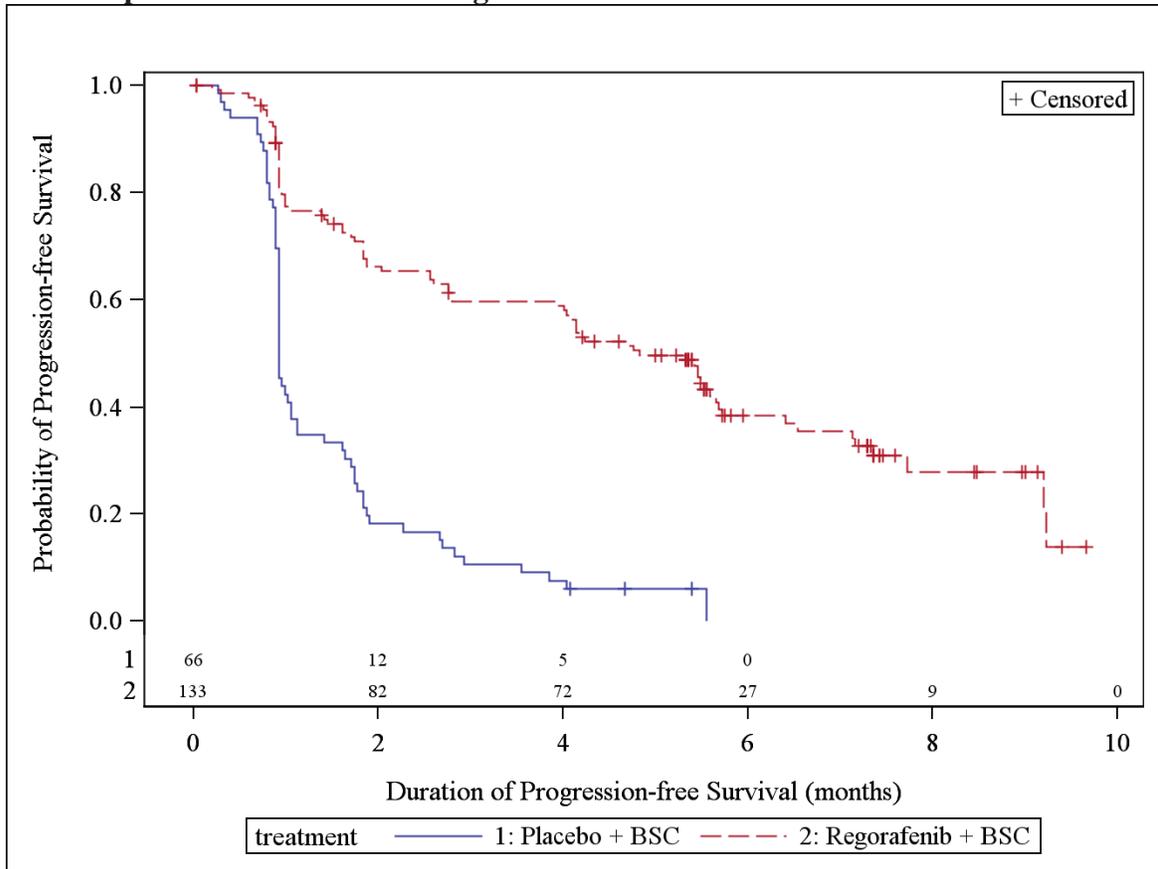
A. Results of Study 14874

- Baseline characteristics of the 199 randomized patients (66 to placebo and 133 to regorafenib) were comparable between treatment arms.
 - Median age: 60 years
 - 68% White
 - All patients had a baseline ECOG performance status of 0 (55%) or 1 (45%).
 - Most patients were from rest of world (76%) versus Asia (24%); North America (17%) and U.S. (13%).
 - Extent of disease at study entry was metastatic (61%), unresectable (8%), or both (23%).
 - Histological diagnosis was spindle cell (48%), epithelioid (8%), and mixed (14%).
 - All patients received prior treatment with imatinib and sunitinib.
- Key efficacy results
 - Statistically significant improvement in progression-free survival
 - No significant difference in overall survival
 - No significant difference in overall response rate (5% vs. 2%)

Table 1. Progression-free Survival Based on BCRR

	Placebo, n=66 (%)	Regorafenib, n=133 (%)
Censored (%)	3 (5)	51 (38)
Events (%)	63 (96)	82 (62)
Number of Progression Events	62	76
Number of Deaths	1	5
Median PFS in days (95% CI)	28 (28, 32)	147 (119, 172)
Median PFS in months (95% CI)	0.9 (0.9, 1.1)	4.8 (3.9, 5.7)
Hazard Ratio (95% CI)	0.27 (0.19, 0.39)	
p-value (stratified log-rank)	<0.0001	

Figure 1. Kaplan-Meier Curves of Progression-free Survival Based on BCRR



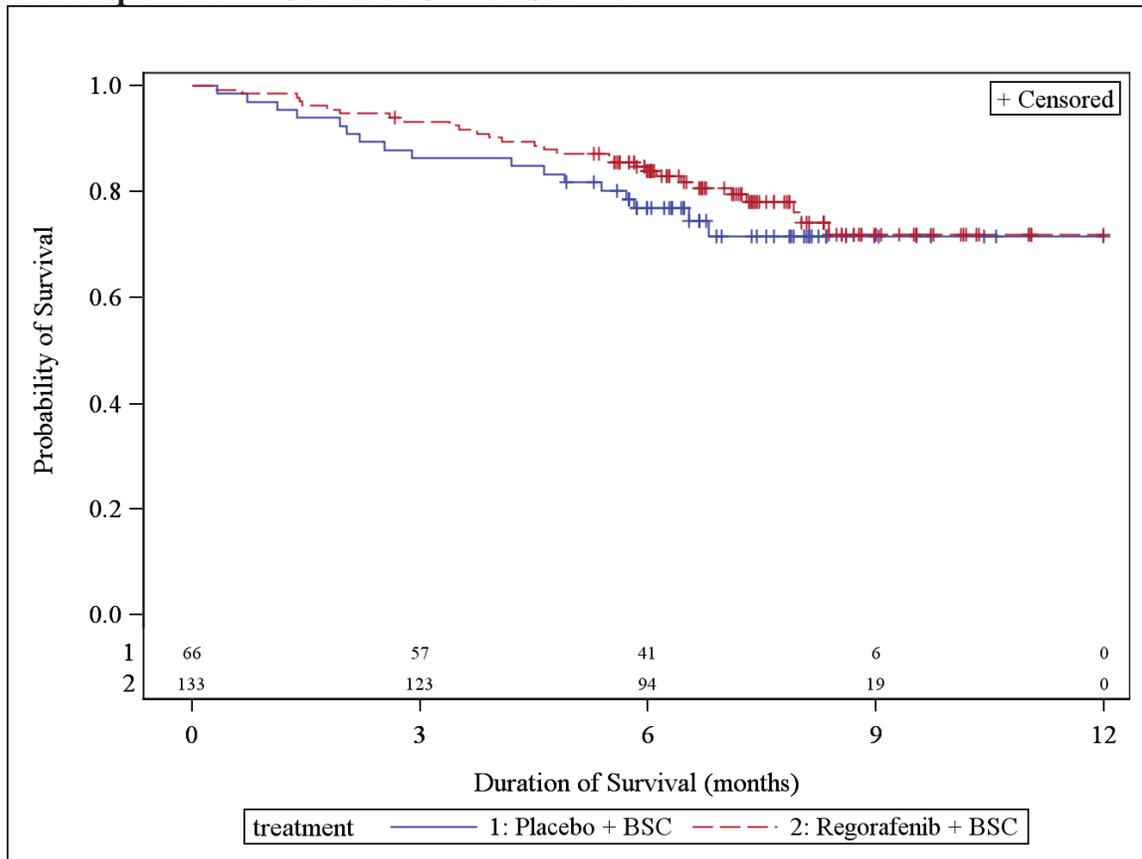
Additional Supportive Analyses of Efficacy

- Key secondary endpoints were overall survival and response rate.

Table 2. Overall Survival

	Placebo, n=66 (%)	Regorafenib, n=133 (%)
Events	17 (26)	29 (22)
Censored	49 (74)	104 (78)
Median OS, months (95% CI)	Not Reached	Not Reached
Hazard Ratio (95% CI)	0.77 (0.42, 1.41)	
p-value (stratified log-rank)	0.4	

Figure 2. Kaplan-Meier Curves of Overall Survival



Tumor Response Rate and Duration of Response

Six (5%) patients in the regorafenib arm and one patient (2%) in the placebo arm had a confirmed partial response. Complete responses were not observed in either arm. The median duration of response was 99 days (range: 42-99) in the regorafenib arm and 30 days in the placebo arm.

B. Analysis of Safety Data from Study 14874

- The overall toxicity profile of regorafenib appeared similar to that of other multi-kinase inhibitors.
- The mean duration of therapy was 20 weeks for the regorafenib arm compared to 9.1 weeks for placebo.
- Treatment-emergent adverse events resulted in dose interruptions in 58% of patients receiving regorafenib; 50% of patients required dose reduction (compared to 26% and 0, respectively, with placebo).
- The most serious adverse reactions of regorafenib are:
 - Drug-induced liver injury: fatal hepatic failure occurred in 0.8% of patients in the regorafenib arm compared to no patients in the placebo arm in Study 14874.
 - Hemorrhage: the overall incidence of hemorrhage (all grades) was 11% in regorafenib-treated patients compared to 3% with placebo in Study 14874. There were no grade 5 events of hemorrhage.
 - Severe dermatologic toxicity including palmar-plantar erythrodysesthesia (PPE): the overall incidence of PPE (67% versus 12%) and the incidence of Grade 3 PPE (22% versus 0%) were increased in regorafenib-treated patients in Study 14874. Stevens Johnson syndrome, erythema multiforme, and toxic epidermal necrolysis were not seen in Study 14874 but have occurred in other clinical studies of regorafenib.
 - Hypertension: hypertension occurred in 59% of regorafenib-treated patients versus 27% with placebo in Study 14874.
 - Gastrointestinal (GI) perforation
- Clinically significant adverse drug reactions observed in $\geq 20\%$ of regorafenib-treated patients across all placebo controlled trials were:
 - Asthenia/fatigue
 - PPE
 - Diarrhea
 - Decreased appetite and food intake
 - Hypertension
 - Mucositis
 - Dysphonia
 - Infection
 - Pain (NOS)
 - Weight loss
 - GI and abdominal pain
 - Rash
 - Fever
 - Nausea

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.

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

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/s/

MONICA L HUGHES
02/04/2013



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

Memorandum

Date: February 4, 2013

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

Subject: NDA 204369: Financial Disclosure

Financial disclosure information submitted under this NDA was reviewed in the clinical review prepared by Drs. Amir Shahlaee and Jennie Change. Please refer to page 22 of the clinical review.



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

Memorandum

Date: February 1, 2013
From: Monica Hughes, M.S., Lead Regulatory Health Project Manager DOP2/OHOP
Subject: NDA 204369: Microbial Purity Test, FDA Proposal for Post-Marketing Commitment (PMC)

On November 29, 2012, Dr. Vinayak Pawar of the FDA proposed the following to Bayer via email communication:

“If your Drug Product Specification includes Microbial Purity test, then each batch needs to be tested according to 21 CFR211.165 (a) & (b). (b) (4)

However, this leaves you with the following options:

- 1.
- 2.
- 3.
- 4.

Please communicate your preference through an official amendment to the NDA.”

On December 11, 2012, Dashan Wariabharaj of Bayer provided the following response via email communication:

“The team has considered the options, as presented in your e-mail of November 29 (re-presented below). Our preferred option is: “include “Microbial Purity” in the “Specification” and test each batch prior to release.

Since the CMC documentation to support the inclusion of “Microbial Purity” in the “Specification” would not be available until January 2013 and given that Bayer has previously committed to submitting to the approved NDA 203085 an updated drug product specification/test procedure (with XRPD testing) by January 31, 2013 (see below - for additional background information), Bayer proposes to include “Microbial Purity” in the “Specification” in the planned submission to the approved NDA 203085.

Given that a change control in support of the planned update to the drug product specification/test procedure (with XRPD testing) has already been initiated, Bayer proposes amending this change control to accommodate the change to the microbial purity test frequency. Implementing the change in such a manner avoids the need to initiate a new separate change control solely to support the change to the microbial purity test frequency.

We hope this proposal is acceptable. Assuming FDA’s acceptance of our proposal, please advise what (if any) official amendment would be required to NDA 204369?

Background - Planned Update To Drug Product Specifications (XRPD)

During the regulatory review of NDA 203085, on August 15, 2012, a teleconference was held between Bayer and FDA to discuss the control of the (b) (4) Agreement was reached to revise the dissolution test acceptance criteria (b) (4) and to develop X-Ray Powder Diffraction (XRPD) testing methodology & specifications to test any batches that do not meet the revised dissolution acceptance criteria. Based on FDA’s guidance for post-approval changes to approved NDAs, these changes would be filed as a CBE supplement.”

