

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204819Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**



Bayer HealthCare
Pharmaceuticals

NDA 204819
BAY 63-2521/ riociguat
1.3.5.2 Patent Certification

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1.3.5.2 Patent Certification

A patent certification pursuant to 21 U.S.C. 355(b)(2) or (j)(2)(A) is not applicable to this New Drug Application 204819 for BAY 63-2521/ riociguat.

EXCLUSIVITY SUMMARY

NDA # 204819

SUPPL #

HFD # 110

Trade Name Adempas

Generic Name riociguat

Applicant Name Bayer Healthcare Pharmaceuticals

Approval Date, If Known Exact date not known

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 X NO

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

505(b)(1)

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

YES X 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.

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:

d) Did the applicant request exclusivity?

YES X NO

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

5

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

YES NO X

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?

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 X

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 X

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

NDA#

NDA#

NDA#

2. Combination product.

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

YES NO X

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

NDA#

NDA#

NDA#

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

IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

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

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If

the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

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

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

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

YES NO

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

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

YES NO

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

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently

demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

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

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

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

Investigation #1 YES NO

Investigation #2 YES NO

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

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

Investigation #1 YES NO

interest provided substantial support for the study?

Investigation #1
!
! YES NO
! Explain: ! Explain:

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: Edward Fromm, R.Ph., RAC
Title: Chief, Project Management Staff
Date: October 3, 2013

Name of Office/Division Director signing form: Norman Stockbridge, M.D., Ph.D.
Title: Director, Division of Cardiovascular and Renal Products

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/

EDWARD J FROMM
10/03/2013

NORMAN L STOCKBRIDGE
10/03/2013



1.3.5.3 Exclusivity Request

Claim for 5 Year Exclusivity - New Chemical Entity

Pursuant to 21 CFR 314.50(j) and with reference to 21 CFR 314.108(b)(2), Bayer HealthCare Pharmaceuticals Inc. claims a period of five years exclusivity (new chemical entity) for riociguat for the treatment of Chronic-Thromboembolic Pulmonary Hypertension and Pulmonary Arterial Hypertension which is the subject of NDA 204819.

Bayer HealthCare Pharmaceuticals Inc. certifies that the two phase 3 studies referenced below, which are contained in this application, meet the definition of a “new clinical investigation”, as set forth in 21 CFR 314.108(a). These studies support a finding of substantial evidence of effectiveness of riociguat for the treatment of Chronic-Thromboembolic Pulmonary Hypertension and Pulmonary Arterial Hypertension.

Study 12934 - Report A62510: *“Randomized, double-blind, placebo-controlled, multi-centre, multi-national study to evaluate the efficacy and safety of oral BAY 63 2521 (1 mg, 1.5 mg, 2 mg, or 2.5 mg tid) in patients with symptomatic Pulmonary Arterial Hypertension (PAH). PATENT-1 Study”*

Study 11348 - Report A62508: *“Randomized, double-blind, placebo-controlled, multi-centre, multi-national study to evaluate the efficacy and safety of oral BAY 63 2521 (1 mg, 1.5 mg, 2 mg, or 2.5 mg tid) in patients with Chronic Thromboembolic Pulmonary Hypertension (CTEPH). CHEST-1 Study”*

Bayer HealthCare Pharmaceuticals Inc. also certifies that riociguat, the active moiety, has not previously been approved under section 505(b) of the Federal Food, Drug and Cosmetic Act.

It is the opinion of Bayer HealthCare Pharmaceuticals Inc. that published studies and publicly available reports do not provide sufficient basis to support the approval of riociguat for the treatment of Chronic-Thromboembolic Pulmonary Hypertension and Pulmonary Arterial Hypertension.

Pediatric Page

No formal pediatric page is needed as orphan designation has been granted for both the CTEPH and PAH indications.



Bayer HealthCare
Pharmaceuticals

NDA 204819
BAY 63-2521/ riociguat
1.3.3 Debarment Certification

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Module 1.3.3: Debarment Certification

Bayer 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 this application, NDA 204819.

Date:

Jan. 15, 2013

Signature:

A handwritten signature in cursive script, appearing to read "S. Brown".

Sharon W. Brown

Director, Global Regulatory Affairs

US Head Womens Healthcare and Cardio Pulmonary

Bayer HealthCare Pharmaceuticals



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Office of Orphan Products Development
Food and Drug Administration
10903 New Hampshire Avenue
WO32- 5271
Silver Spring, MD 20993

SEP 19 2013

Bayer HealthCare Pharmaceuticals, Inc.
PO Box 1000
Montville, NJ 07045-1000

Attention: Carmen Leung, RPh
Deputy Director, Global Regulatory Affairs

Re: Designation request # 13-4069

Amendment Dated: July 12, 2013
Amendment Received: July 16, 2013

Dear Mr. Leung:

This letter responds to your request for orphan-drug designation of riociguat for “treatment of pulmonary hypertension: pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension.”

Pursuant to section 526 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360bb), your orphan-drug designation request of riociguat is granted for *treatment of chronic thromboembolic pulmonary hypertension*. Please be advised that it is the active moiety or principal molecular structural features of the drug¹ and not the formulation of the drug that is designated.

If your drug receives marketing approval for an indication broader than what is designated, it may not be entitled to exclusive marketing rights under section 527 (21 U.S.C. 360cc). Therefore, prior to submission of your marketing application, we request that you compare the drug’s orphan designation with the proposed marketing indication and submit additional information to amend the orphan-drug designation if warranted. 21 CFR 316.26.

If the same drug is approved for the same orphan indication before you obtain marketing approval of your drug, you will have to demonstrate that your drug is clinically superior to the already approved same drug in order to obtain orphan-drug exclusivity. Failure to demonstrate clinical superiority over the already approved same drug will result in your drug not receiving orphan-drug exclusivity. 21 CFR 316.34(c).

¹ The term “drug” in this letter includes drug and biological products.

You must submit to the Office of Orphan Products Development a brief progress report of drug development within 14 months after this date and annually thereafter until marketing approval. 21 CFR 316.30.

Please notify this Office within 30 days of submitting a marketing application for the drug's designated use. Once your marketing application is approved, please contact Stephanie Donahoe, RPh, MPH, at 301-796-8681 or alternatively at 301-796-8660 to assess eligibility for orphan-drug exclusivity.

If you have questions regarding the development of your designated product, please feel free to contact Erica McNeilly, RPh, Health Science Administrator at 301-796-8679 or alternatively at 301-796-8660. Congratulations on obtaining your orphan-drug designation.

Sincerely,

A handwritten signature in cursive script that reads "Gayatri Rao".

Gayatri R. Rao, MD, JD
Director
Office of Orphan Products Development

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 204819 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: 1 (NME)
Proprietary Name: Adempas Established/Proper Name: Riociguat Dosage Form: Tablet		Applicant: Bayer Healthcare Pharmaceuticals Agent for Applicant (if applicable): NA
RPM: Edward Fromm		Division: Division of Cardiovascular and Renal Products
<p><u>NDA 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: October 08, 2013 		<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>Not Applicable</p>
<p>❖ Application Characteristics ³</p>	
<p>Review priority: Standard <input type="checkbox"/> Priority <input checked="" type="checkbox"/></p> <p>Chemical classification (new NDAs only): 1</p> <p><input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch <input checked="" type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC</p> <p>NDA: 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>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><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>REMS: <input checked="" type="checkbox"/> MedGuide <input checked="" type="checkbox"/> Communication Plan <input checked="" 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 checked="" type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other</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	Included
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>)	X Included
Documentation of consent/non-consent by officers/employees	X Included
Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action and date AP October 8, 2013
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. 	NA
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	Included
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	NA

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 checked="" type="checkbox"/> Medication Guide <input 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. 	NA
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	Included (02/08/2013)
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	NA
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)	
<ul style="list-style-type: none"> • Most-recent draft labeling 	August 5, 2013
❖ Proprietary Name <ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) • Review(s) (<i>indicate date(s)</i>) • <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.</i> 	Acceptable-August 7, 2013
❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)	X RPM February 22, 2013 X DMEPA June 25, July 25, 2013 Carton/Container: -Sept 12, 2013 <input type="checkbox"/> DMPP/PLT (DRISK) <input checked="" type="checkbox"/> ODPD (DDMAC)- Sept 17, 2013 <input type="checkbox"/> SEALD <input type="checkbox"/> CSS <input checked="" type="checkbox"/> Other reviews: Patient Labeling: Sept. 17, 2013
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>) ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>) 	RPM Filing Review- December 12, 2012, RPM Summary Review- October 9, 2013 X Not a (b)(2) X Not a (b)(2)
❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)	X Included
❖ 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 X 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 X No <input type="checkbox"/> Not an AP action

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

❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> Date reviewed by PeRC _____ If PeRC review not necessary, explain: _____ Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>) 	Not Applicable-Orphan Exemption <input type="checkbox"/> Included
❖ 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>)	X 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>)	Ack ltr-2/22/13, Late Cycle Meeting Briefing Package-07/08/13
❖ Internal memoranda, telecons, etc.	T-con minutes-December 19, 2012
❖ Minutes of Meetings	
• Regulatory Briefing (<i>indicate date of mtg</i>)	X No mtg
• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)	X N/A
• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)	Written Responses in lieu of meeting-November 01, 2012
• EOP2 meeting (<i>indicate date of mtg</i>)	May 29, 2008
• Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>)	Pre-IND-Feb. 27, 2007, Late Cycle Meeting-July 22, 2013
❖ Advisory Committee Meeting(s)	X AC meeting
• Date(s) of Meeting(s)	August 6, 2013
• 48-hour alert or minutes, if available (<i>do not include transcript</i>)	Not available
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input type="checkbox"/> None October 8, 2013
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None Sept. 9, 2013
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None Sept. 9, 2013
PMR/PMC Development Templates (<i>indicate total number</i>)	<input checked="" type="checkbox"/> None
Clinical Information⁶	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	NA
• Clinical review(s) (<i>indicate date for each review</i>)	July 8, 2013
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	X 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>)	See pgs 25-26 of Dr. Dunmmon's Medical Review
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	X None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	X Not applicable

⁶ Filing reviews should be filed with the discipline reviews.

❖ Risk Management <ul style="list-style-type: none"> REMS Documents and Supporting Statement (<i>indicate date(s) of submission(s)</i>) REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) 	February 8, 2013 July 19, Sept 5,6, & Oct. 7, 2013
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	August 16, 2013
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 checked="" type="checkbox"/> None
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	Concur w/review on July 1, 2013
Statistical Review(s) (<i>indicate date for each review</i>)	July 1, 2013
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)	X None
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)	Concur w/review on July 1, 2013
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	July 1, 2013
❖ DSI Clinical Pharmacology Inspection Review Summary (<i>include copies of OSI letters</i>)	X None
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None Sept. 20, 2013
• Supervisory Review(s) (<i>indicate date for each review</i>)	Concur w/review on June 19, 2013
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	June 19 and July 19, 2013
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	Biometrics-Stat review of Carcinogenicity-April 22, 2013
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	April 22, 2013
❖ ECAC/CAC report/memo of meeting	April 17, 2013
❖ OSI Nonclinical Inspection Review Summary (<i>include copies of OSI letters</i>)	X 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>	X None
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	August 20, 2013
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>	Product Quality-(Drug Substance)-7/17/13, (Drug Product)-6/27/13 Biopharmaceutics-6/11/13
❖ Microbiology Reviews <input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i> <input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>	X Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>	X None
❖ Environmental Assessment (check one) (original and supplemental applications)	
X Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	June 27, 2013
<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	
X NDAs: Facilities inspections (include EER printout) <i>(date completed must be within 2 years of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁷)</i>	Date completed: 02/14/13 X 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) (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>	X Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed (per review)

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

Appendix to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy 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).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.

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/s/

EDWARD J FROMM
10/09/2013

Executive CAC

Date of Meeting: April 16, 2013

Committee: Abby Jacobs, Ph.D., OND IO, Acting Chair
Paul Brown, Ph.D., OND IO, Member
Karen Davis Bruno, Ph.D., DMEP, Alternate Member
Thomas Papoian, Ph.D., DCRP, Team Leader
Elizabeth Hausner, D.V.M., DCRP, Presenting Reviewer

Author of Draft: E. Hausner

The following information reflects a brief summary of the Committee discussion and its recommendations.

IND # 75629/ NDA 204819

Drug Name: riociguat (BAY63-2521)

Sponsor: Bayer Healthcare

Background: Riociguat (BAY63-2521) is a soluble guanylate cyclase activator intended for the indications of chronic thromboembolic pulmonary hypertension (CTEPH) and pulmonary arterial hypertension (PAH). The drug facilitates the conversion of GTP to cGMP with the pharmacologic effect of smooth muscle relaxation. The drug has an active metabolite, BAY60-4552, that appears in both animals and humans as approximately 10% of the plasma AUC for total drug. The parent drug is not highly metabolized and is the predominant molecular form in circulation.

Mouse Carcinogenicity Study:

The mouse study used dietary administration that provided calculated doses of 0, 8, 16, or 32 mg/kg/day riociguat to the female CD-1(ICR)BR mice (n=50 per group) and doses of 0, 6, 12, or 25 mg/kg/day to the male mice (n=50 per group). No new toxicities emerged in the course of the study. A maximally tolerated dose was achieved in both sexes based on mortality.

Rat Carcinogenicity Study:

The rat study used dietary administration to provide doses of 0, 5, 10 or 20 mg/kg/day of riociguat to both sexes of Hsd Cpb:WU rats (n=50 per sex per group). No new toxicities emerged in the course of the study. A maximally tolerated dose was achieved in males based on mortality and in females based on weight loss.

Executive CAC Recommendations and Conclusions:

Mouse:

- The Committee found that the study was acceptable, noting prior Exec CAC concurrence with the protocol.
- The Committee concurred that there were no drug-related neoplasms.

Rat:

- The Committee found that the study was acceptable, noting prior Exec CAC concurrence with the protocol.
- The Committee concurred that there were no drug-related neoplasms.

Abigail Jacobs, Ph.D.
Acting Chair, Executive CAC

cc:\

- /Division File, DCRP
- /Thomas Papoian, Ph.D., DCRP
- /Elizabeth Hausner, D.V.M. DCRP
- /Ed Fromm R. Ph., RPM, DCRP
- /ASeifried, OND IO

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/s/

ADELE S SEIFRIED
04/17/2013

ABIGAIL C JACOBS
04/17/2013



NDA 204819

NDA ACKNOWLEDGMENT

Bayer HealthCare Pharmaceuticals, Inc.
Attention: Carmen Leung, R.Ph.
Deputy Director, Global Regulatory Affairs
P.O. Box 1000
Montville, NJ 07045-1000

Dear Ms. Leung:

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: Riociguat Tablets (BAY 63-2521), 0.5 mg, 1 mg, 1.5 mg, 2 mg, and 2.5 mg

Date of Application: February 8, 2013

Date of Receipt: February 8, 2013

Our Reference Number: NDA 204819

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 April 9, 2013, in accordance with 21 CFR 314.101(a).

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 Cardiovascular and Renal Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

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, please contact:

Dan Brum, Pharm.D., RAC
Regulatory Health Project Manager
(301) 796-0578

Sincerely,

{See appended electronic signature page}

Edward Fromm, R.Ph., RAC
Chief, Project Management Staff
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

EDWARD J FROMM
02/12/2013

Minutes of a teleconference with Bayer

Meeting Date: December 19, 2012
Application: IND 75629
Drug substance: riociguat
Sponsor: Bayer
Purpose: To further discuss CMC and DMEPA items outlined in pre-NDA preliminary responses

FDA Attendees:

Kasturi Srinivasachar, Ph.D.	Pharmaceutical Assessment Lead, Office of New Drug Quality Assessment
Pei-I Chu, Ph.D.	Reviewer, ONDQA
Irene Z. Chan, Pharm.D.	Team Leader, Division of Medication Error and Prevention Analysis
Kimberly Defronzo, RPh, MS, MBA	Reviewer, DMEPA
Dan Brum, Pharm.D., BCPS, RAC	Senior Regulatory Project Manager, DCRP

Sponsor attendees:

Regina Seidel – Lead Global Regulatory Strategist
Carmen Leung, R.Ph. – US Global Regulatory Strategist
Robert Haydu – US CMC Regulatory Affairs
Christine Tarenz – Global Regulatory CMC Manager
Winfried Joentgen, PhD – Chemical and Pharmaceutical Development
Urte Kuhland, PhD – Chemical and Pharmaceutical Development

Background

On November 1, 2012, I emailed Bayer preliminary responses (reference September 10, 2012 correspondence requesting a pre-NDA (including top-line results) meeting. In the November 1, 2012 correspondence, I indicated the meeting had been cancelled but that the sponsor should notify me if they wanted a follow-up teleconference to clarify particular issues.

On November 16, 2012, Bayer requested a teleconference with the Division to follow up on the following two items from the preliminary responses:

Additional CMC Comment: The structure of BAY 63-2521 suggests that this molecule may degrade (b) (4) (b) (4) In your NDA you must address this possibility by providing data showing whether this cleavage is likely to occur (b) (4) (b) (4) Because even small amounts (b) (4) (b) (4) would represent a significant safety concern, analytical methods of appropriate sensitivity should be used in these studies. Failure to address this concern could result in our refusal to file your application.

You propose to market five different strengths of riociguat, and each strength has been formulated to the same tablet weight, size, and shape. You intend to add color to assist in tablet identification; however, it was unclear in your briefing package what colors each of the five strengths will be, and whether the colors will be sufficiently distinct from each other. Therefore, we recommend you use five unique color schemes, not variations of the same hue, to ensure adequate strength differentiation within your product line.

Meeting discussion points

Bayer asked ONDQA to confirm whether Bayer's data to address FDA's concern regarding the possibility for BAY 63-2521 to degrade (b)(4) would be adequate for NDA submission (see sponsor's enclosed slide presentation).

ONDQA said the sponsor's approach was acceptable and the sponsor agreed to provide all the data in the NDA submission.

Bayer asked DMEPA to confirm whether Bayer's product differentiation strategy to reduce medication errors would be acceptable (e.g., colors for the five tablet strengths) – (see sponsor's enclosed slide presentation).

