CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204819Orig1s000

OTHER REVIEW(S)

RHPM NDA Overview
October 8, 2013

Adempas (riociguat) Tablets

NDA 204819

Applicant: Bayer Healthcare Pharmaceuticals

Classification: 1 (NME)

Review Classification: Priority (8 month review)

Proposed Indication: treatment of 1) chronic thromboembolic pulmonary hypertension (CTEPH) World Health Organization (WHO) Group 4 to improve exercise capacity and WHO functional class and 2) pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise capacity, improve WHO functional class and to delay clinical worsening.

Date of Application: February 8, 2013

Receipt Date: February 8, 2013

User Fee Goal Date: October 8, 2013

REVIEW TEAM

Office of New Drugs, Office of Drug Evaluation I, Division of Cardiovascular and Renal Products
- Cross Discipline Team Leader
  - Norman Stockbridge, M.D., Ph.D.
- Medical Reviewer
  - Preston Dunnmon, M.D.
- Pharmacology and Toxicology
  - Elizabeth Hausner, D.V.M.
- Regulatory Health Project Manager
  - Edward Fromm, R.Ph., RAC

Office of New Drug Quality Assessment (ONDQA), Branch 1
- Monica Cooper, Ph.D., (Drug Substance)
- Pei-I Chu, Ph.D., (Drug Product)
- Kareen Riviere, (Biopharmaceutics)

Office of Clinical Pharmacology
- Divya Menon-Andersen, Ph.D.
- Dhananjay Marathe, Ph.D., (Pharmacometrics)

Office of Biostatistics, Division of Biometrics I
- John Lawrence, Ph.D.

Office of Surveillance and Epidemiology
- Kim Defronzo, Pharm.D., (DMEPA)
- Sharon Mills, RN, BSN, (Medication Guide)
- Somya Dunn, M.D., (Risk Evaluation and Mitigation Strategy - REMS)

Office of Medical Policy, Office of Prescription Drug Promotion
- Emily Baker, Pharm.D.

Office of Compliance, Division of Scientific Investigations (DSI)
- Sharon Gershon, Pharm.D.

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).

This 505(B)(1) 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.

User Fee

The user fee for this application was paid in full on February 1, 2013 (ID 3013017).

Pediatrics

The Office of Orphan Products, on September 19, 2013 granted orphan designation for both the PAH and CTEPH indications.

Advisory Committee

The riociguat ADCOM was held on August 6, 2013. The committee was asked a number of discussion questions ranging from the design and conduct of the CHEST-1 and PATENT-1 trials, to the use of riociguat with other vasodilators such as sildenafil and nitrates. There were two voting questions, “Should riociguat be approved for the treatment of PAH of WHO Group 1?” and “Should riociguat be approved for the treatment of CTEPH of WHO Group 4?” Both questions yielded eleven “yes” responses and zero “no” or “abstain” votes.

Trade name

Adempas was deemed conditionally acceptable for use on May 8, 2013, and fully acceptable on August 7, 2013. The review Division did not have any concerns with the proposed name.

REGULATORY TIMELINE

- IND submitted February 15, 2007
- End of Phase 2 Meeting: May 29, 2008
- Pre-NDA Meeting: November 1, 2012
- NDA submitted: February 8, 2013

- Filing Meeting: March 8, 2013
- 74-day Letter issued: April 3, 2013
- Executive Carcinogenicity Assessment Committee (CAC) Meeting: April 16, 2013
- Mid-Cycle T-Con: May 10, 2013
- Late Cycle Meeting: July 22, 2013
- Advisory Committee: August 6, 2013
- PDUFA Date: October 8, 2013
- Approval Date: October

REVIEWS

Office Memorandum (dated October 08, 2013)
Dr. Unger recommended approval for both the CTEPH and PAH indications.

Divisional Memorandum
(see CDTL review)

Cross-Discipline Team Leader (CDTL) Review (dated September 9, 2013)
Dr. Stockbridge recommends approval. He notes the results are highly persuasive in two studies, and everyone appears to be comfortable with their mutual support for indications in PAH, where there are lots of successful predicates with vasodilators, and in CTEPH, where this would be the first product.

Medical Review (dated July 8, 2013)
Dr. Dunnmon recommends approval for the PAH and CTEPH indications. However, in PAH, he recommends a starting dose of 0.5 mg TID, with titration, if necessary to 1.5 mg TID. In CTEPH, Dr. Dunnmon recommends extending the maximal titrated dose to 2.5 mg in patients that have SBP>110 mg Hg and are not experiencing clinical relief.

- **Financial Disclosure** (pg 25 of Dr. Dunnmon's review)
  financial disclosure information was provided for the pivotal efficacy trials PATENT-1 (Study12934) and CHEST-1 (Study 11348). Of all investigators that participated in the two pivotal trials, only four reported disclosable information on form 3454. All four provided a form 3455 specifying the nature of the potential COI, along with the mitigation steps taken to minimize potential bias. None of these four investigators enrolled more than 3.9% of either of the pivotal studies, and all limited endpoint assessments and/or eCRF data entry. Dr. Dunnmon agrees with the sponsor's conclusions that the potential for the participation of these four investigators in the pivotal trials to influence program results was minimal.

Biostatistics Review (dated July 1, 2013)
Dr. Lawrence noted that the two studies showed a symptomatic benefit in improving 6MWD. His review stated that there are no approved drugs for CTEPH, but the magnitude of the effect in the PAH trial was similar to the magnitude of the treatment effect for other approved drugs (approximately 30 m improvement compared to placebo).

Clinical Pharmacology Review (dated July 7, 2013)
The Clinical Pharmacology team of Drs. Menon-Andersen, Marathe, Rogers, and Yang recommended that riociguat be approved in both the PAH and CTEPH indications with a starting dose of 0.5 mg TID, titrated to a maximum dose 1.5 mg TID. They also recommended a maximum dose of 3.0 mg TID in smokers. They noted that based on the proposed dosing regimen and exposure-safety analysis,

concomitant administration of multi-CYP inhibitors such as ketoconazole with riociguat is acceptable, but that hypotension should be monitored upon initiation of treatment with the inhibitor.

Pharmacology and Toxicology Review (dated June 19, 2013)
Dr. Hausner concluded that the drug is approvable dependant on whether the clinical benefit outweighs potential adverse effects, particularly on developing bone in children, where she advises caution be used. The potential effects of the drug on bone in children and adults will be monitored in the post-marketing setting.

The Division met with the Executive Carcinogenicity Assessment Committee (CAC) on April 16, 2013 and their recommendations were as follows (minutes dated April 17, 2013):

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.

Office of New Drug Quality Assessment (ONDQA), Branch 1 Review (four reviews dated June 11and 27, July 5, and August 20, 2013)

- **Tertiary Review CMC Review** (dated August 20, 2013)
  Dr. Sood noted in his summary review that the riociguat application is approvable from a CMC perspective.

- **Drug Substance Review** (dated July 5, 2013)
  Dr. Cooper recommends approval for the micronized riociguat drug substance.

- **Drug Product Review** (dated June 27, 2013)
  Dr. Chu recommends approval for the riociguat drug product. The proposed shelf life for the drug is 36 month and Dr. Chu said, that based on long-term stability data, this was acceptable.

- **Biopharmaceutics Review** (dated June 11, 2013)
  Dr. Riviere recommends a dissolution acceptance criteria of Q= (b) (4) at 15 minutes and the applicant has accepted this recommendation.

- **Facilities Inspections**
  - ACCEPTABLE recommendation on February 14, 2013.
- **Environmental Assessment**
  - Categorical exclusion granted (see Dr. Chu's review)

CONSULTS

Office of Scientific Investigations (OSI) Review (dated August 16, 2013)
Dr. Gershon noted that 4 clinical investigator sites and the sponsor (Bayer Healthcare Pharmaceuticals). No regulatory violations were found during the inspections at three clinical investigator sites: Dr. D'Armini, Italy; Dr. Wang; China; and Dr. Ghofrani, Germany.

Minor regulatory violations were found during the inspections at Dr. Jing; China where a one observational Form FDA 483 was issued for failure to follow the investigational plan. Minor regulatory violations were found during the inspection of the sponsor, Bayer Healthcare, and a one-observational Form FDA 483 was issued for failure to ensure proper monitoring. Dr. Gershon noted that although regulatory violations were noted as described above, they are unlikely to significantly impact the primary efficacy or safety analysis for this study.
Therefore, the data from this study may be considered reliable based on available information.

Office of Surveillance and Epidemiology Review - REMS (dated September 5 and October 7, 2013)
Dr. Dunn notes that the proposed REMS for Adempas (riociguat) contains the appropriate REMS components. These include a Medication Guide and three ETASU—prescriber certification, pharmacy certification and documentation of safe use.

Overall DRISK recommends a REMS for Adempas for the risk of teratogenicity.

Office of Prescription Drug Promotion (dated September 17, 2013).
Dr. Baker finalized her review and included a number of labeling comments in her review.

CONCLUSION
An approval letter was issued for this application and signed by the Office Director, Ellis Unger, M.D., on October 08, 2013. The approval letter was appended with the agreed-upon labeling text, finalized REMS and Medication Guide.

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Edward J. Fromm, R.Ph., RAC
Regulatory Health Project Manager

dr-ef-10/08/13

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/s/

EDWARD J FROMM
10/09/2013

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	September 17, 2013
To:	Norman Stockbridge, MD, PhD Director **Division of Cardiovascular and Renal Products (DCRP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN, CWOCN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Sharon R. Mills, BSN, RN, CCRP Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Emily Baker, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	Adempas (riociguat)
Dosage Form and Route:	tablets, for oral use
Application Type/Number:	NDA 204819
Applicant:	Bayer Healthcare Pharmaceuticals, Inc.

1 INTRODUCTION

On February 8, 2013, Bayer Healthcare Pharmaceuticals, Inc. submitted for the Agency's review an Original New Drug Application (NDA) 204819 for Adempas (riociguat) tablets. The proposed indication for Adempas (riociguat) is for the treatment of adults with persistent, recurrent, or inoperable chronic thromboembolic pulmonary hypertension (CTEPH) WHO Group 4; and for the treatment of adults with pulmonary hypertension (PAH) WHO Group I, to improve exercise capacity, WHO functional class and to delay clinical worsening.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to requests by the Division of Cardiovascular and Renal Products (DCRP) on February 21, 2013 for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for Adempas (riociguat) tablets.

The Risk Evaluation and Mitigation Strategy (REMS) is being reviewed by the Division of Risk Management (DRISK) and will be provided to DCRP under separate cover.

2 MATERIAL REVIEWED

- Draft Adempas (riociguat) tablets MG received on February 8, 2013, and received by DMPP and OPDP on September 3, 2013.
- Draft Adempas (riociguat) tablets Prescribing Information (PI) received on February 8, 2013, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on September 3, 2013.
- Approved Letairis (ambrisentan) tablets comparator labeling dated August 17, 2013

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the MG the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the MG document using the Verdana font, size 11.

In our collaborative review of the MG we have:

- simplified wording and clarified concepts where possible

- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG is consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

SHARON R MILLS
09/17/2013

EMILY K BAKER
09/17/2013

BARBARA A FULLER
09/17/2013

LASHAWN M GRIFFITHS
09/17/2013

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

******Pre-decisional Agency Information******

Memorandum

Date: September 17, 2013

To: Ed Fromm – CPMS
Division of Cardiovascular and Renal Products (DCRP)

From: Emily Baker, Pharm.D. – Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: **NDA 204819**
OPDP Labeling Comments for Adempas (riociguat) tablets

OPDP has reviewed the proposed Package Insert (PI) submitted for consult on February 21, 2013, for Adempas (riociguat) tablets (Adempas). Our comments on the PI are based on the proposed labeling emailed to us on September 3, 2013.

Thank you for the opportunity to comment on the proposed material.

If you have any questions, please contact Emily Baker at 301.796.7524 or emily.baker@fda.hhs.gov.

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/s/

EMILY K BAKER
09/17/2013

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: August 16, 2013

TO: Preston Dunnmon, Medical Officer
Edward Fromm, Regulatory Project Manager
Division of Cardio-Renal Drug Products

FROM: Sharon K. Gershon, Pharm. D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Susan Leibenhaut, M.D.
Acting Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

Kassa Ayalew, M.D.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 204819

APPLICANT: Bayer Healthcare Pharmaceuticals, Inc.

DRUG: riociguat film-coated tablets (Adempas™)

NME: Yes

THERAPEUTIC CLASSIFICATION: Standard

INDICATIONS: treatment of pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH)

CONSULTATION REQUEST DATE: March 19, 2013

INSPECTION SUMMARY GOAL DATE: August 8, 2013

DIVISION ACTION GOAL DATE: October 8, 2013

PDUFA DATE: October 8, 2013

I. BACKGROUND:

Bayer Healthcare submitted NDA 204819 in February 2013, for riociguat tablets with an indication in the treatment of chronic thromboembolic pulmonary hypertension (CTEPH) and pulmonary arterial hypertension (PAH).

Although there are several FDA-approved products to treat PAH, no drugs are FDA-approved to treat CTEPH, although some drugs are used off-label to treat that indication. Riociguat is a stimulator of the soluble guanylate cyclase (sGC), an enzyme in the cardiopulmonary system and the receptor for nitric oxide (NO). Riociguat restores the NO-sGC-cGMP pathways and leads to increased cGMP. Pulmonary hypertension is associated with impaired synthesis of NO and insufficient stimulation of the NO-sGC-cGMP pathway.

This was an international phase III clinical development program for riociguat that included separate pivotal studies in CTEPH (Study 11348: CHEST-1) and PAH (Study 12934: PATENT-1) with long term extension studies for both. The primary endpoint was the change from baseline to Week 16 (CHEST-1) and Week 12 (PATENT-1) in 6 minute walking distance (6MWD).

Study No. 11348 (CHEST-1): Randomized, double-blind, placebo-controlled, multicentre, multinational 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)

This study randomized (2:1 riociguat vs. placebo) 262 subjects at 89 centers in 26 countries. The primary efficacy variable was the change from baseline in 6MWD after 16 weeks. Key secondary endpoints were the change from baseline in Pulmonary Vascular Resistance (PVR), change from baseline in N-terminal prohormone of brain natriuretic peptide (NT-proBNP), time to clinical worsening, and change from baseline in WHO functional class, Borg CR 10 Scale, EQ-5D questionnaire, and Living with Pulmonary Hypertension questionnaire after 16 weeks.

During the 8-week titration phase, the dose of study medication was titrated every 2 weeks based on the subject's peripheral systolic blood pressure (SBP). According to a prespecified algorithm, starting from a dose of 1.0 mg tid riociguat or placebo, the dose was increased, maintained, or decreased depending on whether SBP was ≥95 mmHg, 90 – 94 mmHg, or <90 mmHg. The "optimal dose" reached at the end of the titration phase was to be maintained for a further 8 weeks in the main study phase. Dose reductions could be made for safety reasons.

No. 12934 (PATENT-1): Randomized, double-blind, placebo-controlled, multi-centre, multinational 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).

This study randomized (2:1 riociguat vs. placebo) 445 subjects at 124 centers in 30 countries. The primary efficacy endpoint was the change from baseline in 6MWD after 12 weeks. Key secondary endpoints are the same as described for Study No. 11348.

During the 8-week titration phase, the dose of study medication was titrated every 2 weeks based on the subject's peripheral systolic blood pressure (SBP). In accordance with a prespecified algorithm, starting from a dose of 1.0 mg tid riociguat or placebo, the dose was increased, maintained, or decreased depending on whether SBP was ≥95 mmHg, 90 – 94 mmHg, or <90 mmHg. The maximum permitted daily dose depended on the treatment to which the subject was assigned. The "optimal dose" reached at the end of the titration phase was to be maintained for a further 4 weeks in the main study phase. Dose reductions for safety reasons were allowed.

Four foreign sites were selected to inspect for NDA 204819. These sites were selected because of high enrollment or high risk score using the Risk Based Site Selection Tool, or both. In particular, the Jing site (China):

- had been a high contributor to other PAH registration studies
- had much lower variability in systolic blood pressure (SBP) measurements within visits for each subject
- had many more patients with a baseline 6MWD close to 450 meters
- had a high number of subjects with large improvements in 6MWD.

II. RESULTS (by Site):

Name of CI	Protocol # and # of Subjects	Inspection Date	Final Classification
Andrea Maria D'Armini Piazzale Golgi, 19 IRCCS Policlinico San Matteo Pavia 27100 Italy	**Study No. 11348** Site # 22001 18 subjects	June 3 – 7, 2013	Pending (Preliminary NAI)
Zhicheng Jing Shanghai Pulmonary Hospital Dept. Pulmonary Circulation Shanghai, China	**Study No. 11348** Site # 54004 7 subjects **Study No. 12934** Site #54002 21 subjects	April 22 – 26, 2013	VAI
Chen Wang Respiratory Diseases Institute Beijing Chaoyang Hospital Pulmonology Dept. No.8 Bai jia zhuang Road, Chaoyang District Beijing China	**Study No. 11348** Site #54002 21 subjects **Study No. 12934** Site #54005 18 subjects	July 1-5, 2013	Pending (Preliminary NAI)
Ardeschir Ghofrani Universitätsklinikum Giessen und Marburg Medizinische Klinik II Ambulanz für Pulmonale Klinikstrasse 33, 35392 Germany	**Study No. 11348** Site 10001 9 Subjects **Study No. 12934** Site 10005 16 subjects	June 10 – 14, 2013	Pending (Preliminary NAI)
Bayer Healthcare 10 Waterview Blvd. Parsippany, NJ	**Sponsor**	June 25 – July 11, 2013	Pending (Preliminary VAI)

Key to Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations.
Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending.

1. Andrea Maria D'Armini, Piazzale Golgi, 19 IRCCS Policlinico San Matteo Pavia 27100 Italy

a. What was inspected: This inspection was conducted according to Compliance Program 7348.811. Only Study 11348 (CHEST-1) was conducted at this site. A total of 20 subjects were screened, 18 subjects enrolled, and 15 subjects completed the study. The field investigator reviewed all subject files during the inspection to ensure the following: informed consent was appropriately obtained; subjects met eligibility criteria; test article accountability records were accurately maintained; randomization procedures were followed; protocol deviations were appropriately reported; subject discontinuation information was accurate; catheter lab data was properly obtained; the site adhered to the dose titration schedule; the peripheral systolic blood pressure (SBP) was measured at trough before test article administration; and the source data corroborated with the data listings and electronic CRFs, with respect to all of the above including adverse events and efficacy endpoints.

b. General observations/commentary: The field investigator saw no evidence of under-reporting of adverse events, and confirmed that the primary efficacy data was verifiable. He reported that the study was well conducted at this site and observed no discrepancies of source data and data listings.

In reviewing the subject records, the FDA field investigator reported that the dose titration scheme (dosing algorithm) was appropriately followed. For example, for Subject 8002, the field investigator reviewed clinic notes documenting a SBP of 127/72 at 9:30 am on June 17, 2009, with a decision to up-titrate by notifying the IVRS at 10:00 am (bottle #520065 dispensed).

For each instance reviewed, the FDA field investigator observed that the SBP was measured at trough, before intake of the test article. He observed good documentation concerning this item.

The FDA field investigator reported that the right heart catheterization (RHC) was done for each subject at the study site by one of the study physicians. He also reported that all hemodynamic measurements were documented in the subject's file, and signed by the responsible physician.