FDA Response: Bayer’s agreement to include microbial purity test as a specification and to test each batch prior to its release is acceptable as a post-marketing commitment (PMC) for NDA 204369.

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

Submit a CMC CBE supplement that includes the addition of a microbial purity test as a drug product specification and test each batch prior to release and the addition of X-Ray Powder Diffraction (XRPD) testing methodology & specifications to test any batches that do not meet the dissolution acceptance criterion of NLT (b)(4) dissolved at 45 minutes.

You will submit this CBE supplement using the following schedule:

Submission of CMC CBE Supplement: MM/YY

We are requesting that you respond to our proposal and provide dates for the timeline listed above by 2PM ET on February 8, 2013

Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to NDA 203085. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled “Postmarketing Commitment Protocol,” “Postmarketing Commitment Final Report,” or “Postmarketing Commitment Correspondence.”

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
02/01/2013



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Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: January 24, 2013
From: Monica Hughes, M.S., Lead Regulatory Health Project Manager DOP2/OHOP
Subject: NDA 204369: Internal Labeling Meeting

Attendees: Monica Hughes, Patricia Keegan, Amir Shahlaee, Jennie Chang, Karen Dowdy, Anuja Patel, Carol Broadnax, Anthony Murgu, Liang Zhou

Discussion:

FDA sent Bayer a draft labeling proposal on December 21, 2012. Bayer provided a response to that proposal via email communication on January 10, 2013. This meeting was a continuation of our previous internal labeling meetings and we continued to review and discuss Bayer's proposal.

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/s/

MONICA L HUGHES
01/30/2013



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

Memorandum

Date: January 24, 2013

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

Subject: NDA 204369

Please find attached FDA's counter proposal to your revised package insert (PI) and patient package insert (PPI) submitted via email communication on January 10, 2013, in response to our December 21, 2012, proposed revisions.

Please provide a response to FDA's proposed changes by close of business on January 31, 2013. In addition to submitting your response to the NDA, please email me MS Word labeling in both clean and redlined versions (showing track changes).

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

Attachment: FDA proposed revisions to the package insert and patient package insert

29 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS)
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/s/

MONICA L HUGHES
01/24/2013



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

Memorandum

Date: January 17, 2013

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

Subject: NDA 204369: Internal Labeling Meeting

Attendees: Monica Hughes, Patricia Keegan, Amir Shahlaee, Jennie Chang, Karen Dowdy, Anuja Patel, Carol Broadnax, Anthony Murgo, Kun He, Janet Jiang

Discussion:

FDA sent Bayer a draft labeling proposal on December 21, 2012. Bayer provided a response to that proposal via email communication on January 10, 2013. Bayer's January 10, 2013, proposal was reviewed and discussed during this meeting.

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/s/

MONICA L HUGHES
01/18/2013



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

Memorandum

Date: January 15, 2013
From: Monica Hughes, M.S., Lead Regulatory Health Project Manager DOP2/OHOP
Subject: NDA 204369; Proposed PMC Language

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

Dear Mr. Wariabharaj:

Please see FDA's post-marking commitment proposals for the Stivarga (regorafenib) NDA application 204369.

Post Marketing Commitments (PMCs) Subject to the Reporting Requirements Under Section 506B

CLINICAL

Overall Survival Assessment:

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

Trial Completion Date: Month/Year
Final Report Submission: Month/Year

CLINICAL PHARMACOLOGY

Exposure-Response Analyses Assessment:

2. Submit an exposure-response analysis for regorafenib and its active metabolites M2 and M5 using relevant available data collected in patients with metastatic or unresectable gastrointestinal stromal tumor (GIST).

Final Report Submission: Month/Year

We are requesting that you respond to our proposal and provide dates for the timelines listed above by 4PM ET on January 22, 2013. To assist you in organizing the submission of final study reports, we refer you to the following resources:

- Guidance for Industry entitled, *Structure and Content of Clinical Reports*
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073113.pdf>
- Guidance for Industry, entitled, *Conducting a Clinical Safety Review of a New Product Application and Preparing a Report on the Review*
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072974.pdf>
- Guidance for Industry, entitled, *Reports on the Status of Postmarketing Study Commitments – Implementation of Section 130 of the Food and Drug Administration Modernization of 1997*
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM080569.pdf>.
- Guidance for Industry, entitled, *Postmarketing Studies and Clinical Trials — Implementation of Section 505(o) of the Food, Drug, and Cosmetic Act*
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM172001.pdf> >

Please note for any multi-study PMC/PMR, results from each study are to be submitted as an individual clinical study report (CSR) to the NDA or BLA as soon as possible after study completion. The cover letter for these individual CSRs should identify the submission as **PMC/PMR CORRESPONDENCE – PARTIAL RESPONSE** in bold, capital letters at the top of the letter and should identify the commitment being addressed by referring to the commitment wording and number, if any, used in the approval letter, as well as the date of the approval letter.

The PMC/PMR final study report (FSR) submission intended to fulfill the PMC/PMR should include submission of the last remaining CSR and all previously submitted individual CSRs. The FSR should also contain an integrated analysis and thoughtful discussion across all studies regarding how these data support the fulfillment of the PMC/PMR. The cover letter should state the contents of the submission.

Furthermore, if a PMC/PMR requests, as a milestone, the submission of individual study reports as interim components of a multi-study PMC/PMR, the cover letter should identify the submission as **PMC/PMR CORRESPONDENCE – INTERIM STUDY REPORT** in bold, capital letters at the top of the letter and should identify the commitment being addressed by referring to the commitment wording and number, if any, used in the final action letter, as well as the date of the final action letter.

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
01/15/2013



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

Memorandum

Date: January 14, 2013
From: Monica Hughes, M.S., Lead Regulatory Health Project Manager
DOP2/OHOP
Subject: NDA 204369: Advisory Committee Meeting

No advisory committee meeting was held for this NDA.



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

Memorandum

Date: January 2, 2013

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

Subject: NDA 204369

On December 21, 2012, FDA sent Bayer initial draft labeling comments for NDA 204369.

On December 21, 2012, via email communication, Bayer asked FDA to clarify the following “In Table 3 of the label FDA included data for Hypothyroidism, Bayer understands the incidence is based on subset of patients with normal TSH and no thyroid supplementation at baseline. Bayer would appreciate if FDA could provide their analyses that formed the basis for the numbers cited”

FDA Response: The number of patients that developed hypothyroidism was derived in the following manner:

1. Subset #1: All patients in the safety population with baseline TSH levels < ULN were identified in the ADLB data set: 106 on regorafenib and 56 on placebo
2. Subset #2: The patients in Subset #1 whose max TSH level rose above the ULN during the double blind treatment period were then identified using the ADLB data set: 25 on regorafenib and 7 on placebo arm
3. Subset #3: The patients who were on T4 supplementation at baseline were identified using the ADCM data set and removed from Subset #2 leaving 19 patients on regorafenib and 4 on placebo who had baseline TSH levels < ULN with a rising TSH (>ULN) during treatment and who were not on T4 supplementation at baseline. The following are the patient numbers for those meeting all the criteria:

260030004	Placebo
140060002	Placebo
140050005	Placebo
120020001	Placebo
220010005	Regorafenib
200030001	Regorafenib
680010002	Regorafenib
560040001	Regorafenib
260010006	Regorafenib
160050005	Regorafenib
220010006	Regorafenib
100010006	Regorafenib
180010010	Regorafenib
160010007	Regorafenib

560040003 Regorafenib
180010003 Regorafenib
220050002 Regorafenib
120020009 Regorafenib
440010001 Regorafenib
200050003 Regorafenib
200040001 Regorafenib
220050006 Regorafenib
200010001 Regorafenib

The final numbers provided in the label:

19/106=18% of patients without baseline elevated TSH on regorafenib

4/56=7% of patients without baseline elevated TSH on placebo

Please let me know if you have additional 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
01/02/2013



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

Memorandum

Date: December 20, 2012

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

Subject: NDA 204369: Internal Labeling Meeting

Attendees: Monica Hughes, Patricia Keegan, Amir Shahlaee, Jennie Chang, Suzanne Demko, Jason Bunting, Stacy Shord, Hong Zhao

Sections covered include:

Section 14: Clinical Studies

Review Highlights and Full Prescribing Information (for consistency)

Review outstanding internal questions

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/s/

MONICA L HUGHES
12/21/2012



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

Memorandum

Date: December 13, 2012

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

Subject: NDA 204369: Internal Labeling Meeting

Attendees: Monica Hughes, Patricia Keegan, Anthony Murgo, Shan Pradhan, Karen Dowdy, Amir Shahladee, Jennie Chang, Suzanne Demko, Jason Bunting

Sections covered include:

Section 6: Adverse Reactions (Continued)

Section 5: Warnings and Precautions (Continued)

Section 8: Use in Specific Populations (Continued)

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/s/

MONICA L HUGHES
12/21/2012



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

Memorandum

Date: December 10, 2012

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

Subject: NDA 204369: Internal Labeling Meeting

Attendees: Monica Hughes, Patricia Keegan, Anthony Murgo, Shan Pradhan, Karen Dowdy, Amir Shahlaee, Jennie Chang, Suzanne Demko, Jason Bunting

Sections covered include:

Section 6: Adverse Reactions (Continued)
Section 5: Warnings and Precautions (Continued)
Section 2: Dosage and Administration
Section 8: Use in Specific Populations
Section 10: Overdosage

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/s/

MONICA L HUGHES
12/21/2012



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

Memorandum

Date: December 6, 2012

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

Subject: NDA 204369: Internal Labeling Meeting

Attendees: Monica Hughes, Patricia Keegan, Anthony Murgo, Shan Pradhan, Stacy Shord, Hong Zhao, Karen Dowdy, Jason Bunting, Amir Shahlaee, Jennie Chang, Suzanne Demko, Elsbeth Chikhale, Janet Jiang, Kun He, Hong Zhao, Carrie Ceresa

Sections covered include:

Section 1: Indications and Usage

Section 14: Clinical Studies

Section 5: Warnings and Precautions

Section 6: Adverse Reactions

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/s/

MONICA L HUGHES
12/21/2012

NDA 204369: Stivarga (regorafenib) for GIST 11/29/12 Mid-Cycle Meeting Summary

Attendees: Monica Hughes, Jennie Chang, Janet Jiang, Anthony Murgo, Amir Shahlaee, Suzanne Demko, Patricia Keegan, Debasis Ghosh, Donghao Lu, Anuja Patel, Karen Dowdy, Hong Zhao, Stacy Shord, Christina Makela, Jason Bunting, Elsbeth Chikhale, Josephine Jee, Frances Fahnbulleh

1. Important Goal Dates

PDUFA Goal Date: February 28, 2013 (Type 9 NDA)

2. Discipline Specific Reviews of Application

- Presentations
 - a. Regulatory/Introduction (Monica Hughes)=less than 5 minutes
 - b. Clinical/Statistical (Jennie Chang: Efficacy & Amir Shahlaee: Safety, and Janet Jiang: statistical)=30 minutes
 - c. Clinical Pharmacology (Stacy Shord), No Presentation.
 - d. Non-Clinical (Anwar Goheer), No Presentation.
 - e. CMC (Josephine Jee and Robert Lu), No Presentation
 - f. Biopharmaceutics (Elsbeth Chikhale), No Presentation

DISCUSSION DURING MEETING: Presentations included: regulatory, clinical, and statistical. Discussion is noted below.

Presentation/Discussion to Include

- Applicable studies/information submitted
- Status of review of the data
- Discussion of findings so far
 - a. Are there issues requiring resolution? No issues were identified.
 - b. Are there any major labeling issues? No issues were identified.
 - c. Are there PMC and Risk Management Plan Issues? There are no plans or need for REMS. The clinical team will have one PMR for an update of the survival results. The clinical pharmacology team will have at least one PMC.
- Identify need for additional consults: none were required
- Information requests to be sent to sponsor: none were identified

DISCUSSION DURING MEETING: The review team members will continue with their reviews and address any outstanding questions during upcoming labeling meetings. No major issues requiring resolution were identified. The review team did discuss the potential need for a clinical pharmacology PMC and a clinical PMR to obtain the final study report and mature overall survival data for Study 14874.

NDA 204369: Stivarga (regorafenib) for GIST 11/29/12 Mid-Cycle Meeting Summary

3. Pending

OC/DMPQ Inspection: DP facility inspection conducted under NDA 203085 in July 2012.

DISCUSSION DURING MEETING: Updated information was received and discussed; there is a scheduled inspection for the API facility, to begin on December 3, 2012.

4. Scheduled Meetings

Team Meetings: December, January, and February.

Wrap-Up: January 28, 2012.

Labeling: Tentatively scheduled for December 6, 10, 13, 2012; and January 3, 2013.

DISCUSSION DURING MEETING: No discussion occurred regarding the upcoming meetings.