DMEPA provided the following response:

We do not agree with the product differentiation strategy you have proposed. Your proposed dosing for titration of riociguat will result in concomitant administration of more than one strength by the same patient during the titration period; therefore, ensuring the physical tablets can be clearly differentiated by patients is important from a safety perspective. Currently, we find some of the colors used for strength differentiation appear too similar and may lead to selection errors by patients. Additionally, you have proposed carrying your color differentiation scheme from your tablets to the labels, labeling, and packaging of your product, which can lead to selection errors by healthcare professionals during the dispensing of your product. Therefore, we recommend you improve the color differentiation of your physical tablets and labels and labeling to minimize the risk of confusion in the marketplace. We recommend not using colors that are varying shades of the same color.

We also have concerns regarding the debossing of the tablets. Specifically, the use of trailing zeros for the 1.0 mg and 2.0 mg strengths may lead to confusion. The Institute for Safe Medication Practices does not recommend the use of trailing zeros for doses expressed in whole numbers since decimal points are easily overlooked. Additionally, by adding the trailing zero, your 1 mg and 2 mg tablets are no longer debossed with a single whole number, or single digit, which may be easier to differentiate from a number that includes two digits. This increases the similarity in debossing of the 1 mg and 2 mg strengths with the debossing of the other strengths proposed in your product line. We also note the debossing on one side of the tablet is identical for all strengths.

The blister packs will be reviewed during the review cycle.

Minutes preparation: *{See appended electronic signature page}*
Dan Brum, Pharm.D., RAC

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following this page

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/s/

DANIEL BRUM
12/21/2012



IND 75629

MEETING PRELIMINARY COMMENTS

Bayer HealthCare Pharmaceuticals, Inc.
Attention: Carmen Leung, R.Ph.
Deputy Director, Global Regulatory Affairs
P.O. Box 1000
Montville, New Jersey 07045-1000

Dear Ms. Leung:

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

We also refer to your September 10, 2012, correspondence, received September 10, 2012, requesting a pre-NDA (including top-line results) meeting.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

If you have any questions, please call me at (301)796-0578.

Sincerely,

{See appended electronic signature page}

Daniel Brum, PharmD, MBA, BCPS, RAC
Senior Regulatory Project Manager
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments

PRELIMINARY MEETING COMMENTS

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: November 2, 2012 @ 1-3 p.m.
Meeting Location: White Oak Bldg 22, Room 1315

Application Number: IND 75629
Product Name: riociguat tablets
Indication(s): pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH)
Sponsor/Applicant Name: Bayer

Introduction:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for November 2, 2012, 1 p.m., White Oak Building 22 Room 1315 between Bayer and the Division of Cardiovascular and Renal Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). Note that if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, we may not be prepared to discuss or reach agreement on such changes at the meeting although we will try to do so if possible. If any modifications to the development plan or additional questions for which you would like CDER feedback arise before the meeting, contact the RPM to discuss the possibility of including these items for discussion at the meeting.

*** Note: The Division does not believe that a meeting is necessary based on the contents of your briefing package and our responses; therefore, we are cancelling the meeting. If you wish to follow up with a teleconference to clarify any particular issues, please notify Dr. Brum.**

1.0 BACKGROUND

IND 75629 for riociguat (BAY 63-2521) was submitted on February 20, 2007 by Bayer Healthcare Pharmaceuticals. This new molecular entity is intended to treat chronic thromboembolic pulmonary hypertension (CTEPH: Group 4) and pulmonary arterial hypertension (PAH: Group 1).

Riociguat is a soluble guanylate cyclase (sGC) stimulator that increases production of cGMP. The phase 3 clinical development program for riociguat included separate studies in CTEPH (Study 11348, CHEST-1 (controlled) and -2 (extension)) and PAH (Study 12934, PATENT-1 (controlled) and -2(extension)). The primary endpoint in both CHEST-1 and PATENT-1 was the change from baseline to Week 16 (CHEST-1) and Week 12 (PATENT-1) in 6 minute walking distance (6MWD). An end of phase 2 (EOP2) meeting was held on May 29, 2008.

Riociguat immediate-release film-coated tablets are presented in the following strengths: 0.5, 1, 1.5, 2, and 2.5 mg.

Although there are several FDA-approved products to treat PAH, no drugs are FDA-approved to treat CTEPH although Bayer suggested in the briefing document that "a high proportion" of patients receive PAH drugs off-label for CTEPH.

Bayer intends to submit an NDA for CTEPH and PAH in 1Q2013 (as early as mid-January 2013). The purpose of this meeting is to discuss the format and content of an NDA to support approval of riociguat for the treatment of CTEPH and PAH. At this meeting*, Bayer also plans to discuss the summary results from the Phase 3 studies.

2. DISCUSSION

CHEMISTRY, MANUFACTURING AND CONTROLS

Question 1: Starting Material

Does the Division agree to the starting material concept for the synthesis of the drug substance?

Preliminary response: Yes, we agree.

Question 2: NDA Stability Package

Does the Division agree that the proposed stability data package is acceptable to support Riociguat tablets packaged in (b) (4) blisters and (b) (4) HDPE bottles?

Preliminary response: Your overall plan for conducting stability studies is acceptable. You will need to clarify if the HDPE bottle dimensions (thickness and size) or blister material of the commercial packaging is identical to the packaging used for the primary stability studies. In addition, any difference in the number of tablets to be packaged in commercial bottles from those in the primary stability studies should be justified by headspace to content ratio. The NDA submission should contain data to support container closure performance in accordance with USP <661> and <671>.

Additional CMC Comment: The structure of BAY 63-2521 suggests that this molecule may degrade (b) (4)

(b) (4) In your NDA you must address this possibility by providing data showing whether this cleavage is likely to occur under (b) (4)
(b) (4) Because even small amounts (b) (4) would represent a significant safety concern, analytical methods of appropriate sensitivity should be used in these studies. Failure to address this concern could result in our refusal to file your application.

NONCLINICAL

Question 3: Nonclinical Studies

Does the Division agree that the non-clinical studies listed in the pre-NDA background document are sufficient to support filing and potential approval of the riociguat NDA?

Preliminary response: They appear adequate.

Question 4: Data Line Listings from Animal Toxicology Studies

Does the Division agree with Bayer's plan to submit data line listings from animal toxicological studies electronically, as scanned appendices within the study reports?

Preliminary response: Yes.

CLINICAL PHARMACOLOGY

Question 5 Clinical Pharmacology Studies

Does the Division agree that the clinical pharmacology studies listed in the pre-NDA background document are sufficient to support filing and potential approval of the riociguat NDA?

Preliminary response: Yes. Please complete and submit the attached Clinical Pharmacology Summary Aid in your NDA.

CLINICAL AND STATISTICAL

Question 6: Indications

Does the Division agree that the pivotal trials (study 11348 - CHEST-1, study 12934- PATENT-1) provide the necessary information to support filing and review of the riociguat NDA for proposed indications in CTEPH and PAH?

Preliminary response: Yes.

Question 7: Multiregional Phase 3 Data

Does the Division agree that the non—US data obtained from the multiregional phase 3 studies are applicable to the US target population to support filing of the riociguat NDA for CTEPH and PAH, and are there specific analyses/or presentation of the current data that the Division would like in the NDA to support review of the 6MWD treatment effects as it applies to the US patient population?

Preliminary response: There is insufficient information in your briefing package to answer your question. We note that the results in the various regions appear heterogeneous. We disagree with your statement that the regional differences are not of concern because a statistical test for regional heterogeneity yielded a p-value > 0.05; the analysis was underpowered to detect a difference. Whether your non-USA data are applicable to patients in our country may be dependent on how different the patient demographics, disease characteristics, background therapies, medical management, and disposition of subjects enrolled outside of the USA are from patients in the USA. Your submission should include sufficient detail so that we can analyze the impact of these elements and characteristics.

Question 8: Dosage and Administration

Does the Division agree that the data from the pivotal phase 3 studies, the proposed PK/PD evaluations, and exposure response analyses will provide the information necessary for the Division's review of the proposed dosing regimen?

Preliminary response: This information will be helpful. We are concerned, however, about the table you propose for adjusting the dose of riociguat (Table A. on page 53 of 62 in your pre-NDA briefing document).

(b) (4)

(b) (4)

Question 9: Integrated Analysis of Efficacy

Can the Division clarify whether TTCW is the only efficacy outcome from the extension trials that need to be updated at the 120 day safety update?

Preliminary response: No. At the time of your submission, please submit the following analyses:

- CHEST-2
 - 6MWD change from baseline at Week 16 of the open label trial, grouping patients by whether they were in the active treatment group or placebo treatment group during the double blind trial using the same imputation methods for missing data as were used for the primary efficacy analysis. We agree with your proposal to use the 6MWD at visit 7 of CHEST-1 as your new baseline for this analysis.
 - TTCW from rollover into CHEST-2 with breakdown of component outcomes.

- PATENT-2
 - 6MWD change from baseline at Week 16 of the open label trial, grouping patients by whether they were in the active treatment group or placebo treatment group during the double blind trial, using the same imputation methods for missing data as were used for the primary efficacy analysis. We agree with your proposal to use the 6MWD at visit 6 of PATENT-1 as your new baseline for this analysis.
 - TTCW from rollover into PATENT-2 with breakdown of component outcomes.

Please re-run these analyses with updated information at the time of the 120-day safety update.

Question 10: SAP for Integrated Analysis of Safety

Can the Division provide guidance on additional relevant laboratory and ECG parameters for inclusion into the mixed model analysis of variance?

Preliminary response: Please provide this information for ALT, AST, Alk Phos, T-bili, serum creatinine, CK and/or troponins (if measured), hemoglobin, hematocrit, platelets, white blood cell count (total), diastolic blood pressure, systolic blood pressure, heart rate, and any electrolytes of special interest or where known potentially clinically relevant abnormalities are seen or suspected.

Analysis of ECG parameters by this method will not be necessary based on your previously submitted QT information.

Question 11: 4 Month Safety Update

Does the Division agree with the proposed plans for the content and data to be included in the 4-Month Safety Update?

Preliminary response: Yes

Question 12: Risk Management

Does the Division have any potential concerns that may merit a REMS at this time?

Preliminary response: Based on the information available at this time, we believe that a risk evaluation and mitigation strategy (REMS) will be necessary to ensure that the benefits of the drug outweigh the risk of embryo-fetal toxicity. Therefore, we encourage you to submit a proposed REMS with your application. A complete review of the REMS, in conjunction with the full clinical review of the NDA will be necessary to determine that the REMS adequately addresses the safety risks and meets the criteria set forth in section 505-1 of the Federal Food, Drug, and Cosmetic Act.

Question 13: Priority Review

Does the Division agree that the NDA could meet the classification for Priority Review?

Preliminary response: Your summary of the results of CHEST-1 indicates that riociguat is an effective treatment for a condition where no satisfactory alternative therapy exists, i.e., for treatment of CTEPH. If our preliminary estimate at the time of filing your NDA is that riociguat has the potential to provide effective therapy for CTEPH, then we will designate the review as priority.

Question 14: Pediatrics

Does the Division have any comments to the proposed pediatric strategy?

Preliminary response: If you request a waiver of studies required under PREA for CTEPH, we believe that it is likely to be granted because it appears the condition is rare in children.

However, we are uncertain that a full waiver of pediatric studies in PAH is appropriate. If you request a full waiver in your NDA submission then you should include supportive information such as data regarding the incidence, prevalence, and available therapies for pediatric patients with PAH. We note that non-clinical studies have demonstrated adverse effects in developing bone; information on how these findings would affect the conduct of studies in pediatric patients may be relevant. If you do not have adequate data to support a full waiver, you should submit a pediatric plan that includes a plan to study all relevant pediatric populations.

Finally, we remind you that the final decision to waive or defer pediatric studies will be made by FDA's Pediatric Review Committee (PeRC) after you submit your NDA.

Question 15: ISS / ISE

The Sponsor will provide the ISE and ISS text, attachments and appendices in Module 5.3.5.3 as per the FDA “Guidance for Industry, Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Documents” (April 2009). The Sponsor proposes a link in Modules 2.7.3 (Summary of Clinical Efficacy) and 2.7.4 (Summary of Clinical Safety) to the ISE and ISS, respectively and not to provide summaries of the integrated analyses in these sections. Does the Division agree with this proposal?

Preliminary response: Yes.

Question 16: Financial Disclosure

Does the Division agree with Bayer’s proposal to submit financial disclosure information from only the two pivotal studies PATENT-1 (Study 12934) and CHEST-1 (Study 11348) in the NDA?

Preliminary response: Yes.

Question 17: Applicant Orientation Meeting/Advisory Committee Meeting

Does the Division anticipate requesting an Applicant Orientation meeting for the riociguat NDA and/or that the NDA will be subject to an Advisory Committee meeting?

Preliminary response: We may request an Applicant Orientation meeting once the NDA is submitted. You should prepare for the possibility that the NDA will be discussed at an Advisory Committee meeting although a final decision has not been made at this time.

Additional Comments:

You propose to market five different strengths of riociguat, and each strength has been formulated to the same tablet weight, size, and shape. You intend to add color to assist in tablet identification; however, it was unclear in your briefing package what colors each of the five strengths will be, and whether the colors will be sufficiently distinct from each other. Therefore, we recommend you use five unique color schemes, not variations of the same hue, to ensure adequate strength differentiation within your product line.

As stated in our September 14, 2012 communication granting this meeting, this new molecular entity will be subject to “The Program” under PDUFA V. We believe our responses to your questions constitute an agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or

other risk management actions. Based on your questions, we anticipate no minor application components to be submitted after the submission of the original application.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities. Information on PDUFA V and “The Program” is available at <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm>.

The sponsor made no request that minor components of the NDA be submitted after NDA submission. And as much as possible, an agreement on the content of a complete application was made during preliminary discussions.

As noted above in Response 12, a preliminary discussion on the need for a REMS occurred.

PREA PEDIATRIC STUDY PLAN

The Food and Drug Administration Safety and Innovation Act of 2012 changes the timeline for submission of a PREA Pediatric Study Plan and includes a timeline for the implementation of these changes. You should review this law and assess if your application will be affected by these changes. If you have any questions, please email the Pediatric Team at Pedsdrugs@fda.hhs.gov.

PRESCRIBING INFORMATION

Proposed prescribing information (PI) submitted with your application must conform to the content and format regulations found at 21 CFR 201.56 and 201.57.

Summary of the Final Rule on the Requirements for Prescribing Information for Drug and Biological Products, labeling guidances, sample tool illustrating Highlights and Table of Contents, an educational module concerning prescription drug labeling, and fictitious prototypes of prescribing information are available at: <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>. We encourage you to review the information at this website and use it as you draft prescribing information for your application.

ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the draft guidance for industry, “Guidance for Industry Assessment of Abuse Potential of Drugs,” available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf>

MANUFACTURING FACILITIES

To facilitate our inspectional process, the Office of Manufacturing and Product Quality in CDER's Office of Compliance requests that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

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

/s/

DANIEL BRUM
11/01/2012

Meeting Minutes

Meeting Date: October 9, 2009
Application: IND 75,629
Drug: riociguat (BAY 63-2521)
Sponsor: Bayer
Purpose/indication: PAH (b) (4)
Meeting Type: C

FDA Attendees:

Norman Stockbridge, MD, PhD	Director, DCRP
Shari Targum, MD	Team Leader, Medical Officer
Nancy Xu, MD	Medical Officer
Fanhui Kong, PhD	Statistician
Raj Madabushi, PhD	Team Leader, Clinical Pharmacology
Islam Younis, PhD	Clinical Pharmacologist
Pravin Jadhav, PhD	Team Leader, Pharmacometrics
Satjit Brar, PhD	Pharmacometrician
Edward Fromm, RPh, RAC	Chief, Project Management Staff
Dan Brum, PharmD, RAC	Regulatory Project Manager

Bayer

Dr. Francis Boateng, Deputy Director, Global Clinical Statistics

Dr. Janet Herrington, Director Global Regulatory Affairs, US Head General Medicine

Dr. Mel Lederman, US Medical Director

Dr. Wolfgang Mueck, Clinical Pharmacologist

Ms. Alexandra Park, Deputy Director, Global Regulatory Affairs

Dr. Maria-Luisa Rodriguez, Global Project Leader

Ms. Regina Seidel, Director, Senior Global Regulatory Strategist

Dr. Max Wegner, Vice President Global Regulatory Affairs, Therapeutic Area Head General Medicine

Dr. Gerrit Weimann, Global Clinical Leader

Background:

On February 20, 2007, Bayer Healthcare Pharmaceuticals submitted an IND for riociguat (BAY 63-2521). According to the sponsor, riociguat stimulates the enzyme soluble guanylate cyclase (sGC) independently of nitric oxide (NO), the endogenous activator of the enzyme.

On May 29, 2008, DCRP met with the sponsor during an EOP2 meeting to discuss the use of riociguat for the treatment of chronic thromboembolic pulmonary hypertension (CTEPH) and pulmonary arterial hypertension (PAH) (see FDA meeting minutes dated June 15, 2008 for details).

With regard to this meeting, Bayer is developing riociguat for the following indication:

(b) (4)

- Meeting Request received July 14, 2009
- Meeting Package received September 8, 2009
- Preliminary Responses sent October 8, 2009
- Meeting held October 9, 2009 (**sponsor's slide presentation enclosed**)

The sponsor requested responses to the following questions listed in the meeting briefing package. The questions are repeated below, and the Division's **preliminary responses** are in **bold, black font**. Bold green text reflects **discussion during the meeting**.

Meeting: The following questions were addressed:

Clinical Pharmacology

Question 1

As presented in Section 4.6, does the Agency agree that no additional pharmacology studies are needed to support the clinical development in PH associated with left ventricular disease?

FDA Response: No. It depends on the design of the clinical bone metabolism study.

Discussion during the meeting: See "additional comments" below.*

Also, apart from the conducted and on-going clinical pharmacology studies, you will need to address the following issues:

I. Pharmacokinetic drug-drug interactions between riociguat and:

1. Digoxin
2. Bosentan
3. Oral contraceptives
4. Ritonavir
5. Rifampin

Discussion during the meeting: The sponsor proposed to use an in vitro study to explore the P-gP inhibitory potential before conducting an in vivo study with digoxin. The approach is acceptable.

The drug interaction potential with bosentan will be explored in the phase 2 and 3 studies. Sparse PK samples of riociguat and the active metabolite will be collected to characterize the interaction. The potential induction effect of bosentan is expected to provide information pertaining to the interaction potential with rifampicin. The approach is acceptable.