No regulatory violations were noted and a Form FDA 483 was not issued. There were two instances of potential blind breaking during the study, and Dr. D'Armini was given a verbal warning each time. The first instance involved a Certificate of Analysis of the test articles, that was mistakenly sent to the site by the sponsor. This document provided enough information to deduce which materials were placebo and which were test article. However, both the principal investigator and study coordinator signed statements saying they were unaware of which was which, and the situation was quickly corrected. (discussed below under the sponsor inspection)

The second instance involved subject management in the study extension for CHEST-2. Subjects 8001 and 8002 were both maximally up-titrated on CHEST-1 when they finished and entered CHEST-2. Subject 8001, who was on placebo, was allowed to be up-titrated in

CHEST-2, while Subject 8002, on test article, was not. CHEST-2 entrance retained dose type and concentration in use at the end of CHEST-1. This issue was detected and corrected after Subjects 8001 and 8002 had completed CHEST-1 and before Subject 8003 had completed CHEST-1.

c. Assessment of data integrity: Overall, the study was conducted adequately and no regulatory violations were cited at this site during the inspection. OSI recommends the data from this site be accepted in support of the respective indication.

NOTE: Observations noted above are based on communications with the field investigator; an inspection summary addendum will be generated if conclusions change upon receipt and review of the Establishment Inspection Report (EIR).

2. **Zhicheng Jing, Shanghai Pulmonary Hospital, Dept. Pulmonary Circulation No. 507 Zhengmin Road, Shanghai China 200433**

a. What was inspected: This inspection was conducted according to Compliance Program 7348.811. The inspection audited records for two clinical studies: Protocol 11348 (CHEST-1) and Protocol 12934 (PATENT-l). (b) (4)

For Protocol No. 11348 (CHEST-1), 14 subjects were screened, 7 subjects enrolled, and 7 subjects completed the study. The field investigator reviewed subject files for all 7 subjects, including progress notes, tests performed during each visit such as blood pressure measurements, 6-minute walk test (6-MWD) and blood chemistry results. He verified that the dose titration scheme was followed, as per the protocol specified dosing algorithm. The field investigator visited the hallway where the 6MWD was performed and made introduction with the person who was responsible for administering the 6MWD.

For Protocol 12934 (PATENT-1), 23 subjects were screened, 21 subjects enrolled, and 20 subjects completed the study. One subject (Subject 005) experienced a SAE (fatal cardiac arrest) and did not complete the study.

The field investigator reviewed subject files for protocol deviations, informed consent documents, and corroborated source documents with data listings with respect to adverse events and primary efficacy endpoints for each subject. In addition, he reviewed the right heart catheterization (RHC) tracings and printouts, and ensured that the dosing algorithm was followed.

b. General observations/commentary: For Protocol 11348 (CHEST-1), there were no serious adverse events. The field investigator confirmed that the pre-assessment angiogram data and right heart catheterization data was administered by (b) (4) for Subject 54004003 and by (b) (4)

(b) (4) for all other subjects (009 to 0014). There were no deficiencies observed relating to the conduct of this clinical study (No. 11384, CHEST-1) at this site.

For Protocol 12934 (PATENT-1), the FDA field investigators observed that all subjects had their right heart catheterization (RHC) performed and read at (b) (4) The tracings included the hospital and patient names, but were not signed by the physician performing the procedure. During the inspection, review of records revealed that the RHC tracings and printouts were filed separately from the signed RHC summary reports. The tracings and printouts were not signed, as required by the RHC manual. This item was cited on a Form FDA 483.

In general, the source documents were clean, legible, and adequate. The field investigator reviewed all adverse events and found them accurately documented and reported. There was one serious adverse event (SAE) that occurred during Study 12934, whereby Subject 005 experienced a fatal cardiac arrest. The data was well-reported.

c. Assessment of data integrity: No deficiencies were observed relating to the conduct of study No. 11384 (CHEST-1); only minor regulatory violations were noted for Study No. 12934 (PATENT-1). The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indications.

3. Chen Wang, Respiratory Diseases Institute, Beijing Chaoyang Hospital, Pulmonology Dept. Chaoyang District, Beijing China 100020

a. What was inspected: This inspection was conducted according to Compliance Program 7348.811. The inspection audited records for two clinical studies: 11348 (CHEST-1) and 12934 (PATENT-l).

For Study 11348 (CHEST-1), 32 subjects were screened, 21 subjects enrolled, and 19 subjects completed the study. The FDA field investigator reviewed records for 19 subjects,

For Study 12934 (PATENT-1), 19 subjects were screened, 18 subjects enrolled, and 18 subjects completed the study. The FDA field investigator audited subject records for all 18 enrolled subjects.

For each study, the field investigator reviewed the catheter lab data for each subject to determine where the RHC was performed, when it was performed, and if the physician signed the form. He reviewed subject records to ensure that the titration scheme was followed according to the SBP measurements at visits, and according to the protocol specified dosing algorithm. He corroborated the data listings with the source documents with respect to adverse events and efficacy endpoints.

b. Commentary/Observations: The FDA field investigator observed that for both studies, the right heart catheterization for the diagnosis of PAH was performed at the investigator site, and that the hemodynamic measurements were documented in the subject files. He reported that the dosing schedule was followed, as per the dosing algorithm in the protocol. The primary and secondary efficacy endpoint data was verifiable, and there was no evidence of underreporting of adverse events. Subject records were adequate and protocol deviations were documented.

c. Assessment of data integrity: No deficiencies were observed relating to the conduct of study 11384 (CHEST-1 or Study 12934 (PATENT-1) at this site. The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indications.

NOTE: Observations noted above are based on communications with the field investigator; an inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

4. Ardeschir Ghofrani, Klinikstrasse 33, Giessen Germany 35392

a. What was inspected: This inspection was conducted according to Compliance Program 7348.811. The inspection audited records for two clinical studies: 11348 (CHEST-1) and 12934 (PATENT-l). Subject records were in German and were translated during the inspection.

For Study 11348 (CHEST-1), 11 subjects were screened, 9 subjects enrolled, 8 subjects completed the study. The FDA field investigator reviewed 9 subject records for this study. For Study 12934 (PATENT-1), 16 subjects were screened, 16 subjects enrolled, and 15 subjects completed the study. The FDA field investigator reviewed 16 subject records for this study.

For both studies, the FDA field investigator corroborated the source data with the data listings with respect to adverse events, primary and secondary efficacy endpoints, protocol deviations, subject randomization, subject discontinuations, and concomitant medications. As per special instruction, he confirmed that the dosing algorithm was followed, that blood pressure measurements were made at trough before intake of the morning dose, and that the right heart catheterization was performed within the protocol required time period and the printouts were signed.

b. Commentary/Observations: The FDA field investigator observed that for both studies, the right heart catheterization for the diagnosis of PAH was performed at the investigator site, and that the hemodynamic measurements were documented in the subject files. He reported that the dosing schedule was followed, as per the dosing algorithm in the protocol. The primary and secondary efficacy endpoint data was verifiable, and there was no evidence of underreporting of adverse events. Subject records were adequate and protocol deviations were documented

No FDA 483 was issued at this site. One item was discussed at the end of the inspection, for Study 11348. This concerned a discrepancy observed between the source documents and data

listings for Borg scale (a secondary efficacy endpoint) for Subject 8005. The data listing documented a BORG score of three on September 22, 2009 at 14:25, whereas the source document documented a value of four. OSI considers this finding minor, isolated and unlikely to impact data integrity at this site.

c. Assessment of data integrity: No deficiencies were observed relating to the conduct of study 11384 (CHEST-1 or Study 12934 (PATENT-1) at this site. The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indications.

5. Bayer Healthcare Pharmaceuticals, Inc., 10 Waterview Blvd., Parsippany, NJ

a. What was inspected: This inspection was conducted according to Compliance Program 7348.810. (b) (4)

During the inspection the FDA field investigator reviewed study trial oversight and all study documents relating to Study 11348 (CHEST-1) and Study 12934 (PATENT-1). The inspection reviewed Standard Operating Procedures for clinical study monitoring and management; study drug accountability and destruction, site closeout visits; protocol deviation documentation and handling; archiving of subject data and eCRFs; and investigator site audits. In general, Bayer was responsible for providing monitoring of all the sites for both studies, with the exception of Japan where monitoring was provided by (b) (4) during the beginning of both studies. Also, monitoring for all sites in Israel was provided by (b) (4). She reviewed the contracts and Master Service Agreements for the various vendor CROs. To determine adequacy of monitoring, the FDA field investigator focused on the four foreign sites where inspections were conducted. She was provided a listing of the CRAs who conducted monitoring at those sites, and reviewed their CVs, and the Investigator Meeting logs. The FDA field investigator reviewed the dose titration schedule for both trials, and collected documents relating to discussion of dose titration. She also reviewed Annual Reports to ensure these Reports were submitted in a timely manner.

b. Commentary/Observations: In general, the sponsor maintained adequate oversight of the pivotal study trials for this NDA. She observed that the CRAs conducted monitoring visits, drug accountability, and eCRF queries throughout the studies. However, the field investigator observed that, because the monitoring plan was broad and did not provide required timeframes for monitoring, some sites did not have a monitoring visit for several months, although she observed that there was no new enrollment during this time. There was no evidence of underreporting of adverse events, and the primary efficacy endpoints were verifiable.

At the end of the inspection a one observational Form FDA 483 was issued for failure to ensure proper monitoring and ensure the study is conducted according to the investigational plan. Specifically, the FDA field investigator noted that several protocol deviations were noted during monitoring that were not included in the Clinical Study Report.

For Study 11348, at Site 10001 (Ghofrani, Germany), Subject 8001 was 77 years old, and did not meet the inclusion criteria of 18 – 75 years old at screening. Although the inclusion criteria changed during the study to include subjects up to 80 years old, at the time of this subject's enrollment, the inclusion criteria was 18 – 75 years of age. Also at Site 10001 (Ghofrani, Germany), three subjects (8001, 8002, 8005) and at Site 22001 (D'Armini, Italy), one subject (8009) did not meet the inclusion criteria at screening in that the pulmonary vascular resistance (PVR) was not greater than 480 dyn*sec*cm-5. These subjects were enrolled and did not meet the inclusion criteria. These issues were described within meeting minutes as minor protocol deviations, but were never included in the CSR. Also at Site 22001 (D'Armini, Italy), the resupply of study drugs to the site was mistakenly accompanied by a Certificate of Analysis that which could potentially unblind the staff to study drug. Once this issue was identified, Bayer sent a person to that site to collect the wrongly sent document. This issue was identified during the inspection at that site, and a Note to File was documented by site personnel stating that they were never unblinded during the study. (Discussed under the CI results above.)

For Study 12934, at Site 10005, Subject 100054003, an 80 year old subject did not meet the inclusion criteria of 18-75 yrs old at screening but was enrolled in the study and Subject 100054004 was misdosed when she took two different dosages of study medication for approximately 9 days as per the Site's directions.

In addition, the FDA field investigator found isolated instances (7 subjects from Study 11348; 6 subjects from Study 12934) of discrepancies for pills returned, between the eCRF and study drug dispensing logs and study drug reconciliation and destruction logs. For example, at Site 10001 (Ghofrani, Germany), for Study 11348 (CHEST-1), for Subject 8003, the Study Drug Dispensing log showed 10 tablets of Bottle 521755 returned at Visit 2 and 13 tablets of Bottle 503085 returned at Visit 4, whereas the eCRF page documented 44 tablets and 41 tablets, respectively. Although drug accountability was performed by the study monitor, these discrepancies were not identified during monitoring.

c. Assessment of data integrity: Although the inspection of the Sponsor (Bayer Healthcare) found sporadic instances in which the sponsor failed to ensure proper monitoring and ensure the study is conducted according to the protocol, the issues are minor, and unlikely to impact data integrity. OSI recommends that the data be accepted in support of the studies conducted under this NDA.

NOTE: Observations noted above are based on the Form FDA 483 and communications with the field investigator; an inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Four foreign clinical investigator sites and the sponsor (Bayer Healthcare) were inspected in support of NDA 204819. No regulatory violations were found during the inspections at three clinical investigator sites: Dr. D'Armini, Italy; Dr. Wang; China; and Dr. Ghofrani, Germany.

Minor regulatory violations were found during the inspections at Dr. Jing; China where a one observational Form FDA 483 was issued for failure to follow the investigational plan. Minor regulatory violations were found during the inspection of the sponsor, Bayer Healthcare, and a one-observational Form FDA 483 was issued for failure to ensure proper monitoring. Although regulatory violations were noted as described above, they are unlikely to significantly impact the primary efficacy or safety analysis for this study. Therefore, the data from this study may be considered reliable based on available information.

Note: The final EIRs for Dr. D'Armini, Italy; Dr. Wang; China; and Dr. Ghofrani, Germany, and the Sponsor (Bayer Healthcare) were not available at the time this CIS was written. The observations noted are based on preliminary EIRs or email communications with the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIRs.

{See appended electronic signature page}

Sharon K. Gershon, Pharm.D.
Reviewer
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

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/s/

SHARON K GERSHON
08/16/2013

SUSAN LEIBENHAUT
08/16/2013

KASSA AYALEW
08/16/2013

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Final Label and Labeling Memo

Date:	July 25, 2013
Reviewer:	Kimberly DeFronzo, R.Ph, M.S., M.B.A. Division of Medication Error Prevention and Analysis
Team Leader:	Irene Z. Chan, Pharm.D, BCPS Division of Medication Error Prevention and Analysis
Drug Name and Strength(s):	Adempas (Riociguat) Tablets 0.5 mg, 1 mg, 1.5 mg, 2 mg, and 2.5 mg
Application Type/Number:	NDA 204819
Applicant/Sponsor:	Bayer Healthcare Pharmaceuticals
OSE RCM #:	2013-499-1

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1 INTRODUCTION

This review evaluates the revised container labels, carton, and blister pack labeling for Adempas (Riociguat) Tablets, 0.5 mg, 1 mg, 1.5 mg, 2 mg, and 2.5 mg received on July 9, 2013 (Appendices A through D). DMEPA previously reviewed the proposed labels and labeling under OSE Review # 2013-499 dated June 28, 2013.

2 MATERIAL REVIEWED

DMEPA reviewed the revised labels and labeling received on July 9, 2013. We compared the revised labels and labeling against the recommendations contained in OSE Review # 2013-499 dated June 28, 2013, to ensure all our recommendations were implemented.

3 CONCLUSIONS AND RECOMMENDATIONS

The revised labels and labeling incorporated all of DMEPA's previous recommendations. However, we note the Applicant (b) (4)

3.1 COMMENTS TO THE APPLICANT

DMEPA recommends the following be implemented prior to approval of this NDA:

A. Bottle Labels and Bottle Carton Labeling

1. Remove the phrase (b) (4) from the strength expression on your bottle labels and bottle carton labeling. However, the "per tablet" statement should be (b) (4) for your blister packs.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact Karen Bengtson, OSE Project Manager, at 301-796-3338.

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

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/s/

KIMBERLY A DE FRONZO
07/25/2013

IRENE Z CHAN
07/25/2013

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs - Immediate Office
Pediatric and Maternal Health Staff
Silver Spring, MD 20993
Telephone 301-796-2200
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MEMORANDUM TO FILE

Date: July 23, 2013

From: Amy M. Taylor, MD, MHS Medical Officer
Pediatric and Maternal Health Staff

Through: Lynne P. Yao, MD OND Associate Director
Pediatric and Maternal Health Staff

NDA Number: 204-819 (associated IND number 75,629)

Sponsor: Bayer Healthcare Pharmaceuticals

Drug: riociguat

Dosage form and route of administration: Tablet, oral

Proposed Indications:

- For the treatment of chronic thromboembolic pulmonary hypertension.
- For the treatment of pulmonary arterial hypertension.

Consult request: The Division of Cardiovascular and Renal Products "would like to discuss the issue of a deferred PREA requirement for the PAH indication and how that would work with respect to the PeRC. We need assistance in mapping out a regulatory pathway for assessing the drug in kids with PAH given the potential bone toxicity that was noted in preclinical studies."

Background

The Division of Cardiovascular and Renal Products (DCRP) is currently reviewing riociguat (NDA 204-819) for the treatment of chronic thromboembolic pulmonary hypertension (CTEPH) and pulmonary arterial hypertension (PAH). The applicant submitted a request for a full waiver of required studies under the Pediatric Research Equity Act (PREA) for both indications. For CTEPH, the applicant requested the waiver under the criterion that necessary studies are impossible or highly impracticable because CTEPH is rare in the pediatric population. The request for a waiver for PAH is under the criteria that 1) studies are impossible or highly impracticable and 2) there is evidence strongly suggesting that the product would be ineffective or unsafe in all pediatric age groups. The applicant provides support for the second criterion based on pre-clinical evidence suggesting that riociguat might affect skeletal development in growing children.

Discussion and Conclusion

The waiver for CTEPH appears appropriate under the criterion that necessary studies are impossible or highly impracticable because CTEPH is rare in the pediatric population. (Berger 2012, van Loon 2011)

The waiver for PAH, however, is not appropriate. Currently, there are no approved products for the treatment of PAH in pediatric patients. Recently, sildenafil was not approved for the treatment of PAH in pediatric patients because of an increase in mortality associated with long-term use of the product. Patients completing the 16-week controlled study of sildenafil were followed for a median of 4 years (range 0.3 years to 7.0 years. An increase in mortality was observed with increasing sildenafil doses. The hazard ratio for high dose compared to low dose was 3.5, p=0.015. The labeling for Revatio® states that "use of REVATIO, particularly chronic use, is not recommended in children. Because there are no approved products for the treatment of PAH in pediatric patients, studies in products for the treatment of PAH would represent a public health benefit for pediatric patients.

The applicant listed two criteria under which they believe riociguat would qualify for a waiver. The criterion that necessary studies are impossible or highly impracticable is disputed by the ability of the sponsor of sildenafil to complete pediatric studies of 234 patients aged 1 to 17 years with PAH.

In addition, the applicant stated that a waiver would be indicated under the criterion that there is evidence strongly suggesting that the product would be ineffective or unsafe in all pediatric age groups. The applicant cites the non-clinical data related to possible bone toxicity. The applicant stated in the request for waiver:

> "Any study investigating the effects of riociguat in children would focus on pediatric patients aged 28 days to <18 years suffering from PAH. Clearly, this patient population is undergoing active skeletal system development, especially young children and adolescents. In nonclinical studies the effects of riociguat on bone morphology and bone growth were investigated in pivotal toxicity and mechanistic studies in rats, mice and dogs. In the repeat dose toxicity studies in juvenile and adolescent rats, riociguat-related effects on the skeletal system consistent with stimulation of osteoblasts were restricted to juvenile and adolescent rats and mice. In the repeat-dose studies in adolescent rats up to 26-weeks (chronic) treatment, growth plate alterations, epiphyseal cartilage

thickening and increases in bone mass of the primary and secondary spongiosa were observed after four weeks of riociguat treatment. In addition, after longer term treatment thickening of diaphyseal bone was observed. In juvenile animals, thickening of trabecular bone and hypercellularity consisting of activated osteoblasts and osteoclasts was seen in mice treated for up to 13-weeks in a few animals, epiphyseal growth cartilage changes comparable to those seen in rats were observed, whereas in dogs no treatment-related effects on bones, including the sternum, distal femur, proximal tibia, and central femur diaphysis were observed. As indicated by FDA's letter dated December 14, 2011, if development were to be pursued in children, then additional studies may be needed to address the significance, reversibility, and monitorability of the observed bone pathology in juvenile rats."