5. Goals Remaining

Milestone	6 month review
Send proposed labeling/PMR/PMC/REMS to applicant (Review Planner's Target date)	January 31, 2013
Week after the proposed labeling has been sent, discuss the Labeling/PRM/PMC with Applicant	February 7, 2013
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>	January 31, 2013 February 4, 2013 February 7, 2013 * not required February 28, 2013
Compile and circulate Action Letter and Action Package	February 7, 2013
FINAL Action Letter Due	February 28, 2013

DISCUSSION DURING MEETING: No discussion occurred regarding the timelines noted above.

**NDA 204369: Stivarga (regorafenib) for GIST
11/29/12 Mid-Cycle Meeting Summary**

6. Consults

OPDP	Carole Broadnax- professional reviewer Karen Munoz- consumer reviewer
OSE	Sue Kang-OSE RPM Jason Bunting-Risk Management Plan
Maternal Health	Carrie Ceresa-Reviewer
Pediatric Page/PeRC	**Orphan Exclusivity, no PeRC Meeting
Patient Labeling Team	Karen Dowdy- Reviewer
SGE's or Patient Representatives	Dr. Ephraim Casper

DISCUSSION DURING MEETING: No discussion occurred regarding the consults noted above.

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/s/

MONICA L HUGHES
12/21/2012



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

Memorandum

Date: December 21, 2012
From: Monica Hughes, M.S., Lead Regulatory Health Project Manager DOP2/OHOP
Subject: NDA 204369

Please find attached FDA's counter proposal to your revised package insert (PI) submitted on November 9, 2012, as part of the 90 day safety update.

Please provide a response to FDA's proposed changes by 10:00 AM on January 9, 2013. In addition to submitting your response to the NDA, please email me MS Word labeling in both clean and redlined versions (showing track changes).

Please note these are our preliminary comments, this labeling is currently being reviewed by our counterparts in the Office of Prescription Drug Promotion (OPDP) and the Patient Labeling Team (PLT) and additional comments will follow.

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

Attachment: FDA proposed revisions to the package insert

27 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS)
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/s/

MONICA L HUGHES
12/21/2012

NDA 204369: Meeting Summary for October 25, 2012, Team Meeting

Product: Stivarga (regorafenib)
Submission Date: August 30, 2012 (final rolling portion received)
Received Date: August 30, 2012
PDUFA Date: February 28, 2013

Sponsor: Bayer HealthCare Pharmaceuticals, Inc.

Proposed Indication: GIST

Current Review Team for NDA 204369:

Patricia Keegan, M.D., Director DOP2
Monica Hughes, M.S., Lead Regulatory Health Project Manager
Karen Jones (CPMS)
Jennie Chang, Pharm.D., Senior Clinical Analyst (Efficacy Review)
Amir Shahlaee, M.D., Medical Officer (Safety Review)
Suzanne Demko, Clinical TL
Anthony Murgo, M.D., Associate Director OHOP (CDTL)
Xiaoping (Janet) Jiang, Ph.D., Statistics
Kun He, Ph.D., Statistics (TL)
Stacy Shord, Ph.D., Clinical Pharmacology
Hong Zhao, Ph.D., Clinical Pharmacology (TL)
M.A. Goheer, Ph.D., Non-Clinical
Whitney Helms, Ph.D., Non-Clinical (TL)
Josephine Jee, Ph.D., Product
Donghao (Robert) Lu, Product
Liang Zhou, Ph.D., Product (TL)
Nallaperum Chidambaram, Ph.D., Product (Acting TL)
Jewell Martin, Product (ONDQA RPM)
Angelica Dorantes, Ph.D., Biopharmaceutics (TL)
Elsbeth Chikhale, Ph.D., Biopharmaceutics Reviewer
Sue Kang, OSE RPM
Jason Bunting, OSE/DRISK, Risk Management Reviewer
Cynthia LaCivita, OSE/DRISK, TL
Carol Broadnax, OPDP Professional Reviewer
Karen Munoz, OPDP, Consumer Reviewer
Karen Dowdy, PLT
Barbera Fuller, PLT (TL)
Carrie Ceresa, PMHT
Melissa Tassinari, PMHT (TL)

FDA Attendees: Monica Hughes, Stacy Shord, Patricia Keegan, Whitney Helms, Anthony Murgo, Anwar Goheer, Josephine Jee, Robert Lu, Karen Dowdy, Hong Zhao, Amir Shahlaee, Jennie Chang, Suzanne Demko, Kun He, Elsbeth Chikhale, Frances Famabulleh, Janet Jiang.

Meeting Purpose: This monthly team meeting was used to discuss review discipline specific updates and to prepare for the upcoming mid-cycle meeting.

1. Review Discipline Updates:

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

DISCUSSION DURING MEETING: No updates regarding the efficacy or safety review were discussed during this meeting. Preparations for the mid-cycle presentation are underway.

- b. Statistics

DISCUSSION DURING MEETING: The reviewer noted that we are awaiting a response to a recent information request. Preparations for the mid-cycle presentation are underway.

- c. Clinical Pharmacology

DISCUSSION DURING MEETING: The reviewer noted that some new PK information from a P2 trial was included; however, they do not anticipate updating the labeling unless there is a difference detected from the previous findings.

- d. Nonclinical

DISCUSSION DURING MEETING: The reviewer noted that no new information was submitted with this application that was not provided with the CRC NDA.

- e. CMC

DISCUSSION DURING MEETING: The reviewers noted that no new information was submitted with this application. The EES is pending. (b) (4)

- f. Biopharmaceutics

DISCUSSION DURING MEETING: The reviewers noted that no new information was submitted with this application that was not provided with the CRC NDA.

- g. Regulatory

DISCUSSION DURING MEETING: The RPM review is underway, no comments at this time. Preparations for the mid-cycle presentation are underway.

2. Preparation for upcoming Mid-Cycle Meeting in November

- a. Presentations (clarify who will/will not be presenting at the mid-cycle meeting):
 - Regulatory
 - Clinical
 - Statistical
 - Clinical Pharmacology
 - Non-Clinical

- CMC & Biopharmaceutics

DISCUSSION DURING MEETING: The RPM will present a brief overview of the regulatory history and there will be one combined presentation from the clinical and statistical reviewers. There will be no formal presentations from clinical pharmacology, non-clinical, or CMC and biopharmaceutics.

- b. Discuss OHOP mid-cycle expectations

DISCUSSION DURING MEETING: The review team reviewed the OHOP expectations for information to be presented during the mid-cycle meeting.

- c. Discuss deadline for final slides to be sent to RPM and CDTL for review (Recommendation: at least one week before the mid-cycle meeting).

DISCUSSION DURING MEETING: The team agreed to send the slides to the RPM and CDTL one week before the meeting.

Milestone Reminders:

Milestone	6 month review
Acknowledgment Letter	September 13, 2012
Filing Action Letter	October 29, 2012
Deficiencies Identified Letter (74 Day Letter)	November 12, 2012
Send proposed labeling/PMR/PMC/REMS to applicant (Review Planner's Target date)	January 31, 2013
Week after the proposed labeling has been sent, discuss the Labeling/PRM/PMC with Applicant	February 7, 2013
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>	January 31, 2013 February 4, 2013 February 7, 2013 * not required February 28, 2013
Compile and circulate Action Letter and Action Package	February 7, 2013
FINAL Action Letter Due	February 28, 2013

DISCUSSION DURING MEETING: No discussion during the meeting occurred regarding the timelines noted above.

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/s/

MONICA L HUGHES
12/14/2012



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

Memorandum

Date: November 2, 2012
From: Monica Hughes, M.S., Lead Regulatory Health Project Manager DOP2/OHOP
Subject: NDA 204369: Information Request

We refer to NDA 204369 for Regorafenib Tablets for treatment of GIST. We specifically reference section 2.1.5.5.2 of the Summary of Clinical Safety titled "Severe cutaneous adverse reactions". In this section you identified 7 patients exposed to regorafenib who developed severe cutaneous reactions including erythema multiforme, exfoliative dermatitis and Stevens-Johnson Syndrome. The cutoff date for this analysis was March, 31 2012.

In addition we refer to the following safety reports of severe cutaneous reaction submitted to IND 113896:

- 1) 2012-092453: Fever and Lyell Syndrome: Your Serial Number/eCTD Sequence # 0033 and 0027.
- 2) 2012-104470: Toxidemia: Your Serial Number/eCTD Sequence # 0032.
- 3) 2012-094298: Toxic Epidermal Necrolysis and Hepatitis: Your Serial Number/eCTD Sequence #0027.

Please submit an updated analysis of all "severe cutaneous adverse reactions" that have been reported in patients receiving regorafenib to NDA 204369 as part of your 90 day safety update.

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
11/02/2012



NDA 204369

FILING COMMUNICATION

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

Dear Mr. Wariabharaj:

Please refer to your rolling New Drug Application (NDA), for which the first portion was submitted and received on May 31, 2012, and the final portion dated August 30, 2012, was received on August 30, 2012, as submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Stivarga (regorafenib) tablets, 40 mg.

We also refer to your amendments dated July 3, 2012; July 23, 2012; August 13, 2012; September 6, 2012; September 11, 2012; September 14, 2012; September 25, 2012; September 27, 2012; September 28, 2012; October 3, 2012; October 5, 2012; October 9, 2012; October 10, 2012; and October 24, 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 February 28, 2013.

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, mid-cycle, 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 January 31, 2013.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

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 (as applicable). 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 (as applicable), 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.

Because the drug product for this indication has orphan drug designation, you are exempt from this requirement.

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

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/s/

PATRICIA KEEGAN
10/29/2012

MEMORANDUM OF INTERNAL MEETING MINUTES

MEETING DATE: September 6, 2012
TIME: 10:30 AM-11:00 AM
LOCATION: WO 22, Room 2157
APPLICATION: NDA 204369
DRUG NAME: Stivarga (regorafenib)

FDA ATTENDEES:

Joseph Gootenberg – Deputy Division Director
Amir Shahlaee - Clinical Reviewer
Jennie Chang-Clinical Reviewer
Suzanne Demko- Clinical TL
Anthony Murgo-Associate Director OHOP, CDTL
Monica Hughes- Lead Regulatory Health Project Manager

BACKGROUND: On August 30, 2012, the final portion of the rolling Stivarga NDA 204369 for GIST was received. This is a Type 9 NDA that will be converted to an efficacy supplement to the Stivarga NDA 203085 for CRC. The purpose of this internal meeting is to discuss the following review issues: (1) Do we need OSI clinical site inspections; and (2) do we agree with Bayer's content proposal for the 90 day safety update.

DISCUSSION POINTS:

- (1) Do we need OSI clinical site inspections for this NDA?

DISCUSSION DURING MEETING: The issue of whether an OSI inspection should be conducted for the regorafenib GIST study was discussed at today's meeting. One reason for conducting the study site inspections is that one study was submitted supportive of the GIST indication; however, the number of patients at each study site was <10 and the efficacy results were robust. One hundred ninety-nine patients were enrolled into 2:1 randomization, regorafenib:placebo.

Sites for consideration, based on our discussion with Jean Mulinde in OSI, using the Site Selection Tool are all ex-U.S. One U.S. site (M. von Mehren) was considered, but only 2/7 patients were treated with regorafenib.

<u>Site number</u>	<u>Investigator</u>	<u>Location</u>	<u>Number of pts.</u>
10008*	Bauer	Germany	n=5 (4 tx, 1 placebo)
10007*	Bauer	Germany	n=4 (3 tx, 1 placebo)
18001	Rutkowski	Poland	n=10 (8 tx, 2 placebo)
30001	Gelderblom	Holland	n=9 (7 tx, 2 placebo)

**These two sites would count as a two for one site visit, as Bauer took over the second site at some point because the initial investigator left.*

The team agreed that following review of the information discussed, that clinical site inspections are not needed for this application.

- (2) Do we agree with Bayer's content proposal for the 90 day safety update?

DISCUSSION DURING MEETING: The review team discussed Bayer's proposal noted below:

The 90 day update to the Regorafenib GIST NDA 204,369 will cover the period (April 1 2012 and July 31 2012) and the submission will include:

1. Updated CRFs and narratives for AEs leading to treatment withdrawal and AEs of special interest:

The proposed safety update will only include tables of AEs leading to treatment discontinuation. It won't be possible to provide standard Clinical Study Report (CSR) narratives for all these events in these ongoing studies. Regarding AEs of special interest, all new serious AEs (SAEs) related to the following topics hepatic disorders, cardiac failure, interstitial lung disease, severe cutaneous adverse reactions, hemorrhage, acute renal failure, wound healing complications and GI perforation, will be assessed and presented. For the SAEs of special interest CIOMS-I case narratives in lieu of standard CSR narratives will be provided. CRFs would be available upon request within 48 hours.

2. Updated narratives and CRFs for deaths and SAEs:

The proposed safety update will include SAEs (including SAEs of special interest) and deaths with CIOMS-II line listings and CIOMS-I case narratives in lieu of standard narratives. Updated CRFs would be available upon request. CRFs would be available upon request within 48 hours.