The Division encouraged the sponsor to perform a multiple dose study with ritonavir to understand the interaction potential and help guide dosing in patients with HIV.

The sponsor mentioned that CYP1A1 appears to be responsible for metabolism of the parent compound. To provide the Division with insight into the safety of the active metabolite, the sponsor will submit information from a recently completed Proof of Concept (PoC) study.

II. Pharmacodynamic drug-drug interactions between riociguat and:

1. Alpha blockers
2. Antihypertensives
3. Alcohol

Discussion during the meeting: The Division does not expect the sponsor to conduct a targeted PD drug-drug interaction study for every class of drugs that has the potential to result in blood pressure reduction, but instead to focus on those with overlapping mechanisms of action e.g., nitrates and PDE-5 inhibitors. The sponsor proposed to conduct an in vivo interaction study with nitrates.

III. Dose adjustment of riociguat in geriatric patients.

Discussion during the meeting: The sponsor said that an age and gender study demonstrated a moderate effect of age on exposure (increased by ~40%) in healthy volunteers, and that riociguat exposure is strongly affected by the underlying disease (~3-fold increase when healthy volunteers are compared to elderly patients with PAH). Also, the sponsor contends that high inter-individual variability of exposure will be addressed by titration to effect. The Division noted that a sufficient number of geriatric subjects would be required to gain useful information regarding dose adjustment in elderly patients.

Clinical

Question 1

Does the Agency agree to the overall concept of developing riociguat for the following indication:

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(b) (4)

FDA Response: We agree with the overall concept of developing riociguat

(b) (4)

For your pivotal trial, we will be more assured if the individual components of your combined primary endpoint, hospitalization or death trend in the same direction. The results of the other endpoints may need to be replicated in another trial unless the p-value is highly significant. We will also analyze all-cause mortality, CV mortality, and CV hospitalization separately.

Discussion during the meeting: The sponsor requested clarification on the following statement in the preliminary response: “The results of the other endpoints may need to be replicated in another trial unless the p-value is highly significant.” The Division replied that the level of persuasiveness will depend on the composition of the results. For example, a nominal p-value of 0.05 carried by a large improvement in mortality and perhaps a neutral or even adverse trend on hospitalization *may* be okay; however, the inverse of this situation where hospitalization appears favorable but mortality trends poorly would be viewed negatively. So there is a possibility that the primary endpoint is significant while the drug is not approvable. The Division noted that two trials are likely needed to position symptomatic claims such as 6MW in the indications section of the labeling.

Question 2

Does the Agency concur that the proposed phase II program supports the progression into Phase III?

FDA Response: In the phase 2 dose-finding trial (14308), you propose a randomized, double-blind, placebo-controlled, parallel-group design testing three doses of riociguat against placebo. Your endpoints for trial 14308 will include functional status, invasive hemodynamics, ECHO, vitals and safety. Since your primary endpoint in your phase 3 study is different from those of trial 14308, we recommend that you consider more than one dose in your phase 3 trial. You might consider a functional endpoint as one of your secondary endpoints.

Discussion during the meeting: The sponsor asked for clarification in the preliminary response regarding functional endpoints, if the Division would provide some examples, and whether the comment was respect to Phase 2 or Phase 3. The Division clarified that the comment “consider a functional endpoint as one of your secondary endpoints” was directed at the phase 3 study, but that an adequately powered Phase 2 study with clinically meaningful endpoints might well be considered a Phase 3 study. Hypothetically speaking, the Division mentioned that although 6MW has historically been used as a primary endpoint, other choices of endpoints, ones perhaps more reflective of clinically relevant outcomes (e.g., delay in clinical worsening) would be more influential. In any case, the Division cautioned the sponsor that a win on 6MW would not guarantee a favorable regulatory action; the benefit-to-risk profile of riociguat would be evaluated in the context of approved PAH therapies.

Question 3

Does the Agency agree that additional invasive hemodynamic measurements are not necessary in the pivotal Phase III?

FDA Response: Yes.

No further discussion.

Question 4

Does the Agency concur with Bayer's preliminary proposal for the Phase III trial, and key elements of the Phase III program, as presented?

FDA Response: Please also see comments under questions 1 and 2.

In addition, we recommend that you conduct an event-driven trial.

You are enrolling patients with pulmonary hypertension due to left heart disease from systolic dysfunction, diastolic dysfunction and valvular disease. You might consider stratifying randomization by etiology (e.g., left heart disease).

It is unclear why a 2:1 randomization ratio was selected, given the fact that the statistical power may be compromised with the unbalanced randomization ratio.

Discussion during the meeting: The sponsor explained that they are currently focused on left heart disease from systolic dysfunction and that the 2:1 randomization ratio was proposed for ethical reasons because they expect the drug to demonstrate a sizeable benefit. But this is not fully determined and they will revisit the issue before the Phase III trial according to the Phase II study results. The sponsor also stated that they are not planning to study more than one dose in Phase 3 and there is enormous intersubject (not intrasubject) variability with regard to dose and resultant plasma concentrations. Assuming 2:1 randomization, the Division asked if the sponsor had considered splitting the drug arm into two doses and then pooling the doses for the primary analysis. On a related note, the Division emphasized that dose-response data are important for providing useful dosage and administration information to prescribers.

There was some additional discussion regarding intersubject variability and possible causes; however, since causes for the variability are not well understood, the sponsor plans to titrate patients based on tolerability and safety.

Additional comments:

If you have not done so, please submit the troponin and CKMB data for trial 12166 and other trials using riociguat (BAY-2521).

Discussion during the meeting: The sponsor has submitted the trial report for 12166 and will provide this information for other trials when available. At this point, the sponsor said zero patients have had elevated CKMB levels or ECG changes.

Given osteochondrosis was observed in dogs, and trabecular disorganization and cartilage thickening was observed in rats, you should monitor bone mineral density and fracture incidence in ongoing and planned clinical trials.

Discussion during the meeting *: The sponsor clarified that they did not see any osteochondrosis in dogs, rather the findings noted were in rats and only during the growth phase. The sponsor also apprised the Division of some completed and ongoing studies, as well as monitoring plans, that address this issue (see sponsor's slides for additional details):

- **Preclinical: Mechanistic study on bone density for different age groups (adult rats) ongoing (results available soon). Histologically no findings for any bone alterations so far. No morphological findings after 6 months of treatment.**
- **A 14 day-study on bone metabolism in healthy subjects is in progress and planned to have last patient/last visit end of 2009.**
- **Monitor and analyze fractures reported as adverse events in on-going Phase III studies.**
- **A marker of bone remodeling that has been used to evaluate fracture risk, serum type I collagen C-telopeptide (CTX), is included in the ongoing Phase III studies.**

Additionally, the sponsor said they have not observed any fractures in any of their clinical studies (up to 2 years in duration) and that enrollment criteria specify that patients must be at least 18 years of age. The sponsor asked whether a bone density scan is necessary for their proposed phase 3 trial. The Division questioned the reliability of a 14-day study of bone metabolism in healthy subjects that does not include a positive control. Based on the sponsor's outside experts, they decided that a positive control was not necessary because the test is highly sensitive thereby providing sufficient power to detect small changes. The Division encouraged the sponsor to provide reassurance in this regard.

Because soluble guanylate cyclase is involved in vestibular function and hearing, in addition to the fact that you observed a case of "idiopathic" sudden sensorineural hearing loss in your development program, we expect you to submit reports for all similar cases under this IND.

Discussion during the meeting: The sponsor agreed to collect and submit any such 15-day adverse event reports to the IND. The Division asked the sponsor to not unblind the subjects (except perhaps in unusual circumstances, e.g. sudden hearing loss in a young subject). The Division also asked the sponsor to submit a summary of similar sensorineural hearing loss cases in their completed or ongoing studies with the active metabolite.

Minutes preparation: *{See appended electronic signature page}*
Dan Brum, Pharm.D., RAC

Concurrence, Chair: *{See appended electronic signature page}*
Norman Stockbridge, M.D., Ph.D.

Enclosed: Sponsor's slide presentation

Brum 10/10/09; 10/16/09

Younis 10/13/09

Brar 10/13/09

Madabushi 10/13/09

Jadhav 10/13/09

Xu 10/14/09

Kong 10/16/09

Targum 10/16/09

Fromm 10/16/09

Stockbridge 10/16/09

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
IND-75629	GI-1	BAYER HEALTHCARE PHARMACEUTICA LS INC	BAY 63 2521

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

/s/

DANIEL BRUM
10/19/2009

NORMAN L STOCKBRIDGE
10/19/2009

Meeting Minutes

Date: May 29, 2008
Application: IND 75,629
Drug: riociguot (BAY 63-2521)
Sponsor: Bayer
Purpose: End of Phase 2 (EOP2) Meeting
Meeting Type: B

FDA Attendees:

Norman Stockbridge, M.D., PhD.	Director
Ellis Unger, M.D.	Deputy Director
Thomas Marciniak, M.D.	Team Leader, Medical Officer
Salma Lemtouni, M.D., MPH	Medical Officer
Angelica Dorantes, Ph.D.	Clinical Pharmacologist
Elizabeth Hausner, DVM	Pharmacologist
Fanhui Kong, Ph.D.	Statistician
Edward Fromm, R.Ph.	Chief, Project Management Staff
Dan Brum, Pharm.D., MBA	Regulatory Health Project Manager

Representing Bayer

Dr. John Curram	Statistician
Dr. Reiner Frey	Clinical Pharmacologist
Ms. Margaret Foley	Assistant Director, Global Regulatory
Dr. Volker Geiss	Toxicologist
Dr. Mel Lederman	US Medical Director
Dr. Wolfgang Mueck	Clinical Pharmacologist
Dr. Maria-Luisa Rodriguez	Global Project Leader
Ms. Regina Seidel	Director, Global Regulatory
Dr. Johannes-Peter Stasch	Pharmacologist
Dr. Max Wegner	Global Regulatory Affairs
Dr. Gerrit Weimann	Global Clinical Leader

Background:

An IND was submitted on February 20, 2007 by Bayer Healthcare Pharmaceuticals for riociguot (BAY 63-2521). This new molecular entity is for the treatment of chronic thromboembolic pulmonary hypertension (CTEPH) and pulmonary arterial hypertension (PAH).

- Meeting Request received April 3, 2008
- Meeting Package received May 1, 2008
- Preliminary Responses sent May 22, 2008
- EOP2 Meeting held May 29, 2008

The sponsor requested responses to the following questions listed in the meeting briefing package. The questions are repeated below, and the Division's preliminary responses are in bold, black font. Bold green text reflects discussion during the meeting.

Meeting:

The following questions were addressed:

Clinical Questions

Question 1

Does the agency agree that the pivotal trials (study 11348 – CHEST-1, study 12934 – PATENT-1) could generate adequate information to support the following indications:

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FDA Response: Yes, but only if the primary endpoints are clinically relevant benefits (e.g., six minute walk distance (6MWD), clinical worsening, hospitalizations, mortality, etc.) for both studies. While you have asserted that 6MWD might not be the optimal endpoint for trials in chronic thromboembolic pulmonary hypertension (CTEPH) patients, Table 5-1 in your submission suggests that it should be suitable for trials with BAY 63-2521. Regardless, we will not accept hemodynamic changes as the primary endpoints for your pivotal studies.

Discussion during the meeting: The Division mentioned that a 30 meter change in 6MWD is not an uncommon treatment effect seen in clinical trials for drugs marketed for PAH. The Division cautioned the sponsor that a single trial at, say, $p=0.05$ is unlikely to be sufficient for approval, but that two successful trials (e.g., one in PAH and one in CTEPH both with p -values <0.05) likely would be.

Question 2

Does the agency agree to the study design, the primary and the secondary endpoints, the duration of the double-blind treatment phase, and sample size estimation, and the statistical

analysis plans of the two pivotal trials (study 11348 – CHEST-1, study 12934 – PATENT-1)?

FDA Response:

- **To avoid regression-to-the-mean effects, we recommend not using the 6MWDs used for eligibility determinations as the baseline values.**
- **You must explore more than one dose in your pivotal trials or provide other data showing how dosage relates to clinical benefits (i.e., not just hemodynamic effects.)**

Discussion during the meeting: The Division explained that the sponsor's

proposal to

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cannot help determine the dose

response curve. If the sponsor needs to titrate the dose for reasons of patient safety, then the trial should include multiple treatment arms (to avoid confounding the effects of dose and time). In PAH trials, short-term titrations can be problematic since effects on exercise may take weeks to become evident (e.g., hysteresis) even though changes in PVR can occur almost immediately after administering the drug.

The sponsor proposes to study a dose range, (b) (4) based on changes in hemodynamic effects in earlier studies; however, the difference between doses is quite narrow and the Division recommended studying a broader dose range.

The Division emphasized that even a notion of unblinding (whether true or inferred) will affect how the Division views the integrity of a trial and that the sponsor should also be interpreting such findings cautiously – this is related to a patient in an open label study with a documented 100 m improvement in 6MWD (sponsor's slide).

- **An analysis set including only patients who have taken medication and who have a post-baseline measurement or died is not intent-to-treat (ITT). Please**

do not reference this analysis set as ITT. The appropriate analysis set is true ITT: all patients as randomized. For small PAH trials, dropouts or other deviations from true ITT have been problematic; variations in handling missing data for one or two patients have changed the p-values for 6MWD endpoints from about 0.04 to 0.09. Your studies must be robust to such variations. Please strive to minimize dropouts and insure that the maximum numbers of randomized patients have complete evaluations at the pre-specified endpoint times. Patients who fail to take any study medication should be minimal (one or two). Early dropouts should be included in the analysis set, and it is critical to pre-specify procedures for handling missing data (see below).

- You must describe, clearly and completely, all procedures for handling missing data. You must address all possibilities for the occurrences of missing data. For example, you propose that if the subject stops the study medication prematurely due to clinical worsening, the values recorded for the termination visit will be used. What if the patient does not complete the termination visit? If the clinical worsening and the termination visit are early, how does this value correspond to the desired ITT value at the pre-specified endpoint time? Assigning a worse case (or worse rank if data are non-parametric) endpoint value may be more appropriate.
- If a patient requires oxygen or an increase in oxygen therapy during the study and the patient completes a 6MW at the pre-specified endpoint time without using increased oxygen, the 6MWD may be acceptable as an endpoint value. If such a patient does not complete a 6MW at the pre-specified endpoint time without using increased oxygen, then that patient should be counted as clinical worsening. Hence you should specify that final walks be completed without a change in oxygen therapy—e.g., if the patient had a change in oxygen treatment, revert to the original level immediately prior to conducting the final 6MW.

- You should control the endpoint determinations relative to the administration of study drug. You should include 6MW and other endpoint measurements at trough (prior to next dose) and estimated peak drug levels.

Discussion during the meeting: Based on the TID dosing regimen and resulting plasma profile that appeared to be relatively constant over 24 hours (sponsor's slide), the Division does not require the sponsor to measure endpoints at peak (in addition to trough); however, the Division mentioned that peak and trough results have the potential to support favorable labeling. Also, the Division is not concerned about differences in hemodynamic effects at peak versus trough.

- For clinical worsening, including persistent decrease in 6MWD may make this secondary endpoint identical to your primary endpoint. Decreases in 6MWD should be associated with changes in other factors that indicate unequivocal deterioration (hospitalization, increase in signs and symptoms, etc.). Start of new PH-specific treatment and worsening of functional class are subjective determinations and, due to the unblinded nature of your studies, should not be used alone. To use clinical worsening as an endpoint, you should provide a definition that does not allow subjective determinations alone to define clinical worsening, and all possible clinical worsening cases should be adjudicated by a blinded endpoints committee (including blinding to the hemodynamic effects of BAY 63-2521.)

Discussion during the meeting: Defining clinical worsening is challenging and the Division voiced concern that subjective elements on the part of investigators can creep into measurements and evaluations. If the sponsor believes riociguot can substantially improve functioning independent of potentially biased measurements of 6MWD, clinical worsening should be at the top of the list of secondary endpoints, and 6MWD should not be a major component of it.

Because the imputation methods you are proposing (e.g., 0 for 6MWD in patients who die) are likely to produce non-normal distributions, you should use non-parametric tests for your 6MWD analyses. If you propose the

possibility of switching from a parametric to a non-parametric test based on a post-hoc determination of normality for any analysis, the test and criterion for non-normality must be pre-specified such that no judgment is needed in applying them.

Discussion during the meeting: The Division reiterated the importance of pre-specifying the criterion for using parametric or non-parametric tests.

- Your statistical analysis plan must provide an analysis scheme for the secondary endpoints preserving an overall alpha of 0.05.

Discussion during the meeting: The Division thought the sponsor's overall strategy was reasonable, but stated that winning on PVR was trivial in comparison to demonstrating improvements in patient reported outcomes or other clinically defined events. The sponsor should decide whether pooling doses for power is sensible versus selecting a single dose, but regardless, the sponsor must plan to control the type I error rate.

- Please submit randomization lists for the studies prior to study initiation. You should submit the lists as encrypted files (e.g., using WinZip) and do not submit the encryption key until NDA submission.
- Please submit your final statistical analysis plan, including complete approaches for handling missing data and clinical worsening, prior to enrollment of substantial numbers of subjects.
- We recommend that your long-term safety study (PATENT-2) be controlled. Sildenafil is an appropriate active control.

Discussion during the meeting: The Division clarified that sildenafil was suggested as one example of an active comparator if a placebo arm is not included. To maintain the blind, the Division suggested implementing a double-dummy design as one option. In sum, a study without a control group would not be informative and was discouraged.

The Division recommended the sponsor consider a withdrawal study design and added that since there are no data to support the concept that patients acutely decompensate following abrupt discontinuation of PAH drugs, a randomized withdrawal design will be of particular value, if implemented in a setting of careful monitoring with reassuring escape criteria, a sensible consent form, and an open-minded community in which to conduct the study.

Question 3

Based on “Guidance for Industry Fast Track Development Programs – Designation, Development, and Application Review” (January 2006) and the phase II study 12166 interim results for the 13 CTEPH patients, the sponsor proposes that the clinical development program for BAY 63-2521 in the indication CTEPH be given fast track designation. Does the agency agree?

FDA Response: While the serious and life-threatening nature of the disease supports your request for Fast Track designation, the proposed primary endpoints do not address serious aspects. To obtain a Fast Track designation, your primary endpoints must address a serious aspect of the condition, e.g., mortality, avoidance of hospitalizations, etc.