The available nonclinical data and the issues related to use of riociguat in pediatric patients are summarized in a consult review dated April 26, 2013 from Dr. Eric Andreasen and Dr. Stephen Voss in the Division of Bone, Reproductive, and Urologic Products (DBRUP). DBRUP concluded that:

- Because of the severity of PAH/CTEPH and limitations of other treatments, and the uncertain implications of the riociguat nonclinical bone findings, we do not believe that they should preclude pediatric studies.

- The findings in infant-juvenile rats are of some concern with respect to potential pediatric use, especially in infants and younger children. Skeletal growth and development may be affected by riociguat-related hyperostosis (increased bone mass of cortical and/or trabecular bone) and increased thickness of the growth plate. Potentially, children could experience altered growth or skeletal deformities; the worst-case adverse result might involve impingement of hypertrophic bone on CNS, cranial or peripheral nerves, or bone marrow. Other manifestations might include bone pain, increased susceptibility to fracture or dental complications. Adolescents are less likely to experience any such effects, thus it would be appropriate to assess skeletal effects in adolescents prior to studies in younger children.

- We believe that an adequate assessment of possible skeletal changes in adolescents could be obtained in a study in which skeletal endpoints are assessed at baseline, the end of the double blind phase, and during a safety extension of at least 1 year duration. Study endpoints could include height (using a wall-mounted stadiometer), head circumference, and sequential X-ray, and possibly ultrasound, of the knees in order to provide an assessment of distal femur/proximal tibia growth plate height, morphology and volume, and potential encroachment of hyperostotic bone on marrow spaces. If any evidence of skeletal effects emerges, further studies may be indicated. We do not believe that a BMD study would provide useful data.

- Additional nonclinical study may be warranted to see if the findings in infant-juvenile rats progress with continued dosing beyond 20 days after birth, how

severe findings would be with continued dosing, and if effects on bones are reversible following cessation of treatment.

PMHS concurs with DBRUP that pediatric studies should not be waived for PAH. Rather, pediatric studies should be deferred because the product is ready for approval for use in adults. Pediatric studies should begin in adolescents with careful monitoring of possible skeletal changes. Of note, assessment of any effects of the product on bone may be enhanced by documentation of Tanner Stage. Initiation of studies in younger pediatric patients should be delayed until the adolescent studies are completed and the results analyzed.

All waiver and deferral requests must be reviewed by PeRC. DCRP is reminded that PMHS and PeRC are separate. Generally, the PeRC often provides recommendations that are consistent with advice provided from PMHS. Nevertheless, PMHS cannot make recommendations on behalf of the PeRC.

It is PMHS' understanding that the applicant has applied for orphan designation. If the applicant receives orphan designation before the NDA is approved, the application would be exempt from PREA. In this case, the Division should consider issuing a Written Request since pediatric studies in PAH would represent a public health benefit.

References

Berger RMF, Beghetti M, Humpl T, et al. Clinical features of paediatric pulmonary hypertension: a registry study. *Lancet* 2012; 379: 537–46.

van Loon RL, Roofthooft MTR, Hillege HL, et al. Pediatric pulmonary hypertension in the Netherlands : epidemiology and characterization during the period 1991 to 2005. *Circulation*. 2011;124:1755-1764

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/s/

AMY M TAYLOR
07/24/2013

LYNNE P YAO
07/24/2013

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Label, Labeling and Packaging Review

Date:	June 28, 2013
Reviewer:	Kimberly DeFronzo, RPh, MS, MBA Division of Medication Error Prevention and Analysis
Team Leader:	Irene Z Chan, PharmD, BCPS Division of Medication Error Prevention and Analysis
Associate Director:	Scott Dallas, RPh Division of Medication Error Prevention and Analysis
Drug Name and Strength(s):	Adempas (Riociguat) Tablets 0.5 mg, 1 mg, 1.5 mg, 2 mg, and 2.5 mg
Application Type/Number:	NDA 204819
Applicant/Sponsor:	Bayer Healthcare Pharmaceuticals
OSE RCM #:	2013-499

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Contents

1 INTRODUCTION

This review evaluates the proposed container label, carton, and insert labeling for Adempas (Riociguat) Tablets, 0.5 mg, 1 mg, 1.5 mg, 2 mg, and 2.5 mg, for areas of vulnerability that can lead to medication errors.

1.1 REGULATORY HISTORY

Riociguat (BAY 63-2521) is a new molecular entity (NME) seeking approval for the indications of treating chronic thromboembolic pulmonary hypertension (CTEPH Group 4) and pulmonary arterial hypertension (PAH Group 1). Although there are several FDA-approved products to treat PAH, there are currently no drugs FDA-approved to treat CTEPH.

On December 19, 2012, a teleconference was held where Bayer and DMEPA discussed Bayer's proposed product differentiation strategy under IND 75629. DMEPA provided the following response regarding Bayer's proposed product differentiation strategy:

> 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.

On February 8, 2013, Bayer submitted this New Drug Application (NDA #204819) which is receiving Priority Review under "The Program" due to the CTEPH indication. Bayer also submitted a proprietary name request for the name Adempas, which was reviewed under separate cover in OSE RCM #2013-471 dated May 8, 2013 and found conditionally acceptable.

1.2 PRODUCT INFORMATION

The Applicant proposed to market under a REMS program to minimize the risk of fetal exposure and adverse fetal outcomes in women of childbearing potential (WCBP) that are prescribed this

drug; to ensure that women who are pregnant should not be prescribed this drug; and to ensure women taking this drug do not become pregnant. The product information below is provided in the February 8, 2013 NDA submission.

Active Ingredient: Riociguat

Indication of Use: Treatment of:

- Persistent/recurrent Chronic Thromboembolic Pulmonary Hypertension (CTEPH) (WHO Group 4) after surgical treatment or inoperable CTEPH to improve exercise capacity and WHO functional class.
- Pulmonary Arterial Hypertension (PAH) (WHO Group 1) to improve exercise capacity, improve WHO functional class and to delay clinical worsening.

Route of Administration: Oral

Dosage Form: Tablets

Strength: 0.5 mg, 1 mg, 1.5 mg, 2 mg, and 2.5 mg

Dose and Frequency:

Treatment Initiation

The recommended starting dose is 1 mg taken 3 times daily. Tablets should be taken approximately 6 to 8 hours apart with or without food. The maximum daily dose is 2.5 mg 3 times daily.

If systolic blood pressure is ≥95 mmHg and the patient has no signs or symptoms of hypotension, the dose can be increased. Dosage should be increased in approximately 2-week intervals by 0.5 mg increments. Dosage should be maintained if systolic blood pressure is <95 mmHg without signs or symptoms of hypotension. If at any time during the up-titration phase, systolic blood pressure decreases below 95 mmHg and the patient shows signs or symptoms of hypotension, the current dose should be decreased by 0.5 mg.

Maintenance dose

The established individual dose should be maintained at the highest tolerated dose. If a dose is missed, treatment should be continued with the next dose as planned. Dose reduction at any time (including titration and maintenance) might be considered at the discretion of the healthcare provider.

Treatment Interruption

In case treatment has to be interrupted for 3 days or more, restart treatment at 1 mg 3 times daily, and continue dose titration regimen as described above.

How Supplied: Riociguat tablets are available in the following strengths:

- 0.5 mg-film-coated, round, biconvex, white tablets debossed with the "BAYER" cross on one side and "0.5" and "R" on the other side
- 1 mg-film-coated, round, biconvex, pale yellow tablets debossed with the "BAYER" cross on one side and "1" and "R" on the other side

- 1.5 mg-film-coated, round, biconvex, yellow-orange tablets debossed with the "BAYER" cross on one side and "1.5" and "R" on the other side
- 2 mg-film-coated, round, biconvex, pale orange tablets debossed with the "BAYER" cross on one side and "2" and "R" on the other side
- 2.5 mg-film-coated, round, biconvex, red orange tablets debossed with the "BAYER" cross on one side and "2.5" and "R" on the other side

Riociguat tablets are supplied in bottles of 90 tablets and in blister packages containing 42 tablets in the following configurations:

Strength	Bottles of 90 Tablets	Carded Blisters of 42 Tablets
0.5 mg	NDC 50419-250-01	NDC 50419-250-03
1 mg	NDC 50419-251-01	NDC 50419-251-03
1.5 mg	NDC 50419-252-01	NDC 50419-252-03
2 mg	NDC 50419-253-01	NDC 50419-253-03
2.5 mg	NDC 50419-254-01	NDC 50419-254-03

Storage: Store at 25°C (77°F); excursions are permitted from 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

Container and Closure Systems: The product will be packaged in 45 mL high density polyethylene (HDPE) white opaque bottles closed with screw cap (b) (4)), white, (b) (4) with sealing insert. (b) (4)

2 METHODS AND MATERIALS REVIEWED

Using the principals of human factors and Failure Mode and Effects Analysis,[1] along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Bayer's revised tablet differentiation strategy submitted on March 13, 2013 (Appendix A)
- Insert Labeling submitted February 8, 2013, including Medication Guide (no image)
- Container Labels for bottles submitted on February 8, 2013 (Appendix B)
- Carton Labeling for bottles submitted on February 8, 2013 (Appendix C)

[1] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

- Inner Blister Card Labeling submitted on February 8, 2013 (Appendix D)
- Outer Labeling for Blister Packs submitted on February 8, 2013 (Appendix E)

3 MEDICATION ERROR RISK ASSESSMENT

The Applicant has revised their strength differentiation strategy for the labels and labeling of their product line since the teleconference held on December 19, 2012. The Applicant has selected the following new colors for strength differentiation of the labels and labeling, instead of matching them to the tablet colors:

- 0.5 mg – gray
- 1 mg – green
- 1.5 mg – blue

(b) (4)

Additionally, the Applicant has implemented our previous advice to remove trailing zeros from the debossing of the strength on the tablets. The revised strength differentiation for the labels and labeling is an improvement over what was proposed during the IND application. However, the (b) (4) for the 2 mg labels and labeling and the (b) (4) for the 2.5 mg labels and labeling are within the same color family, and as such, can be more optimally differentiated. Additionally, the actual tablets of Adempas are (b) (4) for the 2 mg strength and (b) (4) (b) (4) for the 2.5 mg strength, which is the exact opposite presentation of the proposed labels and labeling. This inconsistency in the color scheme may lead to confusion. Therefore, we recommend the use of an alternate color scheme for the 2 mg and 2.5 mg labels and labeling that does not overlap with any of the other colors used for strength differentiation within the product line.

With regards to color differentiation of the tablets themselves, DMEPA previously expressed concern that the use of varying hues of a color may not allow for adequate tablet differentiation, especially at the lower strengths of 0.5 mg and 1 mg where the colors are white vs. pale yellow and difficult to distinguish (see Appendix A). However, the Applicant has made no changes to further differentiate the tablet colors. Based on the proposed dosing of this product, the possibility exists for concomitant administration of two strengths by the same patient during the titration period. Dose adjustments are expected to occur in approximately 2-week intervals. Therefore, a patient initiated on Adempas may receive a one-month prescription for 1 mg along with a 2 week prescription for 0.5 mg that would allow them to get a 1.5 mg dose if needed. The patient in this scenario would have in their possession both the 1 mg strength as well as the 0.5 mg strength tablets. Given the similarity in color of the two tablets, DMEPA is concerned that patients who use pillboxes or take their tablets out of the dispensing bottles may inadvertently administer two 1 mg tablets, leading to an overdose. Based on this concern for overdose, we consulted with the Medical Officer (MO) who confirmed that while medication error is undesirable, no serious adverse outcome is expected from this scenario since clinical trials have shown a dose of 2.5 mg three times a day (or 7.5 mg daily dose) to be well tolerated. Although we still consider the appearance of the 0.5 mg and 1 mg tablets to be similar due to the color scheme, we also recognize at this late stage in the product development life cycle, a change

in tablet color is likely unfeasible. We acknowledge the tablets are embossed with their strength, which can help mitigate the look alike similarity between the tablets.

Our review of the blister packs with (b) (4) packaging determined they may be confusing for patients to open. We issued an Information Request on May 7, 2013 to inquire whether the proposed packaging is marketed with any products, and if so, to provide medication errors or complaints related to the (b) (4). The Applicant responded that the Riociguat (b) (4) titration package is unique, and no package with these exact specifications has been introduced into the market. Based on our evaluation, we recommend increasing the prominence of the opening instructions.

Our review of the proposed container label and carton labeling identified areas of vulnerability that may cause confusion leading to medication error. We provide recommendations in Section 4 below to increase clarity, improve readability, and bring prominence to important information to ensure the safe use of this product.

4 CONCLUSIONS AND RECOMMENDATIONS

DMEPA concludes that the proposed strength differentiation for the labels and labeling can be improved. Additionally, the proposed labels and labeling can be improved to clarify information, improve readability, and bring prominence to important information to promote the safe use of the product. We provide recommendations in sections 4.1 and 4.2 below.

If you have further questions or need clarifications, please contact Cherye Milburn, OSE Project Manager, at 301-796-2084.

4.1 Comments to the Division

We provide the following comments for consideration by the review division prior to approval of this supplement.

A. Highlights of Prescribing Information, *Dosage and Administration*

1. To improve clarity regarding titration, we recommend revising (b) (4) to read "Increase dosage by 0.5 mg three times a day (total daily dose increase of 1.5 mg) in approximately 2-week intervals according to the titration guidance."
2. We recommend revising the statement (b) (4) to match the statement found in the Full Prescribing Information Dosage and Administration section, which reads "The *maximum daily dose* of <Tradename> is 2.5 mg TID" for consistency. In addition, we recommend avoiding the use of abbreviations (e.g., TID) in the insert labeling and replacing the abbreviation with the full intended meaning of "three times daily". Therefore, please revise the "The *maximum daily dose* of <Tradename> is 2.5 mg TID" to read "The *maximum daily dose* of <Tradename> is 2.5 mg three times daily."

B. Full Prescribing Information: Section 2, *Dosage and Administration*

1. To improve clarity regarding titration, we recommend revising (b) (4) [redacted] to read "Increase dosage by 0.5 mg three times a day (total daily dose increase of 1.5 mg) in approximately 2-week intervals.

2. The error-prone symbols < and ≥ can be found in Section 2.1, *Recommended Dosage in Adult Patients*. These symbols appear on the ISMP list of Error-Prone Abbreviations, Symbols, and Dose Designations. Consider using the appropriate terms "less than or greater than or equal to, etc…" instead of the symbols because they have been mistaken as the opposite of its intended meaning and practitioners have mistakenly used the incorrect symbol.

C. Full Prescribing Information: Section 16, *How Supplied /Storage and Handling*

We recommend adding the unit of measure (°C or °F) immediately following all numbers, as appropriate. In addition, we recommend replacing the hyphen with the word "to" for improved clarity. Consider revising the storage statement to read: 15°C to 30°C (59°F to 86°F)…"

4.2 Comments to the Applicant

We advise the following recommendations are implemented prior to approval of this application.

A. General Comments (Container Labels, Carton Labeling, and Outer Blister Pack Labeling)

1. We recommend adding the unit of measure (°C or °F) immediately following all numbers, as appropriate. In addition, we recommend replacing the hyphen with the word "to" for improved clarity. Therefore, revise the storage statement to read: "Store at 25°C (77°F); excursions are permitted from 15°C to 30°C (59°F to 86°F)…"

2. Ensure the prominence of the established name (which includes the dosage form "tablet") is at least ½ the size of the proprietary name taking into account typography, layout, contrast, and other printing features to ensure it has prominence commensurate with the proprietary name as per 21 CFR 201.10(g)(2).

3. We note a random color scheme was proposed for the 0.5 mg, 1 mg, and 1.5 mg container labels and carton labeling, which can not be linked to the color scheme for the tablets. However, the proposed colors for the 2 mg and 2.5 mg tablet container labels and carton labeling appears similar to, but are actually opposite to, the colors for these tablet strengths. We recommend selecting two different random colors for the 2 mg and 2.5 mg container labels and carton labeling to further differentiate the product line.

B. General Comment (Inner Blister Pack Labeling, Outer Blister Pack Labeling, Carton Labeling)

Minimize and move or delete the graphic to the left of the proprietary name to prevent misinterpretation of and avoid competing prominence with the proprietary name.

C. Container Labels (all strengths)

Move the strength statements so they are within the color blocks, similar to the strength presentation on the carton labeling, or revise the presentation of the strength on the carton labeling to appear outside the color blocks.

D. Inner Blister Card Labeling

1. Relocate the strength statement so it is directly under the established name to increase prominence of this important information.
2. Revise the presentation of the strength statement to read "x mg per tablet" on all panels for clarity.
3. Include the proprietary name, established name, and strength in close proximity to each other and on both sides of the foldout portion of the blister card to ensure proper identification of the tablets in the event that the foldout portion is separated from the rest of the blister card or pack.
4. The foldout card that contains the blisters has the evening dose listed on top of the reading pane followed by the midday dose, then the morning dose. This proposed pattern is in contrast to the usual reading pattern of top to bottom and left to right for the U.S. population.[2] Therefore, we recommend revising as follows:

Day 1

Morning

Midday

Evening

E. Outer Blister Pack Labeling

1. Increase the prominence of the opening instructions box by relocating the opening instruction box from the upper right hand corner to beneath the arrow on the principal display panel so it is closer to the "1. Press and Hold" statement. Additionally, decrease the prominence of the graphic art work on the bottom of the principal display panel since it is distracting and may provide additional space to accommodate the opening instructions.
2. As currently presented, the black font used for the net quantity statement and route of administration statement is difficult to see on the dark gray

[2] Script direction and languages. http://www.w3.org/International/questions/qa-scripts#directions

background. Revise to a different font (i.e. white) to increase contrast and improve readability of these statements or remove the dark gray background.

3. Revise the strength statement to read "x mg per tablet" to clarify that the strength noted is for each individual tablet.
4. Delete the strength statement at the bottom left-hand side of the principal display panel since it is redundant to the strength statement at the top of the principal display panel.
5. Delete the statement (b) (4) found at the bottom left-hand side of the principal display panel, because that statement is not required by regulation and adds clutter to the label.
6. Revise the Dosage statement to read similar to "Usual Dosage: Take one tablet by mouth three times a day. Please see complete prescribing information." to help inform the user of the proper dosing instructions.

F. Carton Labeling

1. To improve readability, move the strength presentation directly beneath the established name presentation. To accommodate this, minimize or remove the graphic art work on the bottom of the principal display panel since it is distracting and may help reduce clutter on a crowded label.
2. To decrease the cluttered appearance of the principal display panel, move the "Each tablet contains…" statement to the side panel.
3. Delete the statement (b) (4)" found at the bottom left-hand side of the principal display panel, because the statement is not required by regulation and adds clutter to the label.
4. Unbold the "Rx Only" statement to decrease its prominence and avoid distracting other important information.
5. Increase the readability of the net quantity statement by removing the colored background covering the net quantity statement, and remove the hyphen preceding the net quantity.