3. Updated safety data sets:

Consistent with the approach taken for the safety update to the Regorafenib CRC NDA 203,085, updated safety data sets are not planned for inclusion in the safety update to the Regorafenib GIST NDA 204,369. The GIST safety update focuses on an assessment of safety data that may potentially impact on the overall benefit-risk assessment or safety information in the proposed labeling. This includes SAEs (including SAEs of special interest), deaths, and adverse events leading to permanent discontinuation of study drug. The scope and content of the safety update is consistent with discussions between Bayer and FDA via teleconference on April 3, 2012 regarding the CRC NDA safety update. In those discussions, FDA noted they only wanted "big picture items" in the safety update and that the

information was only being reviewed to confirm the safety profile in the original application. A similar approach has been adopted for the GIST NDA safety update.

The clinical team discussed the need for datasets to be included with the 90 day safety update, noting that this proposal does not include datasets. The team noted that the Stivarga CRC NDA currently under review did not require the submission of datasets to be included with 90 day safety update. Following a brief internal discussion, the team agreed to accept Bayer's content proposal noted above. We noted that the update should clearly discuss all new events and how these events could potentially alter the safety profile of this agent. In addition, updated data sets and CRFs should be available within 48 hours of request if the need arises.

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/s/

MONICA L HUGHES
10/24/2012

**1st Planning Meeting Summary
September 4, 2012**

NDA: 204369

Product: Stivarga (regorafenib)
Submission Date: August 30, 2012
Received Date: August 30, 2012, final portion of rolling submission received
Sponsor: Bayer Healthcare Pharmaceuticals

Proposed Indication: GIST

Current Review Team for NDA 204369:

Patricia Keegan, M.D., Director DOP2
Monica Hughes, M.S., Lead Regulatory Health Project Manager
Karen Jones (CPMS)
Jennie Chang, Pharm.D., Senior Clinical Analyst (Efficacy Review)
Amir Shahlaee, M.D., Medical Officer (Safety Review)
Anthony Murgo, M.D., Associate Director OHOP (Acting TL and CDTL)
Xiaoping (Janet) Jiang, Ph.D., Statistics
Kun He, Ph.D., Statistics (TL)
Stacy Shord, Ph.D., Clinical Pharmacology
Hong Zhao, Ph.D, Clinical Pharmacology (TL)
M.A. Goheer, Ph.D., Non-Clinical
Whitney Helms, Ph.D., Non-Clinical (TL)
Josephine Jee, Ph.D., Product
Liang Zhou, Ph.D., Product (TL)
Nallaperum Chidambaram, Ph.D., Product (Acting TL)
Jewell Martin, Product (ONDQA RPM)
Angelica Dorantes, Ph.D., Biopharmaceutics (TL)
Elsbeth Chikhale, Ph.D., Biopharmaceutics Reviewer
Sue Kang, OSE RPM

FDA Attendees: Monica Hughes, Hong Zhao, Stacy Shord, Patricia Keegan, Whitney Helms, Anthony Murgo, Suzanne Demko, Anwar Goheer, Josephine Jee, N. Chidambaram, Kun He, Liang Zhou, Amir Shahlaee, Jennie Chang, Elsbeth Chikhale, Karen Jones, Jeff Summers, Joe Gootenberg, Jewell Martin, Janet Jiang, Lauren Iacono-Conner

Draft Agenda and Discussion Items:

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

1. **Review Status:**

- Fast Track Granted April 17, 2011: Priority Review requested
- Categorical Exclusion requested
- Orphan Designation Granted: January 12, 2011
- The clinical development of regorafenib for GIST has been conducted under IND 113896 (earlier information under IND 75642).

DISCUSSION DURING MEETING: Priority review will be granted. RPM will send the pediatric page to the PeRC for tracking purposes only as this is an orphan designation.

2. **Dates Milestone Letters Must Issue:**

Milestone	6 month review
Acknowledgment Letter	September 13, 2012
Filing Action Letter •Do we have any filing issues that we should discuss today? If so, 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.	October 29, 2012
Deficiencies Identified Letter (74 Day Letter)	November 12, 2012
Send proposed labeling/PMR/PMC/REMS to applicant (Review Planner’s Target date)	January 31, 2013
Week after the proposed labeling has been sent, discuss the Labeling/PRM/PMC with Applicant	February 7, 2013
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>	January 31, 2013 February 4, 2013 February 7, 2013 * not required February 28, 2013
Compile and circulate Action Letter and Action Package	February 7, 2013
FINAL Action Letter Due	February 28, 2013

DISCUSSION DURING MEETING: The review team discussed the key deadlines for this priority review. This is a type 9 NDA that will be converted to a supplement under NDA 203085 at its approval. The review team decided that it will be signed by the division director and that no CDTL review is required.

3. Potential Consults/Collaborative Reviewers Needed:

OPDP	- professional reviewer - consumer reviewer - RPM
OSE	Sue Kang-OSE RPM *DMEPA/CMC/DDMAC to review carton/container, and patient labeling *Risk Management Plan
Maternal Health	-Reviewer
Facility/OMPQ	
QT-IRT	**To be assigned when final report comes in with all data in the PMR submission in November 2012 from NDA 203085.
OSI	Lauren Iacono-Conners assigned, need to select sites if inspections will be conducted.
Pediatric Page/PeRC	**does not apply, orphan designation granted
Patient Labeling Team	*Patient Information Included
SGE's or Patient Representatives	

Are there any additional consults we need?

DISCUSSION DURING MEETING: The review team discussed and agreed to begin the screening process for an SGE to be assigned to this application. The clinical team has met with OSI and an additional internal meeting will be set up to discuss the need for clinical site inspections.

4. Upcoming/TBD Internal Team Meetings:

- **Filing Meeting:** Scheduled for October 9, 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: No discussion occurred; the team noted the date of the scheduled filing meeting and the location of the current filing review memos on the 21st Century Review website.

- **Mid-Cycle Meeting:** TBD.

DISCUSSION DURING MEETING: No discussion occurred during the meeting, the mid-cycle meeting will be scheduled.

- **Labeling Meetings (suggested section groupings):**

- **When should we begin labeling meetings?**
- **How many labeling meetings do we need?**

DISCUSSION DURING MEETING: The team agreed to begin labeling meetings in late November-early December and to schedule 5 initial meetings.

- **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 team agreed to schedule monthly team meetings and to cancel ones not needed. The team agreed not to schedule separate PMC/PMR meetings at this time.

- **Wrap- Up Meeting:** TBD.

DISCUSSION DURING MEETING: No discussion occurred during the meeting, the wrap-up meeting will be scheduled.

5. **Applicant Orientation Presentation:** Scheduled for September 17, 2012.

DISCUSSION DURING MEETING: No discussion occurred during the meeting.

6. **ODAC Needed/Not Needed:**

Target AC date: (month 4-5 for 6 month review)

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

- ***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 an ODAC meeting is needed, we will need to schedule a planning meeting and practice sessions.

DISCUSSION DURING MEETING: At this point, the review team does not believe that an ODAC meeting will be required based on:

- **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**

A final decision will be made at the time of filing.

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/statistical reviewers will meet to discuss potential OSI clinical site reviewers to review potential clinical sites for inspection. Following that meeting, the clinical staff will discuss the need for clinical site inspections with OHOP management in meeting to be scheduled. At this point, it does not appear that preclinical site audits will be necessary.

- b. CMC/Jewell Martin will assist with the following consults:
 - **Establishment (EES)/Coordinate Inspections (if needed)**
 - **Environmental Analysis: Request for Categorical Exclusion**
 - **Labeling (if needed)**

DISCUSSION DURING MEETING: The CMC information is the same as that being reviewed under NDA 203085. Manufacturing site inspections may not be required as they were just conducted in July 2012 under NDA 203085.

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/s/

MONICA L HUGHES
10/24/2012



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

Memorandum

Date: October 23, 2012
From: Monica Hughes, M.S., Lead Regulatory Health Project Manager DOP2/OHOP
Subject: NDA 204369: Information Request

We have the following requests for information:

CLINICAL:

1. The review team has identified two patients (#100040008 and #540020001), in addition to the 45 patients from the safety population described in the GRID study CSR, who had a disposition event of "death". Please confirm the disposition of these patients, and provide further information including CRFs and a brief narrative regarding the cause of death for each of these patients.

STATISTICAL:

2. Please provide the results of sensitivity analyses which assess the impact of the unscheduled tumor assessments on PFS results, including a "worse-case" scenario by potentially moving the PFS dates to an earlier date for the Regorafenib arm but potentially moving to a later date for the placebo arm. Please conduct the sensitivity analyses results based on the datasets with 122 PFS events (independent review) and 144 PFS events (independent review), respectively. Provide the datasets and SAS programs that can be used to replicate your analyses results.
3. Please provide PFS datasets (with 122 and 144 independent review PFS events) that are one record per patient and include the dates of last evaluable tumor assessment and the evaluable tumor assessment prior the last evaluable tumor assessment.

4. Please provide the summary table as follows and provide the datasets and SAS programs that can be used to replicate the results in the tables.

Table 1: Summary of Time to Tumor Assessment from Randomization

Time from randomization to	# (%)		Median		25 th percentile		75 th percentile	
	Placebo + BSC	Regorafenib + BSC	Placebo + BSC	Regorafenib + BSC	Placebo + BSC	Regorafenib + BSC	Placebo + BSC	Regorafenib + BSC
1 st Assessment								
2 nd Assessment								
3 rd Assessment								
4 th Assessment								
...								

Table 2: Summary of Time Between Last Tumor Assessment Visit and PFS Date

	Placebo + BSC (n=66)	Regorafenib + BSC (n=133)
Median		
25th percentile		
75th percentile		

Please submit your responses to your NDA to the comments above by 4:00 PM on October 26, 2012.

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
10/23/2012



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

Memorandum

Date: October 5, 2012
From: Monica Hughes, M.S., Lead Regulatory Health Project Manager DOP2/OHOP
Subject: NDA 204369: Information Request

We have the following request for information:

1. Your submitted ae.xpt data set doesn't include MedDRA HLT and HLGT terms for each reported AE. Please resubmit this file and include MedDRA HLT and HLGT for each reported AE.

Please submit your responses to the comments above by October 9, 2012.

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
10/05/2012



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

Memorandum

Date: October 2, 2012
From: Monica Hughes, M.S., Lead Regulatory Health Project Manager DOP2/OHOP
Subject: NDA 204369: Information Request

We have the following requests for information for NDA 204369:

1. Please explain how AENDT was used to assess PFS in the ADEVTTE dataset. In the TR dataset, the dates of disease progression (PD) under TRDTC differed between independent reviewer 1 and independent reviewer 2 for some patients; however, no adjudicator was used to resolve the discrepancies, except in patient 160010009. When patients were cross-referenced in the ADEVTTE dataset, the earlier Overall (Timepoint) Response RECIST date was selected as the AENDT in the ADEVTTE dataset, but a later AENDT, based on the Overall (Timepoint) Response RECIST was selected in others. An example of this is patient 100040007.

According to the IRRC, p. 52:

6.6.8 The response assessments determined by Reader 1 and Reader 2 will be compared to establish whether an adjudication is required, based on the adjudication variable, the Date of Progression. If the Dates of Progression, as listed, are identical, no adjudication will be required between reads number 1 and number 2, and the results from the first radiology read will be used as the accepted read. If the Dates of Progression are discordant, a third radiologist will perform an adjudication of the radiology results, as described in Section 6.7, Adjudication Paradigm.

2. Please submit the following CRFs:

140060001

200040001

200080002

200080003

220050003

220050006

260030003

440020001

240030001

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
10/02/2012



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

Memorandum

Date: September 26, 2012
From: Monica Hughes, M.S., Lead Regulatory Health Project Manager DOP2/OHOP
Subject: NDA 204369: Information Request

We have the following requests for information for NDA 204369:

- (1) FDA.ADEVTTE dataset provides information used for censoring determining under variable name AENDTSPC; however, an explanation as to why these dates were selected is needed. Please indicate which censoring rule was applied the 55 patients, per the SAP Version 1.1, dated March 22, 2012. If patients were censored due to safety, indicate the adverse event.
- (2) In FDA.ADEVTTE dataset, one of the format decodes is "12"; however the format decode is not provided in the "Define" file. Please clarify.
- (3) Please link the visit date to visit name in FDA.ADEVTUMD dataset.
- (4) Please provide the independent radiologic review charter.

We are requesting that you submit the independent radiologic review charter by the end of the week and the remaining information by Thursday, October 4, 2012.

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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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 204369: Information Request

Please submit the CRFs for the following patients:

100030001
100030002
100060002
100070003
100070004
120020004
140050002
140150002
160020002
160020003
160050005
160050006
180010003
180010004
180010010
180010011
200010001
200030001
200040001
200080002
200080003
220010002
220010006
220030001
220050003
220050006
240030001
260010007
260030003
300010001
300010005
300010006
300010007
300010009
440020001
560040003
590010001

We are requesting that you submit these CRFs to NDA 204369 by 4:00 PM ET on September 25, 2012.