Question 4

Does the agency agree to the dose titration scheme as used already in the phase II study (study 12166) in order to optimize the individual dose for a patient?

FDA Response: We suggest that you study more than one target dose in a parallel design.

Question 5

Does the agency agree that the company defers to conduct clinical trials in adolescents until results of the pivotal trials in adults become available? Does the agency agree to a waiver for preterm, newborns, infants and toddlers and children?

FDA Response: It is premature to make these determinations. We, along with the Pediatric Review Committee, will evaluate your requests during review of your NDA.

Question 6

Does the Agency agree that the series of completed, ongoing and planned clinical pharmacology studies are sufficient to support the clinical program detailed in this submission and in addition will form an adequate basis to reach a decision regarding license approval?

FDA Response: Yes.

Question 7

(b) (4)



FDA Response: No. Since the PK findings of volunteers are different from those in patients, you should consider studying the effect of your drug on QT in a subpopulation of your Phase III studies using the formal QT study design, that is rigorously collecting ECGs at multiple timepoints and including a positive control.

Discussion during the meeting: The Division stressed the importance of including a positive control (single dose moxifloxacin) in a thorough QT study. The Division said that performing the QT study in one of the two planned patient populations (e.g., PAH) would suffice.

Preclinical Questions

Question 8

Does the Agency agree that the series of completed and ongoing preclinical pharmacokinetic and drug metabolism investigations are sufficient to support the clinical program detailed in this submission and in addition will form an adequate basis to reach a decision regarding license approval?

FDA Response: Please see FDA Response to Question 9.

Question 9

Does the Agency agree that the series of completed and ongoing nonclinical safety studies and their results will be sufficient to support the clinical program detailed in this submission and the license approval?

FDA Response: No. You need to conduct a study in non-rodents (e.g., dogs) for nine to 12 months in duration. You should also characterize the endocrine results of your non-clinical studies and describe their relevance to humans (e.g., effects on the uterus, prostate gland, heart, and bone).

Reports for the non-clinical studies of 6 months duration should be submitted prior to beginning the clinical studies of greater than 3 months duration as per the Guidance: M3 Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals.

Discussion during the meeting: Results from the segment III study will help to address many of the Division's concerns regarding effects of riociguot on the endocrine system and bone development. Data from the sponsor's six month dog study is forthcoming and a twelve month dog study is set to begin in two weeks. The Division said that no additional nonclinical information is needed at this time.

Chemistry, Manufacturing and Controls

Question 10

Does the Agency agree to the starting material concept for the synthesis of the drug substance as detailed in the briefing package?

FDA Response: Before we can agree to the starting material concept, we would like you to respond to the following comments:

- **Provide a detailed description of how you synthesize the designated starting material,** (b) (4)
- **Provide structural characterization of** (b) (4)
- **Describe how potential impurities and impurities listed on page 1270 of the meeting package are obtained and structurally characterized in the starting material.**
- **Indicate whether** (b) (4) **will be manufactured or purchased from vendors. If the starting material will be manufactured or purchased from vendors, provide your plans for the qualification of a new vendor. Also, please consider that there may be specific impurities that need to be controlled in the starting material provided by a current or future vendor.**

Discussion during the meeting: The sponsor plans to submit a written response to the preliminary response in Question #10 "in the near future."

Minutes preparation: *{See appended electronic signature page}*
Dan Brum, Pharm.D., MBA

Concurrence, Chair: *{See appended electronic signature page}*
Norman Stockbridge, M.D., Ph.D.

Brum 6/2/08
Hausner 6/3/08
Dorantes 6/4/08
Lemtouni 6/4/08
Kong 6/4/08
Marciniak 6/4/08
Unger 6/10/08
Fromm 6/11/08
Stockbridge 6/11/08
Finalized 6/14/08

Linked Applications

Sponsor Name

Drug Name

IND 75629

BAYER HEALTHCARE
PHARMACEUTICALS
INC

BAY 63 2521

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/s/

DANIEL BRUM
06/14/2008

NORMAN L STOCKBRIDGE
06/15/2008

Executive CAC

Date of Meeting: June 12, 2007

Committee: David Jacobson Kram, Ph.D., OND IO, Member
Joseph Contrera, Ph.D., OPS, Member
Sushanta Chakder R.Ph., Ph.D., DGP Member
Al DeFelice Ph.D., DCRP, Pharm Tox Supervisor
Elizabeth Hausner, D.V.M., DCRP Presenting Reviewer

Author of Minutes: Elizabeth Hausner

The following information reflects a brief summary of the Committee discussion and its recommendations.

Both rat and mouse studies demonstrated that there were no palatability issues. The protocols for both species indicate:

- histopathology is to be performed in all dose groups
- urinalysis will be performed at 6,12, 18 months and near the end of the study
- blood samples will be collected for glucose(rats) determination or hematology (mice)

IND # 75,629

Drug Name: BAY63-2521

Sponsor: Bayer HealthCare Pharmaceuticals

Mouse Dose Selection

The sponsor proposed doses of 0, 50, 100 and 200 ppm by dietary administration based on MTD (mortality at 400 ppm and mild effects at 200ppm).

Rat Carcinogenicity Study or Rat Dose Selection

The sponsor proposed doses of 0, 5, 10 and 20 mg/kg by dietary administration, based on MTD (decreased body weight gain).

Executive CAC Recommendations and Conclusions:

The Executive CAC concurred with the sponsor's proposed doses for both the rat and mouse 2-year carcinogenicity studies.

The Committee noted that hematology samples and urinalysis are not required for the carcinogenicity studies. If the Sponsor chooses to pursue those determinations, blood samples should not be taken from the main study animals. Rather, satellite groups should be used.

Also, if a radio is played in the animal housing, it should be played when the animals are normally awake, i.e. night-time for nocturnal animals.

David Jacobson Kram, Ph.D.
Chair, Executive CAC

cc:\

/Division File, DCRP
/Al DeFelice, DCRP
/Elizabeth Hausner, DCRP
/Dan Brum, DCRP
/ASeifried, OND IO

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/s/

David Jacobson-Kram
6/13/2007 09:51:12 AM

Minutes of a Meeting

Application Number: IND 75,629
Sponsor: Bayer Pharmaceuticals Corporation
Drug: BAY 63-2521

Type of Meeting: Pre-IND
Classification: B

Meeting Date: February 22, 2007
Preliminary Responses Sent: February 15, 2007

List of Attendees:

Division of Cardiovascular and Renal Products

Norman Stockbridge, M.D., Ph.D.	Director Division of Cardiovascular and Renal Products
Abraham Karkowsky, M.D., Ph.D.	Team Leader, Clinical Division of Cardiovascular and Renal Products
Tom Marciniak, M.D.	Team Leader, Clinical Division of Cardiovascular and Renal Products
Charles Resnick, Ph.D.	Team Leader, Pharmacology Division of Cardiovascular and Renal Products
Elizabeth Hausner, D.V.M.	Pharmacologist Division of Cardiovascular and Renal Products
Patrick Marroum, Ph.D.	Team Leader, Clinical Pharmacology Division of Clinical Pharmacology 1
Kasturi Srinivasachar, Ph.D.	Pharmaceutical Assessment Lead Office of New Drug Quality Assessment
Jim Hung, Ph.D.	Director Division of Biometrics 1
Cherry Liu, Ph.D.	Statistician Division of Biometrics 1
Melissa Robb	Regulatory Health Project Manager Division of Cardiovascular and Renal Products

Bayer Pharmaceuticals Corporation

John Curram, Ph.D.	Global Biometry Leader
Julie Dixon, Ph.D.	Associate Director U.S. Regulatory Affairs
Cornelia Middendorf, Ph.D.	Global Regulatory Strategist
Wolfgang Mueck, Ph.D.	Global Clinical Pharmacokineticist
Hans-Peter Stasch, Ph.D.	Senior Research Fellow, Global Pharmacologist
Max Wegner, Ph.D.	Head GRA Global Strategy
Gerrit Weimann, M.D.	Global Clinical Pharmacology Project Leader
Larry Winick, M.A.	Deputy Director, US Regulatory Affairs

Background:

BAY-632521 is a new chemical entity being developed for the treatment of chronic thromboembolic pulmonary hypertension (CTEPH) and the treatment of pulmonary arterial hypertension (PAH) (b) (4)

(b) (4) The sponsor requested this meeting to discuss their proposed Phase 2 clinical

development program. The sponsor would like to specifically address the issues of dose titration, dose selection, and study design. An IND application was received on February 20, 2007.

Questions:

1. *Due to its kinetic properties, BAY 63-2521 requires a dose titration to reach the optimal dose for an individual patient, where the systolic blood pressure will be used as a surrogate for the titration endpoint. Does the FDA agree with this development concept?*

Pre-meeting Response

Ideally dose-response studies should be based on a clinically meaningful endpoint such as six minute walk distance. However, for PAH we can understand why that might not be feasible. Given the PK variability of the drug, your proposal to titrate appears reasonable. We do have the following comments on your proposed titration: The drug effects upon heart rate appear to be the most consistent in normal volunteers and patients, while the effects upon SBP were more variable. We believe that your titration scheme also needs to consider adverse effects (e.g., heart rate, SBP changes) at peak as well as SBP changes at trough. We also note that the titration scheme, as well as the adverse event profile of the drug, may make blinding practically unachievable.

Meeting Discussion

The sponsor stated they agreed with the Division's comments and plan to incorporate them in their development program.

2. *Does the FDA agree that the proposed study design (Appendix 6, Study Outline of CTEPH Pivotal Trial) will form an appropriate basis for approval in the desired indication*

(b) (4)

Pre-meeting Response

One such successful study in CTEPH, combined with a second study in other PAH, may form an appropriate basis for approval for the indication stated above. However, because of the likelihood of unblinding, we are reluctant to state that changes in six minute walk alone for this protocol as proposed will support approval. We would like you to discuss in more details approaches for insuring blinding in your studies; for correlating walk changes with other, less influenceable measures such as hemodynamic changes; and for other endpoints such as time to clinical worsening.

Meeting Discussion

The sponsor stated that the proposed study designs for both patients with CTEPH and PAH involves a 16-week, double-blind trial. The first 8-week period will be for titration and the remaining 8-week period will be a maintenance phase. There will also be a 36-week, open-label extension trial that all patients can enroll in, if desired. This trial will also have an 8-week titration period. The sponsor presented their plans to ensure blinding throughout the trial. The Division noted that it appears that the sponsor is trying as best they can to ensure the trial maintains the blinding. However, in this case, it may be unachievable. Both the patient and the physician may be aware of the treatment group they are in, which may influence their performance on testing for the proposed endpoints. This is especially concerning because of the historically small treatment effect seen with drugs approved for this indication.

The Division stated that if the sponsor was able to demonstrate an effect on exercise and was also able to correlate that finding with hemodynamic effects, it would allow for a greater confidence in the exercise finding (which could

be influenced by unblinding). However, the Division stated that there are currently no data in approved products for PAH that indicates a correlation between exercise and hemodynamic effects. In fact, hemodynamic effects are often seen early before a benefit on exercise has been established. The Division suggested the sponsor conduct early sampling of hemodynamic parameters and try to demonstrate a relationship between increased exercise and decreased PVR.

The Division suggested the sponsor ask both the investigator and the patient prior to any walk test which treatment group they believe the patient is in. If there is little correlation between this finding and the walk test, this would reinforce that the blind seemed to have been maintained.

The Division suggested the sponsor continue to follow all patients who discontinue the study for clinically meaningful events during the 16-week, double-blind trial. The Division stated that often times, patients may deteriorate more after discontinuing the trial and these data will be helpful when imputing for missing data to establish the robustness of the findings. Following patients would also prevent biases in defining the cause of discontinuation, particularly if imputed values as worse outcome are assigned to those who discontinue due to worsening.

3. *Does the FDA agree with the proposed inclusion and exclusion criteria for this study?*

Pre-meeting Response

The Division agrees.

Meeting Discussion

There was no further discussion on this question.

4. *Does the FDA agree that the proposed statistical methods will be sufficient to evaluate BAY 63-2521 for the desired indication?*

Pre-meeting Response

For study of CTEPH, please provide statistical analysis plans for interim analysis and secondary efficacy endpoints.

Meeting Discussion

It was noted that most of the sponsor's proposed secondary endpoints have to do with clinical worsening which can be affected by the potential for unblinding (discussed in Question 2). The Division stated that the sponsor should submit a detailed statistical analysis plan (SAP) that prespecifies an alpha-conserving method to evaluate both the primary and secondary endpoints. The sponsor should also include in their SAP how they want to evaluate the secondary endpoints, by either allocating alpha to each of the endpoints or ranking them and then testing them sequentially until they reach an endpoint that is not significant.

The Division stated that laboratory values should be collected, but not included as a secondary endpoint.

The Division suggested the sponsor consider conducting a randomized withdrawal at the end of the extension trial to demonstrate a sustained effect. The Division stated that many of the drugs approved for PAH seem to need a longer time before an effect on exercise is seen. Therefore, it may take a while for the effect of the drug to go away. The sponsor should consider this if they plan to implement this in their proposed trial.

5. Does the FDA agree that the proposed study design (Appendix 7, study outline of pivotal PAH study) will form an appropriate basis for approval in the desired indication (b) (4)

(b) (4)

Pre-meeting Response

(b) (4)

6. Does the FDA agree that the proposed study design will form an appropriate basis for approval in the second desired indication (b) (4)

(b) (4)

Pre-meeting Response

We disagree that an estimated treatment effect size of (b) (4) is conservative. Hence we believe that your strata sizes are underpowered to detect treatment effects in the individual strata. However, if the study is convincingly

successful and the results in the strata are consistent, we would describe the strata results in the label and, depending upon how convincing the strata results are, include a generic or specific statement in the indications.

Meeting Discussion

This question was discussed with Question 5 above.

7. *Does the FDA agree with the proposed inclusion and exclusion criteria for this study?*

Pre-meeting Response

The Division agrees.

Meeting Discussion

There was no further discussion on this question.

8. *Does the FDA agree to the placebo-controlled study design for all three stratification groups?*

Pre-meeting Response

The Division agrees.

Meeting Discussion

There was no further discussion on this question.

9. *Does the FDA agree that the proposed statistical methods will be sufficient to evaluate BAY 63-2521 for the desired indication?*

Pre-meeting Response

For study of PAH, if a claim for a stratum is intended when the drug effect in all strata combined is not statistically significant, adjustment for multiplicity is needed. An overall $\alpha=0.05$ will need to be split between the overall drug effect and stratum-specific drug effects.

Meeting Discussion

The Division stated that the use of a covariate for the primary endpoint seems acceptable, but that the sponsor should propose a number of sensitivity analyses since a large number of dropouts are anticipated.

The sponsor stated they plan to use the last observation carried forward method when dealing with missing values. The Division noted that they have also seen programs that have used a last rank carried forward method to deal with missing values. The Division stated that the sponsor needs to consider how they will deal with all missing values, including deaths, clinical worsening, and dropouts, in their prespecified SAP. The Division stated that it is important to have a detailed SAP that has been reviewed by the Division long before all data is collected.

There are differing opinions within the Agency regarding imputation for the primary endpoint for the dropouts. Some believe it is a pure measurement of effect on exercise. Meanwhile, others look at a broader way to determine if the drug is a useful therapy. However, the Division stated that if the sponsor gets agreement on a plan that includes an algorithm for imputation, then there will be less difficulty in determining if there is a net benefit.

10. Does the FDA agree that one pivotal study with BAY 63-2521 (b) (4)
(b) (4) will form an appropriate basis for approval in both indications, PAH and CTEPH?

Pre-meeting Response

The Division agrees, but see responses 2 and 5.

Meeting Discussion

There was no further discussion on this question.

11. Does the FDA agree that the total number of patients treated with BAY 63-2521 will be sufficient for safety evaluation to support both New Drug Applications?

Pre-meeting Response

The numbers of patients may be sufficient. However, a final decision regarding of the adequacy of the safety data base depends upon the adverse event profile shown in the proposed studies.

Meeting Discussion

There was no further discussion on this question.

12. Does the FDA agree that for BAY 63-2521, a standard QT-program including a thorough QT/QTc study with a limited dose range and the collection of on-therapy ECGs in accordance with the current practices, will be sufficient?

Pre-meeting Response

The thorough QTc study needs to be a multiple dosing study. We note that the Investigator's Brochure does not describe problems with blood pressure in the normal volunteer studies and states that single dosing to 5 mg was well tolerated. The thorough QTc study must use the maximum tolerated dose.

Meeting Discussion

The Division stated that all thorough QTc trials only use one dose of moxifloxacin on the last day. There are some concerns related to only a single-dose of study drug. The active metabolite effects may not be seen with only one dose and with the variability of half-lives seen with this compound, some people may have accumulation that will only be seen with multiple dosing. The Division suggested the sponsor either study a continuous intravenous infusion or a lower dose more frequently, which would eliminate any peak-related side effects. The sponsor could also consider conducting the thorough QTc trial in patients, if the drug is better tolerated there than in normal volunteers.

The Division stated that the sponsor should collect ECGs at Cmax of both the parent and active metabolite. In addition, ECGs should be collected for at least 24 hours to ensure that drugs that do not have an acute effect will be detected.

The sponsor added that based on their simulations performed, they do not anticipate many patients to be titrated to 2.5 mg TID. In fact, they believe most patients will be on 1-1.5 mg TID.

The Division stated that the sponsor may want to consider rather than titrating the dose, to adjust the dosing interval or even consider developing a sustained-release product. The sponsor stated that they have considered both those options, but due to poor absorption in the colon do not believe a sustained-release product is possible.

13. Bayer will perform a phase IIb study in patients with chronic thromboembolic pulmonary hypertension (CTEPH) using clinical samples of BAY 63-2521 qualified for phase II. The study has sufficient power to be used as the one pivotal trial in this indication (refer to question 2 for study description). Does the FDA agree that this study can be used as the pivotal study for CTEPH although the clinical samples do not fulfill the requirements for phase III with regard to the manufacturing process?