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

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

/s/

KIMBERLY A DE FRONZO
06/28/2013

IRENE Z CHAN
06/28/2013

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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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Maternal Health Team Review

Date: June 24, 2013

From: Tammie Howard, RN, MSN
Regulatory Reviewer, Maternal Health Team
Pediatric and Maternal Health Staff

Through: Melissa S. Tassinari, PhD, DABT
Acting Team Leader, Maternal Health Team
Pediatric and Maternal Health Staff

Hari Cheryl Sachs, MD
Acting Associate Director, OND
Pediatric and Maternal Health Staff

To: Division of Cardiovascular and Renal Products (DCRP)

Drug: TRADENAME (riociguat) NDA 204819

Subject: Riociguat is a new molecular entity (NME) submitted for NDA approval

Applicant: Bayer HealthCare Pharmaceuticals, Inc. (BHP)

Materials Reviewed: Riociguat product labeling, REMS documents and available literature regarding pregnancy and lactation

Consult Question: DCRP requested PMHS-MHT assistance in evaluating the REMS and labeling for riociguat.

INTRODUCTION

Bayer HealthCare Pharmaceuticals, Inc. (BHP) submitted a New Drug Application (NDA) for TRADENAME (riociguat) Tablets on February 8, 2013. Riociguat is a first-in-class New Molecular Entity (NME) with a proposed indication for treatment of patients with chronic thromboembolic pulmonary hypertension (CTEPH); and pulmonary arterial hypertension (PAH).

Per the sponsor, riociguat is a soluble guanylate cyclase (sGC) stimulator that increases vascular sensitivity to nitric oxide (NO), resulting in pulmonary vasodilation and antiproliferative effects. Nitric oxide binds to sGC, catalyzing synthesis of the signaling molecule cyclic guanosine monophosphate (cGMP), which has a role in regulating processes that influence vascular tone, proliferation, fibrosis and inflammation. Endothelin dysfunction, impaired synthesis of NO and insufficient stimulation of the NO-sGC-cGMP pathway is associated with pulmonary hypertension. Riociguat sensitizes sGC to endogenous NO by stabilizing NO-sGC binding and it directly stimulates sGC through a different binding site, independently of NO, increasing generation of cGMP[1,2]. There are no currently approved drug products for treatment of CTEPH. Other approved products for treatment of PAH include: oral agents (bosentan, ambrisentan, sildenafil, tadalafil), inhaled agents (iloprost, treprostinil) and parenteral agents (epoprostenol, treprostinil).

The Pediatric and Maternal Health Staff-Maternal Health Team (PMHS-MHT) was consulted by DCRP on May 1, 2013 to assist the division in evaluating product labeling and REMS documents. This review includes PMHS-MHT comments and recommendations for riociguat labeling and REMS documents.

BACKGROUND

Riociguat and Pregnancy

Riociguat is an NME and there are no human pregnancy data available. There were no reported pregnancies in the clinical development program.

In animal developmental reproductive studies, riociguat was embryotoxic and teratogenic in rats and rabbits. In the rat embryofetal development study, riociguat was administered orally throughout organogenesis. There was an increased incidence of cardiac ventricular-septal defects at an exposure approximately 2.5 times that in humans at the maximum recommended human dose (MRHD) of 2.5 mg three times a day based on AUC comparison. This dose also produced evidence of maternal toxicity (reduced maternal body weight). Incomplete ossification of the 4th sacral vertebrae was noted at an exposure approximately 0.15 times that in humans at the MRHD, in the absence of maternal toxicity. An increase in spontaneous abortions was seen in rabbits given riociguat at exposure approximately 15 times that in humans at the MRHD.

Reviewer Note:

[1] NDA 204819 Adempas (riociguat) Pharmacology/Toxicology NDA Review and Evaluation, June 19, 2013.
[2] NDA 204819 <Tradename> (riociguat) proposed Full Prescribing Information, submitted February 8, 2013.

The data above is based on labeling recommendations in the Pharmacology/Toxicology NDA Review dated June 19, 2013. The reviewer notes that the sponsor's calculations of margins of exposure were based on plasma levels from healthy volunteers (AUC_{0-24} 1446 µg.hr/l). The reviewer's exposure ratios are based on the plasma exposure in pulmonary hypertension patients reported in study 12166 (AUC_{0-24} 4161 µg.hr/l). PMHS-MHT notes that as of the date of this review, these data do not yet appear in the labeling currently under review. PMHS-MHT proposed labeling recommendations are based on the applicant proposed labeling submitted 2/8/2013 and will be revised to include Pharmacology/Toxicology labeling recommendations pending further labeling discussions.

Riociguat and Lactation

It is not known if riociguat is present in human milk. Riociguat and/or metabolites were present in the milk of lactating rats. A search of the Micromedex, LactMed and PubMed databases revealed no human data regarding riociguat and lactation.

REVIEW OF SUBMITTED MATERIALS

Applicant Proposed Riociguat Labeling

The PMHS-MHT reviewed the applicant's proposed riociguat labeling, submitted February 8, 2013 and has participated in labeling/team meetings during the review period. Discussions regarding labeling and the content of REMS documents are ongoing, therefore PMHS-MHT recommendations regarding labeling and REMS documents are subject to amendment, pending the outcome of discussions. A summary of current PMHS-MHT labeling recommendations appear immediately following Discussion and Conclusions with labeling excerpts provided in **Appendix A**.

Applicant Proposed Riociguat REMS Documents

The applicant submitted a proposed REMS program focused on minimizing the risk of fetal exposure and adverse fetal outcomes in females of reproductive potential prescribed riociguat; Women who are pregnant should not be prescribed riociguat and women taking riociguat should not become pregnant.

The proposed riociguat REMS program contains Elements to Assure Safe Use (ETASU), requiring enrollment of females of reproductive potential into the REMS program. Enrolled female patients of reproductive potential are required to have a pregnancy test prior to starting treatment and monthly during treatment. They must also agree to use acceptable contraception during treatment with riociguat and for 1 month after stopping treatment.

Acceptable methods of contraception are as follows[3]:

A patient enrollment guide, describing risks/benefits of riociguat and the REMS program, will be reviewed with the patient by the prescriber. The guide advises patients that: Their doctor will discuss birth control options with them, and to use the table of acceptable contraceptive methods (above) to help decide the best birth control options for the patient. A medication guide with information regarding REMS program requirements for pregnancy testing, contraception use and counseling will be provided with each prescription.

Prescribers must be certified with the program by completing a prescriber enrollment and agreement form, agreeing to read the full prescribing information (FPI) and to review the medication guide with each patient. A prescriber guide describes in detail all prescriber roles and responsibilities. Certified prescribers are responsible for identifying female patients who are of reproductive potential, providing counseling regarding the risk of teratogenicity, required use of contraception and ordering required pregnancy testing.

Determination of female patients reproductive status is based on the following definitions:

[3] Riociguat Risk Evaluation and Mitigation Strategy (REMS) Patient Enrollment Guide (proposed), February 8, 2013.

(b) (4)

Definition of Menopause

(b) (4)

Prescribers must also monitor female patients for changes in reproductive status and re-enroll patients that continue to meet the definition of female of reproductive potential annually. Prescribers are also responsible for reporting any adverse events and pregnancies to the applicant.

Pharmacies will be certified through contracts with the applicant and must only dispense to patients who are enrolled in the REMS program. Certified pharmacies are responsible for counseling female patients of reproductive potential regarding the risk of teratogenicity, required pregnancy testing and required use of contraception. Pharmacies must also confirm pregnancy testing was completed, and only dispense a limited supply of drug if completed. A Medication Guide will be provided each time riociguat is dispensed to a patient.

The applicant proposes to maintain a database of certified prescribers, pharmacies and enrolled patients to monitor and evaluate REMS elements. The applicant will monitor drug shipments, dispensing and compliance with the REMS program.

REMS Assessment Plan

The REMS will be assessed by knowledge, attitudes and behavior (KAB) surveys from a random sample of prescribers and patients. The survey documents were not provided in the NDA submission and will be provided at least 90 days prior to initial survey administration. The applicant proposes to provide REMS assessments at 6 months and 12 months after the initial REMS approval date, then annually thereafter.

The following additional metrics may also be evaluated:

- Summary of issues and complaints received by REMS Coordinating Center; summary of resolution of the issues and complaints.
- With regard to Prescriber Certification:
    - The number of prescribers enrolled in the REMS program (during the reporting period and cumulatively) and stratified by specialty.

- Number of prescribers that had their enrollment revoked during the reporting period and cumulatively and the reason for the revocation.

- With regard to Pharmacy Certification:

  - The number of pharmacies that were under contract with Bayer (during the reporting period and cumulative).

  - Number of pharmacies that had their contract terminated with Bayer during the reporting period and cumulatively and the reason for the termination.

  - The number of instances pharmacies under contract with Bayer dispensed drug to a WCBP using a prescription written by a prescriber who was not certified in the program at the time of dispensing.

  - The number of instances pharmacies under contract with Bayer dispensed drug to a WCBP that was not enrolled in the REMS program at the time of dispensing

- Detailed description of root cause of noncompliance with REMS program and any corrective and/or preventive actions taken to address noncompliance during the reporting period and cumulatively

- Based on the information submitted, an assessment of and conclusion regarding whether the REMS is meeting its goals, and whether modifications to the REMS are needed.

DISCUSSION AND CONCLUSIONS

Labeling

The Proposed Pregnancy and Lactation Labeling Rule (PLLR) published in May 2008. While still complying with current regulations during the time when the Final Rule is in clearance, PMHS-MHT is structuring the Pregnancy and Nursing mothers label information in the spirit of the Proposed Rule. The first paragraph in the pregnancy subsection of labeling provides a risk summary of available data from outcomes of studies conducted in pregnant women (when available), and outcomes of studies conducted in animals, as well as the required regulatory language for the designated pregnancy category. The paragraphs that follow provide more detailed descriptions of the available human and animal data, and when appropriate, clinical information that may affect patient management. The goal of this restructuring is to provide relevant animal and human data to inform prescribers of the potential risks of the product during pregnancy. Similarly for nursing mothers, human data, when available, are summarized. When only animal data are available, just the presence or absence of drug in milk is noted and presented in the label, not the amount. Additionally, information on pregnancy testing, contraception, and infertility that has been located in other sections of labeling are now presented in a subsection, Females and Males of Reproductive Potential.

The PMHS-MHT has reviewed the proposed riociguat labeling submitted 2/8/2013, and labeling recommendations are provided below. Note that these recommendations may be revised while final labeling is negotiated with the sponsor.

Riociguat Proposed REMS Program

The applicant proposed a REMS program, per Agency recommendation (pre-NDA meeting letter November 1, 2012), citing teratogenic risk in humans based on animal reproductive developmental study outcomes. Discussions regarding the details of the REMS program are ongoing. PMHS-MHT has reviewed the proposed REMS documents, and preliminary recommendations are based on review of the proposed program, and subject to amendment at a later date.

MHT Summary of Labeling Comments and Recommendations

Highlights of Prescribing Information

The REMS program for riociguat includes Elements To Assure Safe Use (ETASU). Therefore a boxed warning describing the risk, information mitigating the risk and a statement that the drug is only available through a REMS program appears in the Full Prescribing Information (FPI) and was added to labeling highlights.

Nursing mothers language under "Use in Specific Populations" was revised to display preferred labeling language in a more concise format. A bullet point titled Females and Males of Reproductive Potential was added to reference information regarding contraception use in section 8.9 of the FPI.

Boxed Warning

Language describing the risk was revised to align with risk described in the FPI. A statement regarding mitigating the risk was added.

2.3 Testing Prior to Dosage in Females of Reproductive Potential

Language stating that treatment with riociguat in females of reproductive potential may only begin after a negative pregnancy test was added. Information regarding contraception was deleted. Although the REMS program requires females of reproductive potential to use contraception during treatment and for 1 month after treatment, contraception is not a test required to initiate treatment. Cross reference to section 8.9 Females and Males of Reproductive Potential was added to reference information regarding pregnancy testing.

4 Contraindications

Language was revised to state required regulatory language and remove information regarding contraception, which was moved to section 8.9 Females and Males of Reproductive Potential.

5 Warnings and Precautions

The Warnings and Precautions section was restructured to comply with requirements of the current SEALD labeling review tool for products with REMS. Sub-section 5.1 titled "Embryo-Fetal Toxicity" was added, with a brief description of the risks and reference to the REMS program, described in sub-section 5.2.

8 Use in Specific Populations

8.1 Pregnancy

The Pregnancy section was restructured to align with current labeling recommendations and to provide an organized presentation of data. Information regarding contraception and pregnancy testing was moved to section 8.9 Female and Males of Reproductive Potential.

8.3 Nursing Mothers

The Nursing Mothers section was revised to state the appropriate regulatory language and to replace the term (b) (4) with the term "present".

8.9 Females and Males of Reproductive Potential
Information on pregnancy testing, contraception, and infertility that was located in other sections of labeling are now presented in the subsection, Females and Males of Reproductive Potential. Language was added to describe pregnancy testing and contraception requirements of the riociguat REMS program, according to current proposed REMS documents submitted by the applicant.

Reviewer Note
This section of labeling should align with requirements of the riociguat REMS program at the time of approval. In addition, PMHS-MHT recommends that the information currently in section 8.9 be move up to become section 8.6 and appear after information on geriatric use and prior to information on renal impairment.

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

The data regarding reproductive and developmental toxicology was moved to section 8.1, under sub-heading animal data.

17 Patient Counseling Information
Section titled (b) (4) was re-titled "Embryo-Fetal Toxicity" to align with language used in boxed warning and warnings and precautions. Language revised to comply with current REMS program requirements. Nursing Mothers language added to describe appropriate patient counseling to mitigate risks. Appropriate cross references provided.

MHT Summary of Recommendations for Riociguat Proposed REMS Program

1. The language (b) (4) should be replaced with "females of reproductive potential (FRP)" throughout all REMS documents to promote consistency across labeling and REMS products.

2. The REMS program should be targeted to the "at risk" population and should enroll all females prescribed riociguat. A determination should be made whether the female patient is of reproductive potential or not of reproductive potential. FRPs should follow the pregnancy testing and contraception requirements as described in the proposed REMS program.

3. The REMS program should require, at minimum, annual verification of reproductive status for pre-pubertal females as appropriate.

4. The definitions of females of reproductive potential, females of non-reproductive potential and menopause should be consistent with recent PMHS-MHT recommendations as agreed upon during the DSaRM AC December 2012. PMHS-MHT recommends the following:

    - Female of Reproductive Potential (FRP) Definition:

        - Females of reproductive potential include girls who have entered puberty and all women who have a uterus and have not passed through menopause (as defined below).

        - For the purposes of this REMS, puberty includes those girls who are at least Tanner stage 3 and have not yet had a menses (premenarchal).

    - Females of Non-Reproductive Potential (FNRP) Definition:

        - Pre-Pubertal Females: Females who are at Tanner Stages 1 and 2 are not considered to be of reproductive potential.

        - Post-Menopausal Females: Females who have passed through menopause (as defined below).

    - Definition of Menopause:

    - Menopause is defined as 12 months of spontaneous amenorrhea (not amenorrhea induced by a medical condition or medical therapy) or post-surgical from bilateral oophorectomy.

5. The proposed riociguat REMS program requires use of highly reliable contraception during treatment and for 1 month after treatment with riociguat. A table of "acceptable contraception methods" describing methods that may be used alone, and methods that must be used in combination, is provided to help patients and prescribers decide what birth control options are best for the patient. PMHS-MHT concurs with the applicant's proposed table of "acceptable contraception methods" for use as a tool to help patients and prescribers choose appropriate contraception methods.

PMHS-MHT Comments on Specific Riociguat REMS Documents:

1. Proposed Patient Enrollment and Consent Form:

- Item 1.4, page 2, regarding the check off list indicating whether the patient is of reproductive potential: Recommend stating "For female patients, please indicate the patient's current reproductive status". A check off box for each category of reproductive status should follow, including the category definition and a place to indicate that a pregnancy test has been performed.

2. Proposed Patient Re-enrollment Form:

    - Item 1.2, page 1: The reason for a change in the patient's reproductive status should be stated and the definitions for each category of reproductive potential should be listed for reference. The applicant should consider a more detailed check off list, including the patient's current reproductive status and options indicating the reasons for change to better guide the form user. Include annual verification of pre-pubertal females as in item on this form.

3. Proposed Prescriber Enrollment Form:

    - Item 1.2, page 1: Recommend including the following items as part of the list a prescriber attest to:

        - Agreement to enroll all females in the REMS program, if all females are the target of the REMS.
        - Agreement to determine the reproductive potential status of all female patients using the definitions provided in the prescriber guide.
        - Agreement to counsel all female patients regarding the risk of riociguat and the requirements of the REMS program.
        - Agreement to report any change in patient's reproductive status (*specify minimum time period for reporting of change to applicant*).
        - Agreement to counsel pre-pubertal females and report reproductive potential status annually.
        - Agreement to comply with the requirements of the REMS program.

4. Proposed Patient Guide:

    - Item 1.1, page 1: Recommend the following:

        - Under "What is the TRADENAME REMS?", revise the statement (b) (4) to "You must agree to all of the requirements of the TRADENAME REMS program".

        - Under "How do I enroll in TRADENAME REMS?", revise the statement "Read all the patient information about TRADENAME and TRADENAME REMS program" to "Read all the patient information about TRADENAME and TRADENAME REMS program included in this guide or on the REMS program website (if there will be one). Include a bullet that explains the prescriber's responsibility in the enrollment process.

- Item 1.2, page 2: Recommend the following:

  - Under "Information for women who are able to get pregnant", revise the statement [redacted (b) (4)] to "You are considered a women who is able to get pregnant if you have entered puberty, have a uterus, and have not passed through menopause.

- Add a bullet to the document that provides detailed information regarding how a patient will receive the drug.

Final labeling and REMS will be negotiated with the applicant and may not fully reflect changes suggested here.

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/s/

TAMMIE B BRENT HOWARD
06/24/2013

JEANINE A BEST
06/25/2013
Signing for Melissa Tassinari

HARI C SACHS
06/25/2013
I am signing on behalf of Lynne P. Yao, MD, Associate Director, PMHS

Interdisciplinary Review Team for QT Studies Consultation: Thorough QT Study Review

NDA	204819
Generic Name	BAY 63-2521 (Adempas) (riociguat)
Sponsor	Bayer HealthCare
Indication	Treatment of chronic thromboembolic pulmonary hypertension (CTEPH) and pulmonary arterial hypertension (PAH)
Dosage Form	Tablets
Drug Class	Stimulator of guanylate cyclase
Therapeutic Dosing Regimen	1.0 (0.5) – 2.5 mg three times daily (TID); individual dose titration according to systolic blood pressure and the patient' s well-being
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	2.5 mg TID
Submission Number and Date	SDN 001 8 Feb 2013
Review Division	DCRP

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

There were two studies involved in this review: Study 12934 and Study 13796.

Study 13796 was a randomized, double-blind, 2-way crossover, placebo-controlled study to investigate the moxifloxacin-induced QTcF effect in healthy volunteers at selected centers used in Study 12934.

Study 12934 is a randomized, double-blind, placebo-controlled, multi-center, multinational study in Phase III, to evaluate the efficacy and safety of oral BAY 63-2521 (1 mg, 1.5 mg, 2 mg, or 2.5 mg t.i.d.) in patients with symptomatic pulmonary arterial hypertension (PAH) (PATENT-1).