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
09/19/2012



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

Memorandum

DATE: September 14, 2012

FROM: Patricia Keegan, M.D.
Director
Division of Oncology Products 2
Office of Hematology and Oncology Products
Office of New Drugs
Center for Drug Evaluation and Research

SUBJECT: Designation of NDA application review status
Sponsor: Bayer Healthcare Pharmaceuticals, Inc.
Product: Stivarga (regorafenib)
Proposed Indication:

(b) (4)

TO: NDA 204369

The review status of this file submitted as an original NDA is designated to be:

Standard (10 Months)

Priority (6 Months)

{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

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/s/

MONICA L HUGHES
09/14/2012

PATRICIA KEEGAN
09/14/2012



NDA 204369

NDA ACKNOWLEDGMENT

Bayer HealthCare Pharmaceuticals, Inc.
Attention: Philip Johnson, MBA
Deputy Director, Global Regulatory Affairs
P.O. Box 1000
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: Stivarga (regorafenib) tablets, 40 mg

Date of Application: August 30, 2012

Date of Receipt: August 30, 2012

Our Reference Number: NDA 204369

Proposed Use: For the treatment of gastrointestinal stromal tumors (GIST) in patients who have been previously treated with two tyrosine kinase inhibitors.

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 October 29, 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
09/07/2012



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

Memorandum

Date: September 5, 2012
From: Monica Hughes, M.S., Lead Regulatory Health Project Manager DOP2/OHOP
Subject: NDA 204369

We refer to your submission of August 30, 2012, to NDA 204369. Please submit the SAS programs that can be used to replicate the major efficacy results in the submitted Clinical Study Report. Along with the SAS programs, please provide names of the variables and datasets used in the SAS programs.

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
09/05/2012



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

Memorandum

Date: September 5, 2012
From: Monica Hughes, M.S., Lead Regulatory Health Project Manager DOP2/OHOP
Subject: NDA 20436

We refer to your submission of August 30, 2012, to NDA 204369. The Adverse Events Dataset (AE) and Analysis Datasets for Adverse Events (ADAE) for study 14874 currently include all adverse events for the “double blind” and the “open-label” portions of the study. Please submit AE and ADAE files that include only the adverse events for the “double blind” portion of the study.

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
09/05/2012

Information request for NDA 204,369From: Sickafuse, Sharon
Sent: Tuesday, August 07, 2012 1:08 PM
To: 'philip.johnson@bayer.com'
Subject: NDA 204369 IR

Good Afternoon,

I'm covering for Monica Hughes for your NDA while she's on leave. The clinical team has the following information request regarding your July 23, 2012, submission of information requested by the Office of Scientific Investigation:

Please clarify whether Dr. Sebastian Bauer is the clinical investigator (CI) for site # 10007. There appears to be a discrepancy between the clinsite.xpt file and the file containing the contact information for the clinical investigators, which list Dr. Dr. Jochen Schutte as the CI for this site.

Thanks

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/s/

SHARON K SICKAFUSE
08/07/2012



NDA 204369

NDA PRESUBMISSION ACKNOWLEDGEMENT

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 the first section of your New Drug Application (NDA) under the program for step-wise submission of sections of an NDA (section 506 of the Federal Food, Drug, and Cosmetic Act) for the following:

Name of Drug Product: regorafenib tablet, 40 mg

Date of Submission: May 31, 2012

Date of Receipt: May 31, 2012

Our Reference Number: NDA 204369

We will review this presubmission as resources permit. Presubmissions are not subject to a review clock or to a filing decision by FDA until the application is complete.

Please cite the NDA number listed above at the top of the first page of any communications concerning 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

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

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

/s/

KAREN D JONES
06/18/2012



IND 113896

MEETING MINUTES

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 Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for “regorafenib (BAY 73-4506, DAST).”

We also refer to the teleconference between representatives of your firm and the FDA on May 3, 2012. The purpose of this pre-NDA meeting was to discuss the NDA filing for regorafenib for gastrointestinal stromal tumors (GIST).

A copy of the official minutes of the teleconference is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-9225.

Sincerely,

{See appended electronic signature page}

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

ENCLOSURE: Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: pre-NDA
Meeting Date and Time: Teleconference, May 3, 2012: 12:00 PM-1:00 PM
Meeting Location: WO, 21 Room 3201
Application Number: IND 113896
Product Name: Regorafenib
Indication: The treatment of patients with (b) (4)
(b) (4)

Sponsor/Applicant Name: Bayer Healthcare Pharmaceuticals, Inc. (Bayer)
Meeting Chair: Patricia Keegan, M.D.
Meeting Recorder: Monica Hughes, M.S.

FDA ATTENDEES

Patricia Keegan, M.D., Director, DOP2/OHOP
Joseph Gootenberg, M.D., Deputy Director/Clinical Team Leader, DOP2/OHOP
Anthony Murgo, M.D., Associate Director for Regulatory Science, OHOP
Katherine Thorton, M.D., Clinical Reviewer, DOP2/OHOP
Amir Shahlaee, M.D., Clinical Reviewer, DOP2/OHOP
Jenny Chang, Pharm.D., Clinical Analyst, DOP2/OHOP
Monica Hughes, M.S., Lead Regulatory Health Project Manager, DOP2/OHOP
Jian Wang, Ph.D, Clinical Pharmacology Reviewer, DCP5/OCP/OTS
Hong Zhao, Ph.D., Clinical Pharmacology Team Leader, DCP5/OCP/OTS
Dubravka Kufirin, Ph.D., Pharmacology/Toxicology Reviewer, DHOT/OHOP
Weishi Yuan, Ph.D., Statistical Reviewer, DBV/OB/OTS
Kun He, Ph.D., Statistical Team Leader, DBV/OB/OTS

SPONSOR ATTENDEES

Regulatory Affairs: Philip Johnson, Meni Melek, Stephanie Mondabon
Clinical Pharmacology: Konstanze Diefenbach
Clinical Development: Iris Kuss, Dirk Laurent
Statistics: Minghua Shan, Christian Kappeler, Sabine Fiala-Buskies
Pharmacovigilance: Christian Wuchter-Czerwony
Project Management: Rita Darkow

1.0 BACKGROUND

Bayer describes regorafenib as 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.

CMC

Bayer describes the regorafenib 40 mg film-coated tablet as an immediate-release (IR) dosage form with rapid dissolution under in vitro test conditions. The tablets are oval-shaped (modified oblong), light pink coated tablets with a length of 16 mm and a width of 7 mm. The regorafenib tablets are produced by (b) (4)

(b) (4)

The tablets contain 40 mg of regorafenib (active substance), 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.

CLINICAL

In the April 4, 2012, meeting briefing document Bayer describes that the clinical development program for regorafenib, for use as single agent, was initiated in July 2005 in mCRC (February 2007 in the US) with a Phase 1 dose escalation study in patients with advanced solid tumors (11650) and has progressed to Phase 3 trials in patients with advanced cancers including CRC and GIST.

Bayer also describes a non-randomized, open label, multi-center Phase 2 study (14935), in which the efficacy and safety of regorafenib was evaluated in subjects with metastatic and/or unresectable GIST following failure of at least imatinib and sunitinib. Patients received regorafenib 160 mg orally once daily for 21 consecutive days, followed by 7 days off study drug, for each 28 day cycle (i.e., 3 weeks on study drug, 1 week off). The primary endpoint was clinical benefit rate (CBR) defined as objective responses [complete response (CR) +partial response (PR)] as well as stable disease (SD) \geq 16 weeks. Serial tumor biopsies were obtained in consenting patients whenever possible. From February 2010 - December 2010, 34 patients were enrolled at four US centers. As of July 28, 2011, 33 patients received at least 2 cycles of regorafenib (range 2 -17). CBR was 79% (95% CI: 61%-91%). Four patients achieved PR and 22 exhibited SD \geq 16 weeks. Median progression free survival (PFS) was 10.0 months.

Bayer describes the Phase 3 clinical study (14784 "GRID") in which patients with GIST, received regorafenib administered orally at 160 mg (4 x 40 mg tablets) once daily in repeating cycles for 21 consecutive days followed by a 7 days break. This 160 mg dose had also been used in several Phase 1 trials and Phase 2 trials, including a Phase 2 investigator sponsored study of GIST patients.

At a meeting with the Division of Oncology Products 1 on August 25, 2010, Bayer agreed to the division's recommendation to power the Phase 3 Study 14874 for overall survival (OS), although the primary endpoint remained progression-free survival (PFS). Bayer plans to submit the NDA with final PFS data and interim OS. Additionally, it was agreed that central radiology review for PFS would be blinded, and acknowledged that a 6-week improvement in PFS may not be clinically meaningful. Following this meeting, Bayer modified the design of study 14874 in accordance with the discussion at the meeting, powering the study for overall survival (80%

power to detect a 66.7% increase) while keeping PFS as the primary endpoint, adding an interim analysis for OS, and using an O'Brien-Fleming type alpha spend to control the overall type I error rate. The original protocol was submitted to IND 75,642 on October 13, 2010. The protocol was subsequently amended on February 18, 2011, August 15, 2011, and October 12, 2011.

Bayer's Phase 3 clinical protocol 14874 ("GRID" study) is a randomized, double-blind, placebo-controlled study of regorafenib plus best supportive care versus placebo plus best supportive care for subjects with metastatic and/or unresectable gastrointestinal stromal tumor whose disease has progressed despite prior treatment with at least imatinib and sunitinib. The protocol states that at least 50% of the patients will have had only imatinib and sunitinib as prior treatment for GIST, making regorafenib the third-line treatment for these patients. Other patients will have received additional prior therapies, making regorafenib 4th line therapy or beyond. Patients received regorafenib administered orally at 160 mg (4 x 40 mg tablets) once daily in repeating cycles for 21 consecutive days followed by a 7 days break.

The primary study endpoint was progression-free survival by independent review using modified RECIST 1.1. Secondary endpoints were overall survival, time to progression, disease control rate, response rate, safety and duration of response

There were 199 patients from 17 countries randomized to treatment versus placebo. One hundred and thirty-three patients were randomized to regorafenib and 66 patients to placebo. North America comprised 18% of the study population with 13% from the US and 52% from Canada. Fifty-three percent of patients were from western Europe, 5% from Eastern Europe and 24% from Asia. The demographic groups were well-balanced across both treatment arms.

The sponsor has submitted preliminary data concluding there is a statistically significant improvement in PFS of 4.8 months vs. 0.9 months (HR 0.268, $p < 0.00001$) with a trend towards overall survival improvement (HR 0.77, $p = 0.20$).

The Statistical Analysis Plan (SAP) for this study was submitted to IND 113,896 on February 7, 2012, and comments were received from FDA on March 8, 2012. Bayer's response to comment #1 was e-mailed to FDA on March 13, 2012, and additional feedback was received from FDA on March 20, 2012. Bayer subsequently revised the Statistical Analysis Plan (version 1.1) in accordance with FDA's comments and submitted the revised SAP and a response to FDA's comments in early April 2012. Bayer established a January 26, 2012, data-cut off for the primary analysis for this study. Bayer stated that results from study 14874 were received on March 30, 2012. Bayer provided a summary of the top-line data from this study in Appendix 2 of the April 4, 2012, meeting briefing document. The exposure-response relationship and a biomarker evaluation of regorafenib (additional exploratory objectives) are currently under evaluation and will not be part of the GIST NDA.

As the results of the Phase 3 study 14874 were positive, Bayer intends to submit a complete NDA for the GIST indication in approximately August 2012, and is proposing a rolling NDA submission with an initial submission for select Modules in May 2012. The final portions of the NDA submission would be made approximately 4 months after the April 2012, submission of the NDA for metastatic CRC in August 2012.

Regulatory History: An End-of-Phase 2 meeting to discuss the proposed Phase 3 GIST study was requested under IND 75642 and it was held on August 25, 2010. The Agency issued final meeting minutes on September 23, 2010. Orphan designation was granted on January 12, 2011, for regorafenib for the treatment of gastrointestinal stromal tumors (GIST). Fast-track status for regorafenib for GIST was requested on February 28, 2011, under IND 75642 and was granted on April 17, 2011.

Meeting Purpose: Bayer plans to submit a rolling new drug application (NDA) in electronic Common Technical Document (eCTD) format in approximately August 2012 for patients with gastrointestinal stromal tumors (GIST) after disease progression on or not candidates for imatinib and sunitinib.

The primary purpose of this pre-NDA meeting is to discuss the format/content of a NDA for GIST (in particular the clinical section), as well as to discuss the overall review schedule as we anticipate filing this NDA during the period of time the mCRC NDA will be under review.

Draft FDA comments were sent to Bayer on April 30, 2012, and Bayer provided responses in advance of the teleconference on May 2, 2012.