Pre-meeting Response

The pivotal study should use the to-be-marketed formulation or the clinical study material must be demonstrated to be bioequivalent to the to-be-marketed formulation. It is not clear why you would like to use phase 2 qualified clinical samples for the CTEPH pivotal study when you state that drug product qualified for phase 3 studies will be available mid-2008 to be used in the pivotal study for PAH. We would recommend using the phase 3 supplies for both studies. If for some reason this is not possible, please clarify how the phase 2 material falls short of the requirements for phase 3 with regards to the manufacturing process. In general, our expectation is that clinical supplies for phase 3 trials will conform with the recommendations in Section IV of the *Guidance for Industry: INDs for Phase 2 and Phase 3 Studies, CMC Information*.

Meeting Discussion

The sponsor stated they agreed with the Division's comments and plan use the to-be-marketed formulation in the phase 3 trials.

Additional Comments at the Meeting

The Division noted that they have received the sponsor's IND application. The Division stated that the sponsor will need to submit pre-clinical data to support the duration of their proposed trials. The Division requested data on the receptor-binding studies. The sponsor stated that this data was included in the IND and will provide its' location for review.

Recorder: {See appended electronic signature page}

Chair Concurrence: {See appended electronic signature page}

Drafted: 2/23/07 Finalized: 3/3/07

RD:
Stockbridge 2/26/07
Karkowsky 2/26/07
Marciniak 2/26/07
Resnick 2/26/07
Hausner 2/26/07
Marroum 2/26/07
Srinivasachar 2/26/07
Hung 2/26/07
Liu 2/26/07

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Norman Stockbridge
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MID-CYCLE COMMUNICATION
DOCUMENTS



NDA 204819

LATE-CYCLE MEETING MINUTES

Bayer Healthcare Pharmaceuticals, Inc
Attention: Carmen Leung, R.Ph.
Deputy Director, Global Regulatory Affairs
P.O. Box 1000
Montville, NJ 07045-1000

Dear Ms. Leung,

Please refer to your New Drug Application (NDA) submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Adempas (riociguat) Tablets.

We also refer to the late cycle meeting (LCM) between representatives of your firm and the FDA on July 22, 2013.

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

If you have any questions, please call Edward Fromm, RPh, RAC, Regulatory Project Manager at (301) 796-1072.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division for Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:
Late Cycle Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF LATE-CYCLE MEETING MINUTES

Meeting Date and Time: July 22, 2013, 2 PM – 4 PM
Meeting Location: FDA White Oak, Building 22, Rm. 1313

Application Number: NDA 204819
Product Name: Adempas (riociguat) Tablets
Indication: **PAH (pulmonary arterial hypertension) and CTEPH (chronic thromboembolic hypertension)**
Sponsor/Applicant Name: Bayer Healthcare Pharmaceuticals

Meeting Chair: Norman Stockbridge, M.D., Ph.D.
Meeting Recorder: Edward Fromm, R.Ph., RAC

FDA ATTENDEES

Office of Drug Evaluation I
Robert Temple, M.D., Deputy Director

Office of Drug Evaluation I, Division of Cardiovascular and Renal Products
Norman Stockbridge, M.D., Ph.D., Director & Cross Discipline Team Leader for the NDA
Mary Ross Southworth, Pharm.D., Deputy Director for Safety
Preston Dunnmon, M.D., Medical Officer
Tom Papoian, Ph.D., Supervisory Pharmacologist
Elizabeth Hausner, D.V.M., Pharmacologist
Lori Wachter, RN, BSN, Safety Regulatory Project Manager
Meghan Delmastro-Greenwood, Ph.D., FDA Summer Fellow
Kelley Quesnelle, Ph.D., FDA Summer Fellow
Edward Fromm, R.Ph., RAC, Chief, Project Management Staff

Office of Drug Evaluation III, Division of Reproductive and Urologic Products
Eric Andreasen, Ph.D., Toxicologist
Stephen Voss, M.D., Medical Officer

Office of Biostatistics, Division of Biometrics I
James Hung, Team Leader

Office of Clinical Pharmacology, Division of Clinical Pharmacology I
Raj Madabushi, PhD, Team Leader
Divya Menon-Andersen, Ph.D., Clinical Pharmacologist

Office of Clinical Pharmacology, Division of Pharmacometrics
Yaning Wang, Ph.D., Senior Staff Fellow
Dhananjay D. Marathe, Ph.D., Visiting Associate

Office of Surveillance and Epidemiology, Division of Pharmacovigilance 1
Susan Lu, Pharm.D., Lead Pharmacist

Office of Surveillance and Epidemiology, Division of Epidemiology II
Jie Li, Ph.D., Epidemiologist

Office of Surveillance and Epidemiology, Division of Risk Management
Somya Dunn, M.D., Medical Officer
Kim Lehrfeld, Pharm.D., Pharmacist

Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis
Kim Defronzo, Pharm.D., Pharmacist

Office of Surveillance and Epidemiology, Office of Pharmacovigilance and Epidemiology
Allen Brinker, M.D., Epidemiologist

Office of Medical Policy, Office of Medical Policy Initiatives
Sharon R. Mills, RN, BSN, CCRP, Senior Patient Labeling Reviewer

Office of New Drugs, Pediatric and Maternal Health
Tammie Brent-Howard, M.D., Medical Officer
Amy Taylor, M.D., Medical Officer

Office of Planning & Informatics
Kimberly Taylor, Operation Research Analyst

(b) (4)

BAYER ATTENDEES

Carmen Leung, R.Ph. – U.S. Global Regulatory Strategist, Global Regulatory Affairs
Laila Narouz-Ott, Ph.D. – Lead Global Regulatory Strategist, Global Regulatory Affairs
Todd Paporello, PharmD., MBA, – U.S. Head Regulatory Affairs, Global Regulatory Affairs
Sharon W. Brown - US Head Womens Healthcare and Cardio Pulmonary, Global Regulatory Affairs
Max Wegner, Ph.D. – General Medicine Head, Global Regulatory Affairs
Gesa Schomakers, M.D. – Global Pharmacovigilance
Shaw Lamberson, M.D. - US Head of Pharmacovigilance
Stephan Vettel, Ph.D – Program Head, Global Project Management
Volker Geiss, DVM, Ph.D. – Toxicology Project Leader, Toxicology Project Management
Neil Davie, Ph.D. – Global Clinical Leader, Global Clinical Development

Nancy Cook Bruns, M.D. – Head, Cardiovascular Group, Global Clinical Development
David Muccino, M.D. – US Medical Affairs
Reiner Frey, M.D. – Clinical Pharmacology Leader, Global Clinical Pharmacology
Corina Becker, Ph.D- Global Clinical Pharmacology
John Curram, Ph.D. – Project Statistician, Global Biostatistics
Robert Haydu – U.S. CMC Regulatory Affairs
Winfried Joentgen, PhD – Chemical and Pharmaceutical Development
Friedrich W. Jekat, M.D., Ph.D. – Global Early Development
Joseph Scheeren, PharmD- Head of Global Regulatory Affairs

1.0 BACKGROUND

Riociguat is a soluble guanylate cyclase (sGC) stimulator proposed for the treatment of pulmonary arterial hypertension (PAH, WHO group I) and chronic thromboembolic pulmonary hypertension (CTEPH, WHO group IV).

The NDA contains two phase 3 trials to support two separate but related indications. Trial 12934 (PATENT-1) was a randomized, double-blind, placebo-controlled, multi-center, multinational study to evaluate the efficacy and safety of oral riociguat (1 mg, 1.5 mg, 2 mg, or 2.5 mg tid) in patients with symptomatic pulmonary arterial hypertension (PAH). Trial 11348 (CHEST-1) was a randomized, double-blind, placebo-controlled, multicenter, multinational study to evaluate the efficacy and safety of oral riociguat (1 mg, 1.5 mg, 2 mg, or 2.5 mg tid) in patients with chronic thromboembolic pulmonary hypertension (CTEPH).

The primary endpoint in both trials was change from baseline in six minute walk distance (6MWD) at end of study.

The IND (75629) for riociguat was submitted on February 15, 2007. An End-of-Phase 2 meeting was held on May 29, 2008; a pre-NDA meeting took place on November 1, 2012.

This 505(B)(1) application was submitted on February 8, 2013, and has a PDUFA goal date of October 8, 2013.

2.0 LCM

Introductory Comments

Welcome, Introductions, Ground rules, Objectives of the meeting

Discussion of Substantive Review Issue(s)

Starting Dose and Dose Range

The Division continues to be concerned that no incremental benefit in the primary efficacy endpoint in these studies was seen when the dose of riociguat was escalated above 1.5 mg TID

(either by exposure-response analyses of both CHEST-1 and PATENT-1, or by separate efficacy analysis of the 1.5 mg TID fixed-capped dose arm that was included in PATENT-1). Between approximately 1/4 and 1/3 of patients in the phase 2 and phase 3 trials supporting this NDA did not tolerate the 2.5 mg TID dose, presumably because of low blood pressure, and ended up on lower doses of riociguat. The dose-responsive nature of SBP <90 mmHg events and adverse events of hypotension have been previously demonstrated, and observed again in the phase 3 program.

Bayer asked if the FDA was proposing a starting dose of 0.5 mg for all patients, or just selected patients. Dr. Dunnmon replied that our preference is for initiation of riociguat at 0.5 mg TID in all patients, as it is difficult to identify prospectively those patients who will tolerate higher doses, and patients taking CYP3A4 inhibitors and/or CYP1A1 inhibitors may experience important increases in riociguat serum concentrations. Dr. Marathe added that another reason for recommending the 0.5 mg starting dose for all patients is that there is considerable variability in blood pressure, which makes it impractical to choose a starting dose based on a specific systolic blood pressure threshold in a clinical setting.

Bayer stated that approximately 90% of the CHEST-1 and PATENT-1 patients tolerated doses of riociguat at or above 2.0 mg three times daily. They believe that there are subgroups of patients that can benefit from higher doses of riociguat and that the drug is well tolerated at the higher doses. Dr. Dunnmon responded that 10% of patients experiencing hypotensive episodes and/or adverse events is a large number of patients, that patients with coronary artery disease, cerebral vascular disease, and peripheral vascular disease could be particularly susceptible to the harmful impact of hypotensive episodes, and probably most importantly, doses above 1.5 mg TID have not been shown to have an increased effect. He did note, however, that patients with baseline SBP >110 mmHg did not appear to experience excessive hypotension on the higher dose.

Bayer asked for clarification on whether FDA thought 1.5 mg TID should be a target dose or the maximal dose for all patients. Dr. Dunnmon told the sponsor that he favors 1.5 mg TID for all patients because no data have been provided on either a dose- or exposure-response basis that identify a subgroup that gains additional efficacy at doses above 1.5 mg TID. Furthermore, patients who were treated with 1.5 mg TID in the double-blind phase of PATENT-1 did not demonstrate any incremental clinical benefit from being dose-escalated to 2.5 mg TID in the open-label extension trial, PATENT-2. Dr. Stockbridge noted that the dosing issue is complex for the following reasons: (1) there is PK variability in patients taking the drug and (2) the 1.5 mg and 2.5 mg doses are too close together to determine an exposure-response relationship, if in fact there is one. Dr. Temple noted that a trial in which non-responders at 1.5 mg were randomized to the 2.5 and 1.5 mg dose of riociguat could determine whether the higher dose was of any value.

Bayer referred to Attachment 1, where they listed subgroups of patients in PATENT-1 that appeared to show greater clinical response with the 2.5 mg TID dose. The firm noted that patients on background therapy of bosentan during the trial benefited from the 2.5 mg dose. Dr. Marathe noted that although bosentan co-therapy decreased riociguat exposure by ~25% compared to therapy-naïve patients, there was still overall a higher incidence of hypotension events (SBP<90 mmHg) in patients with bosentan pre-treatment as compared to therapy-naïve population.

Dr. Temple noted that the subgroup of patients that achieved >380 meters for their 6 minute walk distance may have had a more favorable response on the 2.5 mg dose (the point estimate favored higher dose on the subgroup analysis but the confidence intervals crossed the line of no difference). Bayer replied that there was a 3-fold difference in exposure between healthy volunteers and patients with PAH, so that higher doses of riociguat appeared to be needed to overcome the lower blood levels of the healthier subjects. Dr. Dunnmon asked whether baseline walk distance or serum drug levels could be used for titration of the study drug. Bayer said they would further study the suggestion as a means of dose titration. Bayer committed to send FDA their analysis of drug levels versus baseline walk capacity.

Dr. Stockbridge said the description of the trials and the doses used in those trials would appear in the Clinical Trials section of the labeling. He said he would consider mentioning the 2.5 mg dose in the Dosing and Administration section, but with cautions about hypotension with the higher dose, and a notation that there may be very little difference in efficacy when compared to the 1.5 mg dose. A further discussion of the starting dose and dosing range is planned for the upcoming Advisory Committee meeting.

Blister Packs

Dr. Dunnmon noted that the 14-day supply blister pack is potentially a very useful aid in ensuring that patients return for blood pressure checks during the periods of dose-escalation and dose-reduction. This may be a particularly important issue during hypotension-driven dose reductions. In addition to reminding patients that they need to return to their care provider for blood pressure re-checks, the blister packs could help prevent medication errors during up and down titrations. DMEPA has communicated their concerns to Bayer that patients having multiple large capacity medication bottles at home may become confused during dosing changes, given that the 5 riociguat dosage formulations the sponsor plans to market are similar in appearance. DCRP has been concerned about dosing errors, specifically for patients with hypotension for whom dose reductions have been directed by their physicians. It is the opinion of both the DCRP medical and DMEPA reviewers that the limited-dose blister pack could be integrated into a physician and patient education program in a way that could importantly decrease medication errors in these patients. As it stands now, the only mention of this potentially very helpful dosing aid is under dosage formulations in the proposed label.

The firm plans to distribute riociguat through two specialty pharmacies in the United States and considers patient education a priority. FDA and Bayer agreed to discuss appropriate placement of the blister pack instructions in the labeling and/or medication guide.

Dosing Instructions and Smokers

FDA has proposed that the maximal dose in smokers be increased to 3 mg TID of riociguat because smoking induces CYP1A1, reducing drug exposure by up to 2/3. Bayer agrees with the Division's conclusion that the maximal dose should be increased beyond 1.5 mg TID for smokers, but they prefer not to recommend 3 mg, given that the data from PATENT-1 and CHEST-1 support safe use up to only 2.5 mg. Bayer therefore proposes a maximum dose of 2.5 mg TID for smokers. It was pointed out to Bayer that increasing the dose to 3 mg tid would result in plasma concentrations similar to those seen with the 1.5 mg tid dose in non-smokers, where most of their safety experience from PATENT-1 and CHEST-1 exist. Furthermore, it was

pointed out that riociguat will be titrated in increments of 0.5 mg tid in smokers, based on tolerability (similar to that in non-smokers), which should alleviate the safety concerns with a nominally higher dose.

Bayer asked that if the Agency recommends dosing up to 3 mg for smokers, whether they would be required to have a separate 3 mg dosage strength. Dr. Stockbridge said that we would have further discussions internally about dosing for smokers, but assured the applicant that producing a 3 mg dosage strength prior to the action date would not be a condition for approval.

Drug Interactions (CYP1A1 inhibitors and ketoconazole)

Bayer asked how the TKIs (e.g., erlotinib, gefitinib) should be listed in the labeling; their preference is to have some type of warning regarding them. Dr. Madabushi said that because there are no *in vivo* data to show that TKIs are CYP1A1 inhibitors, the Agency is hesitant to include them as such in the labeling. He added that discussions are ongoing internally regarding this issue. Dr. Menon-Andersen noted that titration of riociguat in 0.5 mg increments with TKIs could ease concerns about exposure differences when these drugs are used together.

Bayer mentioned that their data showed 2- to 2.5-fold exposure increases when riociguat and ketoconazole were used together; a larger increase was seen in smokers. Given the variability, the sponsor is concerned about the safety of concomitant use. Dr. Madabushi stated that the proposed titration of dose should take care of potential hypotension effects when riociguat is initiated in patients on background of a strong multi-CYP inhibitor. Furthermore, with appropriate monitoring instructions, the impact of starting a strong multi-CYP inhibitor like ketoconazole in patients stabilized at an optimal dose of riociguat could be managed, although the most obvious step is to reduce the dose. Dr. Temple said it was his impression that ketoconazole is rarely prescribed and asked if the firm had done studies with other 3A4 inhibitors. Bayer said they had done studies with clarithromycin, a moderate 3A4 inhibitor, and increases in exposures were observed when used with riociguat.

Protease Inhibitors

Bayer stated that they were also worried about the impact of allowing for concomitant use of ketoconazole and anti-HIV agents such as protease inhibitors with riociguat. The applicant stated that based on the *in vitro* study results, they expect the increase in riociguat exposures with protease inhibitors to be similar to that seen with ketoconazole. Dr. Madabushi stated that the potential decrease in blood pressure can be monitored and labeling instructions similar to that proposed for ketoconazole would be applicable for protease inhibitors. Bayer replied that they are open to discussion about this plan, but their view now is that patients should avoid using protease inhibitors with riociguat. Dr. Dunnmon noted that HIV/AIDS is a cause of Group I PAH, but HIV+ subjects were excluded from PATENT-1. Consequently, there is no clinical experience dosing riociguat in patients also taking protease inhibitors.

PDE5 Inhibitors

Bayer said they agree with the contraindication of PD5 inhibitors and nitrates with riociguat but disagreed with the FDA proposed contraindication for patients with coronary artery disease (CAD) who may potentially use nitrates for angina. Dr. Dunnmon said that if riociguat were approved, there would be many patients with coexisting CAD in the CTEPH patient group, given

that 40% of these patients were over the age of 65 years in CHEST-1. Although many of these patients might not be taking nitrates regularly, virtually all of them will be supplied with some form of SL nitroglycerin to abort an acute angina attack. If this population is not contraindicated, instructions must be included in the labeling on what these patients should do when taking sublingual nitrates with riociguat. Bayer replied that they have data from a heart failure study where about 90% of the subjects were on drugs that lowered blood pressure (e.g., ACE inhibitors, ARBs) and that they tolerated the concomitant administration with riociguat well, and one of them was using a nitroglycerin patch, apparently unknown to the investigator. Dr. Dunnmon emphasized to the sponsor that the PK and PD of sublingual nitroglycerin are very different than those of the transdermal product, and that an “N of 1” in the heart failure study does not outweigh the hypotension and syncope that occurred in the trial performed by the sponsor to test the riociguat-nitroglycerin interaction (which led to the contraindication for nitroglycerin in the proposed label). The applicant should address the need to provide instructions for patients with CAD who may need nitroglycerin to abort an attack of angina as an alternative to the FDA position that this population should be specifically excluded from taking riociguat.