From the QT data in Study 12934, there was no mean QTcF change from baseline larger than 10 ms on any visit in any treatment group. At the concentrations observed in this study, no concentration-response relationship was observed for change from baseline in QTcF. However, we do not believe that the results of Study 12934 and Study 13796 have ruled out small changes in QTc (i.e., 10 ms) for the following reasons:

- The moxifloxacin study (Study 13796) was not conducted concurrently with the study drug
- Single ECGs (not triplicate) were collected in Study 12934
- The timing of ECGs in Study 12934 did not adequately cover T_{max}

On the other hand, we conclude that data collected in Study 12934 provided reasonable evidence that a group of selected therapeutic doses of BAY 63-2521 did not prolong the QTc interval more than 20 ms.

2 PROPOSED LABEL

No labeling language was provided by the sponsor.

QT-IRT's proposed labeling language is a suggestion only. We defer final labeling decisions to the Division.

12.6 Cardiac Electrophysiology

The effect of multiple doses of riociguat (1.0 mg to 2.5 mg three times a day) on the QTc interval was evaluated in a randomized, double-blind study in 320 patients with pulmonary arterial hypertension. No large changes in the mean QTc interval (i.e., > 20 ms) were detected in the study.

3 BACKGROUND

3.1 PRODUCT INFORMATION

Riociguat is the first member of a novel class of compounds, the soluble guanylate cyclase stimulators (sGC stimulators). With its dual mode of action riociguat directly stimulates sGC and synergizes with nitric oxide (NO). Based on its unique mechanism of action riociguat has the potential to provide benefit to patients with many forms of pulmonary hypertension.

3.2 MARKET APPROVAL STATUS

Riociguat is not approved for marketing in any country

3.3 PRECLINICAL INFORMATION

From eCTD 2.6.2

Riociguat was tested for in vitro evaluation of ventricular repolarization in a voltage clamp assay using transfected Chinese hamster ovarian (CHO) cells stably expressing the hERG potassium channel as well as in a rabbit cardiac Purkinje fiber action potential assay. In both assays concentrations of 0 (vehicle control), 0.1, 1, and 10 µM were applied. Riociguat did not show any effect on the hERG K+ current amplitude of transfected CHO cells up to the highest concentration tested (Module 4.2.1.3, R-8313).

Exposure of isolated rabbit cardiac Purkinje fibers to riociguat did not induce changes of resting membrane potential, action potential amplitude, maximal upstroke velocity, plateau potential or action potential duration at 20% and 50% of repolarization (APD20, APD50) in the concentration range tested. At concentrations of 0.1 and 1 µM, APD90

was not altered, whereas APD90 was slightly but statistically significantly ($p<0.05$) prolonged by 14±3% at 10 μM.

3.4 PREVIOUS CLINICAL EXPERIENCE

From ISS

Sponsor submitted to the NDA a safety database with 738 participants. Single dose studies (n=534), multiple dose studies (n=189) and interaction study with nitroglycerin (n=6).

Reviewer's comments: Neither sudden cardiac deaths nor torsade de pointes were reported in these studies. Clinically relevant QTcF prolongation was not reported.

3.5 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of riociguat's clinical pharmacology.

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The QT-IRT reviewed the protocol prior to conducting this study under IND 75629. The sponsor submitted the study report 12934 for the riociguat (1 mg, 1.5 mg, 2 mg, or 2.5 mg t.i.d.) and study report 13796 (for moxifloxacin and placebo), including electronic datasets and waveforms to the ECG warehouse.

4.2 TQT STUDY

4.2.1 Title

CSR12934:

Randomized, double-blind, placebo-controlled, multi-centre, multinational 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).

CSR 13796:

A randomized, double-blind, 2-way crossover, placebo-controlled study to investigate the influence of a single-dose of moxifloxacin on the QTc interval in healthy male and female subjects for positive control validation in selected centers of the PATENT-1 trial

4.2.2 Protocol Number

CSR12934: BAY 63-2521 / Study Impact No.12934

CSR 13796: BAY 63-2521 / IMPACT no. 13796

4.2.3 Study Dates

CSR12934: 17 Dec 2008 -- 14 May 2012

CSR 13796: 25 Nov 2009 -- 25 Jun 2010

4.2.4 Objectives

CSR 13796:

To test the ECG assay sensitivity of PATENT-1 by investigating the influence of a single-dose of 400mg moxifloxacin on the QTc interval relative to placebo in the special ECG setting of PATENT- 1 in a subset of PATENT-1 centers.

4.2.5 Study Description

4.2.5.1 Design

CSR 13796:

This is a randomized, double-blind, 2-way crossover, placebo-controlled study with two dosing occasions. Each dosing occasion will be followed by a 7-day washout period.

Study 12934:

This is a randomized, double-blind, placebo-controlled multi-centre, multinational study.

4.2.5.2 Controls

Study 13796: The Sponsor used placebo controls for (moxifloxacin).

Study 12934: The Sponsor used placebo controls for two drug treatment arm.

4.2.5.3 Blinding

Study 13796 was double blinded.

Study 12934 was a double-blind, placebo-controlled, multi-centre, multinational study

4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms

Study 13796:

a. Moxifloxacin 400 mg tablets
b. Placebo tablets

Study 12934:

- Riociguat 1.0-2.5 mg group (titration between 1.0 mg and 2.5 mg tid based on an individual dose titration scheme) (264 subjects planned)
- Placebo group (placebo tid) (132 subjects planned)
- Riociguat 1.0-1.5 mg group (up-titration from 1.0 mg to 1.5 mg tid, capped dose titration) (66 subjects planned)

4.2.6.2 Sponsor's Justification for Doses

For study 13796, a 400 mg tablet of moxifloxacin, given as a single oral dose, was given.

CSR12934:

The dose range of 1.0–2.5 mg riociguat tid was tested in healthy subjects in a multiple-dose study (study 11260). The highest dose of 2.5 mg tid showed a clear increase in AEs and further escalation was stopped. A dose of 0.5 mg was identified in healthy subjects (study 11258) as the no-effect dose, while 1.0 mg already showed clinically relevant hemodynamic effects in some patients in the proof of concept study 11874. In the same study, a strong lowering of systemic blood pressure was observed in one patient at the highest dose level (5 mg). Therefore 1.0 mg tid was selected as the minimal dose and 2.5 mg tid as the maximum dose for further studies in patients. In a Phase II trial (12166) in patients with PAH and CTEPH, the 1.0–2.5 mg tid dose range was tested in combination with an individual dose titration scheme. Interim results available at the time of preparation of the PATENT-1 protocol indicated that riociguat doses between 1.0 mg tid and 2.5 mg tid were effective and safe. Final analysis of the main part of the study showed that riociguat exerted strong effects on pulmonary hemodynamics and functional capacity (6MWD) in patients with PAH and CTEPH. This was supported by evidence from echocardiographic data, the 6MWD test, a biomarker (NT-proBNP), and functional class assessment. In addition, riociguat at total daily doses between 3 and 7.5 mg was generally safe and well tolerated. The long-term extension part of study 12166 is still ongoing.

During the titration phase, an SBP-based individual dose titration was performed. After the subjects reached their optimal dose level at Visit 5, they entered the 4-week main study phase. Dose reductions for safety reasons were allowed in the main study phase, but a subsequent re-increase was not possible.

At the end of the 12-week treatment phase, eligible subjects were given the option to participate in a long-term extension study (PATENT-2, study 12935) where all subjects were treated with an individual optimal dose of riociguat.

Reviewer's Comment: For riociguat, the dosing regimens evaluated are appropriate. The dose range between 1.0 mg and 2.5 mg covers the range from the minimum effective dose to the maximum tolerated dose in healthy volunteers. An individual dose titration scheme for riociguat was used with a starting dose of 1.0 mg of riociguat then titrated in 2-week intervals by increments of 0.5 mg according to systolic blood pressure measured at trough and administered within a dose range covering doses from 0.5 mg to 2.5 mg riociguat t.i.d. This titration was designed to ensure the safety and tolerability, and optimal efficacy for each patient.

The QT effects of a supra-therapeutic dose were not evaluated in Study 12934. The dosing regimens evaluated for the QT assessment in the study do not cover the expected worst case clinical scenario.

The absolute bioavailability of riociguat is high (94%). Riociguat is cleared mainly via cytochrome P450 mediated (CYP1A1, CYP3A4, CYP2C8, CYP2J2) oxidative metabolism, direct biliary/fecal excretion of the unchanged drug, and renal secretion of the unchanged drug via glomerular filtration.

Concomitant administration of 400 mg once daily ketoconazole led to a 150% (range up to 370%) increase in riociguat mean AUC and a 46% increase in mean C_{max}. The sponsor states that concomitant administration of azole antimycotics (for example, ketoconazole, itraconazole) or HIV protease inhibitors (e.g., ritonavir) is not recommended.

Riociguat exposure was higher in subjects with renal impairment compared to subjects with normal renal function. In individuals with mild (creatinine clearance 80–50 mL/min), moderate (creatinine clearance <50–30 mL/min) or severe (creatinine clearance <30 mL/min) renal impairment, riociguat plasma concentrations (AUC) were increased by 43%, 104% or 44%, respectively. Patients with mild hepatic impairment (Child Pugh A) had similar riociguat plasma concentrations compared to healthy controls. In cirrhotic subjects with moderate hepatic impairment (classified as Child Pugh B), riociguat mean AUC was increased by 50–70% compared to healthy controls.

The sponsor recommends to not use riociguat in patients with severe renal and hepatic impairment.

4.2.6.3 Instructions with Regard to Meals

CSR13796:

The treatment part was comprised of two periods (Period 1 and Period 2) with one treatment day each. Treatment periods were to be separated by a washout period of at least seven days.

Subjects were to be admitted to the site for Period 1 and 2 at 7:00 a.m. in the morning. After an overnight fast of at least 10 hours, the study medication was to be administered on the profile day at about 8:00 a.m. (0d00h) with 240 mL of non-sparkling water.

The intake of water was not permitted for up to 2 hours post-administration. Between 2 hours and 4 hours after dosing, the subject was allowed to drink up to 250 mL of non-sparkling water. After 4 hours post-administration a late breakfast was served and the subject was allowed to drink water ad libitum.

CSR12934:

Riociguat and placebo were administered orally tid as film-coated tablets with or without food. The starting dose at the beginning of the 8-week titration phase was 1 mg riociguat or placebo tid. The respective single daily doses were to be taken 6-8 hours apart.

Reviewer's Comment: For study 13796, the reviewer agrees with the administration of moxifloxacin under fasting conditions. Moreover, the reviewer agrees that riociguat can be administered without regard to meals. A high-calorie, high-fat breakfast had only a minor impact on the AUC of riociguat. In the Phase 3 pivotal clinical trials, riociguat tablets were administered three times daily, irrespective of food intake.

4.2.6.4 ECG and PK Assessments

CSR13796:

Study Day	-1	1
Intervention	No treatment (Baseline)	400 mg tablet of moxfloxacin given as a single oral dose or matching placebo tablet
12-Lead ECGs	Screening and -0.5 hours relative to the starting time (clock time) of study medication on Day 1	-0.5, 0.5, 1, 2, 3, 4, 6, 8, 24 hours relative to the starting time (clock time) of study medication on Day 1
PK Samples for drug	None collected	Predose, 0.5, 1, 2, 3, 4, 6, 8, 24 hours relative to the starting time (clock time) of study medication on Day 1

CSR12934:

Study Day	-1	1
Intervention	No treatment (Baseline)	Riociguat 1.0-2.5 mg group (titration between 1.0 mg and 2.5 mg tid based on an individual dose titration scheme) Riociguat 1.0-1.5 mg group (up-titration from 1.0 mg to 1.5 mg tid, capped dose titration) Placebo TID
12-Lead ECGs	Pre-treatment	Visit 1 (day 0): before intake of first and second dose; 2-3 hours post second dose. Visits 2 and 6 (2 weeks and 12 weeks) ECG recorded before administration and 2-3 hours post study medication.
PK Samples for drug	None collected	Sparse sampling employed. Visit 1 (day 0): before intake of first dose. For second dose, immediately before and within 2-3 hours after dosing. Visits 2-6 (2 weeks and 12 weeks) PK taken before administration of study medication.

Reviewer's Comment: For study 13796 *the PK and ECG assessments are adequate to capture QT at peak concentrations of moxifloxacin. For study 12934, ECG was recorded at trough concentrations and within 2-3 hours of dosing riociguat. The reported* T_{max} *is 1-1.5 hours after dosing. Therefore, it is unlikely the study was able to capture the* C_{max} *related effects of riociguat on QT.*

4.2.6.5 Baseline

Study 13796: The average of triple ECG measures taken before drug dosing on treatment day were used as baseline

Study 12934: The average of triple ECG measures taken at baseline visit before drug dosing were used as baseline

4.2.7 ECG Collection

12-Lead ECGs were assessed centrally. Safety single ECGs were collected.

4.2.8 Sponsor's Results

4.2.8.1 Study Subjects

Study 12934

From the total 237 patients treated with Riociguat 1.0-2.5 mg, 57 (1.5mg) and 111 with placebo completed treatment. Data on changes from baseline to last visit were available for 193 subjects in the riociguat 1.0-2.5 mg group, 43 subjects in the riociguat 1.0-1.5 mg group, and 84 subjects in the placebo group.

4.2.8.2 Statistical Analyses

4.2.8.2.1 Primary Analysis

Study 13796:

Text Table 9-1 summarizes the results of the primary analysis of variance (ANOVA), i.e. point estimates (LS-means) and the 95% confidence intervals, for the differences between BAY 12-8039 and placebo in QTcF and QTcB changes from baseline to 3 hours after dosing. The LS-mean differences between BAY 12-8039 and placebo in QTcF and QTcB changes from baseline to 3 hours after dosing was more than 2 times the expected QTc prolongation of approximately 7 ms. Since the lower bound of both 95% confidence intervals is greater than 7 ms, the treatment effect of BAY 12-8039 on QTcF and QTcB prolongation is both statistically and clinically significant at the one-sided significance level of 2.5%.

Table 1: Sponsor's Results: LS-mean differences ('BAY 12-8039 minus placebo') for change in QTcF and QTcB from baseline to 3 hours after dosing (all subjects valid for PD, n=51)

Correction method	Difference 'BAY 12-8039 minus placebo'	
	Point estimate [ms]	95% confidence interval [ms]
Fridericia (QTcF)	15.37	11.92 to 18.81
Bazett (QTcB)	15.55	10.09 to 21.01

Source: CSR 13796 Text Table 9-1

Study 12934:

Data on changes from baseline to last visit were available for 193 subjects in the riociguat 1.0-2.5 mg group, 43 subjects in the riociguat 1.0-1.5 mg group, and 84 subjects in the placebo group. At the regular study visits, the mean QTcF duration was in the range between 420 and 435 msec, which is as expected in the normal range. As can be seen in Table 10-28, changes from baseline did not exceed a mean increase of more than 7 msec and did not show a strong trend to increase during the study period. In addition, the maximum change vs. baseline was <60 msec at all measurements (except for one measurement in the riociguat 1.0- 2.5 mg group at the safety follow-up visit). Overall, there was no clinically relevant change in QTcF duration nor was there a difference between the riociguat treatment groups and placebo.

Table 1: Sponsor's Results: Electrocardiogram: Summary statistics and changes from baseline by visit - QTcF (Fridericia's correction) duration (msec) - safety analysis set

Treatment group	Visit	Value at visit			Change from baseline		
		n	Mean	SD	n	Mean	SD
Riociguat 1.0-2.5 mg (N=254)	Baseline	195	429	21			
	Visit 1 post 1st dose	79	425	19	78	-1	10
	Visit 1 pre 2nd dose	165	427	19	164	-2	12
	Visit 1 post 2nd dose	74	427	19	74	1	9
	Visit 2 pre dose	170	428	21	165	-1	14
	Visit 2 post dose	78	423	20	73	-3	13
	Visit 6 pre dose	163	431	19	154	1	14
	Visit 6 post dose	67	426	20	63	0	16
	Last visit	211	430	21	193	0	15
Placebo (N=126)	Baseline	89	431	26			
	Visit 1 post 1st dose	36	423	21	36	-4	9
	Visit 1 pre 2nd dose	76	427	25	75	-4	11
	Visit 1 post 2nd dose	32	425	22	31	-3	10
	Visit 2 pre dose	71	431	22	71	1	13
	Visit 2 post dose	34	424	21	33	-4	10
	Visit 6 pre dose	64	434	24	61	1	14
	Visit 6 post dose	24	430	24	23	0	14
	Last visit	89	432	25	84	1	13
Riociguat 1.0-1.5 mg (N=63)	Baseline	43	432	23			
	Visit 1 post 1st dose	17	425	27	17	-4	14
	Visit 1 pre 2nd dose	39	433	23	37	0	12
	Visit 1 post 2nd dose	17	424	19	16	0	9
	Visit 2 pre dose	35	431	24	33	-3	16
	Visit 2 post dose	16	428	18	15	1	19
	Visit 6 pre dose	39	435	21	34	3	15
	Visit 6 post dose	17	425	19	16	7	16
	Last visit	52	435	20	43	2	16

pre dose= 1-0 hours before study drug administration; post dose = 2-3 hours after study drug administration

Source: CSR12934 Table 10-28

Reviewer's Comments: FDA reviewer's results are similar and presented in section 5.2.

4.2.8.2.2 Categorical Analysis

Study 12934:

No increases in QTcF of >60 msec from baseline were seen in any of the treatment groups during the treatment phase, but 1 subject from the riociguat 1.0-2.5 mg group had an increase in QTcF of >60 msec from baseline at the safety follow-up visit (see Table 10-29 and Table 14.3.5/23).

Increases in QTcF of >30 msec from baseline were not frequently seen (<5% at most of the regular measurements) and were evenly distributed between the treatment groups. QTcF prolongations >450 msec were already present at baseline (riociguat 1.0-2.5 mg: 15% of subjects; riociguat 1.0-1.5 mg: 19%; placebo: 19%). There was no trend to increase during the treatment phase and there were also no clinically relevant differences between the treatment groups.

QTcF prolongations >480 msec (riociguat 1.0-2.5 mg: 1% of subjects; riociguat 1.0-1.5 mg: 5%; placebo: 1%) and QTcF prolongations >500 msec (riociguat 1.0-2.5 mg: 1% of subjects; riociguat 1.0-1.5 mg: 0%; placebo: 1%) were already present at baseline. There was no trend to increase during the treatment phase. Especially QTcF prolongations >500 msec were seen only in single subjects during the treatment phase. There were no clinically relevant differences between the treatment groups.

4.2.8.3 Safety Analysis

Six deaths occurred during the study. Table 1 summarizes details of the TEAEs leading to death for the 6 subjects. No sudden cardiac deaths were reported.