2. DISCUSSION

Sponsor Submitted Questions and FDA Response:

1. QUESTION 1 – ISS / ISE WITH GIST DATA

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
 - Bayer Analysis 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

Details regarding the content of these documents can be found in Question 2 below.

Question 1: Can FDA confirm that the proposed organization of the Module 2.7.3, 2.7.4, and 5.3.5.3 documents above is acceptable?

FDA RESPONSE SENT ON 4/30/12: Yes, FDA agrees that the proposed organization is acceptable.

BAYER RESPONSE RECEIVED ON 5/2/12: Bayer stated that no additional discussion was required.

DISCUSSION DURING TELECONFERENCE: No discussion occurred during the teleconference.

2. QUESTION 2 – DATA POOLS FOR ISS

ISS Data Pool

Similar to the approach presented by Bayer at the Pre-NDA Meeting for mCRC on August 23, 2011 (Appendix 3: FDA Meeting Minutes from August 23, 2011 Pre-NDA Meeting are attached), Bayer intends to prepare three major analysis sets containing data from company-sponsored studies in oncology patients:

Pool 1: All patients who have received regorafenib monotherapy in any Phase 1 – 3 studies. This includes open-label or double-blind, and intermittent or continuous dosing, data from studies 11650, 11651, 11726, 13172, 14387, 14596, 14874, and 14996.

Pool 2: Patients who received continuous dosing from study 11651

Pool 3: All patients who received regorafenib with intermittent dosing in placebo-controlled Phase 3 studies 14874 (GIST) and 14387 (mCRC) in the blinded treatment (regorafenib or placebo) will be included in Pool 3.

Sub-group analyses within each dataset will be carried out by dose level, ethnicity/race, performance status, region, age, sex, BMI, and baseline renal function and hepatic function.

In accordance with the agreements with FDA at the mCRC Pre-NDA meeting, Bayer does not intend to pool data from studies combining regorafenib with other anti-cancer therapies, data from healthy volunteer studies, or data from non-company sponsored studies in the 3 pools above. However, any Serious Adverse Event and any death considered related to regorafenib from these studies, including the Phase 2 Investigator Sponsored Study 14935, will be discussed and presented separately in the ISS.

Question 2a: Does the Agency concur with this proposed strategy for the ISS?

FDA RESPONSE SENT ON 4/30/12: Yes, FDA agrees that the proposed strategy is acceptable.

BAYER RESPONSE RECEIVED ON 5/2/12: Bayer stated that no additional discussion was required.

DISCUSSION DURING TELECONFERENCE: No discussion occurred during the teleconference.

ISE Data Pool

For efficacy, Bayer plans to write a new ISE that focuses on the GIST indication, with the majority of the discussion on the results from the Phase 3 study 14874. In addition, where appropriate, Bayer will discuss the available efficacy results from the Phase 2 Investigator Sponsored Study 14935.

Question 2b: Does the Agency concur with this proposed strategy for the ISE?

FDA RESPONSE SENT ON 4/30/12: Yes, FDA agrees that the proposed strategy is acceptable.

BAYER RESPONSE RECEIVED ON 5/2/12: Bayer stated that no additional discussion was required.

DISCUSSION DURING TELECONFERENCE: No discussion occurred during the teleconference.

3. **QUESTION 3 – CLINICAL CUT-OFF DATE FOR GIST NDA**

Bayer plans to submit the GIST NDA in approximately August 2012. In accordance with the FDA advice provided at the mCRC Pre-NDA Meeting, Bayer will use a clinical cut-off date of not more than 6 months prior to the submission, with the cut-off currently planned for March 31, 2012.

For studies that are ongoing at the time of the clinical cut-off date, any Serious Adverse Event and any death considered related to Regorafenib available within Bayer GPV safety database at clinical cut-off date will be included in the NDA.

Question 3: Does the Agency agree with the proposed cut-off date?

FDA RESPONSE SENT ON 4/30/12: Yes, FDA agrees that the proposed cut-off date is acceptable.

BAYER RESPONSE RECEIVED ON 5/2/12: Bayer stated that no additional discussion was required.

DISCUSSION DURING TELECONFERENCE: No discussion occurred during the teleconference.

4. QUESTION 4 – SUBMISSION OF COMPLETE GIST NDA

In accordance with the agreement between Bayer and FDA at the Pre-NDA meeting for the mCRC indication on August 23, 2011, Bayer intends to submit a separate NDA for the GIST indication. As the mCRC NDA will be under review by FDA during the planned submission date, Bayer intends to submit a complete, stand-alone NDA for the GIST indication. This NDA will consist of the same documents as the Regorafenib mCRC NDA with the following modifications / additions:

Module 1

Most existing Module 1 documents will be revised / updated based on the completion of the GIST filing. In particular, Bayer plans to submit a Physician's Package Insert that will focus on the GIST data (Indication and Clinical Trials), and the Risk Management Plan will be updated to reflect the additional GIST information. Additionally, financial disclosure/certification forms will be provided for the GIST Phase 3 study 14874.

Module 2

Most clinical-related Module 2 documents will be updated, including:

- 2.2 Introduction
- 2.5 Clinical Overview
- 2.7 Clinical Summary

No substantial updates are currently planned for Modules 2.3, 2.4 or 2.6. A minor update to Module 2.6.2 is planned to include efficacy data on regorafenib in a pre-clinical in vivo GIST model.

Module 3

No updates are currently planned.

Module 4

As compared to the mCRC NDA, the only new study Bayer plans to include in Module 4 is a non-clinical study report on the efficacy of regorafenib in an in vivo GIST model.

Module 5

Bayer will resubmit the entire Module 5 from the Regorafenib mCRC NDA. Additions to Module 5 compared to the mCRC NDA include the following:

1. Phase 3 GIST study 14874 study report and associated documents are planned to be included:

- Clinical Study Report, excluding biomarker evaluation and exposure-response data.
- Case Report Forms for patients who died, had a serious adverse event, or withdrew due to adverse events.
- Datasets as specified below, 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 (bankcrf.pdf)]
 - Bayer analysis datasets (ADS) with define.pdf documentation. 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, and statistical programs will be submitted during the NDA review upon request from FDA.

2. Phase 2 Investigator Sponsored Study 14935

- Manuscript accepted for publication to JCO
- All serious adverse events received by Bayer as of the March 31, 2012 data cut-off as CIOMS-I + CIOMS-II listings. Additionally, all related fatal cases will be reported in a separate listing.
- Pharmacokinetic profiling

The following final Clinical Pharmacology study reports are currently not planned to be included in the GIST NDA, as the reports will not be available at the time of the GIST NDA submission. Bayer intends to submit the interim reports as is planned for the mCRC NDA, and will submit a justification as to why the available data support the determination of benefit-risk for regorafenib for GIST:

- Probe substrate study 12434
- Cardiovascular safety study 14814

Question 4a: Does the Agency concur with the above proposal for submission of a complete NDA for the GIST indication without cross-reference to the mCRC NDA?

FDA RESPONSE SENT ON 4/30/12: Yes, FDA agrees that the proposed strategy is acceptable.

BAYER RESPONSE RECEIVED ON 5/2/12: Bayer stated that no additional discussion was required.

DISCUSSION DURING TELECONFERENCE: No discussion occurred during the teleconference.

Question 4b: Does the Agency agree with the proposed outline above regarding the scope, format, and documentation of the electronic datasets to be submitted?

FDA RESPONSE SENT ON 4/30/12: No, FDA does not agree with your proposal, in part, because more information is needed. FDA believes that Bayer should limit the scope of the NDA to what is supportive of the GIST indication and should not repeat the information that is submitted in the mCRC NDA. For example, FDA does not want the mCRC final study reports in Module 5 as implied by your statements above, including “Additions to Module 5 compared to the mCRC NDA.”

The package insert should be limited to the GIST indication and the Risk Management Plan should be limited to what will support the GIST indication.

In addition, FDA strongly recommends that the analysis of exposure-response relationship for the GIST indication be included in the GIST NDA submission as it will provide important information regarding dose selection and product labeling for the proposed indication.

BAYER RESPONSE RECEIVED ON 5/3/12: Bayer did not provide a response on 5/2/12, but noted via email communication on 5/3/12 that they wish to discuss our response as it relates to the exposure-response analysis, which was conveyed in our additional comment 25.

DISCUSSION DURING TELECONFERENCE: FDA stated that the regorafenib GIST NDA should be a stand alone submission and should only contain mCRC information if it supports the GIST application. Bayer stated that the mCRC data in the clinical study report (CRC) plays no role with respect to GIST efficacy; however, the safety information included in the ISS includes approximately 500 CRC and 100 GIST patients and therefore will be included in the GIST NDA. The SAE information will not repeat what is in the CRC NDA, however, cross reference will be provided in the GIST NDA to the CRC NDA to ensure access to all SAE information.

Bayer agreed that the package insert will contain only GIST indication information. Bayer asked for clarification regarding the adverse events section, should it summarize/characterize the exposure information for both safety populations, i.e., mCRC and GIST in a pooled analysis and for GIST alone. FDA stated yes.

Bayer proposed that the safety presentation for the risk management and proposed ISS will contain 3 pools as described in the April 4, 2012, meeting briefing document: **Pool 1:** All patients who have received regorafenib monotherapy in any Phase 1– 3 studies. This

includes open-label or double-blind, and intermittent or continuous dosing, data from studies 11650, 11651, 11726, 13172, 14387, 14596, 14874, and 14996; **Pool 2:** Patients who received continuous dosing from study 11651; and, **Pool 3:** All patients who received regorafenib with intermittent dosing in placebo-controlled Phase 3 studies 14874 (GIST) and 14387 (mCRC) in the blinded treatment (regorafenib or placebo) will be included in Pool 3. FDA asked Bayer if it would be possible to have a pool consisting of data from the GIST Phase 3 study 14874 alone, and Bayer agreed to discuss internally to see if this would be possible and follow up with FDA.

POST MEETING FOLLOW-UP TO POOLED DATA DISCUSSION: In an email communication from Bayer on May 9, 2012, Bayer proposed to replace Pool 2 noted above with a new Pool 2 that would contain only GIST Phase 3 data from study 14874. On May 14, 2012, FDA responded via email communication that this proposal was acceptable and asked if it would be possible to have a Pool 4 inclusive of all patients with GIST treated with regorafenib (including studies 14935 and 14874). Bayer responded via email communication on May 14, 2012, stating that FDA's proposed Pool 4 would not be possible as Bayer does not have the database for Study 14935, so pooling safety data from Studies 14935 and 14874 will not be possible. Bayer agreed to discuss the relevant efficacy & safety summary data from the Phase 2 study 14935 in the Summaries of Efficacy/ Safety. FDA found the proposal acceptable.

The following clinical pharmacology discussion during the teleconference involved questions 4b and additional comments 23-25. FDA stated that Bayer's response provided to these comments (noted under additional comment 23 below) was acceptable but noted that Bayer should analyze all available data (Phase 3 data will not be available at the time of the NDA submission) and include that information in the NDA submission. Bayer noted that the intrinsic factors analysis will be conducted with pooled Phase 1 and Phase 2 data. Bayer noted that the dose-response and exposure-response analysis will be based on Phase 1 data for efficacy (biomarker activity) and for safety. Bayer noted that the PK analysis is ongoing, Bayer is looking at M2 and M5 (regorafenib metabolites) in ongoing Phase 3 studies and will provide ER and pop PK from the Phase 3 studies in December 2012. Bayer asked if clinical pharmacology becomes available during the review of the NDA should the information be submitted to the NDA during the review period or as a PMR. FDA requested that Bayer ask FDA this question as appropriate as data becomes available and FDA will advise on whether to submit the data as an amendment to the NDA or as a PMR.

5. **QUESTION 5: SUBMISSION OF A ROLLING NDA FOR REGORAFENIB GIST INDICATION**

Bayer received notification on April 17, 2011 that our application for Fast Track designation for Regorafenib for the treatment of patients with metastatic and/or unresectable gastrointestinal stromal tumors (GIST) whose disease has progressed despite

at least imatinib and sunitinib as prior treatments was approved. Bayer proposes to submit a rolling NDA for the GIST indication, with the following proposed schedule:

Module 1 – Submission with the final documents for the NDA (August 2012)

Module 2 – Submission of 2.3 at the same time as the submission of Module 3 (end May 2012), submission of 2.4 and 2.6 at the same time as the submission of Module 4 (end May 2012), and submission of 2.2, 2.5 and 2.7 with the final submission of the NDA (August 2012)

Module 3 – Submission by the end of May 2012

Module 4 – Submission by the end of May 2012

Module 5 – Submission with the final documents for the NDA (August 2012)

Question 5: Does the Agency agree with our proposed timing of the rolling NDA documents as outlined above?

FDA RESPONSE SENT ON 4/30/12: Yes, FDA finds the proposed timing of the rolling NDA acceptable. However, in order to plan for OSI inspections FDA requested to receive additional information in advance of the final documents planned for the August 2012 submission (see attachment).

BAYER RESPONSE RECEIVED ON 5/2/12: Bayer stated that no additional discussion was required.