Bone Toxicity/Pediatrics

Bayer said their decision to ask for a waiver of pediatric studies for the PAH indication was based on the preclinical data showing bone toxicity in animals and the contraindication of riociguat with PDE5 inhibitors, a common background therapy in PAH patients. They noted that there was a potential, unpredictable risk in conducting a study in children and they were uncertain how to monitor risk in a short-term trial.

Dr. Dunnmon noted that from a medical point of view, he supports the sponsor’s request for a pediatric waiver for the CTEPH indication, as CTEPH is not a pediatric presentation. However, he does not agree with the sponsor’s request for a waiver to study PAH in the pediatric population. Unlike CTEPH, children do have PAH and have few approved medical treatment alternatives. He voiced the Division’s concern about not studying riociguat in this population because they may be treated off-label with sildenafil, noting that sildenafil is not recommended for use in children because an increase in mortality with increasing dose was observed in a long-term trial in pediatric patients with PAH. Furthermore, the safety and effectiveness of tadalafil in pediatric patients have not been established. Therefore, the argument that pediatric studies should not be done with riociguat so that children might continue being dosed with a PDE5I inhibitor is unconvincing. Showing that riociguat could be safely used in children would be an important advance. Other sponsors have successfully completed pediatric PAH studies. The bone findings with riociguat appear to be dose-related, were not seen in the dog at all, and may not be an issue for humans, particularly if pediatric doses targeting an exposure analogous to the 1.5 TID dose in adults (as opposed to the 2.5 TID dose) are used. Dr. Dunnmon agrees with the consultant from the Division of Bone, Reproductive and Urologic Products, that it would be reasonable to test riociguat in adolescent children prior to testing it in the very young.

Dr. Stockbridge said that even if the firm receives orphan designation for both indications DCRP would still consider a post-marketing commitment/requirement for a PAH study in pediatric patients.

Advisory Committee Meeting

Dr. Stockbridge outlined several issues likely to be discussed at the Advisory Committee meeting for riociguat. The starting dose, dose range, and dosing for subgroups (e.g, smokers, CY1A1 inhibitors) for riociguat will be discussed. In addition, we will ask the committee to comment on the strength of evidence case for the PAH and CTEPH indications. The CETPH claim is a novel one and the applicant will need to demonstrate that one pivotal trial is enough along with other supportive trial data. Dr. Temple said that the firm should present pharmacological evidence that effects of riociguat are supportive of both indications. Dr. Stockbridge encouraged the firm to explore other development programs for CTEPH to make the case that riociguat is unique in providing benefit in the CTEPH population. Dr. Dunnmon noted that hemodynamic data from phase 2 trials could be introduced as supporting evidence that the drug works in a similar manner in both PAH and CTEPH.

Dr. Stockbridge said that we do not plan to discuss the bone toxicity issue at the committee meeting. There are also no plans to discuss possible thyroid effects of riociguat. He did note however, that we could ask for more information regarding thyroid effects as a post-marketing commitment/requirement.

Bayer asked if it would be possible to see FDA's slides prior to the meeting. Dr. Stockbridge said that we would try to send our draft slides prior to the meeting.

REMs

Bayer acknowledged that they had received FDA's comments regarding a REMs for the drug and will be replying to the comments in the next few weeks.

Bayer said they consider the bone findings 'incomplete ossification' rather as a sign of retarded development reflecting the reduced fetus weights rather than a true malformation. Dr. Hausner said she agreed with the applicant's classification.

LCM Regulatory Note

This application has not yet been fully reviewed by the signatory authority, Division Director, or Cross-Discipline Team Leader; therefore, the proceedings of this meeting do not address the final regulatory decision for the application.

Topic for Discussion	Points of Clarification and Discussion from Bayer
<p>Introductory Comments – 5 minutes Welcome, Introductions, Ground rules, Objectives of the meeting</p>	
<p>Discussion of Substantive Review Issue(s) – 60 minutes Each issue will be introduced by FDA and followed by a discussion.</p>	
<ul style="list-style-type: none"> • Starting dose and dose range 	<p>Starting Dose The Sponsor acknowledges the Division’s analysis of the data. We seek to understand whether the Division’s recommendation of 0.5 mg starting dose is for all patients, or selected patients.</p> <ul style="list-style-type: none"> • If 0.5 mg is for all patients how do we communicate the 0.5 mg as well as the 1mg in the label (considering the pivotal trials Patent and Chest had a starting dose of 1 mg)? • If 0.5 mg is for selected patients, which patients would the Division recommend? <p>Dose Range (see Attachment 1 and Attachment 2; pages 5-6) It is the Sponsor’s understanding that you recommend a target dose of 1.5 mg for both indications, and for patients not showing an adequate efficacy response, further dose increases to 2.5 mg is possible. Does the Division agree?</p> <p>The data from CHEST and PATENT support that all 5 dose strengths provide clinical benefit for the studied patients. About 90% of patients in CHEST-1 and PATENT-1 reached doses above 1.5 TID using the IDT scheme. In the long term extension studies, the vast majority of patients are maintained at 2.5mg TID with sustained efficacy, low rate of discontinuation and good long-term tolerability. For patients not showing an adequate efficacy response to 1.5 mg TID (e.g. due to reduced exposure, low biological sensitivity and different etiologies) further dose increases to 2 and 2.5 mg TID would be beneficial. Although 1.5 mg TID could be an appropriate target dose for patients, given that the majority of our patients achieved doses of 2 and 2.5 mg TID, how does the Division recommend we communicate this important information to physicians in the label?</p>

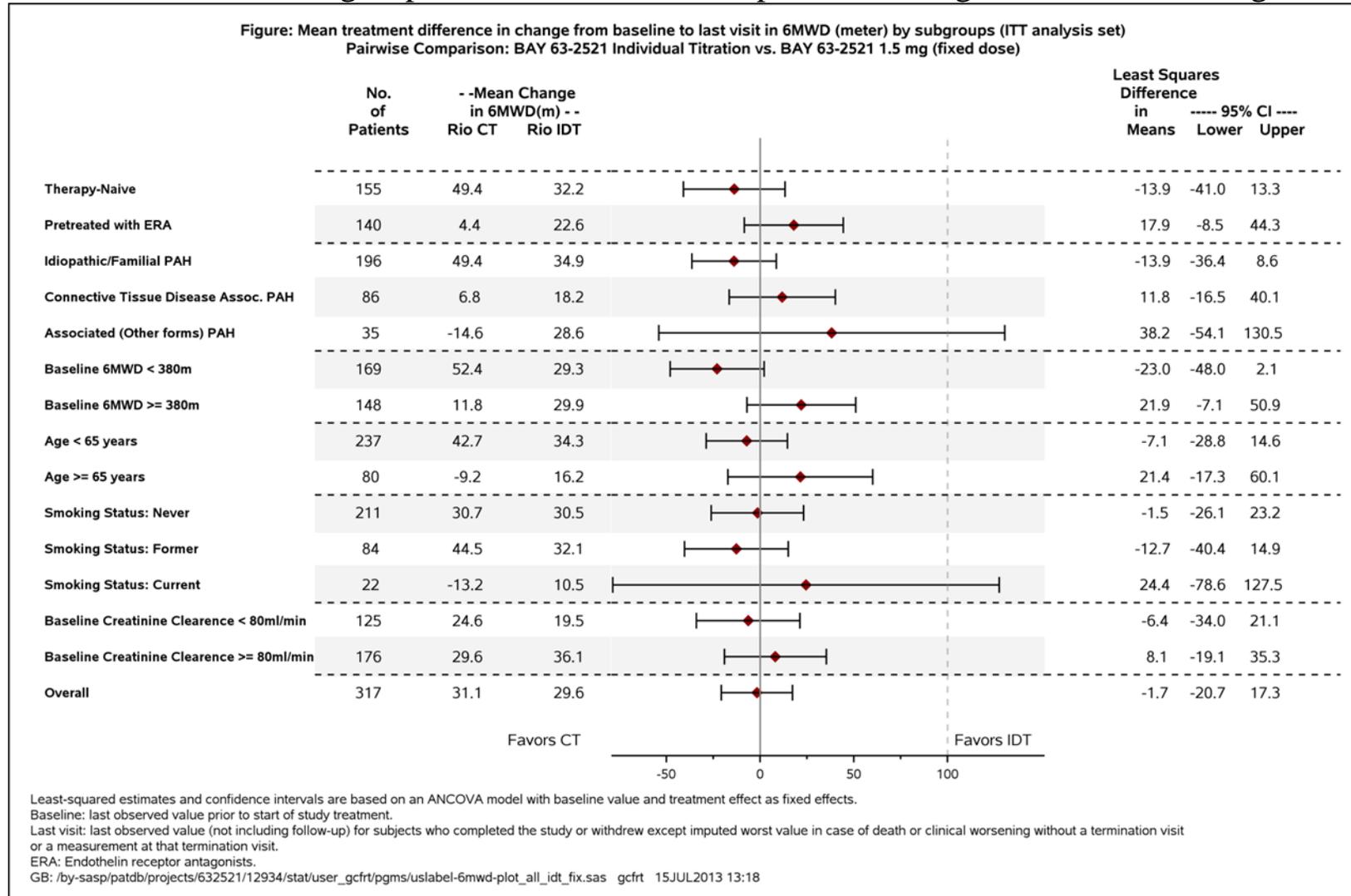
<ul style="list-style-type: none">• Use of Blister Packs	<p>Bayer had proposed in the NDA both bottles and blisters for drug distribution</p> <p>We would be happy to engage with FDA on the best way to provide instructions on how to best use the blister packs (e.g. in the Medication Guide).</p>
<ul style="list-style-type: none">• Exposure calculations	<p>The Sponsor would like to clarify with the Division that we used the same exposure ratios as those used by FDA to calculate the plasma exposure in pulmonary hypertension patients. (See Module 2.6.6 and Module 2.7.2. Study 12166)</p>
<ul style="list-style-type: none">• Dosing instructions and smokers	<p>The Sponsor agrees with the Division's assessment that recommends increasing the maximal dose beyond 1.5 mg TID for smokers is appropriate. However, as the data from PATENT and CHEST support safe use up to 2.5mg, we propose the maximum dose of 2.5 mg TID for smokers.</p>
<ul style="list-style-type: none">• Drug Interactions (CYP1A1 inhibitors and ketoconazole)	<p>CYP1A1 inhibitors (TKI interaction) data is important information for the patients and physicians. We would like to ask FDA how this interaction should be described in the label.</p> <p>Regarding ketoconazole, the Sponsor acknowledges the FDA's proposal and will address during our labeling negotiations.</p>
<ul style="list-style-type: none">• Use with PDE5 Inhibitors	<p>The Sponsor agrees to add a contraindication for PDE5 inhibitors to the proposed package insert.</p>
<ul style="list-style-type: none">• Use in patients with preexisting coronary artery disease	<p>The Sponsor has already recommended a contraindication for nitrates. This broad contraindication should cover patients with CAD who take nitrates for angina pectoris.</p> <p>The Sponsor seeks clarification from the Division on the rationale for an additional proposed contraindication for patients with CAD who may require nitrates.</p>

<ul style="list-style-type: none"> • Bone issues with adolescents and children 	<p>See below.</p>
<ul style="list-style-type: none"> • Pediatrics and waivers 	<p>Based on preclinical and clinical data, the Sponsor concludes there is no risk for adults. However, preclinical data suggests that there could be a potential risk for pediatric use. Based on discussions with bone experts and pediatric experts, bone follow-ups should be between 1-5 years depending on the pediatric age groups being studied, and challenging to implement. In addition, there are only very limited methods available for early detection of bone effects.</p> <p>Based on discussions with pediatric experts, sildenafil is used widely in the US in pediatrics, despite the warning with regard to pediatrics included in the US label. Many children diagnosed with PH in the US are prescribed sildenafil. (Reference: Abman SH, Kinsella JP, Rosenzweig EB, Krishnan U, Kulik T, Mullen M, et al. Implications of the U.S. Food and Drug Administration warning against the use of sildenafil for the treatment of pediatric pulmonary hypertension. Am J Respir Crit Care Med. 2013 Mar 15;187(6):572-5.)</p> <p>In summary, the Sponsor reaffirms their request for a full pediatric waiver for PAH.</p>
<p>Discussion of Upcoming Advisory Committee Meeting- 10 minutes</p>	
<p>Overview of potential questions or discussion topics that FDA expects the AC to address</p>	<p>Can the Division help us prioritize the topics of focus, and are there any other topics that we should be prepared to address?</p>
<p>Review of Agenda and order of presentations by applicant and FDA</p>	
<p>Current Assessment of the need for REMS or other risk management actions- 10 minutes</p> <p>a. Bone and cardiac teratogenicity will be addressed in the product REMS.</p>	<p>The Sponsor has received the Division’s feedback on our proposed REMS and is in agreement.</p> <p>For clarification, we consider the bone findings ‘incomplete ossification’ rather as a sign of retarded development reflecting the reduced fetus weights rather than a true malformation.</p>

Major labeling issues – 15 minutes Indications section	
Postmarketing Requirements/Postmarketing Commitments – Bone Toxicity- 10 minutes	
Wrap up and Action Items- 5 minutes	

Attachment 1:

PATENT-1: Some sub-groups demonstrate better response to 2.5mg TID vs CT to 1.5mg TID



Attachment 2:

PATENT-1: Similar AE profile in IDT vs CT

Type of AE	Placebo N=126 n (%)	Riociguat IDT N=254 n (%)	Riociguat CT N=63 n (%)
Any AE	111 (88.1)	230 (90.6)	59 (93.7)
Any serious AE	23 (18.3)	29 (11.4)	11 (17.5)
Discontinuation due to AE	9 (7.1)	8 (3.1)	1 (1.6)
AE with outcome Death	3 (2.4)	2 (0.8)	1 (1.6)

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

/s/

NORMAN L STOCKBRIDGE
08/15/2013



NDA 204819

**LATE CYCLE MEETING
BACKGROUND PACKAGE**

Bayer Healthcare Pharmaceuticals, Inc
Attention: Carmen Leung, R.Ph.
Deputy Director, Global Regulatory Affairs
P.O. Box 1000
Montville, NJ 07045-1000

Dear Ms. Leung:

Please refer to your New Drug Application (NDA) submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Adempas (riociguat) Tablets.

We also refer to the Late-Cycle meeting (LCM) meeting scheduled for July 22, 2013. Attached is our background package, including our agenda for this meeting.

If you have any questions, please call:

Edward Fromm, RPh, RAC
Regulatory Project Manager
(301) 796-1072

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE:
Late-Cycle Meeting Background Package

LATE-CYCLE MEETING BACKGROUND PACKAGE

Meeting Date and Time: July 22, 2013, 2 PM
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1313
Silver Spring, Maryland 20903

Application Number: NDA 204819
Product Name: Adempas (riociguat) Tablets
Indication: Chronic Thromboembolic Pulmonary Hypertension and
Pulmonary Arterial Hypertension
Sponsor/Applicant Name: Bayer Healthcare Pharmaceuticals

INTRODUCTION

The purpose of a Late-Cycle meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, Advisory Committee (AC) meeting plans (if scheduled), and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

During the meeting, we may discuss additional information that may be needed to address the identified issues, whether it will be reviewed by the Agency in the current review cycle, and, if so, whether the submission would constitute a major amendment and trigger an extension of the PDUFA goal date. If you submit any new information in response to the issues identified in this background package prior to this LCM or the Advisory Committee meeting, if an AC is planned, we may not be prepared to discuss that new information at this meeting.

OVERVIEW OF ISSUES IDENTIFIED TO DATE

Non-Clinical

Thyroid findings in preclinical toxicology studies: In the 26-week dog study, T3 and T4 values were slightly depressed for the high dose group. There was no histological correlate for this and it is possible that the values are simply “sick euthyroid” or a basically healthy thyroid in a stressed animal. Changes in thyroid hormones can also occur secondary to gastrointestinal changes. Since thyroid functions were not evaluated in the clinical development program, we

cannot assess this toxicology finding adequately. Guidance should be included in the labeling for ruling out drug-induced thyroid toxicity with chronic use.

Bone Issues: The bone toxicity reported for rats is incompletely described. There was minimal examination of bones other than the sternum, femur, and tibia. These bones were examined in standard approaches used for safety assessment studies. A study that includes examination of bones such as the mandible, nasal turbinates, calvarium, vertebrae, humerus, femur (including the neck) and tibia and clinical chemistry data such as parathyroid hormones and calcium excretion might help to address the issue of possible exacerbation of osteoporosis.

CLINICAL PHARMACOLOGY

Exposure calculations: Your calculations of margins of exposure were based on plasma levels from healthy volunteers (AUC₀₋₂₄ 1446 µg.hr/L). FDA's exposure ratios are based on the plasma exposure in pulmonary hypertension patients reported in study 12166 (AUC₀₋₂₄ 4161 µg.hr/L).

Dosing instructions in smokers: FDA evaluation of data from PATENT-1 suggests that Δ 6MWD is similar between smokers and non-smokers. To illustrate the point, smokers (n=9) who received 2.5 mg on day 84 had a mean Δ 6MWD (SD) of 46.8 (37.8) m while that in non-smokers (n=115) was 40.4 (52.5) m. Based on the exposure-response analyses, a maximal dose of 1.5 mg *tid* is proposed. Given that exposures in smokers is about half that in non-smokers, a maximum dose of 1.5 mg *tid* in smokers will result in exposures similar to that achieved with 0.75 mg *tid* in non-smokers, but because there is not enough information at this lower dose level, increasing the maximal dose to 3 mg *tid* should be considered in smokers.

CYP1A1 inhibitors (TKIs): While the TKIs erlotinib and gefitinib may have shown to be inhibitors of CYP1A1 in studies conducted by Bayer, these drugs cannot be specifically listed as CYP1A1 inhibitors in the riociguat USPI absent the same information being presented in the respective TKI labels.

Dosing recommendation for ketoconazole: Based on our proposed dosing regimen of starting with 0.5 mg *tid* with a maximum dose of 1.5 mg *tid* and exposure-safety analysis, concomitant administration of multi-CYP inhibitors such as ketoconazole with riociguat is acceptable. Additional monitoring for hypotension is recommended upon initiation of the multi-CYP inhibitor.