Table 1: Listing of subjects who died during the study - safety analysis set

Subject No.	Randomized treatment	Age/ Sex	Event description (MedDRA preferred term)	Day of onset of AE	Day of death	Day of stop of study med.	AE related to study med.?
220024001	RIOC 1.0-2.5	61/F	Sepsis	5	8	3	No
540044008	RIOC 1.0-2.5	26/M	Haemoptysis	55	55	55	No
140054001	Placebo	73/F	Pulmonary arterial hypertension	5	8	8	No
400084010	Placebo	66/M	Anxiety	60	63	63	No
540024005	Placebo	59/F	Respiratory failure	3	5	3	No
			Circulatory collapse	3	5	3	No
440034006	RIOC 1.0-1.5	65/M	Right ventricular failure	52	52	41 [a]	No
			Pulmonary arterial hypertension	52	52	41 [a]	No

RIOC 1.0-2.5 = Riociguat 1.0-2.5 mg; RIOC 1.0-1.5 = Riociguat 1.0-1.5 mg
[a] Day indicated is day of end of last study drug interval. Day of last study drug intake is unknown.
Source: Tables 14.3.2/2 and 14.3.2/7

Source: CSR 12934, Table 10-11

Reviewer's comments: No torsade de pointes, ventricular fibrillation or ventricular flutter were reported in these studies. No sudden cardiac deaths were reported.

4.2.8.4 Clinical Pharmacology

4.2.8.4.1 Pharmacokinetic Analysis

The PK results are presented in Table 2 (riociguat) and Table 3 (moxifloxacin). The concentration-time profile for moxifloxacin is illustrated in Figure 1.

Table 2: Summary statistics for pre-dose (top table) and post-dose (bottom table) concentrations of plasma riociguat

Visit	N	Riociguat 0.5 mg	N	Riociguat 1.0 mg	N	Riociguat 1.5 mg	N	Riociguat 2.0 mg		Riociguat 2.5 mg
V1 pre 2nd dose			297	19.5/51.9 (2.2-56.6)						
V1 pre 4th dose			129	35.3/80.2 (<LLOQ-116.2)						
V2 pre dose	7	18.4/110.9 (6.9-69.6)	295	34.6/119.7 (<LLOQ-232.5)						
V3 pre dose	7	26.3/130.5 (4.9-83.7)	22	40.4/164.7 (<LLOQ-171.6)	267	50.3/108.8 (<LLOQ-338.9)				
V4 pre dose			17	39.0/139.9 (3.9-174.7)	74	54.6/125.0 (<LLOQ-321.1)	194	66.3/130.0 (<LLOQ-425.2)		
V5 pre dose			10	34.1/117.9 (7.9-112.1)	64	50.2/114.7 (<LLOQ-235.1)	29	53.7/168.3 (<LLOQ-265.0)	178	80.7/119.6 (<LLOQ-376.2)
V6 pre dose			8	40.8/114.1 (10.4-107.8)	60	57.3/85.9 (10.8-240.4)	34	80.4/125.0 (2.5-438.0)	168	87.5/126.9 (<LLOQ-400.8)

Source: CSR12934, Table 11-1, Page 199

Visit	N	Riociguat 0.5 mg	N	Riociguat 1.0 mg	N	Riociguat 1.5 mg	N	Riociguat 2.0 mg		Riociguat 2.5 mg
V1 post 1st dose			299	25.4/99.7 (<LLOQ–91.4)						
V1 post 2nd dose			279	36.8/56.9 (3.2-124.8)						
V1 post 4th dose			120	59.9/51.8 (11.7-358.6)						
V2 post dose	5	50.2/87.0 (18.0-146.1)	15	75.5/55.3 (25.7-182.1)	105	82.1/56.4 (14.8-277.5)				
V3 post dose			10	87.6/38.3 (47.9-143.3)	36	90.2/55.7 (28.4-231.4)	78	106.4/59.6 (25.2-305.4)		
V4 post dose			5	95.8/53.3 (72.9-233.5)	30	116.2/55.7 (51.3-346.2)	11	123.4/51.3 (55.9-243.4)	71	141.4/63.3 (21.5-522.8)
V5 post dose			5	124.0/32.7 (92.9-187.0)	23	112.2/40.3 (52.1-224.0)	15	110.4/57.9 (37.8-242.8)	68	135.8/65.5 (23.5-387.1)
V6 post dose			5	118.4/50.8 (62.5-203.9)	26	111.8/46.1 (41.5-201.9)	13	148.4/73.1 (32.0-454.3)	59	154.4/61.7 (29.7-362.2)

Source: CSR12934, Table 11-2, Page 200

Table 3: PK Parameters following a single oral dose of 400 mg moxifloxacin

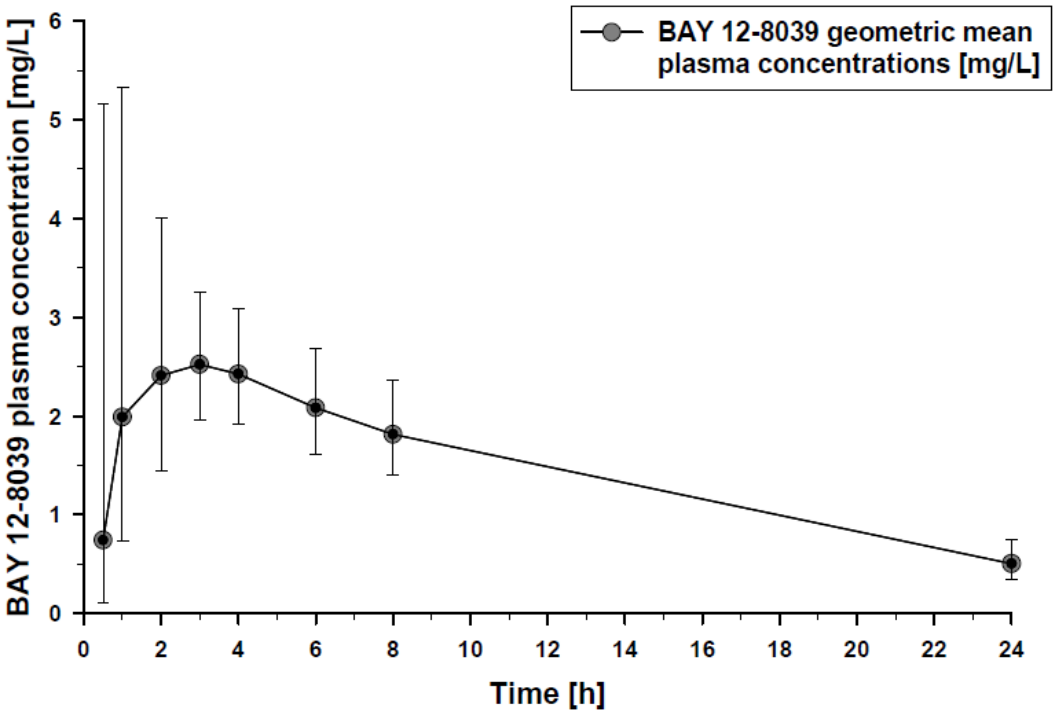
Parameter	Unit	N	BAY 12-8039 geometric mean/CV% (minimum-maximum)
C_{max}	mg/L	51	3.020/29.12 (1.81-6.08)
$C_{max\ norm}$	kg/L	51	0.495/23.20 (0.310-0.841)
T_{max}[a]	h	51	2.00 (0.42-6.0)

Source: Table 14.4/2 and Table 14.4/3 in Section 14

[a] Median (Range)

Source: CSR13796 Table 9-40, Page 95.

Figure 1: Plasma Concentration of Moxifloxacin following a Single 400 mg Dose

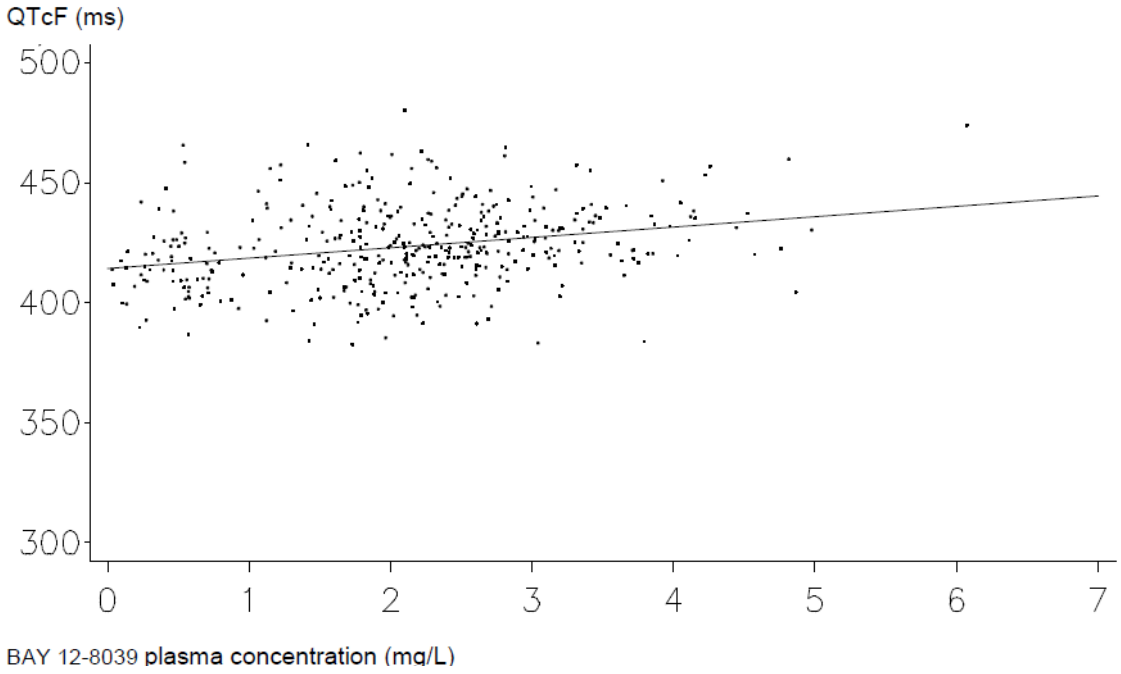


Source: CSR13796, Figure 9-5, Page 94.

4.2.8.4.2 Exposure-Response Analysis

For moxifloxacin, a plot of ΔΔQTc vs. drug concentrations is presented in Figure 2.

Figure 2: ΔΔ QTcF vs. Moxifloxacin concentration



For riociguat, the reviewer was unable to find exposure-response analysis performed by the sponsor.

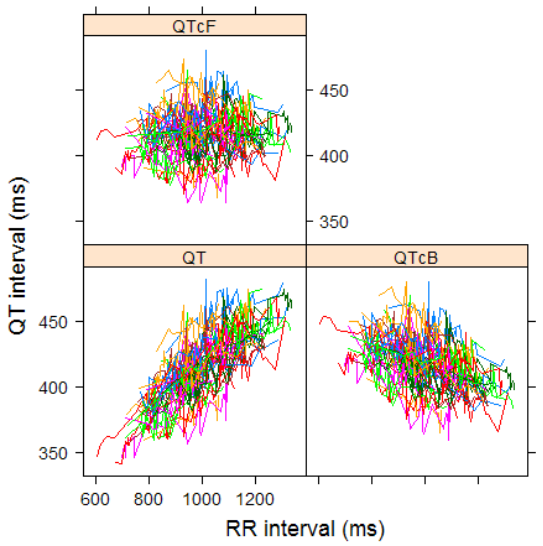
5 REVIEWERS' ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

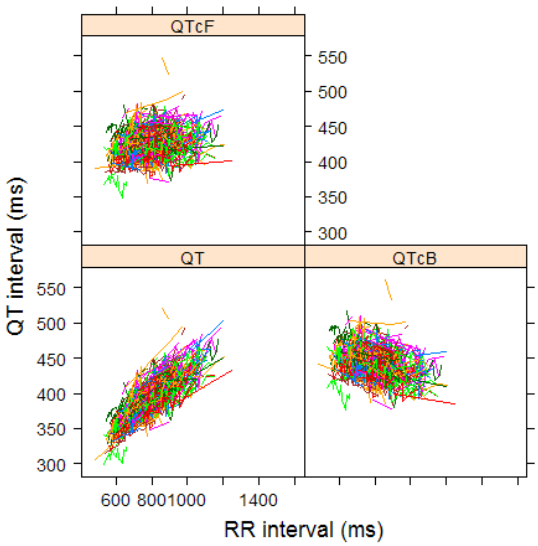
The sponsor used QTcF and QTcB as their outcome. The statistical reviewer used QTcF as outcome for both studies.
The relationship between different correction methods and RR is presented in Figure 3.

Figure 3: QT, QTcB, and QTcF vs. RR (Each Subject's Data Points are Connected with a Line)

Moxifloxacin, Study 13796



Riociguat, Study 12934



5.2 STATISTICAL ASSESSMENTS

5.2.1 QTc Analysis

5.2.1.1 The Primary Analysis

Study 12934:

Descriptive analysis was applied on the QTcF measured before and after dosing at visit 1, 2, 6 and the last visit for each treatment arm. Mean and standard deviation of QTcF and its changes from baseline were displaced. There is no mean QTcF change from baseline larger than 10 ms on any visit in both treatment groups.

Table 4: Summary statistics and changes from baseline by visit - QTcF (Fridericia's correction) duration

Treatment arm	Visit	n	QTcF (mean) (ms)	QTcF (SD) (ms)	QTcF change from baseline (mean) (ms)	QTcF change from baseline (SD) (ms)
BAY 63-2521 1.5 mg (fixed dose)	Visit 1 pre-dose	17	429	26	5	-
	Visit 1 post 1st dose	17	425	27	-4	14
	Visit 1 pre 2nd dose	17	429	26	0.3	13
	Visit 1 post 2nd dose	17	424	19	0.07	19
	Visit 2 pre-dose	16	426	24	0.6	18
	Visit 2 post-dose	16	428	18	0.5	19
	Visit 6 pre-dose	19	426	18	5	18
	Visit 6 post-dose	17	425	18	7	16
	Last visit	19	427	20	6	16
BAY 63-2521 Individual Titration	Visit 1 pre-dose	78	426	20	5	9
	Visit 1 post 1st dose	78	424	19	-2	10
	Visit 1 pre 2nd dose	80	424	18	-0.6	9
	Visit 1 post 2nd dose	74	426	19	1.3	9
	Visit 2 pre-dose	78	424	19	-1.4	13
	Visit 2 post-	78	422	20	-3	13

	dose					
	Visit 6 pre-dose	65	427	18	1.6	12
	Visit 6 post-dose	67	425	20	0.3	16
	Last visit	72	426	16	0.13	16

5.2.1.2 Assay Sensitivity Analysis

Study 13796:

The statistical reviewer used mixed model to analyze the ΔQTcF effect. The model includes time point and sequences as fixed effects and each subject as a random effect. Baseline values are also included in the model as a covariate. The analysis results are listed in the following tables.

Table 5: Analysis Results of ΔQTcF and ΔΔQTcF for Study 13796

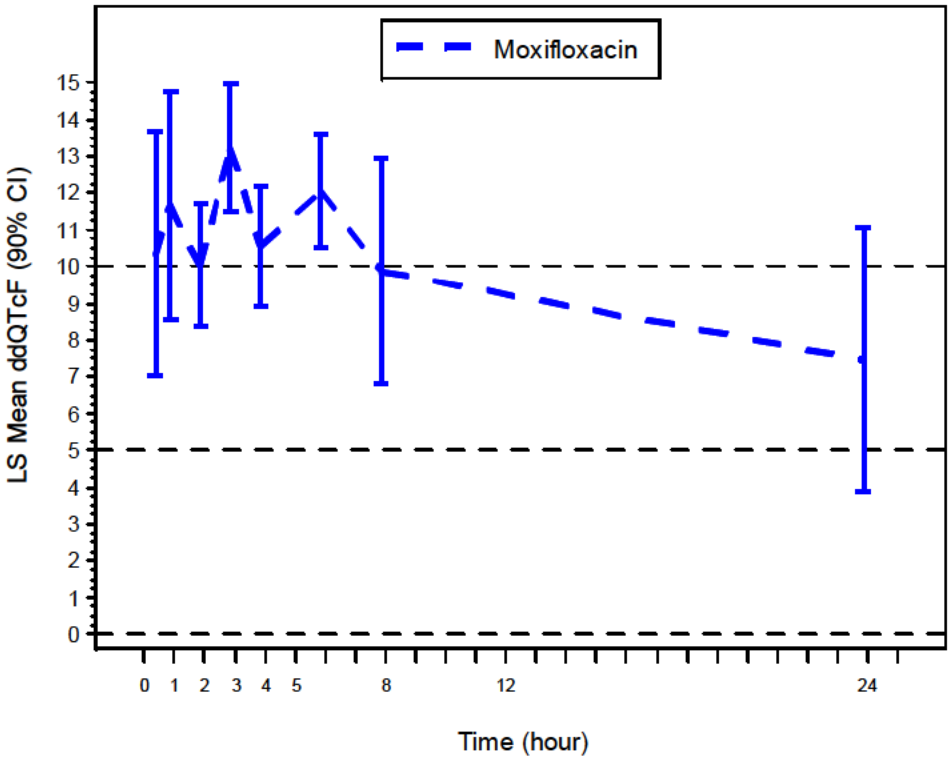
	Treatment Group			
	Moxifloxacin 400 mg			
	dQTcF	Placebo	ddQTcF	
Time (hrs)	LS Mean (ms)	LS Mean (ms)	Diff LS Mean (ms)	90% CI (ms)
0.5	11.9	1.5	10.4	(7.0, 13.7)
1	15.8	4.1	11.7	(8.6, 14.7)
2	16.8	5.1	11.7	(8.4, 15.0)
3	18.0	3.0	15.0	(11.5, 18.5)
4	16.4	4.2	12.2	(8.9, 15.5)
6	7.7	-5.9	13.6	(10.5, 16.8)
8	7.5	-2.3	9.9	(6.8, 13.0)
24	6.1	-1.4	7.5	(3.9, 11.0)

The largest lower bounds of the 2-sided 90% CI for the mean difference between Moxifloxacin 400 mg and placebo were 11.5 ms at 3 hour after dose after multiplicity adjustment for 3 time points.

5.2.1.3 Graph of ΔΔQTcF over Time

The following figure displays the time profile of ΔΔQTcF for study 13796.

Figure 4: Mean and 90% CI ΔΔQTcF Timecourse of Moxifloxacin



(Note: CIs are all unadjusted)

5.2.1.4 Categorical Analysis

Study 12934:

Table 6 lists the number of subjects as well as the number of observations whose QTcF values are ≤ 450 ms, between 450 ms and 480 ms. No subject's QTcF was above 480 ms.

Table 6: Categorical Analysis for QTcF

	Total N		Value<=450 ms		450 ms<Value<=480 ms		480 ms<Value<=500 ms		Value>500	
Treatment Group	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
BAY 63-2521 1.5 mg (fixed	24	155	17 (70.8%)	134 (86.5%)	6 (25.0%)	20 (12.9%)	1 (4.2%)	1 (0.6%)	0 (.%)	0 (0.0%)
BAY 63-2521 Individual Ti	92	670	71 (77.2%)	603 (90.0%)	21 (22.8%)	67 (10.0%)	0 (0.0%)	0 (0.0%)	0 (.%)	0 (0.0%)
Placebo	38	187	30 (78.9%)	165 (88.2%)	8 (21.1%)	22 (11.8%)	0 (.%)	0 (0.0%)	0 (.%)	0 (0.0%)

Table 7 lists the categorical analysis results for ΔQTcF. No subject's change from baseline was above 60 ms.