DISCUSSION DURING TELECONFERENCE: No discussion occurred during the teleconference.

6. QUESTION 6 – PEDIATRIC WAIVER

As an orphan drug designation for treatment of gastrointestinal stromal tumors (GIST) was previously granted in January 2011 by the Office of Orphan Products Development in January 2011, Bayer plans to request a waiver the evaluation of Regorafenib in children (< 18 years).

Question 6: Does the Agency concur with this proposal?

FDA RESPONSE SENT ON 4/30/12: Yes, FDA agrees with the proposed strategy.

BAYER RESPONSE RECEIVED ON 5/2/12: Bayer stated that no additional discussion was required.

DISCUSSION DURING TELECONFERENCE: No discussion occurred during the teleconference.

7. QUESTION 7 – NDA RECONCILIATION FOLLOWING APPROVALS

Bayer currently plans to submit 2 separate NDAs for Regorafenib (mCRC indication in April 2012, and GIST indication in approximately August 2012), with each NDA fully self-contained.

At such point when the first NDA is approved, Bayer would propose to submit an amendment to the second NDA to align the second NDA with all information approved in the first NDA. Regorafenib would be marketed under the first NDA until such time the second NDA were to be approved, at which time Bayer would market regorafenib under the second NDA from that point forward. The first NDA would then be inactivated.

Question 7: Does the Agency agree in principal to the proposed plan above? Does the Agency have any recommendations regarding this transition?

FDA RESPONSE SENT ON 4/30/12: No, FDA does not agree with this proposal. If the CRC NDA is approved, then the second NDA (GIST indication) will become a supplement to the first NDA.

BAYER RESPONSE RECEIVED ON 5/2/12: Bayer stated that no additional discussion was required.

DISCUSSION DURING TELECONFERENCE: No discussion occurred during the teleconference.

Additional FDA Comments Sent on 4/30/12:

Statistical:

8. In Bayer's April 10, 2012, submission which contained a response to FDA's March 9 and 20, 2012, letters, Bayer agreed that the study objective would only be considered to have been met if both 122 and 144 PFS events are statistically significant. Therefore, Bayer should modify the study protocol and statistical analysis plan to reflect the agreements reached in the April 10, 2012, submission.

BAYER RESPONSE RECEIVED ON 5/2/12: As previously agreed with the agency, the primary analysis of PFS would include 144 events and a supportive analysis including only 122 events would also be provided. Bayer agreed to the FDA's position that, for the NDA submission, the FDA would consider the primary objective fulfilled only if tests at both 122 and 144 PFS events are statistically significant. The final SAP, submitted to FDA on April 10, 2012, includes both the 144 event primary analysis and the 122 event supportive analysis as suggested by FDA. Even though for the US GIST NDA submission, both analyses need to be statistically significant in order to meet the primary

objective of the study, for submissions to other regions of the world, the 144 event analysis remains the only primary analysis, and amending the protocol now to formally state that both analyses would need to be positive to fulfill the primary endpoint would require new discussions with all global Health Authorities. Additionally, as a protocol amendment requires significant operational effort, and given the study has already been unblinded for the purposes of the primary analysis, Bayer would prefer to not undertake this amendment without better understanding the benefits of such a change. For these reasons, Bayer prefers not to amend the clinical study protocol to add the 122 event supportive analysis.

DISCUSSION DURING TELECONFERENCE: FDA acknowledged the issues raised by Bayer above. FDA agreed that the protocol and SAP do not need to be amended and FDA will rely on agreements reached with Bayer as stated in FDA's March 9 and 20, 2012, letters and subsequently agreed to by Bayer in the April 10, 2012, submission.

9. FDA acknowledges the receipt of the proposed gate-keeping procedure for secondary endpoints; however, the inclusion of any specific secondary endpoint in labeling will be a review issue.

BAYER RESPONSE RECEIVED ON 5/2/12: Bayer stated that no additional discussion was required.

Clinical Pharmacology Comments:

Please address the following clinical pharmacology related questions in the Summary of Clinical Pharmacology Studies in Module 2 of the NDA submission:

10. What is the basis for selecting the dose(s) and dosing regimen used in the registration trial(s)?

BAYER RESPONSE RECEIVED ON 5/2/12: Bayer stated that no additional discussion was required.

DISCUSSION DURING TELECONFERENCE: No discussion occurred during the teleconference.

11. What are the exposure-response relationships (dose-response, exposure-response) for efficacy?

BAYER RESPONSE RECEIVED ON 5/2/12: Bayer stated that no additional discussion was required.

DISCUSSION DURING TELECONFERENCE: No discussion occurred during the teleconference.

12. What are the exposure-response relationships (dose-response, exposure-response) for safety?

BAYER RESPONSE RECEIVED ON 5/2/12: Bayer stated that no additional discussion was required.

DISCUSSION DURING TELECONFERENCE: No discussion occurred during the teleconference.

13. How is the QT prolongation potential of regorafenib assessed? What are the conclusion and proposed labeling description?

BAYER RESPONSE RECEIVED ON 5/2/12: Bayer stated that no additional discussion was required.

DISCUSSION DURING TELECONFERENCE: No discussion occurred during the teleconference.

14. What are the characteristics of absorption, distribution, metabolism and excretion of regorafenib?

BAYER RESPONSE RECEIVED ON 5/2/12: Bayer stated that no additional discussion was required.

DISCUSSION DURING TELECONFERENCE: No discussion occurred during the teleconference.

15. What are the effects of food on the bioavailability of regorafenib and dosing recommendation with regard to meals or meal types?

BAYER RESPONSE RECEIVED ON 5/2/12: Bayer stated that no additional discussion was required.

DISCUSSION DURING TELECONFERENCE: No discussion occurred during the teleconference.

16. What influence do the intrinsic factors (as listed below but not limited to) have on regorafenib exposure and/or its pharmacodynamic response? What is their clinical impact? What dose and dosing regimen adjustments are recommended?

- a. gender
- b. race
- c. weight
- d. disease
- e. genetic polymorphism
- f. hepatic impairment

- g. renal impairment

BAYER RESPONSE RECEIVED ON 5/2/12: Bayer stated that no additional discussion was required.

DISCUSSION DURING TELECONFERENCE: No discussion occurred during the teleconference.

17. What influence do the extrinsic factors (as listed below but not limited to) have on regorafenib exposure and/or its pharmacodynamic response? What is their clinical impact? What dose and dosing regimen adjustments are recommended?
- a. concomitant medications
 - b. CYP and/or transporter based drug-drug interactions
 - c. diet
 - d. smoking

BAYER RESPONSE RECEIVED ON 5/2/12: Bayer stated that no additional discussion was required.

DISCUSSION DURING TELECONFERENCE: No discussion occurred during the teleconference.

In addition, please apply the following advice in preparing clinical pharmacology sections of the NDA submission:

18. Submit bioanalytical method(s) and validation reports for clinical pharmacology and biopharmaceutics studies.

BAYER RESPONSE RECEIVED ON 5/2/12: Bayer stated that no additional discussion was required.

DISCUSSION DURING TELECONFERENCE: No discussion occurred during the teleconference.

19. Provide complete datasets for clinical pharmacology and biopharmaceutics studies. The datasets should not be limited to PK/PD. For example, domains related to safety (e.g., AE's), demographics, non-PK laboratory values, concomitant drug use should be included. All of these are important in identifying patterns of potential clinical pharmacology related causes of clinical safety outcomes.

BAYER RESPONSE RECEIVED ON 5/2/12: Bayer stated that no additional discussion was required.

DISCUSSION DURING TELECONFERENCE: No discussion occurred during the teleconference.

20. Provide all concentration-time and derived PK parameter datasets as SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.

BAYER RESPONSE RECEIVED ON 5/2/12: Bayer stated that no additional discussion was required.

DISCUSSION DURING TELECONFERENCE: No discussion occurred during the teleconference.

21. Present the PK parameter data as geometric mean with coefficient of variation (and mean \pm standard deviation) and median with range as appropriate in the study reports.

BAYER RESPONSE RECEIVED ON 5/2/12: Bayer stated that no additional discussion was required.

DISCUSSION DURING TELECONFERENCE: No discussion occurred during the teleconference.

22. Provide a table listing of patients with renal or hepatic impairment who have received regorafenib, organized by trial number. Include available renal and hepatic function parameters such as SCr, CLCr calculated by the Cockcroft Gault equation and/or eGFR calculated by MDRD, AST/ALT, Total Bilirubin, etc for each patient in the listing. Also, provide a summary of the following information for each patient: PK and PD data, safety, and clinical efficacy.

BAYER RESPONSE RECEIVED ON 5/2/12: Bayer stated that no additional discussion was required.

DISCUSSION DURING TELECONFERENCE: No discussion occurred during the teleconference.

23. Submit the following datasets to support the population PK analysis:
- SAS transport files (*.xpt) for all datasets used for model development and validation
 - A description of each data item provided in a Define.pdf file. Any concentrations and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets
 - Model codes or control streams and output listings for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. Submit these files as ASCII text files with *.txt extension (e.g., myfile_ctl.txt, myfile_out.txt)
 - A model development decision tree and/or table which gives an overview of modeling steps

For the population analysis reports, submit:

- The standard model diagnostic plots
- Individual plots for a representative number of subjects including observed concentrations, the individual prediction line and the population prediction line
- Model parameter names and units in tables. For example, oral clearance should be presented as CL/F (L/h) and not as THETA(1).
- A summary of the report describing the clinical application of modeling results.

BAYER RESPONSE RECEIVED ON 5/2/12 FOR COMMENTS 23-25: Dose-exposure-response relationship for safety and efficacy was mainly assessed from data of the dose-escalation trial 11650 and from the pooled analysis of Phase 1 and 2 patients. This evaluation will be submitted with the initial NDA submission for GIST.

In the pivotal phase 3 study 14874, two pre-dose pharmacokinetic samples from all subjects (one on Day 15 of Cycle 1 and one on Day 15 of Cycle 2) were scheduled. The pharmacokinetic assessment visit was to be scheduled after at least 14 days of uninterrupted stable dosing of study drug. The objective of pharmacokinetic sampling was to determine the concentrations of parent drug regorafenib and its metabolites M-2 (BAY 75-7495) and M-5 (BAY 81-8752). These concentrations will be used to assess clinically relevant covariates using the population PK approach. In addition, exposure-response relationships will be explored.

Subjects receiving placebo who experienced disease progression (per blinded central radiology review) were offered open-label regorafenib (cross-over option). For cross-over subjects, all study assessments (incl. pharmacokinetic sampling) were to be performed during the first two cycles of regorafenib treatment (i.e. as if the subjects were restarting the study at cycle 1 day 1).

The population PK and exposure-response analysis will be conducted according to the available principles and guidelines. These analyses of the pivotal study 14874 will be started once all relevant PK samples and response parameters are available:

- The cut-off date for primary and secondary efficacy endpoints and safety end-points was on 26 January 2012. Therefore, these data are available.
- PK sampling is still ongoing due to the cross-over option offered to subjects treated with placebo who experienced disease progression. The same cut-off date of 26 January 2012 was selected retrospectively for population PK and exposure-response analysis. PK samples are currently being shipped and analyzed.
- FDA has also suggested assessing exposure-response relationship for biomarkers. So far, no biomarker that is predictive of regorafenib activity has been identified. Exploratory biomarker analyses for the pivotal phase 3 study 14874 is planned to be available in Q4/2012. Bayer believes that an exposure-response analysis of

biomarkers would not be considered of value in case no predictive biomarker is identified.

As discussed with the agency during the End of Phase II meeting, evaluation of the exposure-response data as well as reporting will require about 12 months after the end of the study and therefore, the corresponding reports will not be available for the initial GIST NDA submission. Bayer would commit to providing this report to FDA as a Post-Marketing Requirement, as was proposed in the Regorafenib mCRC NDA 203,085 filed on April 27, 2012.

Population PK and exposure-response analyses are considered exploratory and do not constitute a primary or secondary endpoint of this clinical study. Furthermore, this exploratory assessment cannot provide any definitive information about the benefit-risk for regorafenib. Bayer will submit a justification with the initial NDA as to why the data submitted with the initial NDA is adequate to support the determination of benefit-risk for regorafenib for GIST.

DISCUSSION DURING TELECONFERENCE: Discussion regarding additional comments 23-25 is captured under question 4b above.

24. Refer to the following pharmacometric data and models submission guidelines <http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm> for more information.

BAYER RESPONSE RECEIVED ON 5/2/12: Bayer's response for Additional Comments 23-25 was grouped together and therefore is captured under Additional Comment 23.

DISCUSSION DURING TELECONFERENCE: Discussion regarding additional comments 23-25 is captured under question 4b above.

25. Explore exposure-response (measures of effectiveness, biomarkers and toxicity) relationships for regorafenib and its major active metabolite(s) in the targeted patient population and include the results of this exploratory analysis in the NDA submission. Refer to Guidance for Industry found at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072137.pdf> and <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072109.pdf> for more information.