PHARMACOMETRICS

Highest titration/stable dose of riociguat: In the Phase 3 trial for the PAH population, the dose-response relationship showed similar efficacy in the 1.5-mg fixed dose arm and the 2.5-mg individual dose titration (IDT) arm, and both arms had clinically significant benefit in efficacy over placebo (**Figure 1**). The exposure-response (E-R) relationship for efficacy (change in 6 minute walk distance, 6MWD) was also flat for the exposures (AUC) corresponding to the 1.5-mg and 2.5-mg doses. The lowest quartile of the 1.5-mg dose arm showed lower efficacy, but the

investigation of efficacy in the lowest quantiles of the 2.5-mg stable dose (which matched the exposure in lowest quantile of the 1.5-mg stable dose) showed similar efficacy as at higher exposures, confirming the flat E-R relationship (**Figure 2**). In the CTEPH phase 3 trial, similar flat exposure-response relationship for efficacy (change in 6 minute walk distance, 6MWD) was also seen in the CTEPH population (**Figure 3**).

Regarding safety, in the PAH phase 3 trial, the preliminary evaluation of event-rates, adjusted for the sample size (patients) and the approximate average time they were exposed to a particular dose, suggest a numerical trend towards increase in hypotension (defined by SBP <90 mmHg) event-rates with >1.5 mg as compared to the 1.5-mg dose (**Table 1**). Thus, we believe the highest titration dose of 1.5 mg would be optimal from a benefit-risk perspective.

Starting dose for titration of riociguat: Approximately 45% of all hypotension events (defined by SBP <90 mmHg) on riociguat in the PAH phase 3 trial are occurring on day 1 and day 2 when the subjects are taking 1 mg *tid*. Risk of hypotension was statistically significantly correlated with C_{trough} exposure on day 1 (**Figure 4**). Almost all of these events are occurring in subjects with baseline SBP of ≤ 110 mmHg (median SBP in the PAH trial). Based on this exposure-safety relationship, we believe it would be appropriate to start the patients on an initial starting dose of 0.5 mg, which would lower patients' systemic exposure by 50% on day 1/day 2 and reduce the risk of immediate hypotensive events on riociguat.

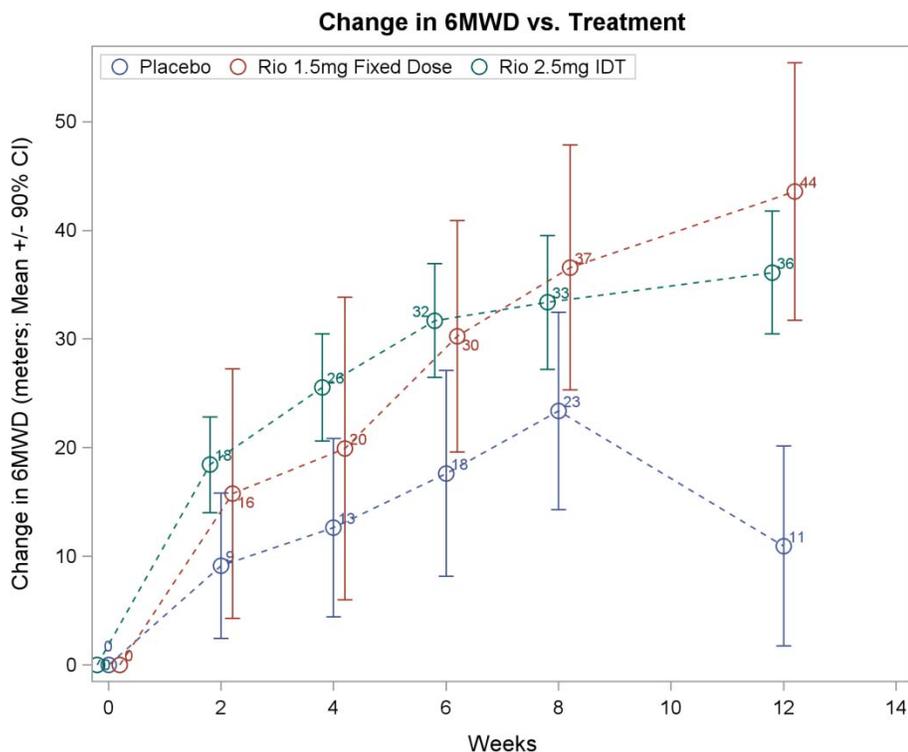
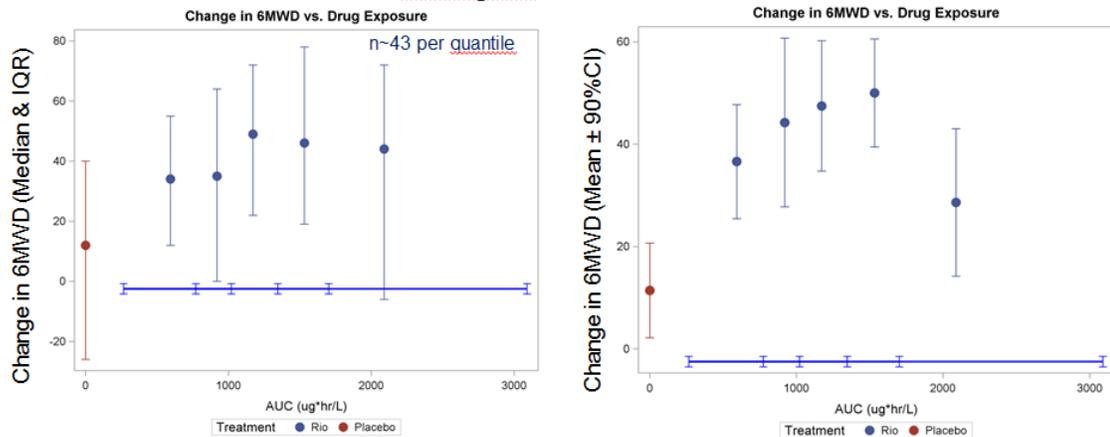


Figure 1 Temporal evolution of efficacy (change in 6MWD) from baseline to the end of the study (12 weeks) in three arms of PAH phase 3 trial (PATENT-1)- ITT population.

Exposures combined from highest stable dose (1.5 and 2.5 mg) in two Riociguat treatment arms



Exposures separated across Riociguat arms

Evidence from 2.5mg dose arm shows flat E-R relationship

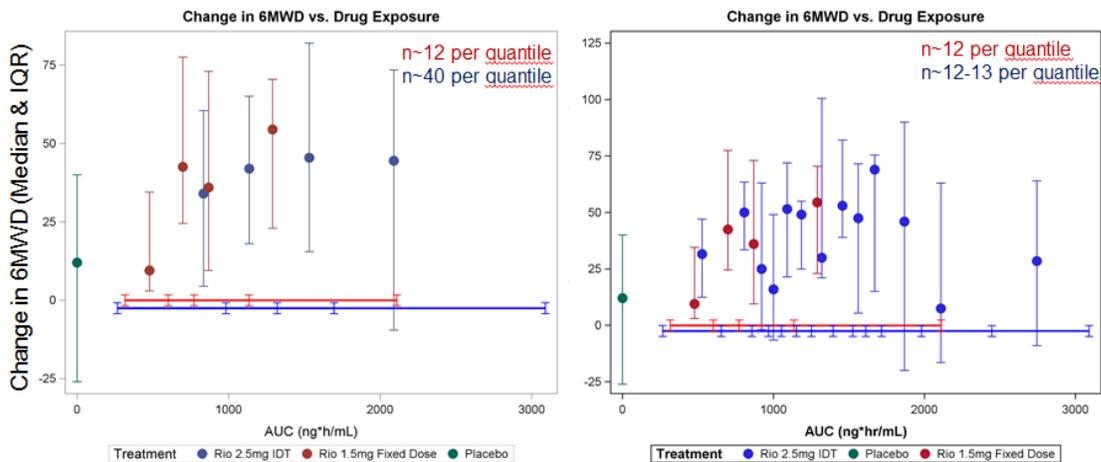
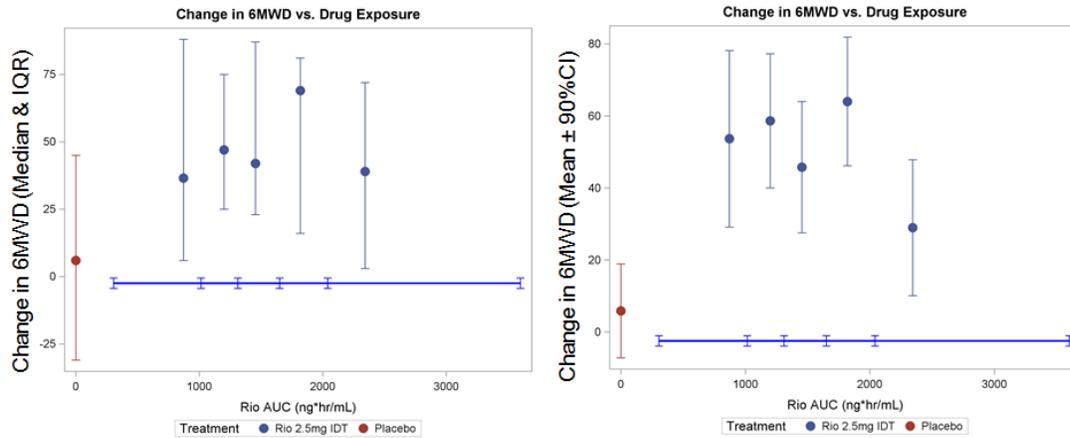


Figure 2 Change from baseline in 6MWD: by quantiles of combined exposure for highest stable doses (1.5 and 2.5 mg) allowed in each of the two riociguat arms (Upper panel); and by quantiles of exposure for 1.5- and 2.5-mg maximum dose arms separately (lower left panel) for subjects maintained on the highest possible dose of riociguat in each arm at the end of the study (12 weeks) in the PAH phase 3 trial. The lower right panel shows smaller exposure quantiles for the 2.5-mg dose, where the median exposure in lowest quantile is similar to median exposure in lowest quantile of the 1.5-mg dose group, but the efficacy is higher and similar to other exposure quantiles.

Exposures combined from all stable doses of Riociguat



Exposures from stable dose of 2.5 mg Riociguat

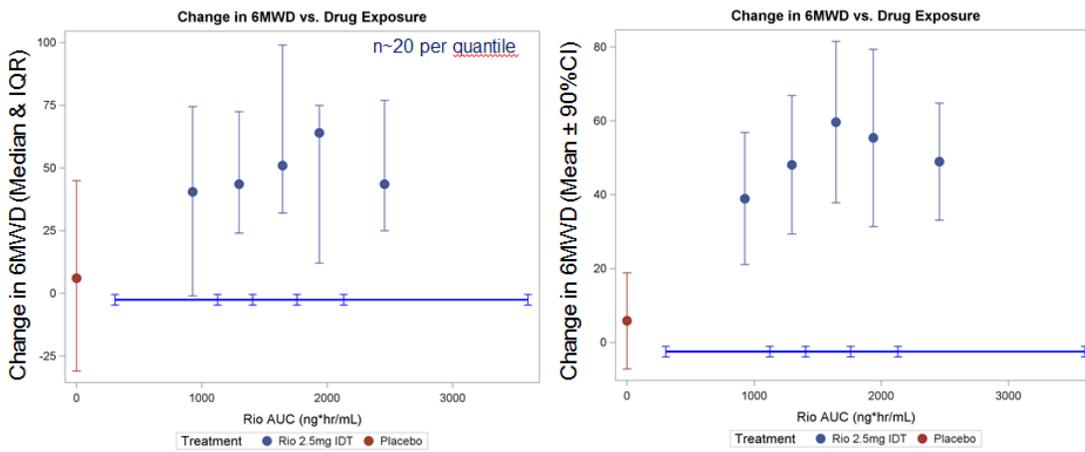
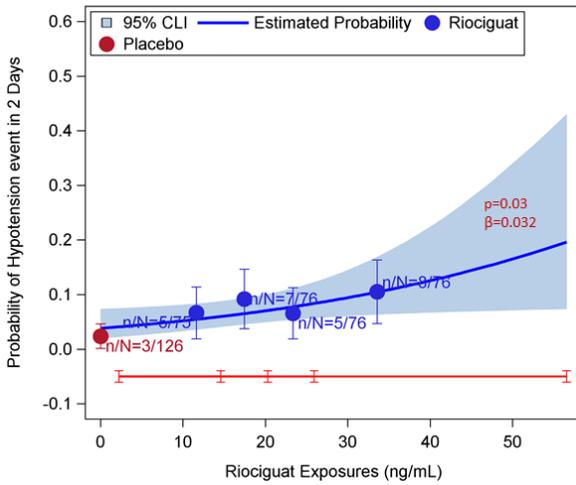
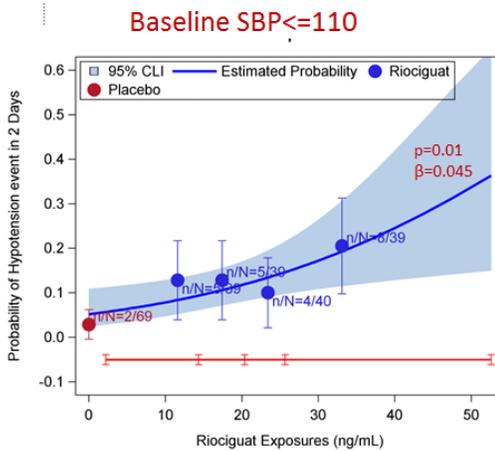


Figure 3 Change from baseline in 6MWD (efficacy) by quantiles of exposure in subjects on all stable doses (upper panels) or maintained on the highest stable dose of 2.5 mg (lower panels) at the end of the study (16 weeks) in the CTEPH phase 3 trial. The median (left panels) as well as mean (right panels) of efficacy data are shown.

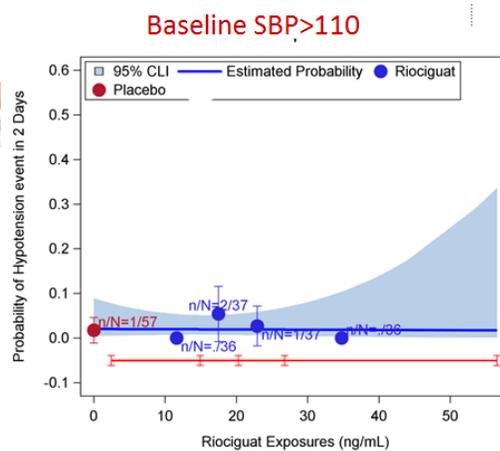
A.



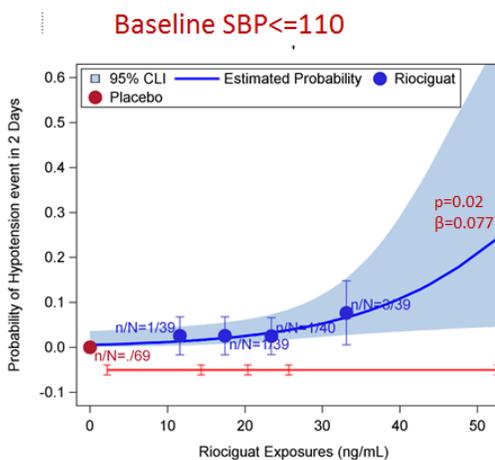
B.



C.



D.



E.

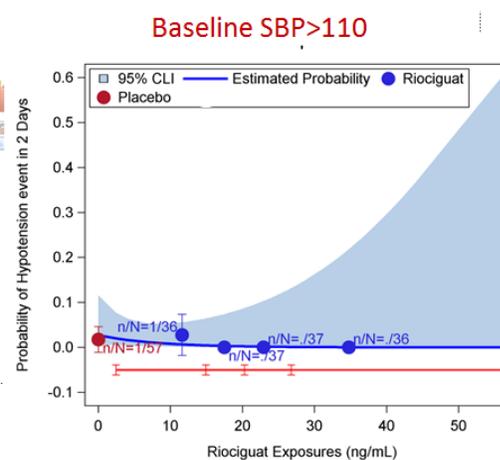


Figure 4 Exposure-response analysis for hypotension events defined by SBP < 90 mmHg (Panels A-C) and hypotension AEs as reported by CSR protocol (Panels D-E) occurring within 2 days of the start of

treatment in PATENT-1. Panel A shows E-R for all the subjects/events while panels B-C and panels D-E show E-R for subjects categorized by baseline SBP. Most of the hypotension events are occurring in subjects with lower baseline SBP (Panels B and D) compared with higher baseline SBP (Panels C and E), and in this former subgroup there is significantly increased probability of event with a higher C_{trough} on the first dose.

Table 1 Hypotension event-rates with different doses in PATENT-1

Hypotension SBP <90*	1.5 mg Fixed Dose Arm	2.5 mg Ind. Titration Dose Arm		
	1.5 mg	1.5 mg	2 mg	2.5 mg
Dose				
Events (n)	1	3	10	13
Patients (N)	52	245	222	189
Exposure in Weeks	10	2	2	6
Events per 100 person-year	10	32	117	60

*Only events after 2 days from start of treatment are considered here

Hypotension AE*	1.5 mg Fixed Dose Arm	2.5 mg Ind. Titration Dose Arm		
	1.5 mg	1.5 mg	2 mg	2.5 mg
Dose				
Events (n)	2	4	6	6
Patients (N)	52	245	222	189
Exposure in Weeks	10	2	2	6
Events per 100 person-year	20	42	70	28

*Only events after 2 days from start of treatment are considered here

CLINICAL

Dose: As was discussed in the mid-cycle communication, it is our point of view, that the IDT dosing strategy, which was adopted to address the high inter-subject variability in PK, is not justified because of the flat exposure-response in the primary efficacy analyses of both PATENT-1 and CHEST-1 on one hand, and the dose-related occurrence of blood pressure below 90 mmHg events on the other, particularly in patients whose baseline SBP is less than 110 mmHg. Between approximately 1/4 to 1/3 of patients in your phase II and phase III studies supporting this application did not tolerate the 2.5 mg tid dose due to low blood pressures. It is our point of view that your data supports a lower dose range, starting at 0.5 mg tid, escalating

every two weeks by 0.5 mg tid to a target of 1.5 mg tid. This will undoubtedly improve the safety experience for unselected patients who are dosed with riociguat who may harbor asymptomatic coronary artery disease, cerebral vascular disease, and peripheral vascular disease – patients who may tolerate drug-induced hypotension poorly. It will likewise increase the margin of safety for patients who may ingest important CYP3A4 inhibitors, which may substantially raise their serum riociguat concentrations. Finally, due to the marked smoking induction of CYP1A1, it is reasonable to advise medical providers in the product label that doses of riociguat as high as 3.0 mg po tid may be required to compensate for the smoking-induced increase in drug clearance.