Table 7: Categorical Analysis of ΔQTcF

	Total N		Value<=30 ms		30 ms<Value<=60 ms		Value>60 ms	
Treatment Group	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
BAY 63-2521 1.5 mg (fixed	19	130	18 (94.7%)	126 (96.9%)	1 (5.3%)	4 (3.1%)	0 (.%)	0 (0.0%)
BAY 63-2521 Individual Ti	84	570	80 (95.2%)	562 (98.6%)	4 (4.8%)	8 (1.4%)	0 (.%)	0 (0.0%)
Placebo	37	187	36 (97.3%)	184 (98.4%)	1 (2.7%)	3 (1.6%)	0 (.%)	0 (0.0%)

5.2.2 HR Analysis

Study 12934:

The same statistical analysis was performed based on HR measured before and after dosing at visit 1, 2, 6 and the last visit for each treatment arm. Mean and standard deviation of HR and its changes from baseline were displaced. There is no large mean HR change (>10 bpm) from baseline on any visit in both treatment groups.

Table 8: Summary statistics and changes from baseline by visit - Heart Rate

Treatment Group	Analysis Visit	# Subj.	HR (mean) (bpm)	HR (SD) (bpm)	HR change from baseline (mean) (bpm)	HR change from baseline (SD) (bpm)
BAY 63-2521 1.5 mg (fixed dose)	Baseline	41	73.4	11.0	.	.
	Last Visit	17	76.9	9.1	0.3	10.8
	Visit 1 - 1-0 HR PRE 1ST DOSE	17	78.3	7.8	-3.0	.
	Visit 1 - 1-0 HR PRE 2ND DOSE	17	82.0	10.4	3.7	8.3
	Visit 1 - 2-3 HRS POST 1ST DOSE	17	83.0	8.1	4.5	7.7
	Visit 1 - 2-3 HRS POST 2ND DOSE	17	82.0	8.7	3.5	6.2
	Visit 2 - 1-0 HR PRE DOSE	16	78.4	10.2	1.4	10.7
	Visit 2 - 2-3 HR POST DOSE	16	81.2	9.0	3.4	10.4
	Visit 6 - 1-0 HR PRE DOSE	19	72.7	7.5	-4.5	7.4
	Visit 6 - 2-3 HR POST DOSE	17	76.9	9.1	0.3	10.8
BAY 63-2521 Individual Titration	Baseline	180	74.8	11.4	.	.
	Last Visit	68	78.6	11.5	2.2	10.9
	Visit 1 - 1-0 HR PRE 1ST DOSE	78	76.0	11.5	-6.2	7.2
	Visit 1 - 1-0 HR PRE 2ND DOSE	80	77.7	11.8	1.0	7.9
	Visit 1 - 2-3 HRS POST 1ST DOSE	78	79.4	12.8	3.0	8.6
	Visit 1 - 2-3 HRS POST 2ND DOSE	74	79.5	11.6	2.1	7.5
	Visit 2 - 1-0 HR PRE DOSE	78	78.6	12.5	2.6	8.8
	Visit 2 - 2-3 HR POST DOSE	78	81.0	12.5	4.7	11.0
	Visit 6 - 1-0 HR PRE DOSE	65	75.5	9.7	-0.0	9.0
	Visit 6 - 2-3 HR POST DOSE	67	78.7	11.5	2.2	11.0

Table 9: Categorical Analysis for HR

	Total N		Value<=100 bpm		Value>100 bpm	
Treatment Group	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
BAY 63-2521 1.5 mg (fixed	22	153	21 (95.5%)	152 (99.3%)	1 (4.5%)	1 (0.7%)

	Total N		Value<=100 bpm		Value>100 bpm	
Treatment Group	**# Subj.**	**# Obs.**	**# Subj.**	**# Obs.**	**# Subj.**	**# Obs.**
BAY 63-2521 Individual Ti	90	666	78 (86.7%)	636 (95.5%)	12 (13.3%)	30 (4.5%)
Placebo	38	184	35 (92.1%)	179 (97.3%)	3 (7.9%)	5 (2.7%)

5.2.3 PR Analysis

Study 12934:

The same descriptive analysis was applied on the PR measured before and after dosing at visit 1, 2, 6 and the last visit for each treatment arm. Mean and standard deviation of PR and its changes from baseline were displaced. There is no large mean PR change from baseline on any visit in both treatment groups.

Table 10: Summary statistics and changes from baseline by visit - PR duration

Treatment Group	Analysis Visit	# Subj.	PR (mean) (ms)	PR (SD) (ms)	PR change from baseline (mean) (ms)	PR change from baseline (SD) (ms)
BAY 63-2521 1.5 mg (fixed dose)	Baseline	41	173.2	24.9	.	.
	Last Visit	17	167.1	19.1	-2.0	17.7
	Visit 1 - 1-0 HR PRE 1ST DOSE	17	171.3	25.7	2.7	.
	Visit 1 - 1-0 HR PRE 2ND DOSE	17	165.7	15.6	-4.3	15.5
	Visit 1 - 2-3 HRS POST 1ST DOSE	17	164.5	17.8	-5.5	9.8
	Visit 1 - 2-3 HRS POST 2ND DOSE	17	166.8	18.7	-1.9	11.8
	Visit 2 - 1-0 HR PRE DOSE	16	170.7	21.2	-0.2	15.4
	Visit 2 - 2-3 HR POST DOSE	16	167.3	21.7	-1.8	16.5
	Visit 6 - 1-0 HR PRE DOSE	19	171.2	18.5	3.8	13.1
	Visit 6 - 2-3 HR POST DOSE	17	167.1	19.1	-2.0	17.7
BAY 63-2521 Individual Titration	Baseline	180	169.1	26.5	.	.
	Last Visit	69	167.6	22.6	0.3	13.1
	Visit 1 - 1-0 HR PRE 1ST DOSE	78	168.8	20.3	7.6	7.9
	Visit 1 - 1-0 HR PRE 2ND DOSE	80	164.7	20.0	-2.1	9.4
	Visit 1 - 2-3 HRS POST 1ST DOSE	78	166.0	21.2	-2.5	8.6
	Visit 1 - 2-3 HRS POST 2ND DOSE	74	165.7	21.6	-1.8	9.9
	Visit 2 - 1-0 HR PRE DOSE	78	167.5	19.4	0.4	10.1
	Visit 2 - 2-3 HR POST DOSE	78	166.4	20.7	-0.6	12.7
	Visit 6 - 1-0 HR PRE DOSE	65	170.2	22.7	2.8	12.5
	Visit 6 - 2-3 HR POST DOSE	67	167.5	22.1	0.2	13.2

Table 11: Categorical Analysis for PR

	Total		Value<=200 ms		Value>200 ms	
Treatment Group	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
BAY 63-2521 1.5 mg (fixed	22	153	19 (86.4%)	146 (95.4%)	3 (13.6%)	7 (4.6%)
BAY 63-2521 Individual Ti	90	667	77 (85.6%)	626 (93.9%)	13 (14.4%)	41 (6.1%)
Placebo	38	184	30 (78.9%)	161 (87.5%)	8 (21.1%)	23 (12.5%)

5.2.4 QRS Analysis

The same descriptive analysis was applied on the QRS measured before and after dosing at visit 1, 2, 6 and the last visit for each treatment arm. Mean and standard deviation of QRS and its changes from baseline were displaced. There is no large mean QRS change from baseline on any visit in both treatment groups.

Table 12: Summary statistics and changes from baseline by visit - QRS duration

Treatment Group	Analysis Visit	# Subj.	QRS (mean) (ms)	QRS (SD) (ms)	QRS change from baseline (mean) (ms)	QRS change from baseline (SD) (ms)
BAY 63-2521 1.5 mg (fixed dose)	Baseline	41	97.3	10.2	.	.
	Last Visit	17	95.6	10.4	0.2	3.3
	Visit 1 - 1-0 HR PRE 1ST DOSE	17	94.5	7.7	0.7	.
	Visit 1 - 1-0 HR PRE 2ND DOSE	17	94.0	8.3	-0.5	3.0
	Visit 1 - 2-3 HRS POST 1ST DOSE	17	94.4	8.0	-0.1	3.2
	Visit 1 - 2-3 HRS POST 2ND DOSE	17	94.5	8.9	-0.7	2.3
	Visit 2 - 1-0 HR PRE DOSE	16	95.7	9.4	1.2	3.6
	Visit 2 - 2-3 HR POST DOSE	16	94.9	11.0	-1.9	5.4
	Visit 6 - 1-0 HR PRE DOSE	19	96.9	10.9	-0.7	5.4
	Visit 6 - 2-3 HR POST DOSE	17	95.6	10.4	0.2	3.3
BAY 63-2521 Individual Titration	Baseline	181	94.3	9.4	.	.
	Last Visit	69	92.6	7.7	0.7	5.1
	Visit 1 - 1-0 HR PRE 1ST DOSE	78	93.0	7.9	3.1	4.7
	Visit 1 - 1-0 HR PRE 2ND DOSE	80	92.7	7.5	0.3	2.6
	Visit 1 - 2-3 HRS POST 1ST DOSE	78	92.7	8.1	-0.2	3.9
	Visit 1 - 2-3 HRS POST 2ND DOSE	74	92.2	8.2	-0.4	3.2
	Visit 2 - 1-0 HR PRE DOSE	78	92.1	8.2	0.0	4.4
	Visit 2 - 2-3 HR POST DOSE	78	92.0	8.1	0.1	4.3
	Visit 6 - 1-0 HR PRE DOSE	65	94.0	8.4	1.6	5.0
	Visit 6 - 2-3 HR POST DOSE	67	92.4	7.7	0.9	5.0

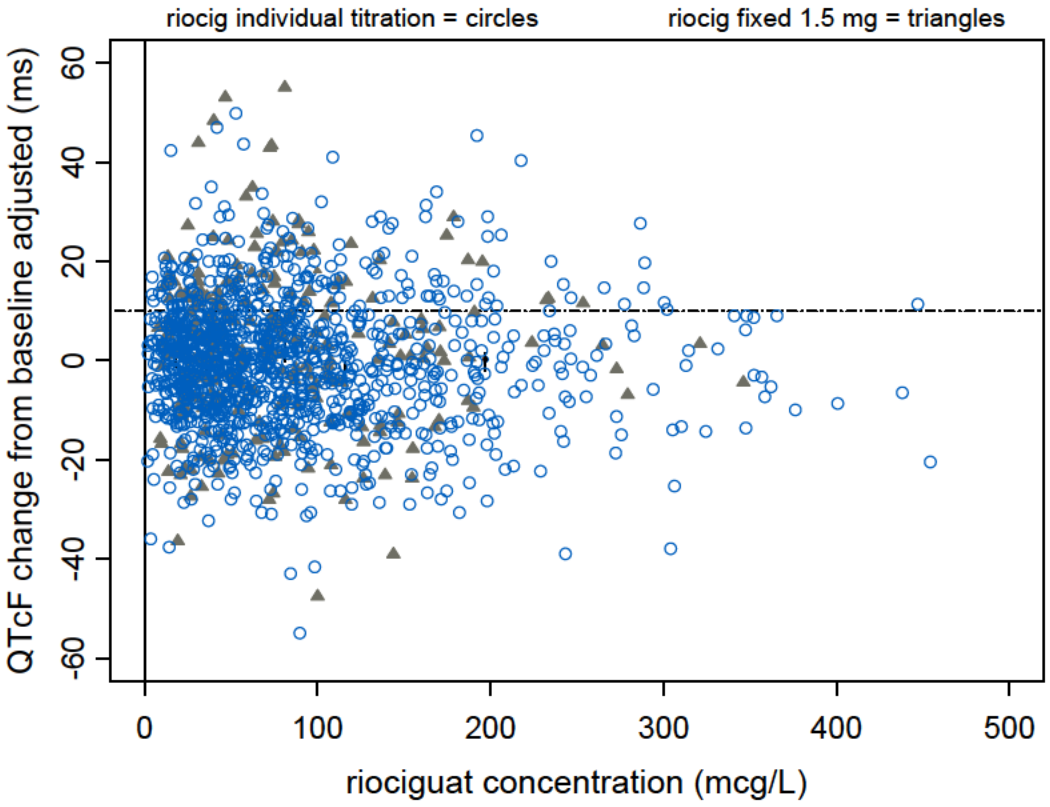
Table 13: Categorical Analysis for QRS

	Total		Value<=100 ms		100 ms<Value<=110 ms		Value>110 ms	
Treatment Group	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
BAY 63-2521 1.5 mg (fixed	22	153	13 (59.1%)	104 (68.0%)	7 (31.8%)	40 (26.1%)	2 (9.1%)	9 (5.9%)
BAY 63-2521 Individual Ti	90	667	65 (72.2%)	565 (84.7%)	21 (23.3%)	96 (14.4%)	4 (4.4%)	6 (0.9%)
Placebo	38	184	28 (73.7%)	153 (83.2%)	10 (26.3%)	31 (16.8%)	0 (0.0%)	0 (0.0%)

5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

The relationship between ΔQTcF and riociguat concentrations is visualized in Figure 5 with no evident exposure-response relationship.

Figure 5: ΔQTcF vs. Riociguat Concentrations



5.4 CLINICAL ASSESSMENTS

5.4.1 Safety assessments

None of the events identified to be of clinical importance per the ICH E 14 guidelines i.e. syncope, seizure, significant ventricular arrhythmias or sudden cardiac death occurred in this study.

5.4.2 ECG assessments

Study 12934

Waveforms from the ECG warehouse were reviewed. According to ECG warehouse statistics 61% of the ECGs were annotated in the primary lead II, with less than 7% of ECGs reported to have significant QT bias, according to the automated algorithm. Overall ECG acquisition and interpretation in this study appears acceptable.

Sponsor collected single instead of replicate ECGs per time-point.

5.4.3 PR and QRS Interval

No subject had a postbaseline PR > 220 ms or a QRS > 120 ms.

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Therapeutic dose	1.0 (0.5) – 2.5 mg three times daily (TID); individual dose titration according to systolic blood pressure and the patient' s well-being
Maximum tolerated dose	In Caucasian subjects, riociguat doses up to 2.5 mg were safe and well tolerated by healthy male subjects. A single dose of 5 mg riociguat was safe but not well tolerated by healthy subjects as the frequency of adverse events related to the pharmacological effects of riociguat, ie orthostatic hypotension, increased to a clinically relevant extent. Therefore, the dose level of 2.5 mg riociguat was considered the maximum well-tolerated dose in healthy subjects and dose escalation was stopped at a dose level of 5 mg riociguat. The dose range of 1.0 - 2.5 mg TID proved to be safe in healthy subjects in a multiple-dose study. The highest dose of 2.5 mg TID in healthy subjects showed an increase in adverse events and further dose escalation was stopped. A 2.5 mg single dose of riociguat was safe and well tolerated in subject with pulmonary hypertension (PH). A total dose of 5 mg was associated with a decrease in systemic blood pressure in 1 patient.
Principal adverse events	Comparing placebo with active drug in multiple dose studies, the most common single adverse events > 5% reported in Phase-I studies for riociguat were: • Headache – placebo 17.1%, active 23.5%. • Dyspepsia – placebo 1.3%, active 12.7% • Gastro-esophegeal reflux disease – placebo 2.6%, active 7.8% Most treatment-emergent adverse events were of mild intensity. In most cases they were attributable to the pharmacological properties of the test compound, and had resolved by the end of the observation period. Adverse events like headache or dyspepsia are considered secondary pharmacological effects of riociguat due to its mechanism of action: relaxation of the smooth muscle cells in vessels and various organs. Duration and intensity disappeared with its declining plasma concentrations of riociguat.

Maximum dose tested	Single Dose	5 mg single dose
	Multiple Dose	2.5 mg TID for 10 consecutive days
Exposures Achieved at Maximum Tested Dose	Single Dose	Mean (%CV); 5 mg in healthy subjects C_{max}: 109.4 (36.1) µg/L AUC: 665.9 (125.8) µg*h/L 2.5 mg in PH patients C_{max}: 119 (16.1) µg/L AUC: 1411 (39.2) µg*h/L
	Multiple Dose	Mean (%CV); 2.5 mg TID in healthy subjects C_{max}: 106 (58.6) µg/L $AUC_{\tau(0-7)}$: 482 (76.9) µg*h/L 2.5 mg TID in PH patients C_{max}: 203 (42.3) µg/L $AUC_{\tau(0-7)}$: 1387 (50.7) µg*h/L (dosing interval τ of 7 h for TID)
Range of linear PK	Following multiple-dose escalation, riociguat maximum plasma concentrations and AUC values showed consistent dose-proportional increases when escalating the dose from 0.5 mg to 2.5 mg tid under fasted conditions. Dose-proportionality from 0.5 to 2.5 mg was confirmed in a specifically designed single-dose crossover study. In patients with PH, riociguat shows long-term linearity in PK and consistency of riociguat exposure (over 4 years).	
Accumulation at steady state	Geometric means for the accumulation ratio RA_{AUC} of riociguat ranged between 110% and 157 and for the accumulation ratio RA_{Cmax} they ranged between 105% and 146, ie, were in the expected range taking into account the dosing interval and the half life of about 8 hours in healthy subjects in the MD study.	
Metabolites	N-demethylation, catalyzed by CYP3A4, CYP1A1, CYP2C8 and CYP2J2, is the major biotransformation pathway of riociguat leading to metabolite M-1 (BAY 60-4552). Parent drug, M-1 as major circulating active (pharmacological activity: 1/10th to 1/3rd of riociguat) metabolite, and its (pharmacologically inactive) N-glucuronide M-4 are the most important moieties present in human plasma. Besides unchanged riociguat, metabolite M-1 and its N-glucuronide M-4 were also identified as main metabolites in the excreta of animals. No significant species differences in metabolism were observed; specifically, all metabolites observed in humans were also observed in preclinical species.	

Absorption	Absolute/Relative Bioavailability	The absolute bioavailability of the 1.0 mg tablet is complete (riociguat: 94%). There were no relevant differences in bioavailability for riociguat when 2.5 mg of the drug was given either as an oral solution or an immediate-release tablet.
	Tmax	0.5 to 1.5 h after tablet intake
Distribution	Vd/F or Vd	The volume of distribution at steady-state (Vss) was approximately 30 L (0.38 L/kg) for riociguat indicating a low affinity to tissues. VZ/f after oral administration of a 2.5 mg tablet was 0.67/37.3 (0.4205-1.013) L/kg.
	% bound	Plasma protein binding of riociguat in human plasma is approximately 95%, with serum albumin and α1-acidic glycoprotein being the main binding components.
Elimination	Route	Riociguat is metabolized via CYP3A4, CYP2C8, CYP2J2 and CYP1A1. N-demethylation of the drug leading to M 1 (BAY 60-4552) is the major pathway of biotransformation leading to M 1 (BAY 60-4552) and its N-glucuronide M-4. In addition, N debenzylation of riociguat (leading to M-3) is observed as an additional minor biotransformation pathway. Riociguat and metabolites are excreted via both renal (33 to 45%) and biliary/fecal routes (48 to 59%). Approximately 4 to 19% of the administered dose was excreted as unchanged riociguat via the kidneys by mainly glomerular filtration.
	Terminal t½	Riociguat mean terminal half-live in healthy subjects ranges from 5 - 10 h with high inter-individual variability, and was on average approximately 14 h in PH patients.
	CL/F or CL	CL/F after oral administration of the 2.5 mg tablet was 7.2/83.3 (2.78-17.1) L/h. CL after intravenous administration of the 1.0 mg was 3.9/78.3 (1.44-15.3) L/h.