BAYER RESPONSE RECEIVED ON 5/2/12: Bayer's response for Additional Comments 23-25 was grouped together and therefore is captured under Additional Comment 23.

DISCUSSION DURING TELECONFERENCE: Discussion regarding additional comments 23-25 is captured under question 4b above.

26. Submit the following items for QTc study/assessment:
- Copy of the clinical protocol
 - Copy of the Investigator's Brochure
 - Annotated CRF
 - A Define file which describes the contents of the electronic data sets
 - Electronic data sets as SAS transport files (in CDISC SDTM format – if possible) and all the SAS codes for the analyses
 - ECG waveforms to the ECG warehouse (www.ecgwarehouse.com)
 - A completed Highlights of Clinical Pharmacology Table

BAYER RESPONSE RECEIVED ON 5/2/12: Bayer plans to submit the same interim QT study report information for the GIST NDA as we have last week for the mCRC NDA 203,085. The clinical study report, including the datasets and waveforms, would be submitted in the 4th quarter of 2012.

DISCUSSION DURING TELECONFERENCE: FDA stated it was acceptable for this information to be submitted under a PMR.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion associated with this teleconference.

4.0 ACTION ITEMS

There was no action items associated with this teleconference. Post meeting follow-up regarding the pooled analyses is discussed under question 4b.

5.0 ATTACHMENTS AND HANDOUTS

There were no attachments or handouts associated with this teleconference.

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
05/23/2012



FOOD AND DRUG ADMINISTRATION

Meeting Date and Time: August 25, 2010 1:00 p.m.
Meeting Type: Type B
Meeting Category: End of Phase 2
Meeting Location: Bldg. 22, Room 1313
Application Number: IND 75,642
Product Name: Regorafenib (BAY 73-4506)
Received Briefing Package July 19, 2010
Sponsor Name: Bayer HealthCare
Meeting Requestor: Meni Melek, Ph.D., Regulatory Affairs, Bayer HealthCare Pharmaceuticals, Inc., US
Meeting Chair: John R. Johnson, M.D., Lead Medical Officer
Meeting Recorder: Diane Hanner, M.P.H., M.S.W.
Meeting Attendees:
BAYER

Attendee	Title
Gerhard Schlueter, Ph.D.	Regulatory Affairs, Bayer HealthCare Pharmaceuticals Inc., US
Meni Melek, Ph.D.	Regulatory Affairs, Bayer HealthCare Pharmaceuticals Inc., US
Laura Park	Regulatory Affairs, Bayer HealthCare Pharmaceuticals Inc., US
Dietmar Berger, M.D.	Clinical Development, Bayer Schering Pharma AG, Germany
Iris Kuss, M.D.	Clinical Development, Bayer Schering Pharma AG, Germany

Dirk Laurent, M.D.	Clinical Development, Bayer Schering Pharma AG, Germany
Minghua (Michael) Shan, Ph.D.	TA Expert Statistician, Oncology, Bayer HealthCare Pharmaceuticals Inc., US
Rita Darkow, Ph.D.	Project Management, Bayer Schering Pharma AG, Germany
George Demetri, M.D.	Center for Sarcoma and Bone Biology, Dana-Farber Cancer Institute
Lou Mylecraine, Ph.D.	Toxicology, Bayer HealthCare Pharmaceuticals Inc., US

FDA Attendees

Attendee	Title
Robert Justice, M.D., M.S.	Director DDOP
Amna Ibrahim, M.D.	Acting Deputy Division Director
Anthony Murgio, M.D., M.S., FACP	Associate Director OODP IO, Acting Deputy Director DDOP
John R. Johnson, M.D.	Lead Medical Officer, DDOP
Amy McKee, M.D.	Clinical Reviewer, DDOP
Katherine Delorenzo, M.D.	Clinical Reviewer, DDOP
Shenghui Tang, Ph.D,	Acting Team Leader, DB 5
Diane Hanner, M.P.H., M.S.W.	Senior Program Management Officer

BACKGROUND

Bayer HealthCare Pharmaceuticals, Inc., originally submitted IND 75642 to the Division of Oncology Drug Products for BAY 73-4506 (Regorafenib) for the patients with metastatic and unresectable GastroIntestinal Stromal Tumors (GIST) on July 19, 2006. On August 25, 2010, the Division of Oncology Drug Products held a teleconference with representatives of Bayer HealthCare Pharmaceuticals, Inc., to discuss the proposed Phase 3 study.

DISCUSSION

Question 1

Regorafenib is proposed as monotherapy for the treatment of patients with (b) (4)

(b) (4)

The clinical program will consist of the proposed multinational, multicenter, blinded single Phase 3 study, as well as a Phase 2 study in patients with advanced GIST (study currently ongoing), and additional supportive data to be provided by other Phase 1 and Phase 2 data in over 250 patients with different types of advanced cancer.

Does the Agency agree that the proposed clinical program is adequate for the registration of regorafenib as monotherapy treatment of patients with metastatic and/or unresectable GIST whose disease has progressed despite at least imatinib and sunitinib as prior treatment regimens?

FDA Response: No; please see responses to questions 4 and 5.

Question 2

To date, approximately 250 patients have been treated with regorafenib with different dosing schedules and at different dose levels. At the time of a potential NDA submission, it is anticipated that reported safety data from >400 patients treated with regorafenib will be available. This includes approximately 150 patients with GIST. In addition, available safety data from the ongoing CRC Phase 3 study will be included at the time of filing NDA for GIST; enrollment of 690 patients are planned.

Does the Agency agree that the safety data base will be of sufficient size to support the New Drug Application for the proposed patient population?

FDA Response: Yes.

Question 3

This Phase 3 study is intended to enroll patients with advanced GIST who have shown disease progression or intolerance to imatinib as well as documented disease progression while on sunitinib treatment.

Patients with exposure to other investigational new agents as well as other systemic therapies will also be eligible for the trial as long as prior failure of both imatinib and sunitinib has been documented. Patients with prior exposure to any vascular endothelial growth factor receptor (VEGFR) inhibitor, (except sunitinib) are excluded from study participation. Patients included in the proposed phase 3 study will receive either regorafenib with best supportive care or placebo with best supportive care (2:1).

Does the Agency agree with the intended patient population and the proposed comparator arm?

FDA Response: Yes. However, due to the nature of the side effect profile of regorafenib, it is highly likely that most patients and investigators will be unintentionally unblinded to treatment assignment. Please confirm that the central radiology review for the primary endpoint of PFS is blinded. Also, consider whether a placebo is required in the control arm due to the likely unintentional blinding.

Meeting Discussion: The sponsor clarified that the central radiology review for the primary endpoint will be blinded.

Question 4

Does the Agency agree that PFS as the primary endpoint for the planned Phase 3 clinical trial is acceptable for approval?

FDA Response: Yes. However, only a six-week improvement in PFS in this patient population is unlikely to be clinically significant and adequate to support approval.

Question 5

The planned sample size of 170 randomized patients and approximately 122 PFS events for final analysis is based on a targeted improvement in median time of PFS of 100%, from 6 weeks to 12 weeks. The one-sided type I error is set to 0.01, the power is set to 0.90, and a 2:1 randomization ratio for subjects in the regorafenib versus the placebo arm is assumed. There is no planned interim analysis for efficacy. After documented objective progression confirmed by central imaging review, patients initially randomized to the placebo arm may be eligible to receive open-label regorafenib as cross-over extension.

Secondary efficacy endpoints will be overall survival, time to progression, disease control rate, response rate, and duration of response.

Does the Agency agree with the statistical design for this trial?

FDA Response: Yes. However, please note that a statistically significant difference in PFS may not necessarily demonstrate a clinically meaningful difference. Please see our response to question 4.

With PFS as the primary endpoint, we recommend that the study be powered for overall survival (OS) as well and that an interim analysis for OS be performed at the final PFS analysis to demonstrate the right trend of the OS. We also recommend that a log-rank test be used in analyzing OS and Rank-preserving structural failure time method (RPSFTM) be used as sensitivity analysis.

In addition, if you plan to include secondary endpoints in the label, a statistical plan controlling overall type I error rate at 0.05 for those secondary endpoints needs to be pre-specified providing those secondary endpoints are agreed to by the Agency. Please note that Disease Control Rate (DCR) is unlikely to be included in the label.

Meeting Discussion:

FDA reiterated that the 6 week PFS difference may not be adequate for approval. However, the revised statistical analysis plan for OS (see attached slide) submitted by the sponsor appears to be acceptable. Any final decisions on a NDA submission will be dependant upon the trial results.

Question 6

Tumor assessments for PFS will be based on RECIST criteria, version 1.1 and will be done by central review. To reduce the amount of random deviations between the local and central tumor assessment procedures, we propose to present the central reviewers with the target lesions which were selected by the local investigators. In order to determine continuation or discontinuation of blinding for a specific patient (based on progression), local investigators will be required to use the results of central imaging analysis rather than the local imaging assessment for the decision relating to continuation or discontinuation of blinded study drug (regorafenib or placebo) based on radiological disease progression. Radiological assessments will be performed every 4 weeks for 3 assessments, followed by assessments every 6 weeks for 2 times and thereafter every 8 weeks.

Does the Agency agree with the proposed plans regarding tumor assessment?

FDA Response: Yes. However, the frequency of assessments appears to be designed to detect small differences that are not clinically significant.

The selection of target lesions by the local investigators should occur at baseline prior to randomization.

Meeting Discussion:

The sponsor acknowledged that small differences may not be clinically meaningful. The intent of the tumor assessment schedule was to reduce unscheduled scans.

Question 7

For randomization, it is planned to stratify patients according to two criteria: geographical region (Asia versus rest of the world) and lines of prior systemic treatment: 3rd line versus 4th line or beyond; there will be a cap on the 4th line and beyond stratum to prevent a potential overrepresentation of these heavily pre-treated line patients.

Does the Agency agree with the stratification plan for randomization?

FDA Response: Yes.

Question 8

The pharmacokinetics of regorafenib at the 160 mg 21-day on/7-day off dosing regimen has been evaluated in a Phase 1 dose-escalation study in patients with solid tumors.

An investigator sponsored study (ISS) 14935 evaluating the same dosing regimen in patients with GIST is currently being conducted. In the ISS study, patients have the option of providing samples for full profile pharmacokinetic analysis. It is expected that approximately 10-15 patients will provide samples.

In the proposed Phase 3 GIST study, trough samples will be collected on Cycle 2, Day 15 (23-24h after the Cycle 2, Day 14 dose). Trough concentrations will be used to assess clinically relevant covariates and explore exposure-response relationships.

Does the Agency agree with the plan for characterizing the pharmacokinetics, assessing clinically relevant covariates and exploring the exposure- response relationships of regorafenib in patients with GIST?

FDA Response: Yes, your plan appears generally acceptable.

Question 9

The complete clinical pharmacology development plan was discussed with the Division on September 3, 2009 during the End of Phase 2 meeting for the regorafenib CRC Phase 3 study (see EoP2 CRC meeting minutes).

Due to timing of completion of the planned Phase 3 study in GIST patients and, therefore, anticipated NDA submission, it is possible that not all clinical pharmacology studies planned in cancer patients will be completed at the time of filing. Of note, only interim data may be available for Study 12434 – probe substrate study and Study 14814 – QTc cardiovascular safety study. The analysis of trough concentration versus response data from the proposed Phase 3 GIST study data will be available approximately 12 months after the end of the study.

Does the Agency agree that the previously discussed studies/evaluations, with interim data from any on-going studies at the time of filing NDA, will be adequate to provide the complete clinical pharmacology package necessary to support the approval and labeling of the proposed indication?

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

Question 10

A comprehensive program of pharmacology including safety pharmacology, pharmacokinetics and toxicology studies was performed to support clinical trials in subjects with cancer with orally administered regorafenib. The studies and brief results are outlined in the background section. This program is considered sufficient to support for filing of an NDA for regorafenib in the targeted indication.

Does the Agency agree?

FDA Response: Your non-clinical program is generally acceptable. A final decision, including the need for a confirmatory embryofetal toxicity study in a second species, will be made after review of data submitted with the NDA.

Additional comment:

Please justify why patients who progress on regorafenib will be allowed to continue on regorafenib after progression is documented.

Meeting Discussion: The agency finds the sponsor's justification acceptable.

Attachment

Bayer Response to Power for Overall Survival as Secondary Endpoint



	Original Plan	Revised Plan
NDA Submission	PFS + available OS data	PFS + interim OS data
Interim Analysis of OS	None	Time of PFS analysis (~60 deaths)
Time of Final Analysis	Time of PFS analysis (~60 deaths)	136 deaths
Alpha (1-sided)	0.025	0.025
Alpha Spending	None	O'Brien-Fleming-Type
Power	Not powered	80% power to detect 66.7% increase
Long-Term Survival Data Analysis	None	Planned

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/s/

JOHN R JOHNSON
09/23/2010

Reference ID: 2840048

Reference ID: 3273355