Indications: The following table compares the populations included in the phase III clinical trials with the treatment indications being sought in the proposed labeling:

Study	Inclusion/Exclusion	Label
CHEST-1	<p>Thromboembolic obstruction of proximal or distal pulmonary arteries:</p> <ul style="list-style-type: none"> ○ Inoperable, with a PVR >300 dyn*sec*cm-5 measured at least 90 days after start of full anticoagulation and a PAPmean >25 mmHg persisting, or ○ recurrent PH after PEA (subjects must have a PVR >300 dyn*sec*cm-5 measured at least 180 days after surgery) <p><u>Excluded:</u> All types of PH except subtypes 4.1 and 4.2 of the Venice Clinical Classification of PH {Non-thrombotic pulmonary embolism (tumor, parasites, foreign material)};</p>	<p>Persistent/recurrent Chronic Thromboembolic Pulmonary Hypertension (CTEPH) (WHO Group 4) after surgical treatment or inoperable CTEPH to improve exercise capacity and WHO functional class.</p>
PATENT-1	<p>Male and female subjects with symptomatic PAH (Group I/Venice Clinical Classification of Pulmonary Hypertension), an eligibility and baseline 6MWD test between 150 m and 450 m, a PVR >300 dyn*sec*cm-5, and a PAPmean >25 mmHg either due to: <i>Idiopathic PAH, Familial PAH, Associated PAH due to connective tissue disease, Associated PAH due to congenital heart disease (i.e. atrial septal defect, ventricle septal defect, persistent ductus arteriosus), if subjects</i></p>	<p>Pulmonary Arterial Hypertension (PAH) (WHO Group 1) to improve exercise capacity, improve WHO functional class and to delay clinical worsening.</p>

	<p>underwent surgical correction more than 360 days before study inclusion, <i>Associated</i> PAH due to portal hypertension with liver cirrhosis (Note: Subjects with clinical relevant hepatic dysfunction are excluded), <i>Associated</i> PAH due to anorexigen or amphetamine use</p> <p><u>Excluded:</u> All types of PH except subtypes of Venice Group I specified in the inclusion criteria (HIV, thyroid disorders, glycogen storage disease, Gaucher disease, hereditary hemorrhagic telangiectasia, hemoglobinopathies, myeloproliferative disorders, splenectomy, venous or capillary disease)</p>	
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Clinical supplies: The hypotension induced in some patients by riociguat appears to be front loaded, with almost half of these occurrences taking place in the first two days of therapy in the PAH indication. Relative to this finding, you communicated to our medical reviewer that blister packs of 14 tablets were manufactured to a) encourage follow up BP checks on escalated doses b) to prevent patients from having to purchase full prescriptions of doses that might be changed and c) to help prevent medication errors during and following dose adjustments, given the very similar appearance of the different riociguat pill sizes. However, your proposed label is completely silent with respect to all of the above, and so should be modified to address these issues (otherwise all that is seen in labeling is that the blister pack exists). We believe that this caution is warranted not only for the up-titrations of riociguat, but also for down-titrations which are made necessary by SBP < 90 mmHg events (or symptomatic hypotension regardless of what the blood pressure readings are).

Phosphodiesterase inhibitors: Part I of PATENT-PLUS failed to demonstrate clinical benefit for subjects on the combination of sildenafil plus riociguat. In the setting, the interim Bayer review identified decreases in blood pressure (systolic and diastolic) in both treatment groups with a tendency to more reports in the active group, especially during the long-term extension (LTE) period of the study following Part I. In Part I of that study, both AEs involving hypotension occurred in 2 of 12 patients randomized to active therapy (17%). Another subject discontinued study medication due to “vision blurred”. Of the 17 subjects that rolled over into the long term extension (LTE) during the interim data review from the blinded Part I of the trial, 7 subjects experienced TEAEs of hypotension, 4 of these dropped out of the study, and one experienced frank loss of consciousness. Three additional subjects died in the LTE during this interim period between Part 1 and Part 2 of the study. As a result, Part 2 was not initiated, and

you have proposed a warning in your label against concomitant use of PDE inhibitors. Given that both NO donors and PDE inhibitors increase cGMP, and you have contraindicated NO donors of any kind because of drug-induced hypotension when taken with riociguat, we recommend contraindications for both NO donors and PDE inhibitors, as opposed to a contraindication for one, and a warning for the other.

CAD: Patients with severe proven or suspected coronary artery disease (subjects with Canadian Cardiovascular Society Angina Classification class 2-4, and/or requiring nitrates, and/or myocardial infarction within the last 90 days before Visit 1), and subjected with an LVEF <40% were excluded from your trials. There is a contraindication for all NO donors in your proposed label (and specifically for nitroglycerin due to hypotension/syncope with the combination). Given the above, it is our view that a contraindication should be added to your label for patients with coronary artery disease who may need to take nitrates, and specifically nitroglycerin, for the treatment of angina pectoris.

MEDICATION ERROR PREVENTION AND ANALYSIS

DMEPA Information Request letter dated 06/28/2013.

ADVISORY COMMITTEE MEETING

An Advisory Committee meeting is planned on August 6, 2013, 8 AM to 4:30 PM.

REMS OR OTHER RISK MANAGEMENT ACTIONS

- Bone and cardiac teratogenicity may be addressed in the product REMS.

LCM AGENDA

1. Introductory Comments – 5 minutes (RPM/CDTL)
Welcome, Introductions, Ground rules, Objectives of the meeting
2. Discussion of Substantive Review Issue(s) – 60 minutes
Each issue will be introduced by FDA and followed by a discussion.
 - Starting dose and dose range
 - Use of Blister Packs
 - Exposure calculations
 - Dosing instructions and smokers
 - Drug Interactions (CYP1A1 inhibitors and ketoconazole)
 - Use with PDE5 Inhibitors
 - Use in patients with preexisting coronary artery disease
 - Bone issues with adolescents and children
 - Pediatrics and waivers
3. Discussion of Upcoming Advisory Committee Meeting – 10 minutes
 - Overview of potential questions or discussion topics that FDA expects the AC to address
 - Review of Agenda and order of presentations by applicant and FDA
4. Current Assessment of the need for REMS or other risk management actions – 10 minutes
 - a. Bone and cardiac teratogenicity will be addressed in the product REMS.
5. Major labeling issues – 15 minutes
 - Indications section
6. Postmarketing Requirements/Postmarketing Commitments – Bone Toxicity – 10 minutes
7. Wrap up and Action Items – 5 minutes

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/s/

NORMAN L STOCKBRIDGE
07/08/2013



NDA 204819

MID-CYCLE COMMUNICATION

Bayer Healthcare Pharmaceuticals, Inc
Attention: Carmen Leung, R.Ph.
Deputy Director, Global Regulatory Affairs
P.O. Box 1000
Montville, NJ 07045-1000

Dear Ms. Leung:

Please refer to your New Drug Application (NDA) submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Adempas (riociguat) Tablets.

We also refer to the teleconference between representatives of your firm and the FDA on May 10, 2013. The purpose of the teleconference was to provide you an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

If you have any questions, please call:

Edward Fromm, R.Ph., RAC
Regulatory Health Project Manager
(301) 796-1072

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:
Mid-Cycle Communication

MID-CYCLE COMMUNICATION

Telecon Date and Time: May 10, 2013, 10- 11:00 AM

Application Number: 204819

Product Name: Adempas (riociguat) Tablets

Indication: PAH (Pulmonary Arterial Hypertension) and CTEPH (Chronic Thromboembolic Pulmonary Hypertension)

Applicant Name: Bayer Healthcare Pharmaceuticals

Meeting Chair: Norman Stockbridge, M.D., Ph.D.

Meeting Recorder: Edward Fromm, R.Ph., RAC

FDA ATTENDEES

Office of Drug Evaluation 1, Division of Cardiovascular and Renal Products

Norman Stockbridge, MD., Ph.D., Director
Preston Dunnmon, MD, Medical Officer
Thomas Papoian, Ph.D., Supervisory Pharmacologist
Elizabeth Hausner, DVM, Pharmacologist
Lori Wachter, RN, BSN, Regulatory Safety Project Manager
Edward Fromm, R.Ph., RAC, Chief, Project Management Staff

Office of Biostatistics, Division of Biometrics I

John Lawrence, Ph.D., Statistician

Office of Clinical Pharmacology, Division of Clinical Pharmacology I

Divya Menon-Andersen, Ph.D., Clinical Pharmacologist
Raj Madabushi, PhD, Team Leader, Clinical Pharmacology

Office of Surveillance and Epidemiology, Division of Risk Management

Reema Mehta, Pharm.D., Lead Pharmacist
Somya Dunn, MD, Medical Officer

Office of Surveillance and Epidemiology, Division of Error Prevention and Analysis

Kim Defronzo, Pharm.D., Pharmacist

Office of New Quality Drug Assessment

Pei-I Chu, Ph.D., Chemist
Monica Cooper, Ph.D., Chemist
Kareen Riviere, Ph.D., Biopharmaceutics Reviewer

Office of Planning & Informatics

Kimberly Taylor, Operation Research Analyst

BAYER ATTENDEES

Carmen Leung, R.Ph. – U.S. Global Regulatory Strategist, Global Regulatory Affairs
Laila Narouz-Ott, Ph.D. – Lead Global Regulatory Strategist, Global Regulatory Affairs
Max Wegner, Ph.D. – U.S. Regulatory Affairs Interim Head and General Medicine Head, Global Regulatory Affairs
Regina Seidel - Cardio Pulmonary Head, Global Regulatory Affairs
Sharon W. Brown - US Head Womens Healthcare and Cardio Pulmonary, Global Regulatory Affairs
Robert Haydu – U.S. CMC Regulatory Affairs
Winfried Joentgen, PhD – Chemical and Pharmaceutical Development
Christine Tarenz – Global Regulatory CMC Manager
Gesa Schomakers, M.D. – Global Pharmacovigilance
Shaw Lamberson, M.D. - US Head of Pharmacovigilance
Stephan Vettel, Ph.D – Project Head, Global Project Management
Volker Geiss, DVM, Ph.D. – Toxicology Leader, Toxicology Project Management
Friedrich W. Jekat, M.D., Ph.D. – Global Early Development
Neil Davie, Ph.D. – Global Clinical Leader, Global Clinical Development
Dieter Neuser, M.D., Ph.D. – Global Clinical Development
David Muccino, M.D. – US Medical Affairs
Reiner Frey, M.D. – Clinical Pharmacology Leader, Global Clinical Pharmacology
Corina Becker, Ph.D- Global Clinical Pharmacology
John Curram, Ph.D. – Project Statistician, Global Biostatistics
Kai Voglaender – Global Integrated Analysis Project Leader, Global Biostatistics

1.0 INTRODUCTION

We are providing these comments to you before we complete our review of your NDA in order to inform you of issues that we currently believe to be important. In conformance with the prescription drug user fee reauthorization agreements, these comments are not our final assessments of the information reviewed and should not be construed to be so. The issues identified are preliminary and may change as we complete our review of your application. In addition, we may later identify additional information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

2.0 REVIEW ISSUES (to date)

CMC (Chemistry, Manufacturing & Controls)

Dr. Cooper reiterated some items from the IR (Information Request) letter dated May 3, 2013:

Drug Substance

1. Provide additional data to support the most stable polymorph (b) (4) with a discussion of any differences in the solubility and stability of the different morphic forms of riociguat.
2. Provide experimental data to show that certain impurities are not carried over into the drug substance (the specific impurities are detailed in the IR letter).
3. Revise the drug substance specification to include a limit for heavy metals, tighter residual solvent limits, and a polymorph limit.

Additional drug substance issues are listed in the IR letter.

Drug Product

1. Some process parameters specified in the master and executed batch records were inconsistent with the proposed manufacturing process parameters determined in the pharmaceutical development section.
2. Clarify the primary and secondary identification methods for the drug product.
3. Provide data to demonstrate the tablets that have been stored till the expiry date (b) (4)

Bayer replied that they had not yet received the May 3, 2013 IR letter, but would respond once they received it. Dr. Cooper invited the applicant to correspond with the chemists as needed to resolve the outstanding issues.

Biopharmaceutics

Dr. Cooper noted that the dissolution data provided in the application appear to support (b) (4) of the dissolution acceptance criterion to $Q = (b) (4)$ at 15 minutes and thus we recommend that this criterion be revised when responding to our IR letter dated May 3, 2013.

NonClinical Pharmacology

Dr. Hausner noted that there was an outstanding IR letter (April 29, 2013) regarding changes in bone tissues in the animal studies. She also referred to Study A43289, a 26-week mechanistic study in rats and asked for detailed descriptions of the findings in the vertebrae, costae and humerus as well as an assessment of the findings from a veterinary pathologist with expertise in bone histopathology. Dr. Hausner asked the applicant to provide photomicrographs of the findings in juvenile and adult animals to illustrate what Bayer is describing and to show the spectrum of lesions from mild to severe. If Bayer feels that these findings are not relevant to the clinical situation, a detailed explanation of that position should be provided. Dr. Hausner added that the requested items would be sent to the firm in writing.

Bayer said they will provide a response to the April 29, 2013 IR letter by the following week and would respond quickly to today's request from Dr. Hausner after receiving it.

Carcinogenicity

Dr. Hausner said the Executive CAC (Executive Carcinogenicity Committee) reviewed the carcinogenicity studies for riociguat and did not find any evidence of neoplasms. The Division said they will send the minutes of the Executive CAC meeting to Bayer.

Clinical Pharmacology

The three points listed below were discussed.

Dose/dosing regimen The Division stated that a preliminary evaluation of exposure-response relationship (6MWD being the outcome of interest) suggested that there was no additional benefit with 2.5 mg tid over 1.5 mg tid and enquired if the applicant had performed similar analyses (efficacy or safety variables) in support of 2.5 mg tid. Bayer replied that exposure-response analyses (hemodynamics and 6MWD) were performed and were included in the submission. In addition, they pointed to the large between subject variability in pharmacokinetics of the riociguat as a reason for the need for a higher dose. Bayer also cited hemodynamic data from PATENT-1 where a dose-response was observed.

Dosing instructions in smokers The Division thought that the instructions for dosing in smokers currently in the label were impractical. Further, given that elevated CYP1A1 activity/level does not reverse immediately following cessation of smoking, instructions beyond what was currently in the label are required. Bayer replied that they will provide hemodynamic and 6MWD (6 minute walk distance) data to support dosage adjustments for smokers taking the drug.

CYP1A1 inhibitors It was noted that the label currently cited tyrosine kinase inhibitors erlotinib and gefitinib as strong CYP1A1 inhibitors. Data supporting this statement and also the implications of concomitant administration with a strong CYP1A1 inhibitor on riociguat concentrations was requested.

Clinical

The Division continues to have concern that the individual dose titration strategy to 2.5 mg po TID may not be warranted because:

- We agree with Bayer's conclusion from POC study 11874: BAY 63-2521 2.5 and 1 mg led to clinically relevant and statistically significant reductions in PAP, SBP, PVR, and SVR and to a clinically relevant and statistically significant increase in CI (P between 0.0047 and <0.0001) with no clinically relevant differences between the 2.5 and 1 mg dose groups.
- There is no evidence of dose-responsive efficacy in PATENT-1 between the 1.5 mg po TID dose-capped arm and the IDT arm. In fact, the 6MWD increment over baseline was numerically higher in the 1.5 mg TID capped arm.
- This is of concern because:

- there is evidence for a higher incidence of low blood pressure events in patients in the IDT arm compared to the 1.5 mg TID capped arm in PATENT, as well as dose-responsive decreases in blood pressure seen in both study 11260 (multidosing in healthy normals) as well as POC study 11874. The phase II trial 12166 was non-randomized, non-blinded, and non-controlled, so somewhat limited in addressing this issue.
- While 40% of subjects in the CTEPH trial, CHEST-1, were 65 years of age or greater, this experience is not entirely reassuring regarding older patients who will undoubtedly harbor coronary artery disease, cerebral vascular disease, and/or peripheral vascular disease, and who may tolerate systemic hypotension poorly.

Statistical

There were no statistical issues for discussion.

Patient Labeling

Mr. Fromm said the initial assessment of the Medication Guide was that the grade level was somewhat higher and the reading level lower than what we usually prefer.

3.0 INFORMATION REQUESTS

Please see previous discussion under **2.0- Review Issues (to date)**

The Division of Medication Error and Prevention Analysis (DMEPA) said they were reviewing the label, labeling, and packaging of the product and that there was one pending IR regarding the blister packaging. Bayer said they were working on a response to this request and hoped to submit the information in the next week or so. Bayer also confirmed that the blister packaging proposed for Riociguat has not been used on other products marketed by Bayer but the supplier of the blister package indicated that the same packaging has been used by other pharmaceutical companies and Bayer is waiting for this vendor to provide data on any complaints received regarding this blister packaging.

4.0 SAFETY CONCERNS/RISK MANAGEMENT

Please see previous discussion under **2.0- Review Issues (to date)**

The Division of Risk Management (DRISK) is reviewing the REMS submitted with the application and will provide comments and requests to the applicant if needed.

5.0 ADVISORY COMMITTEE MEETING

Dr. Stockbridge said that since riociguat was a new molecular entity and the first member of a new class of pharmacological agents, the agent would be presented before the Cardiovascular and Renal Products Advisory Committee on August 6, 2013. We will share our draft questions for the Advisory Committee meeting with Bayer closer to the time of the meeting.

Bayer asked if any panel members from specific clinical disciplines were being recruited for the Advisory Committee Meeting. Dr. Stockbridge said that recruitment for the Advisory Committee Meeting was standard and no specific clinical disciplines were being targeted.

6.0 LATE-CYCLE MEETING/OTHER PROJECTED MILESTONES

The internal Late-Cycle meeting is scheduled for July 11, 2013 and the Late-Cycle face-to-face meeting with Bayer is scheduled for July 22, 2013. The Division hopes to send draft labeling to the applicant by the beginning of July 2013.

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/s/

NORMAN L STOCKBRIDGE
05/29/2013