Intrinsic Factors	Age (elderly ≥ 65 y vs young ≤ 45 y)	Elderly subjects exhibited higher plasma concentrations than young subjects, with mean AUC values being approximately 38% greater in elderly men and 42% higher in elderly women, compared to young subjects of the same gender, mainly due to reduced (apparent) total body clearance and renal clearance. No relevant age effects were observed for C_{max} or t_{max}.
	Sex (male versus female)	There were no relevant differences in pharmacokinetics between male and female subjects, especially when taking into account common body-weight differences.
	Race	Data on ethnic differences between Japanese, Chinese, African-American and Caucasian subjects suggest that inter-ethnic differences in PK parameters of riociguat are small. In the light of the high inter-individual variability of riociguat PK in general. Ethnic differences in riociguat PK of PH patients were moderate (AUC ≤ 30%) and did not merit any dose adjustment beyond the individual dose titration.
	Hepatic Impairment (according to Child Pugh classification)	Exposure in cirrhotic subjects with mild hepatic impairment (classified as Child Pugh A) was not clinically relevant different to healthy subjects. In cirrhotic subjects with moderate hepatic impairment (classified as Child Pugh B), riociguat mean AUC was increased by 50-70% compared to healthy. There are no data in patients with severe hepatic impairment (classified as Child Pugh C).
	Renal Impairment	Mean dose- and weight- normalized exposure values for riociguat were higher in subjects with renal impairment compared to subjects with normal renal function. Corresponding values for the main metabolite were higher in subjects with renal impairment compared to healthy subjects. In individuals with mild (creatinine clearance 80–50 mL/min), moderate (creatinine clearance <50 30 mL/min) or severe (creatinine clearance <30 mL/min) renal impairment, riociguat plasma concentrations (AUC) were increased by 43%, 104% or 44%, respectively. There are no data in patients with creatinine clearance <15 mL/min or on dialysis. Due to the high plasma protein binding riociguat is not expected to be dialyzable.

Extrinsic Factors	Drug interactions (combined/alone)	Clinically relevant pharmacokinetic interactions were observed between riociguat and: **Multi-pathway CYP and P-gp/ Bcrp (transporter)inhibitors** In vitro, ketoconazole, classified as strong CYP3A4 and P-glycoprotein (P-gp) inhibitor, has been shown to be a 'multi-pathway CYP and P-gp/'breast cancer resistance protein' (BCRP) inhibitor' for riociguat metabolism and excretion. Concomitant administration of 400 mg once daily ketoconazole led to a 150% (range up to 370%) increase in riociguat mean AUC and a 46% increase in mean Cmax. Terminal half-life increased from 7.3 to 9.2 hours and total body clearance decreased from 6.1 to 2.4 L/h. **P-gp/BCRP inhibitors** Based on in vitro studies, riociguat was found to be a substrate for the membrane transport proteins P gp/BCRP. Inhibitors or inducers of these enzymes or transporters may affect riociguat exposure. **CYP1A1 inhibitors** From the recombinant CYP isoforms investigated in vitro CYP1A1 most effectively catalyzed formation of riociguat main metabolite. The class of tyrosine kinase inhibitors was identified as potent inhibitors of CYP1A1, with erlotinib and gefitinib exhibiting the highest inhibitory potency in vitro. Drug-drug interactions by inhibition of CYP1A1 could result in increased riociguat exposure, especially in smokers with increased CYP1A1 activity. **Strong CYP3A4 inhibitors** Co-administration of clarithromycin (500 mg twice daily), classified as strong and selective CYP3A4 inhibitor and also reported to be a weak-to-moderate P-gp inhibitor, moderately increased riociguat mean AUC by 41% without significant change in Cmax. This is not considered clinically relevant **Antacids** Riociguat exhibits a reduced solubility at neutral pH vs. acidic medium. Co-medication of drugs increasing the upper gastro intestinal pH may lead to lower oral bioavailability. Co-administration of the antacid aluminum hydroxide / magnesium hydroxide reduced riociguat mean AUC by 34% and mean Cmax by 56%.

		Pre and co treatment with the proton pump inhibitor omeprazole (40 mg once daily) reduced riociguat mean AUC by 26% and mean Cmax by 35%. This is not considered to be clinically relevant. **Smoking** Cigarette smoking has been shown to reduce riociguat exposure by 50–60%. **CYP3A4 inducers** Bosentan, reported to be a moderate inducer of CYP3A4, led to a decrease of riociguat steady-state plasma concentrations in PH patients by 27% without compromising the efficacy of the combination.
	Food Effects (fed/fasted)	Intake with food does not affect riociguat exposure (AUC); Cmax was reduced to a minor extent (35% lowering). This is not considered clinically relevant. Therefore riociguat can be taken with or without food.
Expected High Clinical Exposure Scenario	Following oral administration of riociguat to patients with pulmonary hypertension, exposure in these (elderly) subjects is markedly higher (AUC up to 3-fold, C_{max} up to 2-fold) in comparison to young healthy male subjects, most probably due to alterations in drug clearance by the underlying disease. Due to the simultaneous reduction of systemic vascular resistance (SVR) parallel to the reduction of PVR an individual titration scheme was chosen for riociguat to treat PH patients: A bi-weekly increase of dose in steps of 0.5 mg TID at the discretion of the treating physician (as pharmacokinetic steady-state is reached after 3 days and pharmacodynamic steady-state (blood pressure) is reached after 5 days) is considered to be appropriate. This slow and stepwise up-titration allows for adaptation to the altered hemodynamic state with decreasing pulmonary vascular resistance and increasing cardiac output compensating for the simultaneous decrease in systemic vascular resistance. The tight correlation of PVR and SVR with reduction of SVR translating into lowering of systemic blood pressure allows for the use of systolic blood pressure as a safety parameter. The up-titration will be performed as long as patient's trough blood pressure remains above 100 mmHg. This individual dose titration also takes into account the high variability in PK and is therefore deemed appropriate in order to maximize each patient's benefit. Based on the described titration procedure, exposures as assessed in PH patients in Phase II are expected high clinical exposure scenarios. QT/QTc evaluations are therefore implemented into the riociguat Phase III trials in PH patients.	

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/s/

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RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data]

Application Information		
NDA # 204819 BLA#	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: Adempas (proposed) Established/Proper Name: riociguat Dosage Form: immediate-release tablets Strengths: 0.5, 1, 1.5, 2, and 2.5 mg		
Applicant: Bayer HealthCare Pharmaceuticals Agent for Applicant (if applicable):		
Date of Application: February 8, 2013 Date of Receipt: February 8, 2013 Date clock started after UN:		
PDUFA Goal Date: October 8, 2013	Action Goal Date (if different):	
Filing Date: April 9, 2013	Date of Filing Meeting: March 8, 2013	
Chemical Classification: (1,2,3 etc.) (original NDAs only) 1		
Proposed indication(s)/Proposed change(s): Treatment of patients with chronic thromboembolic pulmonary hypertension (WHO Group 4) and pulmonary arterial hypertension (WHO Group 1)		

Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499*** ***and refer to Appendix A for further information.***	☒ 505(b)(1) ☐ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher was submitted, review classification is Priority.***	☐ Standard ☒ Priority ☐ Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☐ Fast Track ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other: The sponsor applied for orphan designations and the designations are pending review by OOPD.	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s): 75629 (PAH and CTEPH)	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.***	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? ***For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm*** ***If no, ask the document room staff to make the appropriate entries.***	X			
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***		X		
If yes, explain in comment column.				
If affected by AIP, has OC/OMPQ been notified of the submission? **If yes,** date notified:				
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.***	Payment for this application: ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☒ Not in arrears ☐ In arrears

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?			X	
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? **[see 21 CFR 314.54(b)(1)].**			X	
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug **[see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs***			X	
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:			X	

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2).Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug Designations and Approvals list at:*** ***http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm***		X		

If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***			X	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: 5 ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	X			
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?		X		
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***			X	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	**X**			
Index: Does the submission contain an accurate comprehensive index?	**X**			
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including:	**X**			

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #				
Applications in "the Program" (PDUFA V) (NME NDAs/Original BLAs)	**YES**	**NO**	**NA**	**Comment**
Was there an agreement for any minor application components to be submitted within 30 days after the original submission?		**X**		
• If yes, were all of them submitted on time?			**X**	
Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	**X**			**see eCTD 5.3.5.4**
Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	**X**			**see signed form 356h**
Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	X			
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X			
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	X			

Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)]. ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*				
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."*** ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***	X			
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***Note:*** *Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies 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." Applicant may not use wording such as, "To the best of my knowledge…"*	X			
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***			X	eCTD

Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* <u>For non-NMEs</u>: *Date of consult sent to Controlled Substance Staff*:		**X**		

Pediatrics	**YES**	**NO**	**NA**	**Comment**

PREA Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)***[2] ***Note**: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*	X			Yes, however, the sponsor submitted a request for orphan designation that is pending review by OOPD.
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?	X			
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? ***If no, request in 74-day letter***			X	
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? ***If no, request in 74-day letter***	X			
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]		X		
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	X			"Adempas" proposed
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***	X			
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☒ Medication Guide (MedGuide) ☒ Carton labels			

[2] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm
[3] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm

	☒ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	X			
Is the PI submitted in PLR format?[4]	X			
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***			X	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	X			
MedGuide, PPI, IFU (plus PI) consulted to patient labeling team? (*send WORD version if available*)	X			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***				
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***				
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***				

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm

All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***	X			QT-IRT 2/21/13
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** May 29, 2008 ***If yes, distribute minutes before filing meeting***	X			
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** November 1, 2012* ***If yes, distribute minutes before filing meeting***		X		* Preliminary responses were sent to the sponsor on 11/1/12.
Any Special Protocol Assessments (SPAs)? **Date(s):** Carcinogenicity SPA only ***If yes, distribute letter and/or relevant minutes before filing meeting***	X			Carcinogenicity

ATTACHMENT

MEMO OF FILING MEETING

DATE: March 8, 2013

BLA/NDA/Supp #: NDA 204819

PROPRIETARY NAME: Adempas

ESTABLISHED/PROPER NAME: riociguat

DOSAGE FORM/STRENGTH: immediate-release tablets / 0.5, 1, 1.5, 2, and 2.5 mg

APPLICANT: Bayer HealthCare Pharmaceuticals

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Treatment of patients with chronic thromboembolic pulmonary hypertension (WHO Group 4) and pulmonary arterial hypertension (WHO Group 1)

BACKGROUND: Bayer submitted this New Molecular Entity (NME) New Drug Application (NDA) for the use of Adempas (riociguat) for the treatment of patients with chronic thromboembolic pulmonary hypertension (WHO Group 4) and pulmonary arterial hypertension (WHO Group 1).

Riociguat is a soluble guanylate cyclase stimulator proposed as 0.5, 1, 1.5, 2, and 2.5 mg mg immediate-release tablets for thrice daily oral administration.

The IND for macitentan was submitted on February 20, 2007. A Pre-IND meeting was held on February 22, 2007. An End-of-Phase 2 meeting was held on May 29, 2008. Preliminary responses for a pre-NDA meeting (that was cancelled by the Division) were sent on November 1, 2012.

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).

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Dan Brum	Y
	CPMS/TL:	Edward Fromm	Y

Cross-Discipline Team Leader (CDTL)	Abraham Karkowsky		Y
Clinical	Reviewer:	Preston Dunnmon	Y
	TL:	CDTL	Y
Social Scientist Review (*for OTC products*)	Reviewer:		
	TL:		
OTC Labeling Review (*for OTC products*)	Reviewer:		
	TL:		
Clinical Microbiology (*for antimicrobial products*)	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	Divya Menon-Anderson	Y
	TL:	Raj Madabushi	Y
Biostatistics	Reviewer:	John Lawrence	Y
	TL:	Hsien "Jim" Hung	N
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Elizabeth Hausner	Y
	TL:	Tom Papoian	Y
Statistics (carcinogenicity)	Reviewer:	Atiar Mohammad Rahman	N
	TL:	Karl Lin	N
Immunogenicity (assay/assay validation) *(for BLAs/BLA efficacy supplements)*	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Monica Cooper Pei-I Chu	Y
	TL:	Kasturi Srinivasachar	Y
Quality Microbiology *(for sterile products)*	Reviewer:		
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Kimberly Defronzo	Y
	TL:	Irene Z. Chan	Y
OSE/DRISK (REMS)	Reviewer:	Jason Bunting	Y
	TL:	Reema Mehta	Y
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:	Sharon Gershon	Y
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers	Jie Li (epidemiology), Kareen Riviere (biopharm), Hobart Rogers (genomics)		Y
Other attendees	Ellis Unger (office director), Norman Stockbridge (director), Steve Grant (deputy director), Mary Ross Southworth (deputy director of safety)		

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues? **If yes,** list issues:	☒ Not Applicable ☐ YES ☐ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**:	☒ Not Applicable
CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☒ YES ☐ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an NME NDA or original BLA , include the reason. For example:***	☒ YES Date if known: August 6 or 7, 2013 ☐ NO ☐ To be determined o ***this drug is not the first in its class***

○ ***this drug/biologic is not the first in its class*** ○ ***the clinical study design was acceptable*** ○ ***the application did not raise significant safety or efficacy issues*** ○ ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	○ ***the clinical study design was acceptable*** ○ ***the application probably will not raise significant safety or efficacy issues*** ○ ***the application probably will not raise significant public health questions on the role of the drug in the diagnosis, cure, mitigation, treatment or prevention of a disease***
• Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL	☐ Not Applicable

(PHARMACOLOGY/TOXICOLOGY) **Comments**:	☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

IMMUNOGENICITY (BLAs/BLA efficacy supplements only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
Environmental Assessment • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
Quality Microbiology (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments**:	☒ Not Applicable ☐ YES ☐ NO
Facility Inspection • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☒ YES ☐ NO
Facility/Microbiology Review (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

CMC Labeling Review **Comments**:	☐ Review issues for 74-day letter

REGULATORY PROJECT MANAGEMENT
Signatory Authority: Ellis Unger, M.D. **Date of Mid-Cycle Meeting** (for NME NDAs/BLAs in "the Program" PDUFA V): May 6, 2013 **21st Century Review Milestones (see attached)** (listing review milestones in this document is optional): **Comments**:

	REGULATORY CONCLUSIONS/DEFICIENCIES
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. List (optional): Review Classification: ☐ Standard Review ☒ Priority Review

	ACTIONS ITEMS
☒	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	BLA/BLA supplements: If filed, send 60-day filing letter
☒	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day

	filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
☒	Send review issues/no review issues by day 74
☒	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☒	Update the PDUFA V DARRTS page (for NME NDAs in "the Program")
☐	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]
☐	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original 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) 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, or
(3) 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) 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, and.

(3) 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) 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, or

(3) 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 OND ADRA or OND IO.

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
03/07/2013

Selected Requirements of Prescribing Information (SRPI)

The Selected Requirements of Prescribing Information (SRPI) version 2 is 48-item, drop-down checklist of critical format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and labeling guidances.

Highlights (HL)

GENERAL FORMAT

YES 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment:

YES 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been is granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

- **For the Filing Period (for RPMs)**
  - *For efficacy supplements:* If a waiver was previously granted, select "**YES**" in the drop-down menu because this item meets the requirement.
  - *For NDAs/BLAs and PLR conversions:* Select "**NO**" in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.
- **For the End-of Cycle Period (for SEALD reviewers)**
  - The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment:

YES 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment:

YES 4. White space must be present before each major heading in HL.

Comment:

YES 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment:

YES 6. Section headings are presented in the following order in HL:

Section	Required/Optional

Selected Requirements of Prescribing Information (SRPI)

• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required
• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a Boxed Warning is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*****
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment:

YES 7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: **"HIGHLIGHTS OF PRESCRIBING INFORMATION"**.

Comment:

Highlights Limitation Statement

YES 9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: "**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE)**."

Comment:

Product Title

YES 10. Product title in HL must be **bolded.**

Comment:

Initial U.S. Approval

YES 11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded,** and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment: *It is worth noting that bosentan and ambrisentan have boxed warnings in labeling.*

Boxed Warning

N/A 12. All text must be **bolded**.

Comment:

N/A 13. Must have a centered heading in UPPER-CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS**").

Comment:

N/A 14. Must always have the verbatim statement "***See full prescribing information for complete boxed warning***." centered immediately beneath the heading.

Comment:

N/A 15. Must be limited in length to 20 lines (this does not include the heading and statement "***See full prescribing information for complete boxed warning.***")

Comment:

N/A 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Comment:

Recent Major Changes (RMC)

N/A 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

Comment:

N/A 18. Must be listed in the same order in HL as they appear in FPI.

Comment:

N/A 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Dosage and Administration, Coronary Stenting (2.2) --- 3/2012".

Comment:

N/A 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage

YES 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: [(Product) is a (name of class) indicated for (indication)]."

Comment: *Please revise as follows: "OPSUMIT is an endothelin receptor antagonist indicated for…"*

Dosage Forms and Strengths

YES 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

Contraindications

YES 23. All contraindications listed in the FPI must also be listed in HL or must include the statement "None" if no contraindications are known.
Comment:

YES 24. Each contraindication is bulleted when there is more than one contraindication.
Comment:

Adverse Reactions

YES 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**".

Comment:

Patient Counseling Information Statement

NO 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product **does not** have FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION"**

If a product **has** FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling."**
- **"See 17 for PATIENT COUNSELING INFORMATION and Medication Guide."**

Comment: *Revise to read "See 17 for PATIENT COUNSELING INFORMATION and Medication Guide". Draft labeling does not refer also to the Medication Guide.*

Revision Date

YES 27. **Bolded** revision date (i.e., "**Revised: MM/YYYY** or **Month Year**") must be at the end of HL.

Comment:

Contents: Table of Contents (TOC)

GENERAL FORMAT

YES 28. A horizontal line must separate TOC from the FPI.

Comment:

YES 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: "**FULL PRESCRIBING INFORMATION: CONTENTS"**.

Comment:

YES 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

Comment:

N/A 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

Comment:

YES 32. All section headings must be **bolded** and in UPPER CASE.

Comment:

YES 33. All subsection headings must be indented, not bolded, and in title case.

Comment:

YES 34. When a section or subsection is omitted, the numbering does not change.

Comment:

YES 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading "**FULL PRESCRIBING INFORMATION: CONTENTS"** must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the Full Prescribing Information are not listed."

Comment:

Full Prescribing Information (FPI)

GENERAL FORMAT

YES 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: "**FULL PRESCRIBING INFORMATION".**

Comment:

YES 37. All section and subsection headings and numbers must be **bolded**.

Comment:

YES 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

YES 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment:

YES 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, [*see Warnings and Precautions (5.2)*].

Comment:

N/A 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

N/A 42. All text is **bolded**.

Comment:

N/A 43. Must have a heading in UPPER-CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS**").

Comment:

N/A 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Contraindications

N/A 45. If no Contraindications are known, this section must state "None".

Comment:

Selected Requirements of Prescribing Information (SRPI)

Adverse Reactions

YES 46. When clinical trials adverse reactions data is included (typically in the "Clinical Trials Experience" subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice."

Comment:

N/A 47. When postmarketing adverse reaction data is included (typically in the "Postmarketing Experience" subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

Comment:

Patient Counseling Information

YES 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:

- "See FDA-approved patient labeling (Medication Guide)"
- "See FDA-approved patient labeling (Medication Guide and Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information)"
- "See FDA-approved patient labeling (Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information and Instructions for Use)"

Comment:

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
02/22/2013